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Odessa National Medical University

Department of General and clinical pharmacology with the pharmacognosy

Educational and methodical manual

for practical classes

in pharmacotherapy with the basics of pharmacokinetics

For the students of the IV course of the pharmaceutical faculty of the specialty "Pharmacy, industrial pharmacy"

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Preface

PHARMACOTHERAPY - a science about the use of drugs for the treatment (diagnosis, prevention and treatment of diseases). From the Greek **pharmakon** - a medicine; **terapeia** - a section of medicine that deals with the study of internal diseases (diagnosis, prevention and treatment).

The main task of pharmacotherapy - familiarization of future pharmacists with the principles of medical therapy of certain nosological groups, which will enhance the professional training of specialists, will play an important role in ensuring the effective and safe use of medicines.

In the process of studying pharmacotherapy on the basis of theoretical material obtained at the departments of physiology, pathology, biochemistry, microbiology, pharmacology, combines knowledge of the etiology, pathogenesis of the main nosological units with the principles of their therapeutic therapy. During the study, students learn at the cognitive level the basic methods of clinical examination of patients, general symptomatology and syndromology of the most common diseases, get acquainted with the general principles of constructing the diagnosis.

Modern pharmacotherapy should be strictly individualized and selective. The golden rule of "Treating the sick, not illness", which until recently was only a good wish, is now becoming more feasible with the help of the current arsenal of medicines.

Pharmacotherapy as an object aims to train specialists who acquire knowledge about the main symptoms and syndromes, diagnostic methods and principles of medical therapy of diseases of internal organs.

The main tasks of the student's study of pharmacotherapy are:

- familiarization with the basic principles of medical ethics and deontology, the rules of the pharmacist's behavior in the clinic, the relationship between the pharmacist and the doctor;
- familiarization with the basic types of medical documentation;
- mastering the basic methods of clinical examination of patients, methods of laboratory and instrumental tracing of patients;
- study of etiopathogenetic features of the most common human diseases;
- assimilation of general syndromology and clinical symptomology of the most common diseases in the clinic of internal diseases;
- study of general principles of pharmacotherapy of the most common diseases of internal organs;
- mastering the general methodology and principles of the choice of drugs for effective and safe pharmacotherapy, taking into account the patient's individual condition and the pharmacological characteristics of the drug;
- assimilation of principles for assessing the effectiveness and safety of the use of drugs during pharmacotherapy.
- Fundamentals of deontology, ethics of relations with medical personnel, patients;
- The main clinical symptoms and syndromes of the most common diseases;

- General principles of diagnostics of diseases of internal organs;
- General principles of interpretation of the results of examination of the patient;
- Types of pharmacotherapy (etiologic, pathogenetic, symptomatic, substitution);
- The main pharmacokinetic parameters of drugs, their changes in different pathologies;
- The main types of medical interaction;
- Major side effects in the appointment of the most commonly used drugs;
- Basic principles and directions of medical therapy of diseases.

This training manual is created in accordance with the curriculum on pharmacotherapy and aims to help the future specialist in pharmacy to develop knowledge about the main symptoms and syndromes, methods of diagnosis and the principles of medical therapy for the most common human diseases. The manual contains information on the basic principles of medical therapy of certain nosological groups of diseases, forms students the general plan of rational and safe therapy in the case of typical pathological processes and their individual manifestations, principles of individual selection of effective and safe drugs based on the data of pharmacodynamics and pharmacokinetics, possible side effects and peculiarities of the use of drugs depending on the course of the disease, its seasonality and age of the patient.

This is necessary for:

- a) understanding of the general principles of interpretation of the results of examination of the patient;
- b) the use of the main types of pharmacotherapy (etiological, pathogenetic, symptomatic, substitution, prophylactic);
- c) the definition of the main directions of pharmacotherapy, rational treatment regimens of diseases, groups of drugs.

This purpose can be achieved by optimally combining a theoretical course with practical classes, in which theoretical information about the etiology, pathogenesis, methods of diagnosis and treatment of diseases are implemented in the process of clinical research, the ability of students to think in terms of pharmacotherapeutic logic is acquired.

TOPIC 1. General methods of clinical examination of patients: subjective (questioning, complaints, anamnesis), physical (examination, palpation, percussion, auscultation). Medicinal, pharmaceutical deontology.

Actuality of topic.

Diagnosis - the science of recognizing various diseases. Doctors of different specialties take part in the diagnostic process. Only recognizing the disease can be successfully treated by the patient. In ancient times, they said: "Who diagnoses well he heals well." Of great importance in conducting the diagnosis are subjective and physical methods of examination.

Purpose of the lesson: The student must know the scheme of the diagnostic process; types of diagnosis; the significance of subjective and physical methods in the diagnosis; interrogation: consistency, provision, basic provisions, meaning for the choice of pharmacotherapy; anamnesis: definitions, species; methods of examination of patients: types, definitions, conditions of conducting; review: species, clinical significance; palpation: types, techniques of conducting; percussion: types, techniques of conducting. auscultation: types, technique of holding, means for conducting. To have the concept of medicinal, pharmaceutical ethics and deontology, to know their significance for pharmacist. To master the aspects of interaction of pharmacist-patient, pharmacist-pharmacist, pharmacist-pharmacist.

Disease - a state of an organism characterized by functional and / or morphological changes due to the action of pathogenetic factors, which lead to the appearance of protective reactions.

The disease is always accompanied by a restriction of adaptation of the organism to the environment, as well as a decrease or loss of ability to work.

Etiology - the doctrine of the causes and conditions of the disease.

Pathogenesis - a set of processes that determine the mechanism of occurrence, course and complication of the disease.

A symptom is a manifestation of a disease that is detected by clinical research methods and is used to diagnose and / or predict a disease.

Allocate symptoms:

- ***subjective*** (indicated by the patient himself) - headache, nausea, etc.
- ***objective*** (detected by means of instrumental, laboratory and other methods of research) - high blood pressure, proteinuria, etc.

In the course of time, the **symptoms** may be **early** and **late**, and, according to the diagnostic meaning, **nonspecific** (fever, general weakness, etc.), **specific** (pain

in the heart, pain in the epigastric) and pathognomonic ones - are manifested in a particular disease (rhythm of the "copper" - with mitral stenosis).

Syndrome - a stable set of a number of symptoms with a single pathogenesis. Syndrome combines a group of symptoms that characterizes one or another disease (dyspnea + heart pain + tachycardia + edema = heart failure syndrome).

Diagnosis - the definition of the disease and condition of the patient on the basis of his comprehensive medical examination.

Before you start the diagnosis you need:

- collect complaints of the patient;
- to find out anamnesis of the disease;
- to evaluate the objective manifestations of the disease (to review the patient and evaluate the data of instrumental and laboratory research)

Complaints - subjective sensations (symptoms) that disturb the patient and, in his opinion, are related to the disease.

Complaints are collected through active patient surveys

The history of the disease (***anamnesis*** - recollection, history) describes its origin and development.

The history of the disease is determined by active patient surveys

An **overview** of the patient can reveal objective manifestations of the disease (change in the shape of the joints, swelling, etc.).

Results from instrumental and laboratory studies can reveal additional objective manifestations of the disease, which can confirm (or refute) the diagnosis of the disease.

For the diagnosis and determination of treatment tactics, the collection of anamnesis of the patient's life and an allergic anamnesis is also of great importance.

Anamnesis of life and allergic history are elucidated by active patient surveys.

The **diagnosis** of the disease can be:

- **previous** (based on complaints, medical history, history of life and allergic history, as well as patient data);
- **final** (based on a preliminary diagnosis, as well as data from instrumental and laboratory studies)

Based on the diagnosis, it is possible to proceed with the definition of those drugs that can be used to treat the disease found in this patient, that is, to the pharmacotherapy.

The diagnosis and appointment of medical treatment to the patient is the prerogative of the MEDICINE !

Medicinal product (drug) or ***drug*** (medicine) - a pharmacological agent (substance) that has undergone clinical trials and is authorized for use in the treatment, prophylaxis and diagnosis of diseases by the authorized body of the country.

Allocate drugs intended for:

- treatment of diseases (pharmacotherapeutic and chemo-therapeutic drugs)

- prevention of diseases
- diagnosis of diseases.

PHARMACOTHERAPEUTIC medicine - used for correction of the disease-affected function (s) of organs and systems;

CHEMOTHERAPEUTIC medicine - used for action on atypical (tumorous) cells, pathogenic microorganisms and helminths in order to suppress their livelihoods.

Medicine is used for:

- actions on the cause of the disease (etiological factor);
- actions on the mechanism of disease development (pathogenic factor);
- elimination of the symptoms of the disease.

Depending on the purpose for which the drug is used, one can distinguish the following directions of pharmacotherapy (**PhT)**:

- **etiotropic PhT**
- **pathogenetic PhT**
- **symptomatic PhT**
- **prophylactic PhT** (used to prevent diseases)
- **substitute PhT** (used to treat diseases associated with insufficient production of hormones, enzymes, etc.).

Etiotropic (Causal) treatment is aimed at eliminating the causes of the disease, for example, apply of antimicrobial agents in infectious diseases and antidotes at governance from toxic substances.

Pathogenetic therapy aimed at eliminating or suppressing mechanisms development of the disease. Most drugs have exactly pathogenetic action - antihypertensive, antiarrhythmic, anti-inflammatory, psychotropic, etc.

Symptomatic therapy is aimed at the elimination or reduction of certain effects of the disease. For symptomatic treatment may include painful drugs, do not affect the cause or mechanism of the disease. However, in some situations (myocardial infarction) they may significantly affect the course of pathological process, providing pathogenetic effect in fact.

Prophylactic (Preventive) therapy is to prevent disease. To preventive means include some antiviral, disinfectant.

Substitution treatment is carried out at a failure of natural biologically active substances. By means of replacement therapy include enzymatic agents, hormones and analogues, vitamins, which are not eliminating the causes of the disease, can provide normal vital functions of the body for many years. For example, insulin preparations.

If a single drug is used to treat a patient, such a FT is called **monotherapy**.

When conducting PhT usually use two or more drugs, in this case it is a **combined pharmacotherapy**.

Combined (compatible) use of a drug can lead to a change in the effects of the means. There are two variants of mutual influence of the drug: synergism and antagonism.

Synergism - promotion of drugs to each other, as a result of which there is an increase in their effects.

The basis of synergy can be the effect of one drug on the pharmacokinetics of another: acceleration or slowing of absorption, displacement from the connection with the protein, inhibition of enzymes involved in biotransformation of drugs, delayed withdrawal.

Synergism may also be due to the pharmacodynamic interaction of the drug. In this case, medicines that have a unidirectional action bind to different molecular substrates. Synergism is the most common reason for using a combination of drugs.

For example, for the treatment of arterial hypertension, a combination of alpha-blockers (reducing the overall peripheral vascular resistance) and beta-blockers (reducing the minute volume of the heart), which effectively lowering high blood pressure, is used.

Antagonism is the complete elimination or partial reduction of the effect of one drug to another.

Allocate physical, chemical and functional antagonism.

Physical antagonism, for example, is detected when one drug is absorbed on the surface of another.

The practical use of physical antagonism - absorption of activated charcoal (or toxins) from poisoning.

Due to the chemical interaction of two drugs, a new combination (with other properties or inactive) is formed - **chemical antagonism**.

Functional antagonism is realized through the functional systems of the organism, among which the drug does not interact, and their counteraction is realized with the help of biosubstrat.

Functional antagonism is used in practice to eliminate the side effects of drugs, as well as with their overdose.

Taking a history

Taking (or receiving) histories is what most of us spend most of our professional life doing, and it is worth doing well. A good history is the biggest step towards correct diagnosis. Try to put the patient at ease: a good rapport may relieve distress. Introduce yourself and check whether the patient is comfortable. Be conversational rather than interrogative in tone. Start with open questions, allow the patient to tell their story, but if they stray off topic, try to gently steer them back towards the important points.

Presenting complaint (PC) Open questions: “Why have you come to see me today?” Record the patient’s own words rather than medical terms.

History of presenting complaint (HPC) When did it start? What was the first thing noticed? Progress since then. Ever had it before? 'SOCRATES' questions: site; onset (gradual, sudden); character; radiation; associations (eg nausea, sweating); timing of pain/duration; exacerbating and alleviating factors; severity (eg scale of 1–10, compared with worst ever previous pain). Direct questioning (to narrow list of possible diagnoses). Specific or 'closed' questions about the differential diagnoses you have in mind (+risk factors, eg travel) and a review of the relevant system.

Past medical history (PMH) Ever in hospital? Illnesses? Operations? Ask specifi - cally about MIJTHREADS: MI, jaundice, TB, high BP, rheumatic fever, epilepsy, asthma, diabetes, stroke, anaesthetic problems.

Drug history (DH) Any tablets, injections, 'over-the-counter' drugs, herbal remedies, oral contraceptives? Ask about allergies and what the patient experienced, eg may be an intolerance (nausea, diarrhoea), or may have been a minor reaction of sensitization (eg rash and wheeze) before full-blown anaphylaxis.

Social history (SH) Probe without prying. "Who else is there at home?" Job. Marital status. Spouse's job and health. Housing—any stairs at home? Who visits—relatives, neighbours, GP, nurse? Are there any dependents at home? Mobility—any walking aids needed? Who does the cooking and shopping? What can the patient not do because of the illness? The social history is all too often seen as a dispensable adjunct, eg while the patient is being rushed to theatre, but vital clues may be missed about the quality of life and it is too late to ask when the surgeon's hand is deep in the belly and they are wondering how radical a procedure to perform. It is worth asking a few searching questions of the GP if they are calling to arrange admission. They may have known the patient and/or family for decades. He or she may even hold a 'living will' or advance directive to reveal your patient's wishes if they cannot speak for themselves. As part of the social history, tactfully ask about alcohol, tobacco & recreational drugs. How much? How long? When stopped? The CAGE questionnaire is useful as a screening test for alcoholism. Quantify smoking in terms of pack-years: 20 cigarettes/day for 1 year equals 1 pack-year. We all like to present ourselves well, so be inclined to double stated quantities (Holt's 'law').

Family history (FH) Areas of the family history may need detailed questioning, eg to determine if there is a signifi cant family history of heart disease you need to ask about the health of the patient's grandfathers and male siblings, smoking, tendency to hypertension, hyperlipidaemia, and claudication before they were 60 years old, as well as ascertaining the cause of death. Ask about TB, diabetes, and other relevant diseases. Draw a family tree. Be tactful when asking about a family history of malignancy.

Functional enquiry helps uncover undeclared symptoms. Some of this may

already have been incorporated into the history. Always enquire if your patient has any ideas of what the problem might be, if he/she has any particular concerns or expectations, and give him/her an opportunity to ask you questions or tell you anything you may have missed. Don't hesitate to review the history later: recollections change (as you will fi nd, often on the post-take ward round when the Consultant is asking the questions!).

Just as skilled acrobats are happy to work without safety nets, so experienced clinicians may operate without the functional enquiry. But to do this you must be experienced enough to understand all the nuances of the presenting complaint.

General questions May be the most signifi cant, eg in TB, endocrine problems, or cancer:

- Weight loss
- Night sweats
- Any lumps
- Fatigue/malaise/lethargy
- Sleeping pattern1
- Appetite
- Fevers
- Itch or rash
- Recent trauma.

Cardiorespiratory symptoms

- Chest pain.
- Exertional dyspnoea (=breathlessness): quantify exercise tolerance and how it has changed, eg stairs climbed, or distance walked, before onset of breathlessness.
- Paroxysmal nocturnal dyspnoea (PND). Orthopnoea, ie breathlessness on lying flat (a symptom of left ventricular failure): quantify in terms of number of pillows the patient must sleep on to prevent dyspnoea.
- Oedema: ankles, legs, lower back (dependent areas).
- Palpitations (awareness of heartbeats): can they tap out the rhythm?
- Cough: sputum, haemoptysis (coughing up blood).
- Wheeze.

Gastrointestinal symptoms

- Abdominal pain (constant or colicky, sharp or dull; site; radiation; duration; onset; severity; relationship to eating and bowel action; alleviating or exacerbating, or associated features).
- Other questions—think of symptoms throughout the GI tract, from mouth to anus:
- Swallowing
- Indigestion
- Stool: colour, consistency, blood, mucus, difficulty flushing away, tenesmus or urgency.

• Nausea/vomiting
• Bowel habit
• Tenesmus is the feeling of incomplete evacuation of the bowels (eg due to a tumour or irritable bowel syndrome).
• Haematemesis is vomiting blood.
• Melaena is altered (black) blood passed PR, with a characteristic smell.

Genitourinary symptoms

• Incontinence (stress or urge).
• Dysuria (painful micturition).
• Urinary abnormalities: colour? Haematuria (streaks or pink urine?) Frothy?
• Nocturia (needing to micturate at night).
• Frequency (frequent micturition) or polyuria (the frequent passing of large volumes of urine).
• Hesitancy (diffi culty starting micturition).
• Terminal dribbling.
• Vaginal discharge.
• Menses: frequency, regularity, heavy or light, duration, painful? First day of last menstrual period (LMP). Number of pregnancies and births. Menarche. Menopause. Any chance of pregnancy now?

Neurological symptoms

• Special senses: Sight, hearing, smell, and taste.
• Seizures, faints, 'funny turns'.
• Headache.
• 'Pins and needles' (paraesthesiae) or numbness.
• Limb weakness ("Are your arms and legs weaker than normal?"), poor balance.
• Speech problems. • Sphincter disturbance.
• Higher mental function and psychiatric symptoms. The important thing is to assess function: what the patient can and cannot do at home, work, etc.

Too sleepy? Think of myxoedema or narcolepsy. Early waking? Think of depression. Being woken by pain is always a serious sign.

Musculoskeletal symptoms

• Pain, stiff ness, swelling of joints.
• Diurnal variation in symptoms (ie worse mornings).
• Functional deficit.
• Signs of systemic disease: rashes, mouth ulcers, nasal stuffiness, malaise and constitutional symptoms.

In the assessment of an arthritic presentation, pay particular attention to the distribution of joint involvement (including spine) and the presence of symmetry. Also look for disruption of joint anatomy, limitation of movement (by pain or contracture), joint effusions and peri-articular involvement. Ask about, and examine for, extra-articular features: skin and nail involvement (include scalp, hairline,

umbilicus, genitalia, and natal cleft—psoriasis can easily be missed); eye signs; lungs; kidneys; heart; GI (eg mouth ulcers, diarrhoea); GU (eg urethritis, genital ulcers); and CNS.

3 screening questions for musculo-skeletal disease:

1 Are you free of any pain or stiff ness in your joints, muscles or back?

2 Can you dress yourself without too much diffi culty?

3 Can you manage walking up and down stairs?

If yes to all 3, serious infl ammatory muscle/joint disease is unlikely.

Presenting symptoms:

• Pattern of involved joints
• Symmetry (or not)
• Morning stiff ness >30min (eg RA)
• Pain, swelling, loss of function, erythema, warmth.

Extra-articular features:

• Rashes, photosensitivity (eg SLE)
• Raynaud's (SLE; CREST; polymyositis and dermatomyositis)
• Dry eyes or mouth (Sjögren's)
• Red eyes, iritis (eg AS)
• Diarrhoea/urethritis (Reiter's)
• Nodules or nodes (eg RA; TB; gout)
• Mouth/genital ulcers (eg Behçet's)
• Weight loss (eg malignancy, any systemic infl ammatory disease).

Related diseases:

• Crohn's/UC (in ank yl osing spondylitis), gonorrhoea, psoriasis

Current and past drugs:

• NSAIDS, DMARDS
• Biological agents (eg TNF-alpha inhibitors)

Family history:

• Arthritis, psoriasis, autoimmune disease

Social history: • Age • Occupation • Sexual history • Ethnicity (eg SLE is commoner in AfricanCaribbeans and Asians) • Ability to function, eg dressing, grooming, writing, walking • Domestic situation, social support, home adaptations • Smoking (may worsen RA).

Thyroid symptoms

• *Hyperthyroidism:* Prefers cold weather, bad tempered, sweaty, diarrhoea, oligomenorrhoea, weight (though often appetite), tremor, palpitations, visual problems.

• *Hypothyroidism:* Depressed, slow, tired, thin hair, croaky voice, heavy periods, constipation, dry skin, prefers warm weather. History-taking may seem deceptively easy, as if the patient knew the hard facts and the only problem was extracting them; but what a patient says is a mixture of hearsay ("She said I looked very pale"), innuendo ("You know, doctor, down below"), legend ("I suppose I bit my tongue; it was a real fit, you know"), exaggeration ("I didn't sleep a wink"), and improbabilities ("The Pope put a transmitter in my brain"). The great skill (and

pleasure) in taking a history lies not in ignoring these garbled messages, but in making sense of them.

History and examination

Advances in genetics are touching all branches of medicine. It is increasingly important for doctors to identify patients at high risk of genetic disease, and to make appropriate referrals. The key skill is drawing a family tree to help you structure a family history as follows:

1 Start with your patient. Draw a square for a male and a circle for a female. Add a small arrow (see below) to show that this person is the propositus (the person through whom the family tree is ascertained).

2 Add your patient's parents, brothers, and sisters. Record basic information only, eg age, and if alive and well (a&w). If dead, note age and cause of death, and pass an oblique stroke through that person's symbol.

3 Ask the key question "Has anybody else in your family had a similar problem as yourself?", eg heart attack/angina/stroke/cancer. Ask only about the family of diseases that relate to your patient's main problem. Do not record a potted medical history for each family member: time is too short.

4 Extend the family tree upwards to include grandparents. If you haven't revealed a problem by now, go no further—you are unlikely to miss important familial disease. If your patient is elderly it may be impossible to obtain good information about grandparents. If so, fill out the family tree with your patient's uncles and aunts on both the mother's and father's sides.

5 Shade those in the family tree aff ected by the disease. = an affected female; = an aff ected male. This helps to show any genetic problem and, if there is one, will help demonstrate the pattern of inheritance.

6 If you have identified a familial susceptibility, or your patient has a recognized genetic disease, extend the family tree down to include children, to identify others who may be at risk and who may benefi t from screening. You should fi nd out who is pregnant in the family, or may soon be, and arrange appropriate genetic counselling. Refer for genetics opinion. The family tree shows these ideas at work and indicates that there is evidence for genetic risk of colon cancer, meriting referral to a geneticist.

Symptoms

Symptoms are features which patients report. Physical signs are elicited at the bedside. Together, they constitute the features of the condition in that patient. Their evolution over time and interaction with the physical, psychological, and social spheres comprise the natural history of any disease. Throughout this chapter, we discuss symptoms in isolation and attempt to classify them into a 'system' or present them below as 'non-specifi c'. This is unnatural but a good first step in learning how to diagnose. All doctors have to know about symptoms and their relief: this is what doctors are for. Part of becoming a good doctor is learning to link symptoms together, to identify those that may be normal, and those that are

worrying. There are many online tools and books that can help with this, but there is no substitute for experience. If you aren't sure, ask a specialist in that area for advice. The following are common ‘non-specific’ presentations

Itch Itching (pruritus) is common and, if chronic, most unpleasant.

Local causes:

Eczema, atopy, urticaria
Scabies
Lichen planus
Dermatitis herpetiformis
Spinal cord tumours (rare)

Systemic:

Liver disease (bile salts, eg PBC)
Uraemia (eg CKD)
Malignancy (eg lymphoma)
Polycythaemia rubra vera
Iron defi ciency anaemia
Diabetes mellitus
Thyroid disease
HIV infection
Old age; pregnancy
Drugs (eg morphine)

Look for local causes: Scabies burrows in finger webs, lice on hair shafts, knee and elbow blisters (dermatitis herpetiformis).

‘Off -legs’—falls and difficulty walking

Common causes of admission in the elderly, and can lead to loss of confi dence and independence. Causes are often multifactorial:

Intrinsic: typically osteo- or rheumatoid arthritis, but remember fractured neck of femur, CNS disease, vision decrease, cognitive impairment, depression, postural hypotension, periph eral neuropathy, medication (eg antihypertensives, sedatives), pain, eg arthritis, parkinsonism (eg drugs: prochlorperazine, neuroleptics, metoclopramide), muscle weakness (consider vitamin D deficiency), incontinence, UTI, pneumonia, anaemia, hypothyroidism, renal impairment, hypothermia and alcohol.

Environment: Poor lighting, uneven walking surface. Treatment includes addressing injuries, reducing risk factors, and reducing the risk of injury, eg treat osteoporosis. A multidisciplinary multifactorial approach alongside occupational therapists and physiotherapists is likely to be beneficial.

If there is ataxia, the cause is not always alcohol: other chemicals may be involved (eg cannabis or prescribed sedatives). There may be a metastatic or non-metastatic manifestation of malignancy, or a cerebellar lesion.

Bilateral weak legs may suggest a cord lesion. If there is associated urinary or faecal incontinence ± saddle anaesthesia or lower limb sensory loss, urgent imaging (MRI) and treatment for cord compression may well be needed.

Fatigue

So common that it is a variant of normality. Only 1 in 400 episodes of fatigue leads to visiting the doctor. Don't miss depression. Even if depressed, still rule out common treatable causes—eg anaemia, hypothyroidism, diabetes. After history and examination: FBC, ESR, U&E, plasma glucose, TFT, ± CXR. Follow up to see what develops, and to address emotional problems. Take a sleep history.

Fevers, rigors, sweats

While some night sweating is common in anxiety, drenching sweats requiring changes of night-clothes are a more ominous symptom associated with infection (eg TB, brucellosis), lymphoproliferative disease, or other malignancies. Patterns of fever may be relevant

Rigors are uncontrolled paroxysms of shivering which occur as a patient's temperature rises rapidly.

Sweating excessively (hyperhidrosis) may be primary (eg hidradenitis suppurativa may be very distressing to the patient)—or secondary to fever, pain or anxiety (cold & sweaty) or a systemic condition: the menopause, hyperthyroidism (warm & sweaty), acromegaly, malignancy, phaeochromocytoma, amyloidosis, or neuroleptic malignant syndrome (+hyper thermia). Or it may reflect gabapentin or opiate withdrawal, or a cholin er gic or parasympathomimetic side-eff ect (amitriptyline, bethanechol, distigmine, spider bites)—also hormonal drugs, eg levothyroxine, gonadorelin or somatostatin analog ues, vasopressin, and ephedrine. Also amiodarone, ciprofloxacin, L-dopa, lisinopril, rivastigmine, ritonavir, pioglitazone, venlafaxine. At the bedside: Ask about all drugs, examine all over for nodes; any signs of hyperthyroidism? Any spleno megaly? Test the urine; do T°, ESR, TSH, FBC & blood culture. Antiperspirants (aluminium chloride 20%=Driclor®), sympathectomy, or iontophoresis may be tried.

Insomnia

This is trivial—until we ourselves have a few sleepless nights. Then sleep becomes the most desirable thing imaginable, and bestowing it the best thing we can do, like relieving pain. But don't give drugs without looking for a cause.

• ***Self-limiting***: Jet lag; stress; shift work; in hospital. We need less sleep as we age.

• ***Psychic***: Depression; anxiety; mania; grief; psychomotor agitation/psychosis.

• ***Organic***: Drugs (many; eg caffeine; mefloquine; nicotine withdrawal); nocturia; alcohol; pain (eg acid reflux—worse on lying down); itch; tinnitus; asthma; dystonias; obstructive sleep apnoea; dementia; restless leg syndrome (check ferritin). Rarer: encephalitis (eg West Nile virus) and encephalopathy (Whipple's; pellagra; HIV; prion diseases, eg CJD, and fatal familial insomnia).

Sleep hygiene: No daytime naps; don't turn in till you feel sleepy; regular bedtime routines. Keep a room for sleep; don't eat or work in it (not viable for much of the world). Less caffeine, nicotine, late exercise (but sexual activity may give excellent torpor!) and alcohol (its abuse causes paradoxical pro-adrenergic

tremor and insomnia). Try monitoring quality with a sleep diary (unless already overobsessive). Music and relaxation may make sleep more restorative and augment personal resources.

Signs

Over 80% of diagnoses should be made on history alone, with the signs you elicit adding an extra 10% and tests only giving the final 5% or so.8 Do not rely on signs or investigations for your diagnosis, but use them rather to confi rm what you suspected from the history. The following signs are not specific to a particular system:

Cyanosis

Dusky blue skin (***peripheral***—of the fingers) or mucosae (***central***—of the tongue), representing 50g/L of Hb in its reduced (hence hypoxic) form, it occurs more readily in polycythaemia than anaemia. *Causes*:

• ***Lung disease*** with inadequate oxygen transfer, eg luminal obstruction, asthma, COPD, pneumonia, PE, pulmonary oedema—may be correctable by increase inspired O2.

• ***Congenital cyanotic heart disease***, where there is admixture, eg transposition of the great arteries or right-to-left shunt (eg VSD with Eisenmenger's syndrome)—cyanosis is not reversed by increasing inspired oxygen.

• ***Rare causes***: methaemoglobinaemia, a congenital or acquired red cell disorder. Acute cyanosis is an emergency. Is there asthma, an inhaled foreign body, a pneumothorax or pulmonary oedema?

Peripheral cyanosis will occur in causes of central cyanosis, but may also be induced by changes in the peripheral and cutaneous vascular systems in patients with normal oxygen saturations. It occurs in the cold, in hypovolaemia, and in arterial disease, and is therefore not a specific sign.

Pallor

May be racial or familial—or from anaemia, shock/faints, Stokes–Adams attack (pale first, then flushing), hypothyroid ism, hypopituitarism, and albinism.

If it's just one limb or digit, think of emboli. *Anaemia* is haemoglobin concentration below the normal range. It may be assessed from the conjunctivae and skin creases. Koilonychia and stomatitis suggest iron defi ciency. Anaemia with jaundice suggests haemolysis.

Skin discolouration

Generalized hyperpigmentation may be genetic (racial) or due to radiation; increase ACTH (cross-reacts with melanin receptors, eg Addison's disease, Nelson's syndrome, ectopic ACTH in bronchial carcinoma); chronic kidney disease (increase urea); malabsorption; chloasma (seen in pregnancy or with the oral contraceptive pill); biliary cirrhosis; haemochromatosis ('bronzed diabetes'); carotenaemia; or drugs (eg chlorpromazine, busulfan, amiodarone, gold).

Obesity

This is defined by the World Health Organization as a BMI of over 30kg/m^2. A higher waist to hip ratio, indicating central fat distribution, is commoner in men and is associated with greater health risks, which include type 2 diabetes mellitus, IHD, dyslipidaemia, increaseBP, osteoarthritis of weight-bearing joints, and cancer (breast and bowel). The majority of cases are not due to specifi c metabolic disorders. Lifestyle change is key to treatment, to increase energy expenditure and reduce intake. Medication ± surgery may be considered if the patient fulfils strict criteria. Conditions associated with obesity include: genetic (Prader–Willi syndrome, Lawrence–Moon syndrome), hypothyroidism, Cushing's syndrome and hypothalamic damage (eg tumour or trauma to damage to satiety regions).

Lymphadenopathy

Causes of lymphadenopathy are either reactive or infiltrative: **Reactive**

Infective

• Bacterial: eg pyogenic, TB, brucella, syphilis.

• Viral: EBV, HIV, CMV, infectious hepatitis.

• Others: toxoplasmosis, trypanosomiasis.

Non-infective: sarcoidosis, amyloidosis, berylliosis, connective tissue disease (eg rheumatoid, SLE), dermatological (eczema, psoriasis), drugs (eg phenytoin).

Infiltrative

Benign histiocytosis—OHCS, lipoidoses.

Malignant

• Haematological: lymphoma or leukaemia: ALL, CLL, AML.

• Metastatic carcinoma: from breast, lung, bowel, prostate, kidney, or head and neck cancers.

Oedema

Pitting oedema: Fluid can either be squeezed out of the veins (increased hydrostatic pressure, eg DVT, right heart failure) or diffuse out because of reduced oncotic pressure (low plasma proteins, eg cirrhosis, nephrotic syndrome, protein losing enteropathy) leading to an osmotic gradient with the tissues. The cause of oedema is still not completely understood.

Periorbital oedema: Oedema around the face has a very different differential; The eyelid skin is very thin so periorbital oedema is usually the first sign—think of allergies (contact dermatitis, eg from eye make-up, stings), angioedema (can be hereditary), infection (-orbital cellulitis can be life threatening, refer to hospital immediately if concerned, other infections include EBV and sinusitis); if there is proptosis think Graves' disease, connective tissue diseases (eg dermatomyositis, SLE, sarcoid, amyloid); and many others. Assess for systemic disease before putting it down to allergies.

Non-pitting oedema: ie non-indentable, is lymphoedema due to poor lymphatic drainage. Can be due to radiotherapy, malignant infi ltration, infection,

filariasis or rarely primary lymphoedema (Milroy's syndrome).

Weight loss

This is a feature of chronic disease and depression; also of malnutrition, malignancy, chronic infections (eg TB, HIV/enteropathic AIDS), diabetes mellitus and hyperthyroidism (typically in the presence of increased appetite). Severe generalized muscle wasting is also seen as part of a number of degenerative neurological diseases and in cardiac failure (cardiac cachexia), although in the latter, right heart failure may not make weight loss a major complaint. Do not forget anorexia nervosa (OHCS) as an underlying cause of weight loss.

Rule out treatable causes, eg diabetes is easy to diagnose—TB can be very hard. For example, the CXR may look like cancer so don't forget to send bronchoscopy samples for ZN stain and TB culture. Unintentional weight loss should always ring alarm bells, so assess patients carefully.

Cachexia

General muscle wasting from famine, or decrease eating (dementia; stroke; MND; anorexia nervosa), malabsorption (entero pathic AIDS/slim disease/Crypto spor idium; Whipple's) or increase catabolism (neoplasia; CCF; TB; chronic kidney disease; leptin increase).

Dizziness

Dizziness is a loose term, so try to clarify if your patient means:

• *Vertigo*, the illusion of rotation of either the patient or their surroundings ± difficulty walking/standing, patients may fall over.

• *Imbalance*, a difficulty in walking straight but without vertigo, from peripheral nerve, posterior column, cerebellar, or other central pathway failure.

• *Faintness*, ie 'light-headedness', seen in anaemia, decrease BP, postural hypotension, hypoglycaemia, carotid sinus hypersensitivity, and epilepsy.

Method and order for routine examination

1 Look at the patient. Healthy, unwell, or in extremis? This vital skill improves with practice. Beware those who are sicker than they look, eg cardiogenic shock; cord compression; non-accidental injury.

2 Pulse, BP, O2 sats, T°.

3 Examine nails, hands, conjunctivae (anaemia), and sclerae (jaundice). Consider: Paget's, acromegaly, endocrine disease (thyroid, pituitary, or adrenal hypo- or hyper-function), body hair, abnormal pigmentation, skin.

4 Examine mouth and tongue (cyanosed; smooth; furred; beefy, eg rhomboid area denuded of papillae by Candida, after prolonged steroid inhaler use).

5 Examine the neck from behind: lymph nodes, goitre.

6 Make sure the patient is at 45° to begin CVS examination in the neck: JVP; feel for character and volume of carotid pulse.

7 The praecordium. Look for abnormal pulsations. Feel the apex beat

(character; position). Any parasternal heave or thrill? Auscultate (bell and diaphragm) apex in the left lateral position, then the other 3 areas and carotids. Sit the patient forward: listen during expiration.

8 Whilst sitting forward, look for sacral oedema.

9 Begin the respiratory examination with the patient at 90°. Observe (and count) respirations; note posterior chest wall movement. Assess expansion, then percuss and auscultate the chest.

10 Sit the patient back. Feel the trachea. Inspect again. Assess expansion of the anterior chest. Percuss and auscultate again.

11 Examine axillae and breasts, if indicated (+chaperone for all intimate examinations).

12 Lie patient flat (1 pillow) to inspect, palpate, percuss, and auscultate abdomen.

13 Look at the legs: any swellings, perfusion, pulses, or oedema?

14 CNS exam: Cranial nerves: pupil responses; fundi; visual fields; visual acuity. Consider corneal reflexes. “Open your mouth; stick your tongue out; screw up your eyes; show me your teeth; raise your eyebrows.” Limbs (most signs are due to central not peripheral nerve lesions): Look for wasting and fasciculation. Test tone in all limbs. “Hold your hands out with your palms towards the ceiling and fingers wide. Now shut your eyes.” Watch for pronator drift. “Keep your eyes shut and touch your nose with each index finger.” “Lift your leg straight in the air. Keep it there. Put your heel on the opposite knee (eyes shut) and run it up your own shin.” You have now tested power, coordination, and joint position sense. Tuning fork on toes and index fi ngers to assess vibration sense.

15 Examine gait and speech. Any abnormalities of higher mental function to pursue?

16 Consider rectal and vaginal examination.

17 Examine the urine with dipstick if appropriate.

In general, go into detail where you find (or suspect) something to be wrong.

Physical examination

The physical examination is not so much an extension of the history, but more of the first investigation, to confirm, exclude, define, or show the progress of the provisional diagnosis as revealed in the history. Even in the emergency department where the history may be brief, eg “trauma”, the examination is to confi rm a fracture, or to decide that a fracture is less likely. The examination sheds further light on the history. As you get better, your physical examination gets briefer. Establish your own routine—practice is the key.

End of the bed

• Look at the patient—are they well or in extremis? What makes you think this? Are they in pain? If so, does it make them lie still (eg peritonitis) or writhe about (eg colic). What is the pattern of breathing: laboured; rapid; shallow; irregular; distressed? Are they obese or cachectic? Is their behaviour appropriate? Can you detect any unusual smell, eg hepatic fetor, cigarettes, alcohol?

• Also take a moment to look around the bed for other clues, eg inhalers, insulin administration kit, walking aids, etc.

Face and body habitus

• Does the patient's appearance suggest any particular diseases, eg acromegaly, thyrotoxicosis, myxoedema, Cushing's syndrome, or hypopituitarism?

• Is there an abnormal distribution of body hair (eg bearded, or hairless) suggestive of endocrine disease?

• Is there anything about the patient to trigger thoughts about Paget's disease, Marfan's, myotonia, or Parkinson's syndrome? Look for rashes, eg the malar flush of mitral disease and the butterfly rash of SLE.

Peripheral stigmata of disease

Specific signs are associated with different diseases: consider the nails (koilonychia = iron deficiency), subcutaneous nodules (rheumatoid, neurofibroma?), and look for lymph nodes (cervical, axillary, inguinal). See specific systems for features to assess for, but for all systems consider:

Skin colour:

• Blue/purple = cyanosis (can also be central only).

• Yellow = jaundice (yellow skin can also be caused by uraemia, pernicious anaemia, carotenaemia—check the sclera: if they are also yellow it is jaundice).

• Pallor: this is non-specific; anaemia is assessed from the palmar skin creases (when spread) and conjunctivae — usually pale if Hb < 80–90g/L: you cannot conclude anything from normal conjunctival colour, but if they are pale, the patient is probably anaemic.

• Hyperpigmentation: Addison's, haemo chromatosis (slate-grey) and amiodarone, gold, silver, and minocycline therapy.

Charts:

• Temperature: varies during the day; a morning oral temperature >37.2ºC or evening >37.7ºC constitutes a fever. Rectal temperatures are generally 0.6ºC above oral temperatures. Remember that temperatures are generally lower in elderly patients and therefore fevers may not be as pronounced. A core temperature < 35ºC indicates hypothermia; special low-reading thermometers may be required.

• Blood pressure and pulse—trends are more important than one-off values; repeat if concerned.

• Urine: check urinalysis and input/output charts if available.

Fluid status When admitting an unwell patient, don't forget to assess their degree of hydration, check skin turgor and mucous membranes, look for sunken eyes, and check capillary refill (if well perfused < 2s) and JVP.

The cardiovascular system: examination

As with any examination routine, begin by introducing yourself, obtaining consent to examine the patient and position them appropriately: for the cardiovascular system, lying on a bed but sitting up at 45°. Expose them to the waist (for female patients, delay this until examining the praecordium). Explain what you are doing throughout.

Hands Finger clubbing occurs in congenital cyanotic heart disease and endocarditis. Splinter haemorrhages, Osler's nodes (tender nodules, eg in finger pulps) and Janeway lesions (red macules on palms) are signs of infective endocarditis. If found, examine the fundi for Roth's spots (retinal infarcts). Are there nail fold infarcts (vasculitis) or nailbed capillary pulsation (Quincke's sign in aortic regurgitation)? Is there arachnodactyly (Marfan's) or polydactyly (ASD)? Are there tendon xanthomata (hyperlipidaemia)?

Pulse

Feel for radio-femoral delay (coarctation of the aorta) and radioradial delay (eg from aortic arch aneurysm).

Blood pressure

Systolic BP is the pressure at which the pulse is first heard as on cuff deflation (Korotkov sounds); the diastolic is when the heart sounds disappear or become muffled (eg in the young). The pulse pressure is the difference between systolic and diastolic pressures. It is narrow in aortic stenosis and hypovolaemia, and wide in aortic regurgitation and septic shock. Defining hypertension is problematic. Examine the fundi for hypertensive changes. Shock may occur if systolic < 90mmHg. Postural hypotension is defined as a drop in systolic > 20 mmHg or diastolic > 10mmHg on standing.

Face Is there corneal arcus or xanthelasma (signifying dyslipidaemia)? Is there a malar flush (mitral stenosis, low cardiac output)? Are there signs of Graves' disease, eg bulging eyes (exophthalmos) or goitre)? Is the face dysmorphic, eg Down's syndrome, Marfan's syndrome —or Turner's, Noonan's, or William's syndromes?

Carotid pulse and **jugular venous pressure**

Radial and brachial pulses

• *Radial*: rate, rhythm; radio–radial delay (palpate pulse bilaterally simultaneously), radiofemoral delay (palpate ipsilateral pulses simultaneously), collapsing pulse (hold pulse with fingers of one hand, wrap the fingers of other hand around forearm, check "any pain in arm/shoulder?", lift arm up straight collapsing pulse, felt as 'waterhammer' pulsation in forearm).

• *Brachial*: (just medial to tendonous insertion of biceps). Waveform character

Praecordium

Palpate

• Apex beat (lowermost lateral pulsation): usually 5th intercostal space in mid-clavicular line; measure position by counting intercostal spaces (sternal notch = 2nd intercostal space). Undisplaced/displaced? Character: impalpable (?dextrocardia/ COPD), tapping (palpable S1), double impulse, sustained/strong. Count rate if pulse irregular (AF).

• Heaves' and 'thrills': place the heel of the hand flat on chest to left then right of sternum. Heave: sustained, thrusting usually felt at left sternal edge (= right ventricular enlargement).Thrill: palpable murmur felt as a vibration beneath your hand.

Auscultating the heart

Auscultate (palpate carotid pulse at the same time)

• Apex (mitral area): Listen with bell and diaphragm. Identify 1st and 2nd heart sounds: are they normal? Listen for added sounds and murmurs; with the diaphragm listen for a pansystolic murmur radiating to the axilla—mitral regurgitation.

• At apex with bell, ask the patient to "Roll over onto your left side, breathe out, and hold it there" (a rumbling mid-diastolic murmur—mitral stenosis).

• Lower left sternal edge (tricuspid area) and pulmonary area (left of manubrium in the 2nd intercostal space): if suspect right-sided mumur, listen with patient's breath held in inspiration.

• Right of manubrium in 2nd intercostal space (aortic area) ejection systolic murmur radiating to the carotids—aortic stenosis.

• Sit the patient up and listen at the lower left sternal edge with patient held in expiration (early diastolic murmur: aortic regurgitation?).

Lungs Examine the bases for creps & pleural effusions, indicative of cardiac failure.

Oedema Examine the ankles, legs, sacrum, and torso for pitting oedema. (You may prefer to examine ankles whilst standing at the foot of the bed as it is a good early clue that there may be further pathology to be found.)

Abdomen Hepatomegaly and ascites in right-sided heart failure; pulsatile hepatomegaly with tricuspid regurgitation; splenomegaly with infective endocarditis.

Fundoscopy Roth spots (infective endocarditis).

Urine dipstick Haematuria.

The respiratory system: examination I

As with any examination routine, begin by introducing yourself, obtaining consent to examine the patient and position them appropriately: for the respiratory system, lying on a bed but sitting up at 45°. Expose them to the waist (for female patients, delay this until examining the chest itself). Explain what you are doing throughout.

1 ***General inspection*** • Assess general state (ill/well/ cachexic) • Look for clues (oxygen, inhalers) • Colour (pale, cyanosed, fl ushed) • Short of breath? Accessory muscle use? • Scars on chest wall? Ask the patient to take a deep breath in, watch chest movement and symmetry, any coughing?

2 ***Hands*** • Inspect: Tobacco staining, peripheral cyanosis, clubbing, signs of systemic disease (systemic sclerosis, rheumatoid arthritis) • Asterixis: Ask the patient to hold their hands out and cock their wrists back.

3 ***Arms*** • Time pulse rate, with fingers still on the pulse, check respiratory rate (this can increase if the patient is aware you are timing it)—and pattern • Bounding pulse (CO2 retention)? • Check blood pressure.

4 ***Neck*** • Trachea: feel in sternal notch (deviated?), assess cricosternal distance in fingerbreadths and feel for tracheal tug • Lymphadenopathy: from behind with patient sat forward palpate lymph nodes of head and neck • JVP raised

in cor pulmonale, fixed and raised in superior vena cava obstruction.

5 ***Face*** • Inspect: for signs of Horner's, conjunctival pallor, central cyanosis (ask patient to stick out tongue), pursed lip breathing.

6 ***Front of chest***

• Apex beat.

• Expansion: Ask patient to "breathe all the way out", place hands, "now a deep breath in", and note distance of thumbs to midline, is expansion equal? Repeat with hands laid on upper chest, equal?

• Tactile vocal fremitus: Ask patient to repeat "99" each time they feel your hand while palpating the chest wall with your fingertips. This is rarely used as more information can be gained from vocal resonance.

• *Percussion*: Percuss over different respiratory segments, comparing right and left.

• *Auscultation*: Ask patient to "take steady breaths in and out through your mouth" and listen with diaphragm from apices to bases, comparing right and left.

• Vocal resonance: Repeat auscultation, asking patient to repeat "99" each time they feel the stethoscope. If marked increased resonance heard, repeat with asking patient to whisper "99"; if clearly heard this is termed 'whispering pectoriloquy' and is a sensitive sign for consolidation. Outside of exams, the choice of vocal resonance or tactile vocal fremitus is a personal preference. Many clinicians prefer vocal resonance as it is an easier skill to master and provides more information than tactile vocal fremitus..

7 ***Back of chest*** • Expansion • Tactile vocal fremitus • Percussion • Auscultation • Vocal resonance.

8 ***To complete the examination*** • Palpate for sacral and ankle oedema • Check peripheral pulses, observation chart for temperature and O2 sats • Examine the sputum pot and check PEFR.

The respiratory system: examination II

Examining the chest:

Palpation *Apex beat*: impalpable? (COPD/pleural effusion/dextrocardia?) Expansion: < sensitive than vocal resonance).

Percussion

Dull percussion note: collapse, consolidation, fibrosis, pleural thickening, or pleural effusion (classically 'stony dull'). Cardiac dullness usually detectable over the left side. Liver dullness usually extends up to 5th rib, right mid-clavicular line; below this, resonant chest is a sign of lung hyperexpansion (eg asthma, COPD). Hyperresonant percussion note: pneumothorax or hyperinflation (COPD).

Auscultation

Normal 'vesicular' breath sounds have a rustling quality. Bronchial breathing: Harsh with a gap between inspiration and expiration, occurs where lung tissue has become firm/solid, eg consolidation, localized fibrosis, above a pleural effusion, or large pericardial effusion (Ewart's sign). May be associated with increased vocal resonance and whispering pectoriloquy. Diminished breath sounds:

Pleural eff usions, pleural thickening, pneumothorax, bronchial obstruction, asthma, or COPD. Silent chest: In life-threat ening asthma severe bronchospasm prevents adequate air entry. Added sounds: Wheezes (rhonchi): caused by air expired through narrowed airways. May be monophonic (single note, signifying a partial obstruction of one airway, eg tumour) or polyphonic (multiple notes, signifying widespread narrowing of airways of diff ering calibre, eg asthma, COPD). Wheeze is also heard in LVF ('cardiac asthma'). Crackles (crepitations): caused by re-opening, during inspiration, of small airways which have become occluded during expiration. May be fine and late in inspiration if coming from distal air spaces (eg pulmonary oedema, fibrosing alveolitis) or coarse and mid-inspiratory if they originate more proximally (eg bronchiectasis). Early inspiratory crackles suggest small airways disease (eg COPD), whereas late/pan-inspiratory crackles suggest disease confined to alveoli. Crackles disappearing on coughing are insignificant. ***Pleural rubs***: caused by movement of visceral pleura over parietal pleura, when both surfaces roughened, eg by inflammatory exudate. Causes include adjacent pneumonia or pulmonary infarction.

Further examination Sputum, temperature charts, O2 sats, PEFR.

The gastrointestinal system: examination

Inspection

Does your patient appear comfortable or in distress? Look for abnormal contours/distension. Tattoos? Cushingoid appearance may suggest steroid use post-transplant or IBD. Inspect (and smell) for signs of chronic liver disease:

- Hepatic fetor on breath
- Gynaecomastia
- Clubbing (rare)
- Purpura (purple-stained skin)
- Scratch marks
- Muscle wasting
- Spider naevi
- Palmar erythema
- Jaundice
- Asterixis

Look for signs of malignancy (cachexia, masses), anaemia, jaundice, Virchow's node. From the end of the bed inspect the abdomen for:

- Visible pulsation (aneurysm)
- Peristalsis
- Scars
- Masses
- Striae (stretch marks, eg pregnancy)
- Distension
- Genitalia
- Herniae

If abdominal wall veins look dilated, assess direction of flow. In inferior vena caval (IVC) obstruction, below the umbilicus blood flows up; in portal hypertension (caput medusae), flow radiates out from the umbilicus.

The cough test: While looking at the face, ask the patient to cough. If this causes abdominal pain, flinching, or a protective movement of hands towards the abdomen, suspect peritonitis.

Hands

Clubbing, leuconychia (whitening of the nails due to hypoalbuminaemia), koilonychia ('spooning' of the nails due to iron, B12, or folate defi ciency), Muehrcke's lines (transverse white lines due to hypoalbuminaemia), blue lanulae (bluish discolouration seen in Wilson's disease). Palmar erythema (chronic liver disease, pregnancy), Dupuytren's contracture (thickening and fibrous contraction of palmar fascia; alcoholic liver disease). Hepatic flap/asterixis (hepatic encephalopathy, uraemia from renal disease), check pulse (and respiratory rate) (infection/sepsis?), palpate for arteriovenous fistulae in the forearm (access for haemodialysis in end-stage renal failure).

Face

Assess for jaundice, anaemia, xanthelasma (PBC, chronic obstruction), Kayser–Fleischer rings (green-yellow ring at corneal margin seen in Wilson's disease). Inspect mouth for angular stomatitis (thiamine, B12, iron deficiency), pigmentation (Peutz–Jeghers syndrome, telangiectasia (Osler–Weber–Rendu syndrome/hereditary haemorrhagic telangiectasia), ulcers (IBD), glossitis (iron, B12, or folate deficiency).

Cervical lymph nodes

Palpate for enlarged left supraclavicular lymph node (Virchow's node/Troisier's sign) (gastric carcinoma?).

Abdomen Inspect: Look around to the flanks for nephrectomy scars. Palpate: Note any masses, tenderness, guarding (involuntary tensing of abdominal muscles—pain or fear of it), or rebound tenderness (greater pain on removing hand than on gently depressing abdomen—peritoneal infl ammation); Rovsing's sign (appendicitis); Murphy's sign (cholecystitis). Palpating the liver: Assess size, regularity, smoothness, and tenderness. Pulsatile (tricuspid regurgitation)? The scratch test is an another way to find the lower liver edge (if it is below the costal margin): start with diaphragm of stethoscope at right costal margin. Gently scratch the abdominal wall, starting in the right lower quadrant, working towards the liver edge. A sharp increase in trans mission of the scratch is heard when the border of the liver is reached. Palpating the spleen: If suspect splenomegaly but cannot detect it, assess patient in the right lateral position with your left hand pulling forwards from behind the rib cage. Palpating the kidneys. Enlarged? Nodular? Palpating the aorta: Normally palpable transmitted pulsation in thin individuals.

Percussion

Confirm the lower border and defi ne the upper border of the liver and spleen (dull in the mid-axillary line in the 10th intercostal space). Percuss all regions of abdomen. If this induces pain, there may be peritoneal infl ammation below (eg an inflamed appendix). Some experts percuss fi rst, before palpation, because even

anxious patients do not expect this to hurt—so, if it does hurt, this is a very valuable sign. Percuss for the shifting dullness of ascites, but ultrasound is a more reliable way of detecting ascites.

Auscultation

Bowel sounds: absence implies ileus; they are enhanced and tink ling in bowel obstruction. Listen for bruits in the aorta, renal and femoral arteries.

The breast: examination

1 Inspection Assess size and shape of any masses as well as overlying surface. Which quadrant? Note skin involvement; ulceration, dimpling (peau d'orange), and nipple inversion/discharge.

2 Palpation of the breast Confirm size, and shape of any lump. Is it fixed/tethered to skin or underlying structures? Is it fluctuant/compressible/ hard? Temperature? Tender? Mobile (more likely to be fibroadenoma)?

3 Palpation of the axilla for lymph nodes Metastatic spread? Ipsilateral/bilateral? Matted? Fixed?

4 Further examination Examine abdomen for hepatomegaly, spine for tenderness, lungs (metastatic spread).

Neurological examination

Neurological examination of the upper limbs

The neurological system is usually the most daunting examination, so learn at the bedside from a senior colleague, preferably a neurologist. Keep practising. Be aware that books present ideal situations: often one or more signs are equivocal or even contrary to expectation; consider signs in the context of the history and try re-examining the patient, as signs may evolve over time. The only essential point is to distinguish whether weakness is upper (UMN) or lower (LMN) motor neuron. Position the patient comfortably, sitting up at 45° and with arms exposed. The general order of examination should be Tone, Reflexes, Power, Coordination, Sensation.

Neurological examination of the lower limbs

If the patient is able to walk, the best way to begin your examination is to ask the patient to remove their lower garments down to underwear, and to walk across the room. Gait analysis gives you more information than any other test. If they aren't able to walk, start with them lying down, legs fully exposed. The general routine should be Gait, Tone, Reflexes, Power, Coordination, Sensation.

Assessing the locomotor system

This aims to screen for rheumatological conditions primarily aff ecting mobility (as a consequence of underlying joint disease). It is based on the **GALS** locomotor screen (**G**ait, **A**rms, **L**egs, **S**pine).

Essence 'Look, feel and move' (active and passive). If a joint looks normal

to you, feels normal to the patient, and has full range of movement, it usu ally is normal. Make sure the patient is comfortable, and obtain their consent before examination. The GALS screening examination should be done in light underwear.

Spine: Observe from behind: Is muscle bulk normal (buttocks, shoulders)? Is the spine straight? Are paraspinal muscles symmetrical? Any swellings/deformities? Observe from the side: Is cervical and lumbar lordosis normal? Any kyphosis? "Touch your toes, please": Is lumbar spine fl exion normal, eg Schober's test? Observe from in front: "Tilt your head" (without moving the shoulders)—tests lateral neck flexion. Palpate for typical fibromyalgia tender points.

Arms: "Try putting your hands behind your head"—tests functional shoulder movement. "Arms out straight"—tests elbow extension and forearm supination/pronation. Any deformity, wasting, or swellings? Squeeze across 2nd–5th metacarpophalangeal joints. Pain may denote joint or tendon synovitis. "Put your index finger on your thumb"—tests pincer grip. Assess dexterity, eg fastening a button or picking up a coin.

Legs: Observe legs: Normal quadriceps bulk? Any swelling or deformity? With patient lying supine: Any leg length discrepancy? Internally/externally rotate each hip in flexion. Passively flex knee and hip to the full extent. Is movement limited? Any crepitus? Find any knee effusion using the patella tap test. If there is fluid, consider aspirating and testing for crystals or infection. With patient standing: Observe feet: Any deformity? Are arches high or flat? Any callosities? These may indicate an abnormal gait of some chronicity. Squeeze across metatarsophalangeal joints: see above. Also: although not in the GALS system, palpate the heel and Achilles tendon to identify plantar fasciitis and Achilles tendonitis often associated with seronegative rheumatological conditions. Examine the patient's shoes for signs of uneven wear.

Gait: Observe walking: Is the gait smooth? Good arm swing? Stride length OK? Normal heel strike and toe off ? Can they turn quickly?

Range of joint movement is noted in degrees, with anatomical position being the neutral position—eg elbow flexion 0°–150° normally, but with fixed flexion and limited movement, range may be reduced to 30°–90°. A valgus deformity deviates laterally (away from the mid-line); a varus deformity points towards the mid-line.

Pharmaceutical Ethics and Deontology

Pharmacy Ethics

Ethic is the systematic study of what is right and good with respect to conduct and character.

Values relating to human conduct, with respect to rightness and wrogness of certain actions in the parmacy profession.

Respect for autonomy: the patient should make the find decision about whether a procedure will be performed on his/her own body - *Let the patient decide.*

Nonmaleficience: Not taking actions that could inflict harm - *First do not harm.*

Beneficence: To do good, to remove harms, to promote welfare - *Do something to help the patient.*

Justice: Equal opportunity to obtain equal treatment for all people - *Health for all.*

Why is pharmacy ethics important? A pharmacist's primary responsibility is to benefit patients and prevent harm by dispensing the right drug in the right Failure to\amount and with complete use information fulfill these responsibilities can lead to loss of disease control, disability, and/or death.

You must be aware of the fact that you are regarded as professional and ethical role models in society. You can maintain this status only by being responsible and providing a high standard of integrity in your activity, together with public confidence.

Pharmacist's Code of Deontology establish the fundamental principles of practicing the profession and judgment rules for the deontological cases at the level of the professional association.

Regulation of Deontology Pharmacists

- The first task of the pharmacist is to care for the health of humanity and animal life by working with each other physicians and veterinarians in full understanding and cooperation.
- The pharmacist have to show maximum care and attention to the preparation of the patient's medication and the, without discrimination.
- The pharmacist can not disclose the secrets that have learned during the profession and art, unless it is a statutory obligation.
- The pharmacist can not give someone other than the medicine written without the consent of the physician and does not refer to the patient or relatives of the patient other than the request of the physician.
- The pharmacist welcomes the question of patients or patient relatives about the type of illness or whether the treatment is good or not, with promising and consoling words that will enhance their spirituality.
- The pharmacist can not be condemned for failing to heal by the medicines were given as magistral formulas or preparations in accordance with the pharmaceutical regulations.
- The pharmacist avoids actions that are incompatible with professional morality and judgment, both during and after the work of art and profession.
- The pharmacist has to keep the honor of the pharmacy professional superior in blications to be made.
- The pharmacists who work in official and professional institutions can not use the rights and facilities provided by these duties for their personal benefits.
- The pharmacist can not participate in, or assist in, acts contrary to the law.

- The pharmacy owner pharmacist can not sell the medical preparations and magistral formulas above the price determined by the Ministry of Health.
- Pharmacists have a good relationship with their colleagues; they help each other in material and spiritual terms.
- The pharmacist tries to ensure that the internship students are well educated.
- The pharmacist has to comply with the decisions of the Pharmacists' Association regarding all kinds of deontology decisions taken within the provisions of this Regulation and the decisions made by the competent authorities about the opening and closing times of pharmacies, holidays and pharmacy watches.

Control questions

1. Subject, content and basic principles of pharmacotherapy, types of pharmacotherapy.
2. Ethics and deontology in medicine and pharmacy.
3. Basic clinical examination methods of the patient and their importance for the pharmacist.
4. General knowledge about etiology, pathogenesis, symptoms and syndromes of the disease
and their significance for pharmacotherapy.
5. The theory and practice of the diagnostic process. Types of diagnosis and rules its design, the importance of choosing mono- or combination therapy.
6. Algorithm for choosing a pharmacotherapy for a particular patient.
7. Basic legislative documents on the provision of medicinal products
and their importance for the pharmacist.
8. Subjective methods of examination of patients.
9. Physical methods of examination of patients.
10. Types of laboratory and instrumental methods of examination of patients and their value.
11. Anamnesis of the patient, types, values for the implementation of effective and safe pharmacotherapy.
12. General examination of the patient, method of implementation, clinical significance
for pharmacotherapy.
13. Palpation of the heart and peripheral vessels, clinical significance. Significance at
implementation of pharmacotherapy. Key characteristics of the pulse.
14. Anthropometric study of man, methods, clinical significance
for pharmacotherapy.
15. Thermometry of the body, technique, clinical significance in the choice and conducting pharmacotherapy.

Control the level of knowledge

1. Fill in the "Types of Diseases" table.

Types of diseases	Make a definition
1). The main illness 2). Concomitant illness 3). Acute illness 4). Chronic Disease 5). Complications of the disease 6). Relapse	

2. Fill out the "Examples of anamnesis" table.

Types of anamnesis	Definition of the concept	Values for diagnostics	Values for rational medical therapy
1). The history of the disease 2). The history of life 3) .Demand history			

3. Fill in the table "Methods of studying the patient".

Methods of studying the patient	Definition of the concept
Physical: - Review - palpation - percussion - auscultation **Instrumental:** - anthropometry - thermometry - X-ray examination endoscopy - biopsy and cytological examination - electrophysiological - ultrasonic research methods - magnetic resonance imaging	

4. Fill in the table "Types of pharmacotherapy":

Type of pharmacotherapy	Definition of the concept	Examples
1. Etiotropic 2. Pathogenetic 3. Symptomatic 4. Replace 5. Prophylactic		

5. Fill in the table "Types of Diagnoses":

Diagnosis	Definition of the concept
1. Prev 2. Differential 3. Ultimate	

6. Fill in the "Kinds com" table.

Kinds com	Definition of the concept, clinical picture	Examples
1. Alcoholic coma 2. Apoplectic coma 3. Hypoglycemic coma 4. Hyperglycemic coma 5. Liver Coma 6. Urema Coma 7. Epileptic Coma		

7. Give definitions of "Types of patient position".

Types of patient position	Definition of the concept	Examples
1. Active position 2. Passive position 3. Forced position		

8. Fill in the table "Constitutional types".

Constitutional types	Definition of the concept
1. Normostenic type 2. Hypertensive type 3. Asthenic type	

9. Fill in the table "Degree of disturbance of consciousness in the patient".

Degree of disturbance of consciousness in the patient	Definition of the concept	Examples
1. Stupor 2. Sopor 3. Coma		

10. Give the definition of "symptom" and "syndrome".

Concept	Definition of the concept	Examples
1. Symptoms		
2. Syndromes		

11. Fill in the table "Morphological elements of skin rashes":

Elements	Definition of the concept	At what states it occurs
Primitive	Spot Papule Blister Bladder Vesicle Pustule Gorbok Node	
Secondary	 Secondary stains Larva Crust Excoriation Crack Erosion Ulcer Scar	

12. Fill in the table "Pathological forms of the chest".

Forms of the chest	Clinical description	Examples of diseases
1. Emphysematous (barrel) 2. Paralytic 3. Rheatious (rickety) 4. Funnel-shaped		

5. Boat-shaped		

13. Fill in the table "Adverse respiratory noises".

Types of respiratory noises	The mechanism of noise formation	Clinical examples
1. Dry wheezing 2. Wet rales 3. Creation 4. Noise of pleurisy friction		

14. Fill out the "Heart Tone" table.

Heart Tone	The mechanism of the formation of a tone	The place of the best listening
1. The first (I) tone 2. The second (II) tone		

15. Fill in the table "Blood Pressure Measurement".

Blood Pressure	Definition of the concept	Conditional norms of norm
1. Systolic blood pressure 2. Diastolic blood pressure 3. Pulse pressure		

References:

Murray Longmore, Ian B. Wilkinson, Andrew Baldwin, Elizabeth Wallin (2014) Oxford handbook of clinical medicine.— 9th ed. New York © Oxford University Press, P. 22-34.

Graham Douglas, Fiona Nicol, Colin Robertson (2013) Macleod's Clinical Examination — 13th ed. Churchill Livingstone Elsevier, P. 451.

TOPIC 2. General laboratory and functional-instrumental methods of research of patients.

Actuality of topic.

Laboratory and instrumental examination methods are based on the latest advances in modern physics, chemistry, immunology and require more or less complex instruments and equipment for them to be carried out and specially trained medical personnel. The application of these methods allows not only to study more deeply the known diseases, but, more importantly, in some cases provides the diagnosis of the disease in the state of preclinical development. Often instrumental research is used to solve complex diagnostic problems in individual patients. Currently, diagnostic centers are being organized, which accumulate the latest equipment, which allows to use it more for more effective examination of patients and accurate diagnosis.

Purpose of the lesson: The student must know the clinical methods of research; types of additional methods of examination of patients, their importance for pharmacotherapy; namely: general and biochemical blood tests: basic parameters, conditional norms, clinical significance; general urine analysis: basic parameters, conditional norms, clinical significance; bacteriological studies of biological environments; main functional methods of studying the characteristics of external respiration: spirometry, pyclometrium, clinical significance; Electrocardiography: recording techniques, key indicators, clinical significance; endoscopic methods of investigation of diseases of internal organs; ultrasonic research methods, clinical significance; X-ray methods for the study of patients.

The essence of laboratory medicine

Laboratory medicine reduces our patients to a few easy-to-handle numbers: this is the discipline’s great attraction—and its greatest danger. The normal range (reference interval) is usually that which includes 95% of a given population (given a normal distribution). If variation is randomly distributed, 2.5% of our results will be ‘too high’, and 2.5% ‘too low’ on an average day, when dealing with apparently normal people. This statistical definition of normality is the simplest. Other definitions may be *normative*—ie stating what an upper or lower limit *should* be. The upper end of the reference interval for plasma cholesterol may be given as 6mmol/L because this is what biochemists state to be the desired maximum. 40% of people in some populations will have a plasma cholesterol greater than 6mmol/L and thus may be at increased risk. The WHO definition of anaemia in pregnancy is an Hb of < 110g/L, which makes 20% of mothers anaemic. This ‘lax’ criterion has the presumed benefit of triggering actions that result in fewer deaths from

haemorrhage. So do not just ask “What is the normal range?”—also enquire about who set the range, for what population, and for what reason.

General principles

• Laboratory testing may contribute to four aspects of medicine: • diagnosis; • prognosis (eg clotting in liver failure); • monitoring disease activity or progression (eg creatinine in chronic kidney disease); • screening (eg phenylketonuria in newborn babies).

• Only do a test if the result will influence management. Make sure you look at the result.

• Do not interpret laboratory results except in the light of clinical assessment (unless forced to by examiners!).

Laboratory staff like to have contact with you. They are an excellent source of help and information for both requests and results.

• If a result does not fi t with the clinical picture, trust clinical judgement and repeat the test. Could it be an artefact? The ‘normal’ range for a test (reference interval) is usually defi ned as the interval, symmetrical about the mean, containing 95% of results in a given population. The more tests you run, the greater the probability of an ‘abnormal’ result of no signifi cance.

Involve the patient. Don’t forget to explain to them where the test fits into their overall management plan.

Getting the best out of the lab—a laboratory decalogue

1 Interest someone from the laboratory in your patient’s problem.
2 Fill in the request form fully.
3 Give clinical details, not your preferred diagnosis.
4 Ensure that the lab knows who to contact.
5 Label specimens as well as the request form.
6 Follow the hospital labelling routine for crossmatching.
7 Find out when analysers run, especially batched assays.
8 Talk with the lab before requesting an unusual test.
9 Be thoughtful: at 16:30h the routine results are being sorted.
10 Plot results graphically: abnormalities show sooner.

Artefacts and pitfalls in laboratory tests

• Do not take blood samples from an arm that has IV fluid running into it.

• Repeat any unexpected and inconsistent result before acting on it.

• For clotting time do not sample from a heparinized IV catheter.

• Serum K+ is over-estimated if the sample is old or haemolysed (this occurs if venepuncture is difficult).

• If using Vacutainers, fill plain tubes first—otherwise, anticoagulant contam ination from previous tubes can cause errors.

• Total calcium results are affected by albumin concentration.
• INR may be over-estimated if citrate bottles are under-filled.
• Drugs may cause analytic errors (eg prednisolone cross-reacts with cortisol). Be suspicious if results are unexpected.
• Food may affect result, eg bananas raise urinary HIAA.

Haematology reference intervals

White cell count (WCC) 4.0–11.0 $\approx 10^9$ /L
Red cell count men: 4.5–6.5 $\approx 10^{12}$ /L;
women 3.9–5.6 $\approx 10^{12}$ /L
Haemoglobin: men: 130–180g/L; women: 115–160g/L
Packed red cell volume (PCV) or haematocrit men: 0.4–0.54L/L; women: 0.37–0.47L/L
Mean cell volume (MCV) 76–96fL
Mean cell haemoglobin (MCH) 27–32pg
Mean cell haemoglobin concentration (MCHC) 300–360g/L
Red cell distribution width (RCDW, RDW) 11.6–14.6%
Neutrophils 2.0–7.5$\approx 10^9$/L; 40–75%
Lymphocytes 1 . 3–3.5 $\approx 10^9$/L; 20–45%
Eosinophils 0.04–0.44 $\approx 10^9$/L; 1–6%
Basophils 0.0–0.10 $\approx 10^9$/L; 0–1%
Monocytes 0.2–0.8 $\approx 10^9$/L; 2–10%
Platelet count 150–400 $\approx 10^9$/L
Reticulocyte count 0.8–2.0%; 25–100 $\approx 10^9$ /L
Prothrombin time (citrated bottle) (factors I, II, VII, X) 10–14s
Activated partial thrombo-plastin time (VIII, IX, XI, XII) 35–45s
D-dimer (citrated bottle, as for INR) <0.5mg/L

Biochemistry reference intervals

Adrenocorticotrophic hormone < 80ng/L
Alanine aminotransferase (ALT) 5–35U/L
Albumin 35–50g/L
Aldosterone 100–500pmol/L
Alkaline phosphatase 30–150U/L (adults)
Alfa-amylase 0–180 Somogyi U/dL
Alfa -fetoprotein < 10kU/L
Angiotensin II 5–35pmol/L
Antidiuretic hormone (ADH) 0.9–4.6pmol/L
Aspartate transaminase 5–35U/L
Bicarbonate 24–30mmol/L
Bilirubin 3–17μmol/L
Calcitonin <0.1μg/L
Calcium (ionized) 1.0–1.25mmol/L

Calcium (total) to correct for albumin 2.12–2.65mmol/L
Chloride 95–105mmol/L
Cholesterol < 5.0mmol/L
VLDL 0.128–0.645mmol/L
LDL < 2.0mmol/L
HDL 0.9–1.93mmol/L
Cortisol AM 450–700nmol/L; midnight 80–280nmol/L
Creatine kinase (CK) men: 25–195U/L; women: 25–170U/L
Creatinine (to lean body mass) 70–150μmol/L
Ferritin 12–200μg/L
Folate 2.1μg/L
Follicle-stimulating hormone (FSH) 2–8U/L in women (luteal); > 25U/L in menopause
Gamma-glutamyl transpeptidase men: 11–51U/L; women: 7–33U/L
Glucose (fasting) 3.5–5.5mmol/L
Growth hormone < 20mu/L
HbA1c = glycosylated Hb (DCCT) 4–6%. 7% ≈ good DM control
HbA1c IFCC (more specific than DCCT) 20–42mmol/mol; 53 ≈ good DM control
Iron men: 14–31μmol/L; women: 11–30μmol/L
Lactate Venous 0.6–2.4mmol/L; Arterial 0.6–1.8mmol/L
Lactate dehydrogenase (LDH) 70–250U/L
Lead <1.8mmol/L
Luteinizing hormone (LH) (premenopausal) 3–16U/L (luteal)
Magnesium 0.75–1.05mmol/L
Osmolality 278–305mosmol/kg
Parathyroid hormone (PTH) <0.8–8.5pmol/L
Potassium 3.5–5.0mmol/L
Prolactin men < 450U/L ; women < 600U/L
Protein (total) 60–80g/L
Red cell folate B 0.36–1.44μmol/L (160–640μg/L)
Renin (erect/recumbent) 2.8–4.5/ 1.1–2.7pmol/mL/h
Sodium1 135–145mmol/L
Thyroid-binding globulin (TBG) 7–17mg/L
Thyroid-stimulating hormone (TSH) 0.5–5.7mU/L widens with age; 4–5 is a grey area
Thyroxine (T4) 70–140nmol/L
Thyroxine (free) 9–22pmol/L
Total iron-binding capacity 54–75μmol/L
Triglyceride 0.55–1.90mmol/L
Triiodothyronine (T3) 1.2–3.0nmol/L
Troponin T <0.1μg/L
Urate men: 210–480μmol/L; women: 150–390μmol/L
Urea1 2.5–6.7mmol/L
Vitamin B12 S 0.13–0.68nmol/L (>150ng/L)
Vitamin D 60–105nmol/L

Arterial blood gases reference intervals

pH: 7.35–7.45 PaCO2: 4.7–6.0kPa
PaO2: >10.6kPa Base excess: ±2mmol/L
Note: 7.6mmHg = 1kPa (atmospheric pressure ≈ 100kPa)

The peripheral blood film

Many haematological (and other) diagnoses are made by careful examination of the peripheral blood film. It is also necessary for interpretation of the FBC indices.

Anisocytosis is variation in RBC size, eg megaloblastic anaemia, thalassaemia, IDA.

Acanthocytes: Spicules on RBCS (unstable RBC membrane lipid structure); causes: splenectomy; alcoholic liver disease; abetalipoproteinaemia; spherocytosis.

Basophilic RBC stippling: Denatured RNA found in RBCS, indicating accelerated erythropoiesis or defective Hb synthesis. Seen in lead poisoning, megaloblastic anaemia, myelodysplasia, liver disease, haemoglobinopathy, eg thalassaemia.

Blasts: Nucleated precursor cells. They are not normally in peripheral blood, but are seen in myelofi brosis, leukaemia and malignant infi ltration by carcinoma.

Burr cells (echinocytes): RBC projections (less marked than in acanthocytes).

Cabot rings: Seen in: pernicious anaemia; lead poisoning; bad infectionю

Dimorphic picture: Two populations of red cells. Seen after treatment of Fe, B12, or folate defi ciency, in mixed deficiency (decrease Fe with decrease B12 or folate), post-transfusion, or with primary sideroblastic anaemia, where a clone of abnormal erythroblasts produce abnormal red cells, alongside normal red cell production.

Howell–Jolly bodies: DNA nuclear remnants in RBCS, which are normally removed by the spleen. Seen post-splenectomy and in hyposplenism (eg sickle-cell disease, coeliac disease, congenital, UC/Crohn's, myeloproliferative disease, amyloid). Also in dyserythopoietic states: myelodysplasia, megaloblastic anaemia.

Hypochromia: Less dense staining of RBCS due to decrease Hb synthesis, seen in IDA, thalassaemia, and sideroblastic anaemia (iron stores unusable).

Left shift: Immature neutrophils are sent out of the marrow, eg in infection.

Leukoerythroblastic film: Immature cells (myelocytes, promyelocytes, metamyelocytes, normoblasts) ± tear-drop RBCS from marrow infiltration/infection (malignancy; TB; brucella; visceral leishmaniasis; parvovirus B19)—or in UC or haemolysis.

Leukaemoid reaction: A marked leucocytosis (WCC $>50\approx10^9$/L). Seen in severe illness, eg with infection or burns, and also in leukaemia.

Pappenheimer bodies: Granules of siderocytes containing iron. Seen in lead poisoning, carcinomatosis, and post-splenectomy. Poikilocytosis is variation in RBC shape, eg in IDA, myelofi brosis, thalassaemia.

Polychromasia: RBCS of different ages stain unevenly (young are bluer). This is a response to bleeding, haematinic replacement (ferrous sulfate, B12, folate), haemolysis, or marrow infi ltration. Reticulocyte count is raised.

Reticulocytes: (normal range: 0.8–2%; or < $85 \approx 10^9$/L). Young, larger RBCs (contain RNA) signifying active erythropoiesis. Increased in haemolysis, haemorrhage, and if B12, iron or folate is given to marrow that lack these.

Right shift: Hypermature white cells: hypersegmented polymorphs (>5 lobes to nucleus) seen in megaloblastic anaemia, uraemia, and liver disease.

Rouleaux formation: Red cells stack on each other (it causes a raised ESR). Seen with chronic infl ammation, paraproteinaemia and myeloma.

Spherocytes: Spherical cells found in hereditary spherocytosis and autoimmune haemolytic anaemia.

Schistocytes: Fragmented RBCS sliced by fi brin bands, in intravascular haemolysis. Look for microangiopathic anaemia, eg DIC, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura (TTP), or pre-eclampsia.

Target cells: (also known as Mexican hat cells,) These are RBCS with central staining, a ring of pallor, and an outer rim of staining seen in liver disease, hyposplenism, thalassaemia—and, in small numbers, in IDA.

Tear-drop RBCS: Seen in extramedullary haemopoiesis; see leukoerythroblastic film.

Anaemia is defined as a **low haemoglobin (Hb)** concentration, and may be due either to a low red cell mass or increased plasma volume (eg in pregnancy). A low Hb (at sea level) is <135g/L for men and <115g/L for women. Anaemia may be due to reduced production or increased loss of RBCS and has many causes. These will often be distinguishable by history, examination, and inspection of the blood film.

Types of anaemia The fi rst step in diagnosis is to look at the ***mean cell volume*** (MCV, *normal* MCV is 76–96 femtolitres, 1015 fL = 1L).

***Low MCV*—microcytic anaemia** (correlates with mean cell Hb<27 picograms).

1 Iron-deficiency anaemia (IDA, most common cause).

2 Thalassaemia (suspect if the MCV is ‘too low’ for the Hb level and the red cell count is increase). Definitive diagnosis needs DNA analysis, although fi nding a normal HbA2 with normal ferritin in a very microcytic picture is suggestive of possible alpha thalassaemia trait.

3 Sideroblastic anaemia (very rare).

NB: the last two are conditions where there is an accumulation of iron, and so tests will show serum iron increase, ferritin increase, and a low total iron-binding capacity (TIBC).

***Normal MCV* (normocytic anaemia)**

1 Acute blood loss

2 Anaemia of chronic disease (or decrease MCV)

3 Bone marrow failure

4 Renal failure
5 Hypothyroidism (or increase MCV)
6 Haemolysis (or increase MCV)
7 Pregnancy

High MCV **(macrocytic anaemia)**
1 B12 or folate deficiency
2 Alcohol excess—or liver disease
3 Reticulocytosis (eg with haemolysis)
4 Cytotoxics, eg hydroxycarbamide
5 Myelodysplastic syndromes
6 Marrow infi ltration
7 Hypothyroidism
8 Antifolate drugs (eg phenytoin)

Haemolytic anaemias do not fit into the above classification as the anaemia may be normocytic or, if there are many young (hence larger) RBCS and reticulocytes, macrocytic. Suspect if there is a reticulocytosis (>2% of RBCS; or reticulocyte count >100≈10^9/L), mild macrocytosis, haptoglobin decrease, bilirubin increase and urobilinogen increase. Often mild jaundice (but no bilirubin in urine as haemolysis causes pre-hepatic jaundice).

Red cell distribution width (RCDW or RDW)

If all the red cells in a sample are about the same size, the graph of their volumes is narrow, as occurs in health. But in mixed anaemias the graph is broad, and an abnormal RCDW may be the first hint of such an anaemia. In coeliac disease, for example, poor absorption of iron (MCV decrease) and folate (MCV increase) may occur, with microcytes and macrocytes circulating simultaneously, so the RCDW is raised. *Anisocytosis* is the visual analogue of this. RCDW = the standard deviation of MCV divided by the mean MCV, multiplied by 100. Reference interval: 11.5–14.6%. If the MCV is high and the RCDW is normal, the cause is likely to be alcohol, liver disease or a marrow problem (chemotherapy or aplastic anaemia).

The differential white cell count

Neutrophils 2–7.5 ≈ 10^9/L (40–75% of white blood cells: but absolute values are more meaningful than percentages).

Increased in *(*ie ***neutrophilia****):*
• Bacterial infections.
• Inflammation, eg myocardial infarction, polyarteritis nodosa.
• Myeloproliferative disorders.
• Drugs (steroids).
• Disseminated malignancy.
• Stress, eg trauma, surgery, burns, haemorrhage, seizure.

Decreased in (ie ***neutropenia***)

• Viral infections.
• Drugs, eg post chemotherapy, cytotoxic agents, carbimazole, sulfonamides.
• Severe sepsis.
• Neutrophil antibodies (SLE, haemolytic anaemia)— increase destruction.
• Hypersplenism, eg Felty's syndrome.
• Bone marrow failure— disease production.

Lymphocytes 1.5–4.5 ≈ 10^9/L (20–45%).

Increased in (ie **lymphocytosis**):

• Acute viral infections.
• Chronic infections, eg TB, Brucella, hepatitis, syphilis.
• Leukaemias and lymphomas, especially chronic lymphocytic leukaemia. Large numbers of abnormal ('atypical') lymphocytes are characteristically seen with EBV infection: these are T cells reacting against EBV-infected B cells. They have a large amount of clearish cytoplasm with a blue rim that flows around neighbouring RBCS.

Decreased in (ie **lymphopenia**):

• Steroid therapy; SLE; uraemia; Legionnaire's disease; HIV infection; marrow infiltration; post chemotherapy or radiotherapy. T-lymphocyte subset reference values: CD4 count: 537–1571/mm3 (low in HIV infection). CD8 count: 235–753/mm3 ; CD4/CD8 ratio: 1.2–3.8.

Eosinophils 0.04–0.4 ≈ 10^9/L (1–6%).

Increased in (ie **eosinophilia**):

• Drug reactions, eg with erythema multiforme.
• Allergies: asthma, atopy.
• Parasitic infections (especially invasive helminths).
• Skin disease: especially pemphigus, eczema, psoriasis, dermatitis herpetiformis. Also seen in malignant disease (including lymphomas and eosinophilic leukaemia), PAN, adrenal insuffi ciency, irradiation, Löffler's syndrome, and during the convalescent phase of any infection.

The hypereosinophilic syndrome (HES) is a severe disease of unknown cause, in which an increased eosinophil count (>1.5 ≈ 10^9/L for >6 weeks) leads to end-organ damage (endomyocardial fibrosis/restrictive cardiomyopathy, skin lesions, thrombo embolic disease, lung disease, neuropathy, and hepatospleno megaly). Oral steroids ± mepoli zumab (an anti-interleukin-5 monoclonal antibody). If FIP1L1-PDFRA genotype, dia g nose myeloprolif erative HES/eosinophilic leukaemia (imatinib is 1st choice).

Monocytes 0.2–0.8 ≈ 10^9/L (2–10%).

Increased in (ie **monocytosis**): Post chemo- or radiotherapy, chronic infections (eg malaria, TB, brucellosis, protozoa), malignant disease (including M4 and M5 acute myeloid leukaemia, and Hodgkin's disease), myelodysplasia.

Basophils 0–0.1 ≈ 10^9/L (0–1%).

Increased in (ie **basophilia**): myeloproliferative disease, viral infections, IgE-mediated hypersensitivity reactions (eg urticaria, hypo thyroid ism), and inflammatory disorders (eg UC, rheumatoid arthritis).

Leukocytes provide the main defense against bacterial infection. Monocytes and granulocytes are phagocytic cells that can kill ingested bacteria through the generation of reactive intermediates. Monocytes also release inflammatory mediators that increase the activity of lymphocytes.

Neutrophils

Neutrophils (i.e., polymorphonuclear leukocytes) are the predominant white blood cell in the peripheral blood. They are morphologically recognizable by their characteristic segmented nucleus. Neutrophils also contain cytoplasmic granules that give them a characteristic appearance and are functionally important.

Neutrophils achieve intracellular killing of bacteria through chemotaxis, adhesion, and phagocytosis. Chemotaxis is the ordered movement of the cell toward an attracting stimulus, such as bacterial formyl peptides or complement fragments (i. C3b and C5a). Neutrophils adhere to endothelial cells by interaction of neutrophil surface glycoproteins (i.e., CD11b/CD18) with endothelial adhesion molecules (i.e., intracellular adhesion molecule 1 and endothelial leukocyte adhesion molecule 1), a process called margination. In response to a chemotactic stimulus, the adherent neutrophils move toward the target along the endothelial surfacee.

The syndrome of leukocyte adhesion deficiency underscores the importance of neutrophil adhesion as the first step in bacterial killing. This rare congenital disease is caused by the absence of surface expression of the CD11b/CD18 complex on neutrophils. Neutrophils fail to adhere to endothelium, are unable to undergo chemotaxis, and do not phagocytose or kill bacteria. Patients have severe, life-threatening bacterial infections despite high levels of circulating neutrophils.

Phagocytosis requires recognition of target bacteria or debris by the neutrophil. Targets are opsonized by the surface binding of immunoglobulin or complement factor C3b. The neutrophil has surface receptors for C3b and the Fc portion of immunoglobulin G, which allows recognition and binding to the opsonized target. The target then becomes engulfed in a phagocytic vacuole, which fuses with neutrophil granules inside the cell.

Intracellular killing occurs by oxygen-dependent and oxygenindependent mechanisms. Contents of the primary granules, including cathepsin G, defensins, and lysozyme, break down the bacterial cell wall and kill the target organism. However, the major mechanism of bacterial killing is the respiratory burst. Stimulation of the neutrophil activates a membrane-bound oxidase complex, which generates superoxide through the transfer of an electron from reduced nicotinamide-adenine dinucleotide phosphate (NADPH). The interaction of superoxide with water generates hydroxyl ions. Myeloperoxidase catalyzes the formation of hypochlorite ion from hydrogen peroxide and chloride. The NADPH oxidase is a multisubunit enzyme. Absence or decreased activity of any one subunit

impairs bacterial killing and results in chronic granulomatous disease, a congenital illness in which patients are predisposed to life-threatening bacterial infections.

Neutrophil granules give neutrophils their characteristic appearance and have important functions in neutrophil-mediated activation and killing. Primary granules arise early in myeloid differentiation and are found in neutrophils and monocytes. They contain a large number of proteins, including myeloperoxidase, acid hydrolases, and neutral proteases. These granules fuse with the phagocytic vacuole and aid in the digestion of ingested bacteria. Secondary granules arise later in the differentiation pathway and give the neutrophil its characteristic granular (electrondense) appearance. These granules contain lactoferrin, transcobalamin, and the matrix-modifying enzymes collagenase and gelatinase. On neutrophil stimulation, the granules are released into the extracellular space. Lactoferrin and transcobalamin act as antibacterial proteins by sequestering iron and vitamin B12 away from bacteria, and collagenase and gelatinase break down connective tissues at the site of inflammation.

Abnormalities in neutrophil granules have been described in rare clinical syndromes. Absence of myeloperoxidase produces surprisingly mild symptoms and may be associated with defects in control of fungal infections. Secondary granule deficiency is rare and is associated with a slight increase in the risk of bacterial infections.

Eosinophils and Basophils

Eosinophils and basophils arise from myeloid precursors in the bone marrow. They transit rapidly from the marrow to the blood and into the peripheral tissues, where they play a role in allergic and inflammatory reactions. Like neutrophils, they have secondary granules that give them a characteristic appearance and are functionally important. Both cell types occur in small numbers under normal conditions.

Although eosinophils are capable of phagocytosis, most of the activity of these cells is mediated through the release of granule contents. The eosinophil numbers are elevated in parasitic and helminthic infections, in which these cells are thought to play a role in the allergic response to those organisms. Cell numbers are also elevated in allergic reactions and in collagen vascular diseases, linking their function to immunomodulation. Hypereosinophilic syndromes, in which extremely high levels of eosinophils can be seen, are rare, and hypereosinophilia can be associated with damage to the lung, peripheral nervous system, and endocardial tissues.

Basophils appear to play a role in immediate hypersensitivity reactions and chronic inflammatory conditions. Their levels are increased in chronic myeloid leukemias.

Monocytes

Monocytes arise from a common myeloid precursor along with granulocytes under the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colonystimulating factor (M-CSF). Most circulating monocytes are marginated along the walls of blood vessels. They migrate from the vessels into tissues, where they develop into macrophages.

The monocyte-macrophage lineage has many diverse functions. These phagocytic cells perform chemotaxis, phagocytosis, and intracellular killing in much the same manner as neutrophils. They are especially important in killing infectious mycobacterial, fungal, and protozoal species.

Monocytes interact with other components of the immune system. They are antigen-presenting cells for T lymphocytes, they are capable of cellular cytotoxicity, and they secrete certain cytokines. The macrophages (i.e., differentiated monocytes) that process antigens and present them to T lymphocytes take on different forms in different tissues: Langerhans cells in the skin, interdigitating cells in the thymus, and dendritic cells in the lymph nodes. Antigen-presenting cells are nonphagocytic, and the process by which they internalize antigen is not fully understood. Protein antigens are partially digested and expressed on the cell surface in association with major histocompatibility complex class II (Ia) antigens. This feature permits interaction with and activation of helper T cells. Other macrophages, such as Kupffer cells of the liver and alveolar macrophages of the lung, play an important role in removing particulate and cellular debris and senescent erythrocytes from the circulation.

Monocytes are capable of antibody-dependent and antibodyindependent cytotoxicity against tumor cells. Cytotoxicity is increased by tumor necrosis factor, interleukin-1, and interferon, which are secreted by monocytes. Monocytes secrete large numbers of immunomodulatory proteins (e.g., tumor necrosis factor, interleukin-1, interferon), cytokines (e.g., granulocyte colony-stimulating factor [G-CSF], GM-CSF), coagulation proteins, cell adhesion proteins, and proteases.

DETERMINANTS OF PERIPHERAL NEUTROPHIL NUMBERS

Most granulocyte precursors are in the bone marrow, where maturation occurs over 6 to 10 days. Marrow precursors represent 20% of the granulocyte mass, and the storage pool represents 75% of the granulocyte mass. Peripheral neutrophils represent only 5% of the total granulocyte mass.

Neutrophils circulate in transit between the marrow and peripheral tissues. More than one half of the circulating neutrophils adhere to the vascular endothelium (margination). The halflife of a neutrophil in the circulation was thought to be 6 to 12 hours, but in vivo studies suggest it may be as long as 3 to 4 days. After neutrophils migrate into tissues, they survive another 1 to 4 days. The peripheral neutrophil count therefore represents a sampling of less than 5% of the total granulocyte pool and is taken during a very short interval of the total neutrophil lifespan.

The peripheral white cell count is a poor reflection of granulocyte kinetics. Abnormalities in neutrophil number can occur rapidly and may reflect a change in marrow granulocyte production or a shift among various cellular compartments. An elevated peripheral white cell count may result from increased marrow production, or it may reflect mobilization of neutrophils from the marginated pool or release from the marrow storage pool. Similarly, a low granulocyte count may reflect decreased marrow production, increased margination or sequestration in the spleen, or increased destruction of peripheral cells.

The total peripheral white cell count represents the sum of lymphocytes and granulocytes. The significance of an elevated or depressed leukocyte count depends on the nature of the cellular elements that are increased or decreased. Leukocytosis is a nonspecific term that may denote an increase in lymphocytes (i.e., lymphocytosis) or neutrophils (i.e., granulocytosis). In rare cases, increases may reflect excessive numbers of monocytes or eosinophils. Leukocytosis related to an elevation in the neutrophil count is called neutrophil leukocytosis or neutrophilia.

Extreme elevation of the white blood cell count to more than 50,000 cells/µL of blood with the premature release of early myeloid precursors is called a leukemoid reaction, which may be associated with inflammation and infection. It requires consideration of a diagnosis of myeloproliferative disease, especially chronic myelogenous leukemia (CML). Evaluation of the peripheral blood smear may reveal characteristic changes that provide clues to the underlying disorder. A leukoerythroblastic smear shows immature granulocytes, teardrop-shaped erythrocytes, nucleated erythrocytes, and increased platelets. These changes reflect marrow infiltration (i.e., myelophthisis) by fibrous tissue, granulomas, or neoplasm. As with leukocytosis, leukopenia may reflect lymphopenia or neutropenia. Neutropenia is defined by an absolute neutrophil count of less than 1500 cells/µL.

NEUTROPHILIA

Neutrophilia (i.e., leukocytosis) usually results from other processes, and it rarely indicates a primary hematologic disorder However, patients with a persistently elevated neutrophil count, especially associated with an elevated hematocrit or platelet count, should be evaluated to rule out a primary myeloproliferative disorder. Peripheral blood evaluation for the BCR/ABL fusion product can be performed to rule out CML, and assays for JAK2 and calreticulin mutations can help to rule out non-CML myeloproliferative neoplasms. A leukocyte alkaline phosphatase assay was formerly used to rule out CML because the result was 0 in chronic phase CML, but with the advent of BCR/ABL testing, it has become obsolete.

Neutrophilia related to acute infection, stress, or acute steroid administration primarily reflects demargination and is usually transient. Persistent neutrophilia usually reflects chronic bone marrow stimulation. Nevertheless, a bone marrow aspirate and biopsy are rarely indicated in the work-up of neutrophilia. The exception is for patients who demonstrate leukoerythroblastic changes, for which a bone marrow examination and culture may be indicated to rule out tuberculosis or fungal infection, marrow infiltration with tumor, or marrow fibrosis. Cytogenetic and molecular studies should be performed to help eliminate the diagnosis of marrow malignancies, and the marrow should be cultured for mycobacteria and fungi.

NEUTROPENIA

Differential Diagnosis

Neutropenia (i.e., leukopenia) may reflect decreased production, increased sequestration, or peripheral destruction of neutrophils. Patients should first be evaluated for splenomegaly to rule out the possibility of sequestration.

For patients who are completely asymptomatic and for whom previous studies are unavailable, the possibility of constitutional or cyclic neutropenia should be entertained and can be evaluated by serial peripheral blood counts. The normal neutrophil count varies among ethnic groups and is lower in American blacks (i.e., constitutional neutropenia) than it is in whites. Cyclic neutropenia is a relatively benign disorder, in which cyclical changes occur in all hematopoietic cell lines but are most dramatic in the neutrophil lineage. At the nadir of the neutrophil counts, patients may have infections, but the disease is often clinically silent. In contrast, patients with congenital agranulocytosis or severe congenital neutropenia (SCN) exhibit profound neutropenia and infections in the perinatal period. Kostmann's syndrome is a subset of SCN that was described 50 years ago as an autosomal recessive disorder; later studies demonstrated that SCN might be autosomal dominant, autosomal recessive, X-linked, or sporadic and that the causes were also heterogeneous. About 50% of autosomal dominant SCN and almost 100% of cyclic neutropenia cases are associated with inherited mutations in the neutrophil elastase gene. The mutations are thought to produce a misfolded neutrophil elastase protein, which accumulates in the endoplasmic reticulum and activates the unfolded protein response. This complex cellular stress response coordinates the degradation of misfolded protein in the endoplasmic reticulum and can trigger cellular apoptosis if the stress is severe. Later studies have established that autosomal recessive SCN (i.e. Kostmann's syndrome) is caused by mutations in the HAX1 gene, which encodes a mitochondrial protein that is required for stabilization of the mitochondrial membrane. Absence of HAX1 results in loss of the mitochondrial membrane potential and induction of apoptosis recessive disorder; later studies demonstrated that SCN might be autosomal dominant, autosomal recessive, X-linked, or sporadic and that the causes were also heterogeneous.

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Until G-CSF became available, most patients with SCN died in early childhood, but the availability of cytokine therapy has prolonged survival. However, SCN is also associated with a significantly increased incidence of acute leukemia, a complication that has become apparent as patients survive longer. Up to 30% of patients with SCN develop acute myelogenous leukemia over 10 years.

Acute myelogenous leukemia in these patients is often associated with truncation mutations in the G-CSF receptor. These acquired somatic mutations may contribute to the pathogenesis of leukemia but do not contribute to the congenital neutropenia. The role of the G-CSF receptor mutations in the pathogenesis of leukemic transformation is controversial, as is the relationship between G-CSF therapy and the acquisition of these mutations.

Neutropenia may occur during or after viral, bacterial, or mycobacterial infections. Postviral neutropenia is especially common in children and probably reflects increased neutrophil consumption and a viral suppression of marrow neutrophil production. Neutropenia may be seen as a complication of overwhelming sepsis and is associated with a poor prognosis.

Drug-induced neutropenia may reflect dose-dependent marrow suppression or an idiosyncratic immune response. The former is one of the most common complications of chemotherapeutic drugs and is also common with antibiotics such as sulfamethoxazole-trimethoprim. Chloramphenicol causes dose-dependent marrow suppression, although its more ominous complication is the rare idiosyncratic reaction that gives rise to marrow aplasia. Drugs that are most commonly associated with neutropenia include clozapine, sulfasalazine, ticlopidine, and the thionamide antithyroid agents. Most drug-induced neutropenias respond rapidly to discontinuation of the offending agent. The administration of G-CSF speeds recovery.

Autoimmune neutropenia may be seen as a primary disease or as a secondary manifestation of systemic autoimmune disease or lymphoproliferative disease. Primary autoimmune neutropenia is a disorder of infants and young children that resolves spontaneously in more than 90% of patients within 2 years. Secondary autoimmune neutropenia is a common accompaniment to systemic lupus erythematosus. Although not usually clinically severe, neutropenia is often a marker of disease activity.

Neutropenia in rheumatoid arthritis is associated with splenomegaly (i.e., Felty’s syndrome) and is part of the spectrum of large granular lymphocyte (LGL) leukemia. LGL leukemia is a clonal expansion of suppressor T cells. Patients who develop LGL in association with rheumatoid arthritis share a common HLA-DR4 haplotype with patients with Felty’s syndrome, suggesting that they are in a common spectrum of disease. LGL is also a relatively common cause of acquired neutropenia in elderly patients in the absence of rheumatoid arthritis. Recent data have linked LGL to mutations in the STAT3 gene.

Lymphocytes

The central cell of the immune system is the lymphocyte. **Lymphocytes** mediate the adaptive immune response, providing specificity to the immune system by responding to specific pathogens and conferring long-lasting immunity to reinfection. Lymphocytes are derived from pluripotent hematopoietic stem cells that reside in the bone marrow and give rise to all of the cellular elements of the blood. The two major functional classes of lymphocytes—B lymphocytes (B cells) and T lymphocytes (T cells)—are distinguished by their site of development,

antigenic receptors, and function. The major disorders of lymphocytes include neoplastic transformations of specific subsets of lymphocytes that result in an array of lymphomas or leukemias, congenital or acquired defects in lymphocyte development or function with resultant immunodeficiency syndromes, and physiologic responses to infection or antigenic stimulation that may lead to lymphadenopathy, lymphocytosis, or lymphocytopenia.

B Cells

B cells are characterized by cell surface immunoglobulins (i.e., antibodies). Their major function is to mount a humoral immune response to antigens by producing antigen-specific antibodies. B cells develop in the bone marrow in a series of highly coordinated steps that involve sequential rearrangement of the heavy- and light-chain immunoglobulin genes and expression of B-cell–specific cell surface proteins. Rearrangement of the immunoglobulin genes results in generation of a large repertoire of B cells that are each characterized by an immunoglobulin molecule with unique antigenic specificity. Mature B cells migrate from the bone marrow to lymphoid tissue throughout the body and are readily identified by cell surface immunoglobulin and antigens that are B cell specific, including CD19, CD20, and CD21. In response to antigen binding to cell surface immunoglobulin, mature B cells are activated to proliferate and undergo differentiation to end-stage plasma cells, which lose most of their B-cell surface markers and produce large quantities of soluble antibodies. Neoplastic disorders of B cells arise from B cells at different stages of development, and B-cell lymphomas can have highly varied morphology and cell surface expression of B-cell antigens (i.e., immunophenotype).

T Cells

T cells perform an array of functions in the immune response, including those that are regarded as classic cellular immune responses. T-cell precursors migrate from the bone marrow to the thymus, where they differentiate into mature T-cell subsets and undergo selection to eliminate autoreactive T cells that respond to self-peptides. In the thymus, T-cell precursors undergo a coordinated process of differentiation that involves rearrangement and expression of the T-cell receptor (TCR) genes and acquisition of cell surface proteins that are unique to T cells, including CD3, CD4, and CD8.

As T cells mature in the thymus, they ultimately lose the CD4 or CD8 protein. Mature T cells are composed of two major groups: CD4+ and CD8+ cells. After T-cell maturation and selection in the thymus, mature CD4+ and CD8+ T cells migrate to lymph nodes, spleen, and other sites in the peripheral immune system. Mature T cells constitute about 80% of peripheral blood lymphocytes, 40% of lymph node cells, and 25% of splenic lymphoid cells.

Mature CD4+ and CD8+ T-cell subsets mediate distinct immune functions. CD8+ cells kill virus-infected or foreign cells and suppress immune functions; CD8+ cells are called cytotoxic T cells. CD4+ cells activate other immune response cells such as B cells and macrophages by producing cytokines and through direct cell contact; CD4+ cells are caled helper T cells. Similar to B cells, T cells express unique TCR molecules that recognize specific peptide antigens. In contrast to B

cells, T cells respond only to peptides that are processed intracellularly and bound to (or presented by) specialized cell surface antigenpresenting proteins, designated major histocompatibility complex (MHC) molecules. CD4+ and CD8+ T cells are MHC class restricted in their response to peptide-MHC complexes. CD4+ cells recognize antigenic peptide fragments only when they are presented by MHC class II molecules, and CD8+ cells recognize antigenic peptide fragments only when they are presented by MHC class I molecules. Binding of the TCR by a specific peptide-MHC complex triggers activation signals that lead to the expression of gene products that mediate the wide diversity of helper functions of CD4+ cells or cytotoxic effector functions of CD8+ cells.

Lymphoid System

Lymphocytes localize to the peripheral lymphoid tissue, which is the site of antigen-lymphocyte interaction and lymphocyte activation. The peripheral lymphoid tissue is composed of lymph nodes, the spleen, and mucosal lymphoid tissue. Lymphocytes circulate continuously through these tissues through the vascular and lymphatic systems.

The lymph nodes are highly organized lymphoid tissues that are sites of convergence of the lymphatic drainage system, which carries antigens from draining lymph to the nodes, where they are trapped. A lymph node consists of an outer cortex and an inner medulla. The cortex is organized into lymphoid follicles composed predominantly of B cells. Some of the follicles contain central areas or germinal centers, where activated B cells undergo proliferation after encountering a specific antigen, that are surrounded by a mantle zone. The T cells are distributed more diffusely in paracortical areas surrounding the follicles The spleen traps antigens from blood rather than from the lymphatic system and is the site of disposal of senescent red cells. The lymphocytes in the spleen reside in the areas described as the white pulp, which surround the arterioles entering the organ. As in lymph nodes, the B and T cells are segregated into a periarteriolar lymphoid sheath that is composed of T cells and flanking follicles composed of B cells. The mucosa-associated lymphoid tissues (MALTs) collect antigen from epithelial surfaces and include the gut-associated lymphoid tissue (i.e., tonsils, adenoids, appendix, and Peyer’s patches of the small intestine) and more diffusely organized aggregates of lymphocytes at other mucosal sites.

Lymphocytes circulate in the peripheral blood and represent 20% to 40% of peripheral blood leukocytes in adults; the proportion is higher in newborns and children. Between 80% and 90% of peripheral blood lymphocytes are T cells, and the remaining lymphocytes are largely B cells. A small percentage of peripheral blood lymphoid cells represents a third category of lymphoid cells that are referred to as natural killer (NK) cells. These cells do not bear the characteristic cell surface molecules of B or T cells, and their immunoglobulin or TCR genes have not undergone rearrangement. Morphologically, the cells are large, with abundant cytoplasm containing azurophilic granules, and they are often called large granular lymphocytes. Functionally, they are part of the innate immune system, responding nonspecifically to a wide range of pathogens without requiring prior antigenic exposure.

Urinalysis

Perform dipstick urinalysis whenever you suspect renal disease. This is a crude way of checking whether the urine contains anything that it shouldn't, eg protein, blood, glucose. Abnormalities can reflect renal tract or systemic disease and usually require further investigation.

Proteinuria and nephrotic syndrome: Normal protein excretion is 3g/d, hypoalbuminaemia, oedema. Nephrotic range proteinuria (>3g/d) is almost always a sign of glomerular disease. Urine dipstick is unreliable for quantifying protein excretion; use spot protein : creatinine ratio or albumin : creatinine ratio on an early morning MSU.

Proteinuria particularly requires formal quantification.

Proteinuria Consensus is now to avoid 24h collections (costly, inaccurate) and use albumin:creatinine ratio (ACR) or protein:creatinine ratio (PCR) on a random urine sample, ideally an early morning sample as this avoids orthostatic proteinuria. ACR is preferred to PCR, especially in diabetics.

Normal ACR is < 2.5 (men) or < 3.5 (women). Transient rises to ~5 can occur with fever or exercise. Causes of raised ACR/PCR: glomerular or tubular disease (eg nephrotic syndrome), DM, amyloidosis, increase BP, interstitial nephritis, heavy metals, multiple myeloma (though dipsticks do not detect light chains), pregnancy, CCF.

Microalbuminuria: Ultra-sensitive dipsticks are now available to measure microalbuminuria (albumin excretion 30–300mg/24h). Causes: DM, increase BP, minimal change GN.

Haematuria: Blood in the urine may arise from anywhere in the renal tract. Take haematuria seriously, as it may be the only sign of GU malignancy (esp if >40yrs old and a smoker). However, in the majority of cases it has a benign cause (eg infection, renal stones). The question of who to refer haematuria patients to (urologist or nephrologist). It is classified as visible (VH—previously known as macroscopic, frank) or non-visible (NVH—found on dipstick or microscopy). Non-visible is subdivided into symptomatic (sNVH—with LUTS—dysuria, hesitancy, urgency) and asymptomatic (aNVH). Dipstick of fresh urine is more sensitive than MSU, which has a high false –ve rate, therefore no need to confirm every positive dip with microscopy. However, MC&S of urine is useful for further analysis of cause. Patients with one episode of VH, one of sNVH or persistent aNVH require further assessment.

- Exclude transient causes: (UTI, vigorous exercise, menstruation).
- Check creatinine/eGFR, proteinuria (spot ACR or PCR) and BP.
- Painless VH usually means bladder cancer; refer urgently.
- In aNVH or if systemic symptoms, consider FBC, ESR, CRP, blood film, clotting (NB do not simply attribute haematuria to anticoagulants/antiplatelet agents).

• Urine MC&S to look for infection, malignant/infl ammatory cells, casts, crystals.

• USS and rapid referral to nephrology if rapid decline in GFR or haematuria with proteinuria, casts or dysmorphic cells. Red cell casts ≈ glomerular bleeding.

Oliguria and **polyuria**:

Oliguria is a urine output of < 0.5mL/kg/h. Pathological causes: Pre-renal, ie decrease perfus ion; intrinsic renal, ie renal parenchymal disease; post-renal, ie obstruction.

Polyuria is the voiding of abnormally high volumes of urine, usually from high fluid intake—or diabetes mellitus, diabetes insipidus, hypercalcaemia, renal medullary disorders (urine concentrating ability is impaired).

Microalbuminuria (30–300mg albumin/24h) gives early warning of impending renal problems and is also a strong independent risk factor for cardiovascular disease. Standard dipsticks do not detect this, so use specialized dipsticks or estimate using an albumin : creatinine ratio of >2.5 in men or >3.5 in women. Microalbuminuria is a silent harb inger of serious renal and cardiovascular risk. In one study, 30% of those with type 2 diabetes mellitus died within ~5 years of developing micro albuminuria. This is partly preventable by use of ACE-i.

All others should be monitored in primary care with annual review of urine dip, BP, eGFR and proteinuria (ACR/PCR); refer if above features appear. *Causes*: Renal: neoplasia, glomerulonephritis (often IgA nephropathy), tubulointerstitial nephritis, polycystic kidney disease, papillary necrosis, infection (pyelonephritis), trauma. *Extrarenal*: Calculi, infection, neoplasia, trauma (eg from catheter). Some drugs can cause haematuria: eg, captopril, cephalosporins, ciprofloxacin, furosemide, NSAIDS. Ask about risk factors for renal tract cancer (smoking, chronic analgesic use, toxin exposure). *Imaging*: AXR is no longer used for primary assessment of stones, CTKUB is fi rst choice investigation. NB Not all women with recurrent UTI + haematuria need cystoscopy, but have a good reason not to (Reynard's rule).

Others urine reference intervals

- ***Glucose*** DM, pregnancy, sepsis, renal tubular damage.
- ***Ketones***: Starvation, keto acidosis.
- ***Leucocytes*****:** UTI, vaginal discharge.
- ***Nitrites***: UTI, high-protein meal.
- ***Bilirubin*****:** Obstructive jaundice.
- ***Urobilinogen***: Pre-hepatic jaundice.
- ***Specifi c gravity***: Normal range (NR): 1.000–1.030.
- ***pH***: NR: 4.5–8 (acid–base balance).
- ***Cortisol (free)*** < 280nmol/24h

- ***Hydroxyindole acetic acid*** 16–73μmol/24h
- ***Hydroxymethylmandelic acid (HMMA, VMA)*** 16–48μmol/24h
- ***Metanephrines*** 0.03–0.69μmol/mmol
- ***Creatinine*** (or< 5.5μmol/day)
- ***Osmolality*** 350–1000mosmol/kg
- ***17-oxogenic steroids*** men: 28–30μmol/24h; women: 21–66μmol/24h
- ***17-oxosteroids (neutral)*** men: 17–76μmol/24h; women: 14–59μmol/24h
- ***Phosphate*** (inorganic) 15–50mmol/24h
- ***Potassium*** 14–120mmol/24h
- ***Protein***< 150mg/24h
- ***Protein creatinine ratio*** < 3mg/mmol
- ***Sodium*** 100–250mmol/24h

Using dipsticks

Store dipsticks in a closed container in a cool, dry place, not refrigerated. If improperly stored, or past expiry date, do not use. Dip the dipstick briefl y in urine, run edge of strip along container and hold strip horizontally. Read at the specified time—check instructions. For haematuria.

Urine specific gravity (SG) is not a good measure of osmolality. Causes of low SG (<1.003): diabetes insipidus, renal impairment. Causes of high SG (>1.025): diabetes mellitus, adrenal insuffi ciency, liver disease, heart failure, acute water loss.

Sources of error in interpreting dipstick results

Bilirubin: False +ve: phenothiazines. False –ve: urine not fresh, rifampicin.

Urobilinogen: False –ve: urine not fresh. Normally present in urine due to metabolism of bilirubin in the gut by bacteria and subsequent absorption. Excess may give a false +ve test for prophobilinogen.

Ketones: L-dopa aff ects colour (false +ve). 3-Hydroxybutyrate gives a false –ve.

Blood: *False* +ve *dipstick haematuria*: haemo globinuria, dehydration, myoglobinuria (eg in rhabdomyolysis), porphyria, phenindione, phenolphthalein, or contamination with menstrual blood. False –ve: low urinary pH, air-exposed dipsticks.

Urine glucose: Depends on the test strips used, some can give false +ve but can give false +ve to peroxide, chlorine; and false –ve with ascorbic acid, salicylate, L-dopa.

Protein: *False* +ve: urine pH>7.5; concentrated urine; frank haematuria; presence of penicillin, sulfonamides, pus, semen or vaginal secretions. *False* –ve: dilute urine; non-albumin urinary proteins.

Urine microscopy

Usually done by local laboratory. Put a drop of fresh, unspun urine on the slide, cover with a coverslip and examine under low and high power, looking for

red and white cells, bacteria, casts and crystals. Some example images are shown above. When interpreting laboratory results remember:

• >10/mm3 white cells in an unspun specimen is abnormal, often from UTI.

• >2/mm3 red cells is abnormal, see haematuria.

• Casts are cylindrical bodies formed in the lumen of distal tubules, and can bewaxy, granular, hyaline or cellular. Some types can indicate specifi c diseases.

• Crystals are common in old or cold urine and may not signify pathology. They are important in stone formers.

Sputum examination

Always inspect any sputum produced, however unpleasant this task may be. Send suspicious sputum for microscopy (Gram stain and auramine/ZN stain, if indicated), culture, and cytology.

• Black carbon specks in the sputum suggests smoking, the most common cause of increased sputum production.

• Yellow/green sputum suggests infection, eg bronchiectasis, pneumonia.

• Pink frothy sputum suggests pulmonary oedema.

• Bloody sputum (haemoptysis) may be due to malignancy, TB, infection, or trauma, and requires investigation for these causes.

• Clear sputum is probably saliva.

Instrumental examination

Electrocardiogram (ECG) — a methodical approach

ECG—a dditional points

Where to place the chest leads

Note C1 = V1 etc.

V1: right sternal edge, 4th intercostal space

V2: left sternal edge, 4th intercostal space

V3: half-way between V2 and V4

V4: 5th intercostal space, mid-clavicular line; all subsequent leads are in the same horizontal plane as V4

V5: anterior axillary line

V6: mid-axillary line (V7: posterior axillary line)

Good skin preparation (clean with non-alcoholic wipe, shave if hairy, etc.) will improve ECG quality. Finish 12-lead ECGs with a long rhythm strip in lead II.

• ***Rate***: At usual speed (25mm/s) each ‘big square’ is 0.2s; each ‘small square’ is 0.04s. To calculate the rate, divide 300 by the number of big squares per R–R interval.

• ***Rhythm***: If cycles are not clearly regular, use the ‘card method’: lay a card along ECG, marking positions of 3 successive R waves. Slide the card to and fro to check that all intervals are equal. If not, note if: slight but regular lengthening and

then shortening (with respiration)—sinus arrhythmia common in the young; are different rates multiples of each other—varying block; or is it 100% irregular—atrial fibrillation (AF) or ventricular fi bril lation (VF)? Sinus rhythm is characterized by a P wave (upright in II, III, & aVF; inverted in aVR) followed by a QRS complex. AF has no discernible P waves and QRS complexes are irregularly irregular. Atrial flutter has a 'sawtooth' baseline of atrial depolarization (~300/min) and regular QRS complexes. Nodal rhythm has a normal QRS complex but P waves are absent or occur just before or within QRS complexes. Ventricular rhythm has QRS complexes >0.12s with P waves following them.

• ***Axis***: The mean frontal axis is the sum of all the ventricular forces during ventricular depolarization. The axis lies at 90° to the isoelectric complex (ie the one in which positive and negative defl ections are equal). Normal axis is between –30° and +90°. As a simple rule of thumb, if the complexes in leads I and II are both 'positive', the axis is normal. Left axis deviation (LAD) is –30° to –90°. Causes: LVH, left anterior hemiblock, inferior MI, VT from LV focus, Wolff–Parkinson–White (WPW) syndrome (some types). Right axis deviation (RAD) is +90° to +180°. Causes: RVH, PE, anterolateral MI, left posterior hemiblock (rare), WPW syndrome (some types).

• ***P wave*****:** Normally precedes each QRS complex, and upright in II, III, & aVF but inverted in aVR. Absent P wave: AF, sinoatrial block, junctional (AV nodal) rhythm. Dissociation between P waves and QRS complexes indicates complete heart block. P mitrale: bifid P wave, indicates left atrial hypertrophy. P pulmonale: peaked P wave, indicates right atrial hypertrophy. Pseudo-P-pulmonale seen if K+ is decreased.

• ***PR interval*****:** Measure from start of P wave to start of QRS. Normal range: 0.12–0.2s (3–5 small squares). A prolonged PR interval implies delayed AV conduction (1st degree heart block). A short PR interval implies unusually fast AV conduction down an accessory pathway, eg WPW.

• ***QRS complex***: : Normal duration: < 0.12s. If < 0.12s this suggests ventricular conduction defects, eg a bundle branch block. Large QRS complexes suggest ventricular hypertrophy. Normal Q wave < 0.04s wide and < 2mm deep. They are often seen in leads V5 and V6, aVL and I, and reflect normal septal depolarization, which usually occurs from left to right. Pathological Q waves may occur within a few hours of an acute MI.

• ***QT interval***: Measure from start of QRS to end of T wave. It varies with rate. Calculate corrected QT interval (QTc) by dividing the measured QT interval by the square root of the cycle length. Normal QTc: 0.38–0.42s. Prolonged QT interval: acute myocardial ischaemia, myocarditis, bradycardia (eg AV block), head injury, hypothermia, U&E imbalance (decreases K+, Ca2+, Mg2+ are decreased), congenital (Romano–Ward and Jervell–Lange–Nielson syndromes); sotalol, quinidine, antihist amines, macrolides (eg erythromycin), amiodarone, phenothiazines, tricyclics.

• ***ST segment***: Usually isoelectric. Planar elevation (>1mm) or depression (>0.5mm) usually implies infarction or ischaemia, respectively.

• ***T wave****:* Normally inverted in aVR, V1 and occasionally V2. Abnormal if inverted in I, II, and V4–V6. Peaked in hyperkalaemia and flattened in hypokalaemia.

• ***J wave:*** Seen in hypothermia, subarachnoid haemorrhage and hypercalcaemia.

Exercise ECG testing

The patient undergoes a graduated, treadmill exercise test, with continuous 12-lead ECG and blood pressure monitoring. There are numerous treadmill protocols; the 'Bruce protocol' is the most widely used.

Indications:

• To help confirm a suspected diagnosis of IHD. NICE suggests that this should only be used when there is diagnostic uncertainty in people with known CAD (eg previous MI or angioplasty), and not to make a primary diagnosis.

• Assessment of exercise-induced arrhythmias.

Contraindications:

• Recent Q wave MI (<5 days ago) or unstable angina

• Severea aortic stenosis

• Uncontrolled arrhythmia, hypertension, or heart failure

• Acute myocarditis or pericarditis

• Acute aortic dissection, acute pulmonary embolism

Be cautious about arranging tests that will be hard to perform or interpret:

• Complete heart block, LBBB

• Pacemaker patients, digoxin use

• Osteoarthritis, COPD, stroke, or other limitations to exercise

Stop the test if:

• Chest pain, dyspnoea, cyanosis or pallor occurs.

• The patient feels faint, exhausted, or is in danger of falling.

• ST is rising >1mm in leads without diagnostic Q waves (with or without chest pain).

• Atrial or ventricular arrhythmia (not just ectopics).

• Fall in blood pressure >10mmHg from baseline, failure of heart rate or blood pressure to rise with eff ort, SBP >230mmHg and/or DBP >115mmHg.

• Development of AV block or LBBB.

• 90% maximal heart rate for age is achieved: [(220 age) ± 10].

Interpreting the test:

A positive test only allows one to assess the probability that the patient has IHD. 75% of people with signifi cant coronary artery disease have a positive test, but so do 5% of people with normal arteries (the false-positive rate is even higher in middle-aged women, eg 20%). The more positive the result, the higher the predictive accuracy. Down-sloping ST depression is much more signifi cant than up-sloping, eg 1mm J-point depression with down-sloping ST segment is 99% predictive of 2–3 vessel disease.

Morbidity: 24 in 100,000.

Mortality: 10 in 100,000.

Ambulatory ECG monitoring (eg Holter monitor)

Continuous ECG monitoring for 24h may be used to try to pick up paroxysmal arrhythmias. However, >70% of patients will not have symptoms during the period of monitoring. ~20% will have a normal ECG during symptoms and only up to 10% will have an arrhythmia coinciding with symptoms. Give these patients a recorder they can activate themselves during an episode. Recorders may be programmed to detect ST segment depression, either symptomatic (to prove angina) or to reveal 'silent' ischaemia (predictive of re-infarction or death soon after MI).

'Loop' recorders record only when activated by the patient—they cleverly save a small amount of ECG data before the event—useful if the arrhythmia causes loss of consciousness: the patient can press the button when they wake up. They are more expensive but also more cost-eff ective than Holter monitors, as the pick-up rate of signifi cant disease is higher. These may also be implanted just under the skin (eg Reveal Device), and are especially useful in patients with infrequent episodes.

Echocardiography

This non-invasive technique uses the differing ability of various structures within the heart to reflect ultrasound waves. It not only demonstrates anatomy but also provides a continuous display of the functioning heart throughout its cycle. There are various types of scan:

M-mode (motion mode): A single-dimension (time) image.

2-dimensional (real time): A 2D, fan-shaped image of a segment of the heart is produced on the screen, which may be 'frozen'. Several views are possible and the 4 commonest are: long axis, short axis, 4-chamber, and subcostal. 2D echocardiography is good for visualizing conditions such as: congenital heart disease, LV aneurysm, mural thrombus, LA myxoma, septal defects.

3D echocardiography is now possible with matrix array probes, and is termed 4D (3D + time) if the images are moving.

Doppler and colour-flow echocardiography: Different coloured jets illustrate flow and gradients across valves and septal defects.

Tissue Doppler imaging: This employs Doppler ultrasound to measure the velocity of myocardial segments over the cardiac cycle. It is particularly useful for assessing longitudinal motion—and hence long-axis ventricular function, which is a sensitive marker of systolic and diastolic heart failure.

Trans-oesophageal echocardiography (TOE) is more sensitive than transthoracic echocardiography (TTE) as the transducer is nearer to the heart. Indications: diagnosing aortic dissections; assessing prosthetic valves; finding cardiac source of emboli, and IE/SBE. Don't do if oesophageal disease or cervical spine instability.

Stress echocardiography

Echocardiograms performed during supine exercise or immediately following upright exercise may demonstrate exercise-induced segmental wall motion abnormalities as an indicator of ischemia. In experienced laboratories, the test accuracy is comparable to that obtained with scintigraphy—though a higher proportion of tests is technically inadequate. While exercise is the preferred stress because of other information derived, pharmacologic stress with high-dose dobutamine (20–40 mcg/kg/min) can be used as an alternative to exercise.

Uses of echocardiography

Quantifi cation of global LV function: Heart failure may be due to systolic or diastolic ventricular impairment (or both). Echo helps by measuring end-diastolic volume. If this is large, systolic dysfunction is the likely cause. If small, diastolic. Pure forms of diastolic dysfunction are rare. Differentiation is important; as vasodilators are less useful in diastolic dysfunction as a high ventricular filling pressure is required. Echo is also useful for detecting focal and global hypokinesia, LV aneurysm, mural thrombus, and LVH (echo is 5–10 times more sensitive than ECG in detecting this).

Estimating right heart haemodynamics: Doppler studies of pulmonary artery flow and tricuspid regurgitation allow evaluation of RV function and pressures.

Valve disease: The technique of choice for measuring pressure gradients and valve orifice areas in stenotic lesions. Detecting valvular regurgitation and estimating its significance is less accurate. Evaluating function of prosthetic valves is another role.

Congenital heart disease: Establishing the presence of lesions, and significance.

Endocarditis: Vegetations may not be seen if < 2mm in size. TTE with colour Doppler is best for aortic regurgitation (AR). TOE is useful for visualizing mitral valve vegetations, leafl et perforation, or looking for an aortic root abscess.

Pericardial effusion is best diagnosed by echo. Fluid may first accumulate between the posterior pericardium and the left ventricle, then anterior to both ventricles and anterior and lateral to the right atrium. There may be paradoxical septal motion.

HCM: Echo features include asymmetrical septal hypertrophy, small LV cavity, dilated left atrium, and systolic anterior motion of the mitral valve.

Cardiac catheterization

This involves the insertion of a catheter into the heart via the femoral or radial artery or venous system, and manipulating it within the heart and great vessels to:

- Sample blood to assess oxygen saturation and measure pressures.
- Inject radiopaque contrast medium to image cardiac anatomy and blood flow.
- Perform angioplasty (± stenting), valvuloplasty, and cardiac biopsies, or to do procedures, eg transcatheter ASD closure.
- Perform intravascular ultrasound or echocardiography.

During the procedure, ECG and arterial pressures are monitored continuously. In the UK, the majority are performed as day-case procedures.

Indications:

• Coronary artery disease: diagnostic (assessment of coronary vessels and graft patency); therapeutic (angioplasty, stent insertion).

• Valvular disease: diagnostic (to assess severity); therapeutic valvuloplasty (if the patient is too ill or declines valve surgery).

• Congenital heart disease: diagnostic (assessment of severity of lesions); therapeutic (balloon dilatation or septostomy).

• Other: cardiomyopathy; pericardial disease; endomyocardial biopsy

Pre-procedure checks:

• Brief history/examination; NB: peripheral pulses, bruits, aneurysms.

• Investigations: FBC, U&E, LFT, clotting screen, CXR, ECG.

• Consent for angiogram ± angioplasty ± stent ± CABG. Explain reason for procedure and possible complications (below).

• IV access, ideally in the left hand.

• Patient should be nil by mouth (NBM) from 6h before the procedure.

• Patients should take all their morning drugs (and pre-medication if needed) — but withhold oral hypoglycaemics.

Post-procedure checks:

• Pulse, blood pressure, arterial puncture site (for bruising or swelling?), foot pulses.

• Investigations: FBC and clotting (if suspected blood loss), ECG

Complications:

• Haemorrhage: Apply firm pressure over puncture site. If you suspect a false aneurysm, ultrasound the swelling and consider surgical repair.

• Contrast reaction: This is usually mild with modern contrast agents.

• Loss of peripheral pulse: May be due to dissection, thrombosis, or arterial spasm. Occurs in < 1% of brachial catheterizations. Rare with femoral catheterization.

• Angina: May occur during or after cardiac catheterization. Usually responds to sublingual GTN; if not give analgesia and IV nitrates.

• Arrhythmias: Usually transient. Manage along standard lines.

• Pericardial tamponade: Rare, but should be suspected if the patient becomes hypotensive and anuric.

• Infection: Post-catheter pyrexia is usually due to a contrast reaction. If it persists for < 24h, take blood cultures before giving antibiotics.

Mortality: < 1 in 1000 patients, in most centres.

Intra-cardiac electrophysiology

This catheter technique can determine types and origins of arrhythmias, and locate (and ablate) aberrant pathways (eg causing atrial flutter or ventricular tachycardia). Arrhythmias may be induced, and the effectiveness of control by

drugs assessed. Radiofrequency ablation may be used to destroy aberrant pathways or to prevent AF.

CT angiography

CT angiogram permits contrast-enhanced imaging of coronary arteries during a single breath hold. It can diagnose significant (>50%) stenosis in CAD with an accuracy of 89%. Its negative predictive value is > 99%, which makes it an effective non-invasive alternative to routine coronary angiography to rule out CAD.

Coronary Angiography

Selective coronary arteriography is the definitive diagnostic procedure for CAD. It can be performed with low mortality (about 0.1%) and morbidity (1–5%), but due to the invasive nature and cost, it is currently recommended only in patients with a high pretest probability of CAD.

Coronary arteriography should be performed in the following circumstances if percutaneous transluminal coronary angioplasty or bypass surgery is a consideration:

1. Life-limiting stable angina despite an adequate medical regimen.
2. Clinical presentation (unstable angina, postinfarction angina, etc) or noninvasive testing suggests high-risk disease .
3. Concomitant aortic valve disease and angina pectoris, to determine whether the angina is due to accompanying coronary disease.
4. Asymptomatic older patients undergoing valve surgery so that concomitant bypass may be done if the anatomy is propitious.
5. Recurrence of symptoms after coronary revascularization to determine whether bypass grafts or native vessels are occluded.
6. Cardiac failure where a surgically correctable lesion, such as LV aneurysm, mitral regurgitation, or reversible ischemic dysfunction, is suspected.
7. Survivors of sudden death, symptomatic, or lifethreatening arrhythmias when CAD may be a correctable cause.
8. Chest pain of uncertain cause or cardiomyopathy of unknown cause.
9. Emergently performed cardiac catheterization with intention to perform primary PCI in patients with suspected acute myocardial infarction.

Myocardial Stress Imaging

Myocardial stress imaging (**scintigraphy, echocardiography, or MRI**) is indicated (1) when the resting ECG makes an exercise ECG difficult to interpret (eg, left bundle branch block, baseline ST–T changes, low voltage); (2) for confirmation of the results of the exercise ECG when they are contrary to the clinical impression (eg, a positive test in an asymptomatic patient); (3) to localize the region of ischemia; (4) to distinguish ischemic from infarcted myocardium; (5) to assess the completeness of revascularization following bypass surgery or

coronary angioplasty; or (6) as a prognostic indicator in patients with known coronary disease. Published criteria summarize these indications for stress testing.

Myocardial perfusion scintigraphy

This test, also known as radionuclide imaging, provides images in which radionuclide uptake is proportionate to blood flow at the time of injection.

Stress imaging is positive in about 75–90% of patients with anatomically significant coronary disease and in 20–30% of those without it. Occasionally, other conditions, including infiltrative diseases (sarcoidosis, amyloidosis), left bundle branch block, and dilated cardiomyopathy, may produce resting or persistent perfusion defects. False-positive radionuclide tests may occur as a result of diaphragmatic attenuation or, in women, attenuation through breast tissue. Tomographic imaging (single-photon emission computed tomography, SPECT) can reduce the severity of artifacts.

Radionuclide angiography

This procedure, also known as Multi Gated Acquisition Scan, or MUGA scan, uses radionuclide tracers to image the LV and measures its EF and wall motion. In coronary disease, resting abnormalities usually represent infarction, and those that occur only with exercise usually indicate stress-induced ischemia. Exercise radionuclide angiography has approximately the same sensitivity as myocardial perfusion scintigraphy, but it is less specific in older individuals and those with other forms of heart disease. In addition, because of the precision around LVEF, the test is also used for monitoring patients exposed to cardiotoxic therapies (such as chemotherapeutic agents).

LV angiography

LV angiography is usually performed at the same time as coronary arteriography. Global and regional LV function are visualized, as well as mitral regurgitation if present. LV function is a major determinant of prognosis in coronary heart disease.

Ultrasound (US)

Unlike the other methods of imaging, US doesn't use electromagnetic radiation. Instead, it relies on properties of longitudinal sound waves. This has made it a popular and safe form of imaging (eg in obs & gynae, testes, gallbladders, vessels, fistulae, thyroid). High-frequency sound waves (3–15MHz) are made by a piezo-electric quartz crystal; its size, shape, and resonant frequency determine tissue penetration and image quality. NB: transducers act as transmitter and receiver due to the piezo-electric properties of quartz crystal. Passage of sound waves through tissue is affected by *attenuation and reflection*. Attenuation disperses waves out of the receiver's range, but it is the waves reflected to the receiver that

determine the image. Its quality depends on the difference in acoustic impedance between adjacent soft tissues.

Processing: with the help of software a real-time 2D image is made. During processing an average attenuation value is assumed throughout the tissue examined, so if a higherthan-average attenuation structure is in the superficial tissues, then everything deep to it will be in a low intensity (black) acoustic shadow. If a lower-than-average attenuation object is in the superficial tissues then everything deep to it will be high intensity (white) or enhanced. If a tissue interface is strongly disparate, then all the waves are reflected back, making it impossible to image beyond it.

Modes B (brightness) is the most common, giving 2D slices that map the different magnitudes of echo in greyscale. **M** (movement) traces the movement of structures within the line of the sound beam. It is used in imaging, eg heart valves.

Duplex ultrasonography (flow and morphology) By combining Doppler effects (shifts in wavelength caused by movement of a source or reflecting surface) with B-mode ultrasound technology, flow characteristics of blood can be inferred. This is extremely useful in arterial and venous studies, and echocardiography.

Advantages Portable; fast; non-ionizing; cheap; real-time; can be used with intervention; can enter organs, eg rectum, vagina, gut. *Endoscopic US* can be used to stage and biopsy lung and GI tract cancers, eg stomach, pancreas, and also image the heart = transoesophageal echocardiogram or TOE.

Disadvantages Operator dependent—interoperator variability high; poor quality if patient is obese; interference from bone, bowel gas, calculi, or superimposed organs can limit depth and quality of imaging.

Some important rheumatological investigations

Joint aspiration is the most important investigation in any monoarthritic presentation. Send synovial fluid for urgent white cell count, Gram stain, polarized light microscopy (for crystals) and culture. The risk of inducing septic arthritis, using sterile precautions, is < 1:10,000. 2 Look for blood1 , pus, and crystals (gout or CPPD crystal arthropathy). Do not attempt joint aspiration through inflamed and potentially infected skin (eg through a psoriatic plaque).

Radiology Look for erosions, calcifi cation, widening or loss of joint space, changes in underlying bone of affected joints (eg periarticular osteopenia, sclerotic areas, osteophytes). Irregularity of the lower half of the sacroiliac joints is seen in spondyloarthritis. ***Ultrasound*** and ***MRI*** are more sensitive in identifying effusions, synovitis, enthesitis and infection than plain radiographs—discuss further investigations with a radiologist. Do a CXR for RA, vasculitis, TB and sarcoid.

Intravascular ultrasound (IVUS) is useful when the angiogram is equivocal as well as for assessing the results of angioplasty or stenting. In addition, IVUS is the invasive diagnostic method of choice for ostial left main lesions and coronary dissections. In fractional flow reserve (FFR), a pressure wire is used to measure the relative change in pressure across a coronary lesion after adenosine-induced

hyperemia. Revascularization based on abnormal FFR improves clinical outcomes compared to revascularization of all angiographically stenotic lesions. FFR is an important invasive tool to aid with ischemia-driven revascularization and has become the standard tool to evaluate borderline lesions in cases in which the clinical team is evaluating the clinical and hemodynamic significance of a coronary stenosis.

Noninvasive testing for Helicobacter pylori

Although serologic tests are easily obtained and widely available, most clinical guidelines no longer endorse their use for testing for H pylori infection because they are less accurate than other noninvasive tests that measure active infection. Laboratory-based quantitative serologic ELISA tests have an overall accuracy of only 80%. In comparison, the fecal antigen immunoassay and urea breath test have excellent sensitivity and specificity (greater than 95%). Although more expensive and cumbersome to perform, these tests of active infection are more costeffective in most clinical settings because they reduce unnecessary treatment for patients without active infection.

Endoscopy

Upper Endoscopy (EGD): Uses a thin, flexible tube with a camera inserted through the mouth, following the tract to the stomach and upper small intestine, to look for bleeding, ulcers and inflammation. **Esophagogastroduodenoscopy** confirms the presence of varices and detects specific causes of bleeding in the esophagus, stomach, and proximal duodenum.

Endoscopic testing for Helicobacter pylori Endoscopy is not indicated to diagnose H pylori infection in most circumstances. However, when it is performed for another reason, gastric biopsy specimens can be obtained for detection of H pylori and tested for active infection by urease production. This simple, inexpensive test has excellent sensitivity (90%) and specificity (95%). In patients with active upper gastrointestinal bleeding or patients recently taking proton pump inhibitors or antibiotics, histologic assessment for H pylori is preferred. Histologic assessment of biopsies from the gastric antrum and body is more definitive but more expensive than a rapid urease test. Histologic assessment is also indicated in patients with suspected MALTomas and, possibly, in patients with suspected infection whose rapid urease test is negative. However, serologic testing is the most costeffective means of confirming H pylori infection in patients with a negative rapid urease test.

Colonoscopy and Colon Cancer Screening: An exam using a tube-like instrument to look inside the rectum and colon for polyps, abnormal areas or cancer. Tissue samples can be collected (biopsy) and abnormal growths can be removed.

Balloon-Assisted Endoscopy: A balloon inflating the sides of the bowel allows an endoscope to reach farther into the bowel for a visual examination.

Capsule Endoscopy: A capsule containing a camera is swallowed by the

patient to take pictures along the digestive tract not easily reachable by other procedures. (The capsule passes normally in the stool.)

EndoFLIP: EndoFLIP is a technology that simultaneously measures the area across the inside of a gastrointestinal organ (for example, the esophagus) and the pressure inside that organ.

Endoscopic Retrograde Cholangiopancreatography (ERCP): Uses an endoscope to visually examine the pancreas and bile ducts.

Endoscopic Ultrasound: Uses an endoscope to examine the upper and lower gastrointestinal tract, and then creates detailed pictures using ultrasound imaging.

Endoscopic Mucosal Resection (EMR): For people with Barrett's Disease, this procedure uses an endoscope and the injection of a solution into the esophagus or stomach to raise and remove a lesion for examination.

Bravo (catheter-free or wireless) esophageal pH monitoring study: A small capsule is attached to the lining of the esophagus during an upper endoscopy to measure acidic reflux over a 48-hour period. The capsule sends these measurements wirelessly to a small receiver that the patient wears. (The capsule passes normally in the stool.)

Esophageal 24-hour pH/impedance reflux monitoring: A catheter is placed through the nasal passage into the esophagus to record amount of reflux over a 24-hour period.

High Resolution Esophageal Manometry (Esophageal Mano): A catheter is placed through the nasal passage to record the movement and pressures of the esophagus as the patient drinks small amounts of water.

Liver Biopsy: Uses a needle to remove a sample of liver tissue for examination.

Liver Elastography: A non-invasive exam using an ultrasound probe to apply pulse waves to the liver to determine how much scar tissue has accumulated from chronic liver diseases.

Peroral Endoscopic Myotomy (POEM): Peroral endoscopic myotomy (POEM) is an endoscopic therapy for achalasia.

Pneumatic Dilation: An air-filled cylinder-shaped balloon disrupts the muscle fibers of the lower esophageal sphincter, which is too tight in patients with achalasia.

Pouchoscopy: Uses an endoscope to examine a surgically created pouch that serves as a stool reservoir for people whose large bowel has been completely removed.

Radiofrequency Ablation (RFA): Radiofrequency ablation (RFA) is an endoscopic therapy used primarily to treat Barrett's esophagus.

Sigmoidoscopy: Uses an endoscope to examine the lower 20 inches of the colon.

Hydrogen Breath Test (link is external): Tests for bacterial overgrowth and intolerance to sugars (fructose, lactose, sucrose).

Esophageal Manometry: Measures both the movement and pressures in the espophogus.

Anorectal Manometry: Detects problems with bowel movement by

measuring the tone in the anal sphincter and rectal muscles.

Esophageal 24-hour pH Monitoring: During a 24-hour period, both acid and non-acid reflux is monitored in the esophagus.

Secretin Stimulation Test: Measures the ability of the pancreas to respond to secretin, a digestive hormone.

Gastrointestinal Motility Studies: Exam to look at how the stomach and upper small intestinal muscles contract.

Paracentesis: A procedure using a needle to drain fluid from the abdomen.

Barrett's Epithelium Ablation Therapy (HALO®): Uses the advanced HALO system to endoscopically remove diseased tissue from the esophagus of patients with Barrett's Disease.

Confocal Microscopy: An advanced form of imaging using a tiny microscope to perform "virtual biopsies" and other exams, especially useful for patients with Barrett's Disease and those with narrowing of the bile and pancreatic ducts.

Endoscopic Dilation: A technique to open a blocked section of the esophagus.

PEG Tube Placement: Using an endoscope to place into the stomach through the skin.

Cystoscopy

A cystogram is a radiogram showing radiopaque outlining of the bladder cavity. Cystograms are seen as part of ordinary excretory urograms, but direct radiographic cystograms can be obtained by instilling a radipaque fluid directly into the bladder. The contrast medium is usually instilled via a transurethral catheter, but when necessary, it can be administered via percutaneous suprapubic bladder puncture. Radiograms of the filled bladder are taken using standard overhead X-ray tube equipment, or less frequently, "spot" films are taken during real-time, direct image-intensidied fluoroscopy.

Modern cystourethroscopes have a metal sheath ranging in size from 8F to 26F and interchangeable fiberoptic telescopes allowing a view from 0 to 170 degrees. The 0 to 30 degrees lenses are best for visualizing the urethra, whereas the bladder walls are best inspected with the 70 degrees lens. A retrograde (170-degrees0 lens must be used to see the vesical side of the bladder neck, particularly where prostatic tissue obstructs the view. Complete endoscopic studies are among the most precise diagnostic tests in all medicine. Any urethral lesion (e.g, Verrucae, tumors, strictures and diverticular), as well as the size and configuration of the prostate and bladder neck, are noted before the bladder is inspected. When the bladder is entered, the trigone is visualized and the size, shape, position and number of ureteral orifices noted. The bladder wall is carefully inspected for tumors, stones, diverticula, ulcers, trabeculation, hemorrhage, and edema. The normal and abnormal cystourethreoscopic findings must be specifically described.

Urography (KUB)

A plain film of the abdomen, frequnelty called a KUB (Kidney-Ureter-bladder) film, is the simplest uroradiologic study and the first performed in any radiographic examination of the abdomen or urinary tract. It is usually the preliminary radiogram in more extended radiologic examinations of the urinary tract, such as urography. The size of normal kidneys varies widely, not only between like individuals but also with age, sex and body stature. The long diameter of the kidney is the most widely used and most convenient radiographic measurement. The average adult kidney is about 12-14cm long, and the left kidney is ordinarily slightly longer than the right one.

X-ray contrastive stones, and their diagnostics

Identification on the plain film of calcification or calculi anywhere in the urinary tract may help to identify specific kidney diseases (eg, the calcifications occasionally seen in a Kidney cancer) or may suggest primary disease elsewhere (eg, the occasional patient with nephrocalcinosis whose underlying primary disease is hyperparathyroidism) Contrastive substances or radiographic contrast media include Liquids (almost all fo whih contain iodine), gels, solids (eg, barium preparations), and gases (most commonly air nitrous oxide and carbon dioxide). Some contrast media can only be administered by one route, which limits their usefulness for multisystem anatomic imaging.

Excretory Urography

The excretory urogram, formerly called an intravenous pyelogram, is most commonly used. Excretory tables and chairs Rockville MD urograms can demonstrate a wide variety of urinary tract lesions, are simple to perform, and are well tolerate by most patients. Ocassionally, however, retrograde urograms may be required if the excretory urogram is unsatisfactory or the patient has a history of significant adverse reaction to intravascular contrast media. The advent of excretory urography using high volumes of radiopaque contrast media and ureteral compression has decreased the need for retrograde urograms. Abdominal (ureteral) compression devices that temporarily obstruct the upper urinary tracts during excretory urograms dramatically improve the filling of renal collecting structures.

Retrograde Urography

This is a moderately invasive procedure that requires cystoscopy and the placement of catheters in the urethers. A radiopaque contrast medium is introduces into the ureters or renal placement of catheters in the ureters. A radiopaque contrast medium is introduced into the ureters or renal collecting structures through the ureteral catheters and radiograms of the abdomen are then taken. The study, which contemporary furniture Rockville MD is more difficult than an excretory urogram,

must be performed by a urologist. Some type of local or general anesthesia must be used, and the procedure can occasionally cause later morbidity or urinary tract infection.

Infusional Urography

The use od greater than average amounts of standard contrast medium- and thus greater amounts of iodine per Kilogram of body weight- may be indicated in selected patients. The high volumes may be injected either rapidly as a bolus or more slowly as an infusion; the bolus method produces better visualization and a better urographic nephrogram than the infusion method.

Urethrography

This method of outlining the renal collecting structures and ureters is occasionally used when urinary tract imaging is necessary but excretory or retrograde urography has failed or is contraindicated or when there is a nephrostomy tube in place and delineation of the collecting system of the upper urinary tract is desired. The contrast medium is introduced either through nephrstomy tubes, if these are present (nephrostogram), or by direct injection into the renal collecting structures via a percutaneous puncture through the patient's back.

Isotopic renography

Radioisotopic techniques provie a means of investigating the structure and function of internal organs without disturbing normal physiologic processes. Currently, 4 general types of renal readioisotopic labels are used. Classified according to the mechanisms of labeling, they are as follows; renal cortex labels, which are retained in the renal tubular cells,intravascular compartment labels;renal tubular function labels, which briefly lable the renal cortex as they are accumulated by renal tubular cells and then are passed into the urine and cleared from the Kidney; andSubstances cleared solely by glomerular filtration, which allow determination of the glomerular filtration rate.

X-ray diagnostics

X-Ray is the most common test performed today. In 1895, Wilhelm Conrad Roentgen discovered the x-ray. His remarkable achievement radically changed the practice of medicine. For the first time physicians could see beyond the skin and underlying soft tissues to the skeleton without autopsy. Roentgen did not entirely understand these unusual rays. He used the letter "x" to describe the rays because in Algebra "x" refers to an unknown.

When the spine is x-rayed the beams pass through the skin and underlying soft tissues (e.g. muscle, ligaments, tendons). When the beams meet bone (vertebra) it

stops creating a white shadow on the film. A bone abnormality is reflected on the finished film. Shades of gray mirror the density of the different tissues. X-rays are best for looking at bone. They are not helpful for looking at soft trauma.

X-rays are widely used today and are often called radiographs. These tests are not performed at random. An x-ray would most likely be performed when spine or extremity pain (e.g. leg, arm) is severe or chronic and progressive. An x-ray may rule out particular problems involving bone and some soft tissue disorders. When an x-ray proves inconclusive additional tests may be ordered especially if something suspicious is detected.

Computerized Tomography

CT Scan (Computerized Axial Tomography) or CAT Scan was developed in 1970. The CT Scan evolved from Tomograms; multiple x-rays taken at different levels to check the depth of an abnormality. The advent of computers in medicine has meant less radiation exposure and shorter study times. The CT Scan has become an important adjunct to x-rays. The CT Scan uses multiple x-ray beams projected at many angles in conjunction with computer resources to create three-dimensional cross-sectional images. Each image or picture reveals a different level of tissue that resembles slices.

Magnetic Resonance Imaging

MRI (Magnetic Resonance Imaging) is one of the most sensitive diagnostic tools. This medical miracle was first used on humans in 1971.

MRIs differ from CT Scans in that there is no exposure to radiation. The MRI equipment is basically two powerful magnets; one external and one internal. Within the human body there are millions of negative and positive charged atoms. When these atoms are exposed to the electromagnetic waves produced by the MRI equipment, the atoms act like mini-magnets. By means of a computer, the data is collected, combined, and manipulated using complex mathematical equations. The final product reveals detailed anatomical images transferred onto film. MRI represents the gold standard in imaging. MRI is best for looking at soft tissues such as discs or nerves.

To appreciate the details rendered by an MRI consider the following contrast. Under x-ray, an intervertebral disc resembles a pocket of air. Using MRI the structure of the same disc is revealed in fine detail. Additionally, contrast dye introduced into the patient intravenously further defines and highlights particular aspects of the spine.

Lets say the patient is a competitive tennis player without clinical symptoms indicative of a herniated disc. In this case, to give the patient a serious diagnosis based simply on an MRI would be inappropriate. This is why MRI results must support the patient's clinical symptoms for a specific disorder. In some cases, a bulging disc does not cause any pain or problem. If leg pain is present and the MRI

indicates a herniated disc associated with the nerves to the leg, it confirms the herniation as the cause of the leg pain.

For patients who are claustrophobic (claw-stro-foe-bick, fear of confinement) open-air MRI equipment is available. These patient-friendly imaging tables produce an excellent image without confinement in an imaging tube. Medicine to relax the patient is available and can be administered prior to the test.

Patients with internal ferromagnetic (metallic iron) devices such as a pacemaker, metal cardiac valve or metal in the area of the exam cannot be scanned. The powerful MRI magnets would interfere with these metal devices. In these patients a CT Scan is performed.

Fluoroscopy

Fluoroscopy is an imaging technique commonly used by physicians or radiation therapists to obtain real-time moving images of the internal structures of a patient through the use of a fluoroscope. In its simplest form, a fluoroscope consists of an X-ray source and a fluorescent screen, between which a patient is placed. However, modern fluoroscopes couple the screen to an X-ray image intensifier and CCD video camera allowing the images to be recorded and played on a monitor. This method may use a contrast material. Examples include cardiac catheterization (to examine for coronary artery blockages) and barium swallow (to examine for esophageal disorders).

Spirometry

Spirometry is a powerful tool that can be used to detect, follow, and manage patients with lung disorders. Technology advancements have made spirometry much more reliable and relatively simple to incorporate into a routine office visit. However, interpreting spirometry results can be challenging because the quality of the test is largely dependent on patient effort and cooperation, and the interpreter's knowledge of appropriate reference values. A simplified and stepwise method is key to interpreting spirometry. The first step is determining the validity of the test. Next, the determination of an obstructive or restrictive ventilatory patten is made. If a ventilatory pattern is identified, its severity is graded. In some patients, additional tests such as static lung volumes, diffusing capacity of the lung for carbon monoxide, and bronchodilator challenge testing are needed. These tests can further define lung processes but require more sophisticated equipment and expertise available only in a pulmonary function laboratory.

***Spirometric values**:*

- FVC—Forced vital capacity; the total volume of air that can be exhaled during a maximal forced expiration effort.
- FEV_1—Forced expiratory volume in one second; the volume of air exhaled in the first second under force after a maximal inhalation.
- FEV_1/ FVC ratio—The percentage of the FVC expired in one second.

- FEV_6 —Forced expiratory volume in six seconds.
- $FEF_{25–75\%}$—Forced expiratory flow over the middle one half of the FVC; the average flow from the point at which 25 percent of the FVC has been exhaled to the point at which 75 percent of the FVC has been exhaled.
- MVV—Maximal voluntary ventilation.

Lung volumes:

- ERV—Expiratory reserve volume; the maximal volume of air exhaled from end-expiration.
- IRV—Inspiratory reserve volume; the maximal volume of air inhaled from end-inspiration.
- RV—Residual volume; the volume of air remaining in the lungs after a maximal exhalation.
- V_T —Tidal volume; the volume of air inhaled or exhaled during each respiratory cycle.

Lung capacities:

- FRC—Functional residual capacity; the volume of air in the lungs at resting end-expiration.
- IC—Inspiratory capacity; the maximal volume of air that can be inhaled from the resting expiratory
- TLC—Total lung capacity; the volume of air in the lungs at maximal inflation.
- VC—Vital capacity; the largest volume measured on complete exhalation after full inspiration.

Basic spirometry can be performed in the family physician's office with relative ease and inexpensive equipment. In most cases, office spirometry provides an adequate assessment of pulmonary function. In addition, spirometry may be used to address major issues in clinical management and health screening.

Control questions

1. General blood test, clinical significance in diseases.
2. General urinalysis, clinical significance in diseases of the kidneys and other organs and systems.
3. Biochemical analysis of blood, clinical significance.
4. Instrumental methods of examination of circulatory organs and their clinical significance for pharmacotherapy.
5. Instrumental methods of examination of respiratory organs and their clinical significance for pharmacotherapy.

6. Instrumentation methods of examination of urinary organs and their clinical significance for pharmacotherapy.
7. Instrumental methods of examination of the musculoskeletal system and their clinical significance for pharmacotherapy.
8. Methods of endoscopic examination in gastroenterology and their clinical and pharmacotherapeutic value.

Independent work in class:

1. Curation patient in the ward.
2. Consider and discuss his instrumental and laboratory studies.
3. To conduct an analysis of the effectiveness of the study.

Control the level of knowledge

1. Fill in the table "Methods of studying the patient".

Methods of studying the patient	Definition of the concept
Physical: - Review - palpation - percussion - auscultation **Instrumental:** - anthropometry - thermometry - X-ray examination endoscopy - biopsy and cytological examination - electrophysiological - ultrasonic research methods - magnetic resonance imaging	

2. Fill in the table "Types of Endoscopic Research".

Types of endoscopy	Characteristics of the method, object of research	Diagnostic value
1. Esophagoscopy 2. Gastroscopy 3. Duodenoscopy 4. Colonoscopy		

5. Bronchoscopy		

3. Match the terms of urine tests.

1. Proteinuria.
2. Microhematuria.
3. Macro-hematuria.
4. Glucosuria.
5. Ketonuria.
6. Urobilinuria.
7. Leukocyturia.

A. The appearance of erythrocytes in urine, in urine, was detected by macroscopic examination.
B. Increase in the number of leukocytes in the urine.
C. Isolation of urobillinoids with urine to large numbers.
D. Appearance of protein to urine.
E. The appearance of erythrocytes in the urine revealed revealed by microscopic examination.
F. Appearance in urine of acetone bodies.
J. Appearance of glucose in urine.

4. Fill in the table "Diagnostic Value of Radiation Methods in Pulmonology".

Research methods	**Definition, essence, diagnostic possibilities of the method**
1. Roentgenoscopy 2. Roentgenography 3. Tomography 4. Bronchography	

5. Fill in the table "Measuring Respiratory Volume".

Respiratory Volume	**Definition of the concept**	**Number in milliliters**
1. Respiratory volume		

2. Backup volume of exhalation 3. Stand-by volume of inhalation 4. Lifetime lung capacity 5. Residual volume 6. Total maximum capacity of lungs		

6. Fill in the table "Definition of terms in the study of blood test".

Concept	Definition of the concept	Clinical examples
1. Leucocytosis 2. Leukopenia 3. Thrombocytosis 4. Thrombocytopenia 5. Erythrocytosis 6. Anemia		

Test tasks

1. How many red blood cells in a healthy person (male) are normal?

1. 2-3 $x10^{12}$ /l
2. 3-4$x10^{12}$ /l
3. 4-5$x10^{12}$ /l
4. 5-6$x10^{12}$ /l
5. 6-7$x10^{12}$ /l

2. What amount of hemoglobin in a healthy person (woman) is normal?

1. 80-100 g /l.
2. 100-120 g /l.
3. 120-140 g /l.
4. 130-160 g /l.
5. 160-180 g /l.

3. General urine analysis allows you to determine:

1. Additional loss of protein with urine.
2. Number of renin renal secretion.
3. Presence of protein in urine.

4. Level of glomerular filtration.
5. Number of leukocytes in 1 ml of urine.

4. In a urine, a healthy person may have:

1. 1-2 erythrocytes in the field of view.
2. 6-8 red blood cells in the field of vision.
3. Up to 10 erythrocytes in the field of view.
4. Up to 50 red blood cells in sight.
5.The number of red blood cells in the entire field of vision.

5. What are the meanings of leukocyturia?

1. The presence of leukocytes and red blood cells in the urine.
2. The presence in the urine of leukocytes is less than 2-3 in the field of view.
3. The presence of leukocytes in the urine is more than 4-6 in the field of view.
4. The presence of leukocytes in the urine is more than 10-15 in sight.
5. Presence of protein in urine.

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TOPIC 3. The main pharmacokinetic parameters, their importance for the implementation of pharmacotherapy.

Actuality of topic.

Pharmacokinetics studies the processes of biotransformation of pharmacological agents, in particular, of medicines in the body of a healthy and sick person. The subject of her research is their absorption, distribution, association with biochemical structures of the organism, biotransformation and deduction. On the basis of pharmacokinetics, the doses, optimal routes and regimens of drug administration, as well as the duration of treatment, are determined. Knowledge of pharmacokinetics of medicinal products is extremely important in clarifying the causes of ineffectiveness of treatment, their poor tolerability in the patient, metabolic disorders, renal and hepatic insufficiency, in cases of combination therapy and in solving a number of other important clinical tasks. Pharmacokinetics is one of the most important sections of pharmacotherapy and operates with clear quantitative criteria.

Purpose of the lesson: Student should know: ways of administration of drugs: species, clinical significance; absorption of drugs; bioavailability, determination, clinical significance; concept of bioequivalence; transportation of drugs; the distribution of drugs in the body (protein binding, regional circulation, volume distribution, the concept of biotransformation, routes of withdrawal of drugs from the body, the main pharmacokinetic parameters: the rate of absorption rate, the period of the absorption, the time of reaching the maximum concentration, the time of half-output, constant rate of elimination, constant rate of excretion, determination, value for the implementation of pharmacotherapy.

Drugs need not always be administered orally (i.e., by swallowing), but may also be given parenterally. This route usually refers to an injection, although enteral absorption is also bypassed when drugs are inhaled or applied to the skin. For intravenous, intramuscular, or subcutaneous injections, drugs are often given as solutions and, less frequently, in crystalline suspension for intramuscular, subcutaneous, or intraarticular injection. An injectable solution must be free of infectious agents, pyrogens, or suspended matter. It should have the same osmotic pressure and pH as body fluids in order to avoid tissue damage at the site of injection. Solutions for injection are preserved in airtight glass or plastic sealed containers. From ampules for multiple or single use, the solution is aspirated via a needle into a syringe. The cartridge ampule is fitted into a special injector that enables its contents to be emptied via a needle. An infusion refers to a solution being administered over an extended period of time. Solutions for infusion must meet the same standards as solutions for injection. Drugs can be sprayed in aerosol form onto mucosal surfaces of body cavities accessible from the outside (e.g., the

respiratory tract). An aerosol is a dispersion of liquid or solid particles in a gas, such as air. An aerosol results when a drug solution or micronized powder is reduced to a spray on being driven through the nozzle of a pressurized container. Mucosal application of drug via the rectal or vaginal route is achieved by means of suppositories and vaginal tablets, respectively. On rectal application, absorption into the systemic circulation may be intended. With vaginal tablets, the effect is generally confined to the site of application. Usually the drug is incorporated into a fat that solidifies at room temperature, but melts in the rectum or vagina. The resulting oily film spreads over the mucosa and enables the drug to pass into the mucosa. Powders, ointments, and pastes are applied to the skin surface. In many cases, these do not contain drugs but are used for skin protection or care. However, drugs may be added if a topical action on the outer skin or, more rarely, a systemic effect is intended. Transdermal drug delivery systems are pasted to the epidermis. They contain a reservoir from which drugs may diffuse and be absorbed through the skin. They offer the advantage that a drug depot is attached noninvasively to the body, enabling the drug to be administered in a manner similar to an infusion. Drugs amenable to this type of delivery must: (1) be capable of penetrating the cutaneous barrier; (2) be effective in very small doses (restricted capacity of reservoir); and (3) possess a wide therapeutic margin (dosage not adjustable).

Drug Administration by Inhalation

Inhalation in the form of an aerosol, a gas, or a mist permits drugs to be applied to the bronchial mucosa and, to a lesser extent, to the alveolar membranes. This route is chosen for drugs intended to affect bronchial smooth muscle or the consistency of bronchial mucus. Furthermore, gaseous or volatile agents can be administered by inhalation with the goal of alveolar absorption and systemic effects (e.g., inhalational anesthetics). Aerosols are formed when a drug solution or micronized powder is converted into a mist or dust, respectively. In conventional sprays (e.g., nebulizer), the air blast required for aerosol formation is generated by the stroke of a pump. Alternatively, the drug is delivered from a solution or powder packaged in a pressurized canister equipped with a valve through which a metered dose is discharged. During use, the inhaler (spray dispenser) is held directly in front of the mouth and actuated at the start of inspiration. The effectiveness of delivery depends on the position of the device in front of the mouth, the size of aerosol particles, and the coordination between opening of the spray valve and inspiration. The size of aerosol particles determines the speed at which they are swept along by inhaled air, hence the depth of penetration into the respiratory tract. Particles > 100 µm in diameter are trapped in the oropharyngeal cavity; those having diameters between 10 and 60µm will be deposited on the epithelium of the bronchial tract. Particles < 2 µm in diameter can reach the alveoli, but they will be largely exhaled because of their low tendency to impact on the alveolar epithelium. Drug deposited on the mucous lining of the bronchial epithelium is partly absorbed and partly transported with bronchial mucus towards the larynx. Bronchial mucus travels upwards due to the orally directed undulatory beat of the epithelial cilia. Physiologically, this mucociliary transport functions to remove inspired dust

particles. Thus, only a portion of the drug aerosol (~ 10 %) gains access to the respiratory tract and just a fraction of this amount penetrates the mucosa, whereas the remainder of the aerosol undergoes mucociliary transport to the laryngopharynx and is swallowed. The advantage of inhalation (i.e., localized application) is fully exploited by using drugs that are poorly absorbed from the intestine (isoproterenol, ipratropium, cromolyn) or are subject to first-pass elimination (beclomethasone dipropionate, budesonide, flunisolide, fluticasone dipropionate). Even when the swallowed portion of an inhaled drug is absorbed in unchanged form, administration by this route has the advantage that drug concentrations at the bronchi will be higher than in other organs. The efficiency of mucociliary transport depends on the force of kinociliary motion and the viscosity of bronchial mucus. Both factors can be altered pathologically (e.g., in smoker's cough, bronchitis) or can be adversely affected by drugs (atropine, antihistamines).

Dermatologic Agents

Pharmaceutical preparations applied to the outer skin are intended either to provide skin care and protection from noxious influences, or to serve as a vehicle for drugs that are to be absorbed into the skin or, if appropriate, into the general circulation.

Skin Protection

Protective agents are of several kinds to meet different requirements according to skin condition (dry, low in oil, chapped vs moist, oily, elastic), and the type of noxious stimuli (prolonged exposure to water, regular use of alcoholcontaining disinfectants, intense solar irradiation). Distinctions among protective agents are based upon consistency, physicochemical properties (lipophilic, hydrophilic), and the presence of additives.

Dusting Powders are sprinkled onto the intact skin and consist of talc, magnesium stearate, silicon dioxide (silica), or starch. They adhere to the skin, forming a low-friction film that attenuates mechanical irritation. Powders exert a drying (evaporative) effect.

Lipophilic ointment (oil ointment) consists of a lipophilic base (paraffin oil, petroleum jelly, wool fat [lanolin]) and may contain up to 10 % powder materials, such as zinc oxide, titanium oxide, starch, or a mixture of these. Emulsifying ointments are made of paraffins and an emulsifying wax, and are miscible with water.

Paste (oil paste) is an ointment containing more than 10 % pulverized constituents.

Lipophilic (oily) cream is an emulsion of water in oil, easier to spread than oil paste or oil ointments.

Hydrogel and water-soluble ointment achieve their consistency by means of different gel-forming agents (gelatin, methylcellulose, polyethylene glycol). **Lotions** are aqueous suspensions of water-insoluble and solid constituents.

Hydrophilic (aqueous) cream is an emulsion of an oil in water formed with the aid of an emulsifier; it may also be considered an oil-in-water emulsion of an emulsifying ointment.

All dermatologic agents having a lipophilic base adhere to the skin as a water-repellent coating. They do not wash off and they also prevent (**occlude**) outward passage of water from the skin. The skin is protected from drying, and its hydration and elasticity increase.

Diminished evaporation of water results in warming of the occluded skin area. Hydrophilic agents wash off easily and do not impede transcutaneous output of water. Evaporation of water is felt as a cooling effect.

Dermatologic Agents as Vehicles

In order to reach its site of action, a drug (D) must leave its pharmaceutical preparation and enter the skin, if a local effect is desired (e.g., glucocorticoid ointment), or be able to penetrate it, if a systemic action is intended (transdermal delivery system, e.g., nitroglycerin patch). The tendency for the drug to leave the drug vehicle (V) is higher the more the drug and vehicle differ in lipophilicity (high tendency: hydrophilic D and lipophilic V, and vice versa). Because the skin represents a closed lipophilic barrier, only lipophilic drugs are absorbed. Hydrophilic drugs fail even to penetrate the outer skin when applied in a lipophilic vehicle. This formulation can be meaningful when high drug concentrations are required at the skin surface (e.g., neomycin ointment for bacterial skin infections).

From Application to Distribution in the Body

As a rule, drugs reach their target organs via the blood. Therefore, they must first enter the blood, usually the venous limb of the circulation. There are several possible sites of entry.

The drug may be injected or infused **intravenously,** in which case the drug is introduced directly into the bloodstream. In **subcutaneous** or **intramuscular** injection, the drug has to diffuse from its site of application into the blood. Because these procedures entail injury to the outer skin, strict requirements must be met concerning technique. For that reason, the **oral** route (i.e., simple application by mouth) involving subsequent uptake of drug across the gastrointestinal mucosa into the blood is chosen much more frequently. The disadvantage of this route is that the drug must pass through the liver on its way into the general circulation. This fact assumes practical significance with any drug that may be rapidly transformed or possibly inactivated in the liver (first-pass hepatic elimination). Even with **rectal** administration, at least a fraction of the drug enters the general circulation via the portal vein, because only veins draining the short terminal segment of the rectum communicate directly with the inferior vena cava. Hepatic passage is circumvented when absorption occurs buccally or sublingually, because venous blood from the oral cavity drains directly into the superior vena cava. The same would apply to administration by **inhalation**. However, with this route, a local effect is usually intended; a systemic action is intended only in exceptional cases. Under certain conditions, drug can also be applied percutaneously in the form of a **transdermal**

delivery system. In this case, drug is slowly released from the reservoir, and then penetrates the epidermis and subepidermal connective tissue where it enters blood capillaries. Only a very few drugs can be applied transdermally. The feasibility of this route is determined by both the physicochemical properties of the drug and the therapeutic requirements (acute vs. long-term effect).

Speed of absorption is determined by the route and method of application. It is fastest with **intravenous** injection, less fast which **intramuscular** injection, and slowest with **subcutaneous** injection. When the drug is applied to the oral mucosa **(buccal, sublingual** route), plasma levels rise faster than with conventional oral administration because the drug preparation is deposited at its actual site of absorption and very high concentrations in saliva occur upon the dissolution of a single dose. Thus, uptake across the oral epithelium is accelerated. The same does not hold true for poorly water-soluble or poorly absorbable drugs. Such agents should be given orally, because both the volume of fluid for dissolution and the absorbing surface are much larger in the small intestine than in the oral cavity.

Bioavailability is defined as the fraction of a given drug dose that reaches the circulation in unchanged form and becomes available for systemic distribution. The larger the presystemic elimination, the smaller is the bioavailability of an orally administered drug.

Potential Targets of Drug Action

Drugs are designed to exert a selective influence on vital processes in order to alleviate or eliminate symptoms of disease. The smallest basic unit of an organism is the **cell**. The outer cell membrane, or plasmalemma, effectively demarcates the cell from its surroundings, thus permitting a large degree of internal autonomy. Embedded in the plasmalemma are **transport proteins** that serve to mediate *controlled metabolic exchange with the cellular environment.* These include energy-consuming pumps (e.g., Na, K-ATPase), carriers (e.g., for Na/glucose-cotransport), and ion channels e.g., for sodium or calcium.

Functional coordination between single cells is a prerequisite for viability of the organism, hence also for the survival of individual cells. Cell functions are regulated by means of messenger substances for the transfer of information. Included among these are “transmitters” released from nerves, which the cell is able to recognize with the help of specialized membrane binding sites or **receptors**. Hormones secreted by endocrine glands into the blood, then into the extracellular fluid, represent another class of chemical signals. Finally, signalling substances can originate from neighboring cells, e.g., prostaglandins and cytokines.

The **effect of a drug** frequently results from interference with cellular function. Receptors for the recognition of endogenous transmitters are obvious sites of drug action (receptor agonists and antagonists). Altered activity of transport systems affects cell function (e.g., cardiac glycosides, loop diuretics, calcium-antagonists). Drugs may also directly interfere with intracellular metabolic processes, for instance by inhibiting (phosphodiesterase inhibitors) or activating (organic nitrates) an enzyme.

In contrast to drugs acting from the outside on cell membrane constituents, agents acting in the cell's interior need to penetrate the cell membrane.

The **cell membrane** basically consists of a **phospholipid bilayer** (80Å = 8 nm in thickness) in which are embedded proteins (integral membrane proteins, such as receptors and transport molecules). **Phospholipid** molecules contain two long-chain fatty acids in ester linkage with two of the three hydroxyl groups of glycerol. Bound to the third hydroxyl group is phosphoric acid, which, in turn, carries a further residue, e.g., choline, (phosphatidylcholine = lecithin), the amino acid serine (phosphatidylserine) or the cyclic polyhydric alcohol inositol (phosphatidylinositol). In terms of solubility, phospholipids are amphiphilic: the tail region containing the apolar fatty acid chains is lipophilic, the remainder – the polar head – is hydrophilic. By virtue of these properties, phospholipids aggregate spontaneously into a bilayer in an aqueous medium, their polar heads directed outwards into the aqueous medium, the fatty acid chains facing each other and projecting into the inside of the membrane.

The **hydrophobic interior** of the phospholipid membrane constitutes a **diffusion barrier** virtually impermeable for charged particles. Apolar particles, however, penetrate the membrane easily. This is of major importance with respect to the absorption, distribution, and elimination of drugs.

External Barriers of the Body

Prior to its uptake into the blood (i.e., during absorption), a drug has to overcome barriers that demarcate the body from its surroundings, i.e., separate the internal milieu from the external milieu. These boundaries are formed by the skin and mucous membranes.

When absorption takes place in the **gut** (enteral absorption), the intestinal epithelium is the barrier. This singlelayered epithelium is made up of enterocytes and mucus-producing goblet cells. On their luminal side, these cells are joined together by zonulae occludentes (indicated by black dots in the inset, bottom left). A zonula occludens or tight junction is a region in which the phospholipid membranes of two cells establish close contact and become joined via integral membrane proteins (semicircular inset, left center). The region of fusion surrounds each cell like a ring, so that neighboring cells are welded together in a continuous belt. In this manner, an unbroken phospholipid layer is formed (yellow area in the schematic drawing, bottom left) and acts as a continuous barrier between the two spaces separated by the cell layer – in the case of the gut, the intestinal lumen (dark blue) and the interstitial space (light blue). The efficiency with which such a barrier restricts exchange of substances can be increased by arranging these occluding junctions in multiple arrays, as for instance in the endothelium of cerebral blood vessels. The connecting proteins (connexins) furthermore serve to restrict mixing of other functional membrane proteins (ion pumps, ion channels) that occupy specific areas of the cell membrane.

This phospholipid bilayer represents the intestinal mucosa-blood barrier that a drug must cross during its enteral absorption. Eligible drugs are those whose physicochemical properties allow permeation through the lipophilic membrane

interior (yellow) or that are subject to a special carrier transport mechanism. Absorption of such drugs proceeds rapidly, because the absorbing surface is greatly enlarged due to the formation of the epithelial brush border (submicroscopic foldings of the plasmalemma). The absorbability of a drug is characterized by the *absorption quotient*, that is, the amount absorbed divided by the amount in the gut available for absorption.

In the **respiratory tract**, cilia-bearing epithelial cells are also joined on the luminal side by *zonulae occludentes*, so that the bronchial space and the interstitium are separated by a continuous phospholipid barrier.

With sublingual or buccal application, a drug encounters the non-keratinized, multilayered squamous epithelium of the **oral mucosa**. Here, the cells establish punctate contacts with each other in the form of desmosomes (not shown); however, these do not seal the intercellular clefts. Instead, the cells have the property of sequestering phospholipid-containing membrane fragments that assemble into layers within the extracellular space (semicircular inset, center right). In this manner, a continuous phospholipid barrier arises also inside squamous epithelia, although at an extracellular location, unlike that of intestinal epithelia. A similar barrier principle operates in the multilayered keratinized squamous epithelium of the outer **skin**. The presence of a continuous phospholipid layer means that squamous epithelia will permit passage of lipophilic drugs only, i.e., agents capable of diffusing through phospholipid membranes, with the epithelial thickness determining the extent and speed of absorption. In addition, cutaneous absorption is impeded by the keratin layer, the stratum corneum, which is very unevenly developed in various areas of the skin.

Blood-Tissue Barriers

Drugs are transported in the blood to different tissues of the body. In order to reach their sites of action, they must leave the bloodstream. Drug permeation occurs largely in the capillary bed, where both surface area and time available for exchange are maximal (extensive vascular branching, low velocity of flow). The capillary wall forms the **blood-tissue barrier**. Basically, this consists of an endothelial cell layer and a basement membrane enveloping the latter (solid black line in the schematic drawings). The endothelial cells are “riveted” to each other by tight junctions or occluding zonulae such that no clefts, gaps, or pores remain that would permit drugs to pass unimpeded from the blood into the interstitial fluid.

The blood-tissue barrier is developed differently in the various capillary beds. Permeability to drugs of the capillary wall is determined by the structural and functional characteristics of the endothelial cells. In many capillary beds, e.g., those of **cardiac muscle**, endothelial cells are characterized by pronounced **endo-** and **transcytotic activity**, as evidenced by numerous invaginations and vesicles. Transcytotic activity entails transport of fluid or macromolecules from the blood into the interstitium and vice versa. Any solutes trapped in the fluid, including drugs, may traverse the blood-tissue barrier. In this form of transport, the physicochemical properties of drugs are of little importance.

In some capillary beds (e.g., in the **pancreas**), endothelial cells exhibit **fenestrations**. Although the cells are tightly connected by continuous junctions, they possess **pores** that are closed only by diaphragms. Both the diaphragm and basement membrane can be readily penetrated by substances of low molecular weight — the majority of drugs — but less so by macromolecules, e.g., proteins such as insulin (insulin storage granules). Penetrability of macromolecules is determined by molecular size and electrical charge. Fenestrated endothelia are found in the capillaries of the gut and endocrine glands.

In the central nervous system (**brain and spinal cord**), capillary endothelia lack pores and there is little transcytotic activity. In order to cross the **blood-brain barrier**, drugs must diffuse transcellularly, i.e., penetrate the luminal and basal membrane of endothelial cells. Drug movement along this path requires specific physicochemical properties or the presence of a transport mechanism (e.g., L-dopa). Thus, the blood-brain barrier is permeable only to certain types of drugs.

Drugs exchange freely between blood and interstitium in the **liver**, where endothelial cells exhibit large fenestrations (100 nm in diameter) facing Disse's spaces and where neither diaphragms nor basement membranes impede drug movement. Diffusion barriers are also present beyond the capillary wall: e.g., placental barrier of fused syncytiotrophoblast cells; blood: testicle barrier — junctions interconnecting Sertoli cells; brain choroid plexus: blood barrier — occluding junctions between ependymal cells.

Membrane Permeation

An ability to penetrate lipid bilayers is a prerequisite for the absorption of drugs, their entry into cells or cellular organelles, and passage across the bloodbrain barrier. Due to their amphiphilic nature, phospholipids form bilayers possessing a hydrophilic surface and a hydrophobic interior. Substances may traverse this membrane in three different ways.

Diffusion. Lipophilic substances (red dots) may enter the membrane from the extracellular space (area shown in ochre), accumulate in the membrane, and exit into the cytosol (blue area). Direction and speed of permeation depend on the relative concentrations in the fluid phases and the membrane. The steeper the gradient (concentration difference), the more drug will be diffusing per unit of time (Fick's Law). The lipid membrane represents an almost insurmountable obstacle for hydrophilic substances (blue triangles).

Transport. Some drugs may penetrate membrane barriers with the help of transport systems (carriers), irrespective of their physicochemical properties, especially lipophilicity. As a prerequisite, the drug must have affinity for the carrier (blue triangle matching recess on "transport system") and, when bound to the latter, be capable of being ferried across the membrane. Membrane passage via transport mechanisms is subject to competitive inhibition by another substance possessing similar affinity for the carrier. Substances lacking in affinity (blue circles) are not transported. Drugs utilize carriers for physiological substances, e.g., L-dopa uptake by L-amino acid carrier across the blood-intestine and blood-brain barriers, and uptake of aminoglycosides by the carrier transporting basic polypeptides through

the luminal membrane of kidney tubular cells. Only drugs bearing sufficient resemblance to the physiological substrate of a carrier will exhibit affinity for it.

Finally, membrane penetration may occur in the form of small membrane-covered vesicles. Two different systems are considered.

Transcytosis (**vesicular transport**). When new vesicles are pinched off, substances dissolved in the extracellular fluid are engulfed, and then ferried through the cytoplasm, vesicles (phagosomes) undergo fusion with lysosomes to form phagolysosomes, and the transported substance is metabolized. Alternatively, the vesicle may fuse with the opposite cell membrane (cytopempsis).

Receptor-mediated endocytosis. The drug first binds to membrane surface receptors whose cytosolic domains contact special proteins. Drug-receptor complexes migrate laterally in the membrane and aggregate with other complexes by a clathrin-dependent process. The affected membrane region invaginates and eventually pinches off to form a detached vesicle. The clathrin coat is shed immediately, followed by the adaptins. The remaining vesicle then fuses with an "early" endosome, whereupon proton concentration rises inside the vesicle. The drug-receptor complex dissociates and the receptor returns into the cell membrane. The "early" endosome delivers its contents to predetermined destinations, e.g., the Golgi complex, the cell nucleus, lysosomes, or the opposite cell membrane (transcytosis). Unlike simple endocytosis, receptor-mediated endocytosis is contingent on affinity for specific receptors and operates independently of concentration gradients.

Possible Modes of Drug Distribution

Following its uptake into the body, the drug is distributed in the blood and through it to the various tissues of the body. Distribution may be restricted to the extracellular space (plasma volume plus interstitial space) or may also extend into the intracellular space. Certain drugs may bind strongly to tissue structures, so that plasma concentrations fall significantly even before elimination has begun.

After being distributed in blood, macromolecular substances remain largely confined to the vascular space, because their permeation through the blood-tissue barrier, or endothelium, is impeded, even where capillaries are fenestrated. This property is exploited therapeutically when loss of blood necessitates refilling of the vascular bed, e.g., by infusion of dextran solutions. The vascular space is, moreover, predominantly occupied by substances bound with high affinity to plasma proteins (determination of the plasma volume with protein-bound dyes). Unbound, free drug may leave the bloodstream, albeit with varying ease, because the blood-tissue barrier is differently developed in different segments of the vascular tree. These regional differences are not illustrated in the accompanying figures.

Distribution in the body is determined by the ability to penetrate membranous barriers. Hydrophilic substances (e.g., inulin) are neither taken up into cells nor bound to cell surface structures and can, thus, be used to determine the extracellular fluid volume. Some lipophilic substances diffuse through the cell membrane and, as a result, achieve a uniform distribution.

The volume ratio interstitial: intracellular water varies with age and body weight. On a percentage basis, interstitial fluid volume is large in premature or normal neonates (up to 50 % of body water), and smaller in the obese and the aged.

The concentration (c) of a solution corresponds to the amount (D) of substance dissolved in a volume (V); thus, c = D/V. If the dose of drug (D) and its plasma concentration (c) are known, a volume of distribution (V) can be calculated from V = D/c. However, this represents an apparent volume of distribution (Vapp), because an even distribution in the body is assumed in its calculation. Homogeneous distribution will not occur if drugs are bound to cell membranes or to membranes of intracellular organelles or are stored within the latter. In these cases, Vapp can exceed the actual size of the available fluid volume.

Binding to Plasma Proteins

Having entered the blood, drugs may bind to the protein molecules that are present in abundance, resulting in the formation of drug-protein complexes.

Protein binding involves primarily albumin and, to a lesser extent, !-globulins and acidic glycoproteins. Other plasma proteins (e.g., transcortin, transferrin, thyroxin-binding globulin) serve specialized functions in connection with specific substances. The degree of binding is governed by the concentration of the reactants and the affinity of a drug for a given protein. Albumin concentration in plasma amounts to 4.6 g/100 mL or O.6 mM, and thus provides a very high binding capacity (two sites per molecule). As a rule, drugs exhibit much lower affinity (KD approx. 10–5 –10–3 M) for plasma proteins than for their specific binding sites (receptors). In the range of therapeutically relevant concentrations, protein binding of most drugs increases linearly with concentration (exceptions: salicylate and certain sulfonamides).

The albumin molecule has different binding sites for anionic and cationic ligands, but *van der Waals'* forces also contribute. The extent of binding correlates with drug hydrophobicity (repulsion of drug by water).

Binding to plasma proteins is instantaneous and reversible, i.e., any change in the concentration of unbound drug is immediately followed by a corresponding change in the concentration of bound drug. Protein binding is of great importance, because it is the concentration of free drug that determines the intensity of the effect. At an identical total plasma concentration (say, 100 ng/mL) the effective concentration will be 90 ng/mL for a drug 10 % bound to protein, but 1 ng/mL for a drug 99 % bound to protein. The reduction in concentration of free drug resulting from protein binding affects not only the intensity of the effect but also biotransformation (e.g., in the liver) and elimination in the kidney, because only free drug will enter hepatic sites of metabolism or undergo glomerular filtration. When concentrations of free drug fall, drug is resupplied from binding sites on plasma proteins. Binding to plasma protein is equivalent to a depot in prolonging the duration of the effect by retarding elimination, whereas the intensity of the effect is reduced. If two substances have affinity for the same binding site on the albumin molecule, they may compete for that site. One drug may displace another from its binding site and thereby elevate the free (effective) concentration of the

displaced drug (a form of **drug interaction**). Elevation of the free concentration of the displaced drug means increased effectiveness and accelerated elimination.

A decrease in the concentration of albumin (liver disease, nephrotic syndrome, poor general condition) leads to altered pharmacokinetics of drugs that are highly bound to albumin.

Plasma protein-bound drugs that are substrates for transport carriers can be cleared from blood at great velocity, e.g., p-aminohippurate by the renal tubule and sulfobromophthalein by the liver. Clearance rates of these substances can be used to determine renal or hepatic blood flow.

The Kidney as Excretory Organ

Most drugs are eliminated in urine either chemically unchanged or as metabolites. The kidney permits elimination because the vascular wall structure in the region of the glomerular capillaries allows unimpeded passage of blood solutes having molecular weights (MW) < 5000. Filtration diminishes progressively as MW increases from 5000 to 70000 and ceases at MW > 70000. With few exceptions, therapeutically used drugs and their metabolites have much smaller molecular weights and can, therefore, undergo **glomerular filtration**, i.e., pass from blood into primary urine. Separating the capillary **endothelium** from the tubular **epithelium**, the **basal membrane** consists of charged glycoproteins and acts as a filtration barrier for high-molecular-weight substances. The relative density of this barrier depends on the electrical charge of molecules that attempt to permeate it.

Apart from **glomerular filtration**, drugs present in blood may pass into urine by **active secretion**. Certain cations and anions are secreted by the epithelium of the proximal tubules into the tubular fluid via special, energyconsuming transport systems. These transport systems have a limited capacity. When several substrates are present simultaneously, competition for the carrier may occur.

During passage down the renal tubule, urinary volume shrinks more than 100-fold; accordingly, there is a corresponding concentration of filtered drug or drug metabolites. The resulting concentration gradient between urine and interstitial fluid is preserved in the case of drugs incapable of permeating the tubular epithelium. However, with lipophilic drugs the concentration gradient will favor **reabsorption** of the filtered molecules. In this case, reabsorption is not based on an active process but results instead from passive diffusion. Accordingly, for protonated substances, the extent of reabsorption is dependent upon urinary pH or the degree of dissociation. The degree of dissociation varies as a function of the urinary pH and the pKa, which represents the pH value at which half of the substance exists in protonated (or unprotonated) form. This relationship is graphically illustrated with the example of a protonated amine having a pKa of 7.0. In this case, at urinary pH 7.0, 50 % of the amine will be present in the protonated, hydrophilic, membrane-impermeant form (blue dots), whereas the other half, representing the uncharged amine (orange dots), can leave the tubular lumen in accordance with the resulting concentration gradient. If the pKa of an amine is higher (pKa = 7.5) or lower (pKa = 6.5), a correspondingly smaller or larger proportion of the amine will be present

in the uncharged, reabsorbable form. Lowering or raising urinary pH by half a pH unit would result in analogous changes for an amine having a pKa of 7.0.

The same considerations hold for acidic molecules, with the important difference that alkalinization of the urine (increased pH) will promote the deprotonization of -COOH groups and thus impede reabsorption. Intentional alteration in urinary pH can be used in intoxications with proton-acceptor substances in order to hasten of the toxin (alkalinization to phenobarbital; acidification to amphetamine).

Elimination of Lipophilic and Hydrophilic Substances

The terms **lipophilic** and **hydrophilic** (or hydro- and lipophobic) refer to the solubility of substances in media of low and high polarity, respectively. Blood plasma, interstitial fluid, and cytosol are highly polar aqueous media, whereas lipids — at least in the interior of the lipid bilayer membrane — and fat constitute apolar media. Most polar substances are readily dissolved in aqueous media (i.e., are hydrophilic) and lipophilic ones in apolar media. A **hydrophilic drug**, on reaching the bloodstream, probably after a partial, slow absorption (not illustrated), passes through the liver unchanged, because it either cannot, or will only slowly, permeate the lipid barrier of the hepatocyte membrane and thus will fail to gain access to hepatic biotransforming enzymes. The unchanged drug reaches the arterial blood and the kidneys, where it is filtered. With hydrophilic drugs, there is little binding to plasma proteins (protein binding increases as a function of lipophilicity), hence the entire amount present in plasma is available for glomerular filtration. A hydrophilic drug is not subject to tubular reabsorption and appears in the urine. Hydrophilic drugs undergo **rapid elimination**.

If a **lipophilic drug**, because of its chemical nature, cannot be converted into a polar product, despite having access to all cells, including metabolically active liver cells, it is likely to be retained in the organism. The portion filtered during glomerular passage will be reabsorbed from the tubules. Reabsorption will be nearly complete, because the free concentration of a lipophilic drug in plasma is low (lipophilic substances are usually largely proteinbound). The situation portrayed for a lipophilic non-metabolizable drug would seem undesirable because pharmacotherapeutic measures once initiated would be virtually irreversible (poor control over blood concentration).

Lipophilic drugs that are converted in the liver to **hydrophilic metabolites** permit better control, because the lipophilic agent can be eliminated in this manner. The speed of formation of hydrophilic metabolite determines the drug’s length of stay in the body.

If hepatic conversion to a polar metabolite is rapid, only a portion of the absorbed drug enters the systemic circulation in unchanged form, the remainder having undergone **presystemic** (first-pass) **elimination**. When biotransformation is rapid, oral administration of the drug is impossible (e.g., glyceryl trinitate). Parenteral or, alternatively, sublingual, intranasal, or transdermal administration is then required in order to bypass the liver. Irrespective of the route of administration, a portion of administered drug may be taken up into and transiently stored in lung

tissue before entering the general circulation. This also constitutes presystemic elimination.

Presystemic elimination refers to the fraction of drug absorbed that is excluded from the general circulation by biotransformation or by first-pass binding.

Presystemic elimination diminishes the *bioavailability* of a drug after its oral administration. **Absolute bioavailability** = systemically available amount/ dose administered; **relative bioavailability** = availability of a drug contained in a test preparation with reference to a standard preparation.

Drug Concentration in the Body as a Function of Time. First-Order (Exponential) Rate Processes

Processes such as drug absorption and elimination display exponential characteristics. As regards the former, this follows from the simple fact that the amount of drug being moved per unit of time depends on the concentration difference (gradient) between two body compartments (Fick's Law). In drug absorption from the alimentary tract, the intestinal contents and blood would represent the compartments containing an initially high and low concentration, respectively. In drug elimination via the kidney, excretion often depends on glomerular filtration, i.e., the filtered amount of drug present in primary urine. As the blood concentration falls, the amount of drug filtered per unit of time diminishes. The exponential time course implies constancy of the interval during which the concentration decreases by one-half. This interval represents the half-life (t1/2) and is related to the elimination rate constant k by the equation $t1/2 = \ln 2/k$. The two parameters, together with the initial concentration co, describe a first-order (exponential) rate process.

The constancy of the process permits calculation of the plasma volume that would be cleared of drug, if the remaining drug were not to assume a homogeneous distribution in the total volume (a condition not met in reality). This **notional plasma volume freed of drug per unit of time** is termed the **clearance**. Depending on whether plasma concentration falls as a result of urinary excretion or metabolic alteration, clearance is considered to be renal or hepatic. Renal and hepatic clearances add up to total clearance (Cltot) in the case of drugs that are eliminated unchanged via the kidney and biotransformed in the liver. Cltot represents the sum of all processes contributing to elimination; it is related to the half-life (t1/2) and the apparent volume of distribution Vapp by the equation:

$$t1/2 = \ln 2 \times \frac{Vapp}{Cltot}$$

The smaller the volume of distribution or the larger the total clearance, the shorter is the half-life.

In the case of drugs renally eliminated in unchanged form, the half-life of elimination can be calculated from the cumulative excretion in urine; the final total amount eliminated corresponds to the amount absorbed.

Hepatic elimination obeys exponential kinetics because metabolizing enzymes operate in the quasilinear region of their concentration-activity curve;

hence the amount of drug metabolized per unit of time diminishes with decreasing blood concentration.

The best-known exception to exponential kinetics is the elimination of alcohol (ethanol), which obeys a *linear* time course (zero-order kinetics), at least at blood concentrations > 0.02 %. It does so because the rate-limiting enzyme, alcohol dehydrogenase, achieves half-saturation at very low substrate concentrations, i.e., at about 80 mg/L (0.008 %). Thus, reaction velocity reaches a plateau at blood ethanol concentrations of about 0.02 %, and the amount of drug eliminated per unit of time remains constant at concentrations above this level.

Time Course of Drug Concentration in Plasma

Drugs are taken up into and eliminated from the body by various routes. The body thus represents an open system wherein the actual drug concentration reflects the interplay of intake (ingestion) and egress (elimination). When an orally administered drug is absorbed from the stomach and intestine, speed of uptake depends on many factors, including the speed of drug dissolution (in the case of solid dosage forms) and of gastrointestinal transit; the membrane penetrability of the drug; its concentration gradient across the mucosa-blood barrier; and mucosal blood flow. **Absorption** from the intestine causes the drug concentration in blood to increase. Transport in blood conveys the drug to different organs (**distribution**), into which it is taken up to a degree compatible with its chemical properties and rate of blood flow through the organ. For instance, well-perfused organs such as the brain receive a greater proportion than do less well-perfused ones. Uptake into tissue causes the blood concentration to fall. Absorption from the gut diminishes as the mucosa-blood gradient decreases. Plasma concentration reaches a peak when the drug amount leaving the blood per unit of time equals that being absorbed.

Drug entry into hepatic and renal tissue constitutes movement into the **organs of elimination**. The characteristic phasic time course of drug concentration in plasma represents the sum of the constituent processes of **absorption**, **distribution**, and **elimination**, which overlap in time. When distribution takes place significantly faster than elimination, there is an initial rapid and then a greatly retarded fall in the plasma level, the former being designated the alfa-phase (distribution phase), the latter the "-phase (elimination phase). When the drug is distributed faster than it is absorbed, the time course of the plasma level can be described in mathematically simplified form by the Bateman function (k1 and k2 represent the rate constants for absorption and elimination, respectively).

The velocity of absorption depends on the route of administration. The more rapid the administration, the shorter will be the time (tmax) required to reach the peak plasma level (cmax), the higher will be the cmax, and the earlier the plasma level will begin to fall again.

The *area under the plasma level time curve* (AUC) is independent of the route of administration, provided the doses and bioavailability are the same (Dost’s law of corresponding areas). The AUC can thus be used to determine the **bioavailability** of a drug. The ratio of AUC values determined after oral or intravenous administration of a given dose of a particular drug corresponds to the

proportion of drug entering the systemic circulation after oral administration. The determination of plasma levels affords a comparison of different proprietary preparations containing the same drug in the same dosage. Identical plasma level time-curves of different manufacturers' products with reference to a standard preparation indicate **bioequivalence** of the preparation under investigation with the standard.

Time Course of Drug Plasma Levels During Repeated Dosing

When a drug is administered at regular intervals over a prolonged period, the rise and fall of drug concentration in blood will be determined by the relationship between the half-life of elimination and the time interval between doses. If the drug amount administered in each dose has been eliminated before the next dose is applied, repeated intake at constant intervals will result in similar plasma levels. If intake occurs before the preceding dose has been eliminated completely, the next dose will add on to the residual amount still present in the body, i.e., the drug **accumulates**. The shorter the dosing interval relative to the elimination half-life, the larger will be the residual amount of drug to which the next dose is added and the more extensively will the drug accumulate in the body. However, at a given dosing frequency, the drug does not accumulate infinitely and a **steady state** (Css) or **accumulation equilibrium** is eventually reached. This is so because the activity of elimination processes is concentration-dependent. The higher the drug concentration rises, the greater is the amount eliminated per unit of time. After several doses, the concentration will have climbed to a level at which the amounts eliminated and taken in per unit of time become equal, i.e., a steady state is reached. Within this concentration range, the plasma level will continue to rise (peak) and fall (trough) as dosing is continued at a regular interval. The height of the steady state depends upon the amount administered per dosing interval and the clearance.

The speed at which the steady state is reached corresponds to the speed of elimination of the drug. The time needed to reach 90 % of the concentration plateau is about 3 times the t1/2 of elimination.

Time Course of Drug Plasma Levels During Irregular Intake

In practice, it proves difficult to achieve a plasma level that undulates evenly around the desired effective concentration. For instance, if two successive doses are omitted, the plasma level will drop below the therapeutic range and a longer period will be required to regain the desired plasma level. In everyday life, patients will be apt to neglect drug intake at the scheduled time. **Patient compliance** means strict adherence to the prescribed regimen. Apart from poor compliance, the same problem may occur when the total daily dose is divided into three individual doses (tid) and the first dose is taken at breakfast, the second at lunch, and the third at supper. Under this condition, the nocturnal dosing interval will be twice the diurnal one. Consequently, plasma levels during the early morning hours may have fallen far below the desired or, possibly, urgently needed range.

Accumulation: Dose, Dose Interval, and Plasma Level Fluctuation

Successful drug therapy in many illnesses is accomplished only if drug concentration is maintained at a steady high level. This requirement necessitates regular drug intake and a dosage schedule that ensures that the plasma concentration neither falls below the therapeutically effective range nor exceeds the minimal toxic concentration. A constant plasma level would, however, be undesirable if it accelerated a loss of effectiveness (development of tolerance), or if the drug were required to be present at specified times only.

A steady plasma level can be achieved by giving the drug in a constant intravenous infusion, the steadystate plasma level being determined by the infusion rate, dose per unit of time, and the clearance, according to the equation.

This procedure is routinely used in intensive care hospital settings, but is otherwise impracticable. With oral administration, dividing the total daily dose into several individual ones, e.g., four, three, or two, offers a practical compromise.

When the daily dose is given in several divided doses, the mean plasma level shows little fluctuation. In practice, it is found that a regimen of frequent regular drug ingestion is not well adhered to by patients. The degree of fluctuation in plasma level over a given dosing interval can be reduced by use of a dosage form permitting slow (sustained) release.

The time required to reach steadystate accumulation during multiple constant dosing depends on the rate of elimination. As a rule of thumb, a plateau is reached after approximately three elimination half-lives (t1/2).

For slowly eliminated drugs, which tend to accumulate extensively (phenprocoumon, digitoxin, methadone), the optimal plasma level is attained only after a long period. Here, increasing the initial doses (loading dose) will speed up the attainment of equilibrium, which is subsequently maintained with a lower dose (maintenance dose).

Change in Elimination Characteristics During Drug Therapy

With any drug taken regularly and accumulating to the desired plasma level, it is important to consider that conditions for biotransformation and excretion do not necessarily remain constant. Elimination may be hastened due to enzyme induction or to a change in urinary pH. Consequently, the steady-state plasma level declines to a new value corresponding to the new rate of elimination. The drug effect may diminish or disappear. Conversely, when elimination is impaired (e.g., in progressive renal insufficiency), the mean plasma level of renally eliminated drugs rises and may enter a toxic concentration range.

Dose–Response Relationship

The effect of a substance depends on the amount administered, i.e., the dose. If the dose chosen is below the critical threshold (subliminal dosing), an effect will be absent. Depending on the nature of the effect to be measured, ascending doses may cause the effect to increase in intensity. Thus, the effect of an antipyretic or hypotensive drug can be quantified in a graded fashion, in that the extent of fall in

body temperature or blood pressure is being measured. A dose-effect relationship is then encountered.

The dose-effect relationship may vary depending on the sensitivity of the individual person receiving the drug, i.e., for the same effect, different doses may be required in different individuals. Interindividual variation in sensitivity is especially obvious with effects of the “all-or-none” kind.

To illustrate this point, we consider an experiment in which the subjects individually respond in all-or-none fashion, as in the Straub tail phenomenon. Mice react to morphine with excitation, evident in the form of an abnormal posture of the tail and limbs. The dose dependence of this phenomenon is observed in groups of animals (e.g., 10 mice per group) injected with increasing doses of morphine. At the low dose, only the most sensitive, at increasing doses a growing proportion, at the highest dose all of the animals are affected. There is a relationship between the frequency of responding animals and the dose given. At 2 mg/kg, one out of 10 animals reacts; at 10 mg/kg, 5 out of 10 respond. The **dose-frequency relationship** results from the different sensitivity of individuals, which as a rule exhibits a log-normal distribution. If the cumulative frequency (total number of animals responding at a given dose) is plotted against the logarithm of the dose (abscissa), a sigmoidal curve results. The inflection point of the curve lies at the dose at which one-half of the group has responded. The dose range encompassing the dose-frequency relationship reflects the variation in individual sensitivity to the drug. Although similar in shape, a dose-frequency relationship has, thus, a different meaning than does a dose-effect relationship. The latter can be evaluated in one individual and results from an intraindividual dependency of the effect on drug concentration.

The evaluation of a dose-effect relationship within a group of human subjects is compounded by interindividual differences in sensitivity. To account for the biological variation, measurements have to be carried out on a representative sample and the results averaged. Thus, recommended therapeutic doses will be appropriate for the majority of patients, but not necessarily for each individual.

The variation in sensitivity may be based on pharmacokinetic differences (same dose to different plasma levels) or on differences in target organ sensitivity (same plasma level to different effects).

Control questions

1. The subject of pharmacotherapy, its interconnection with medical-biological and clinical disciplines.
2. Basic questions of pharmacodynamics of medicinal products (notion about affinity, structure of chemical receptors, features of interaction of drugs with receptors, selectivity of action).
3. The main questions of pharmacokinetics and their significance in rational pharmacotherapy.
4. Basic pharmacokinetic parameters (total clearance, volume distribution, half-life,

equilibrium concentration, bioavailability).
5. Types of interaction of medicinal products (pharmaceutical, pharmacokinetic, pharmacodynamic).
6. Factors influencing the interaction of drugs with biological systems and determine the final pharmacotherapeutic efficacy.
7. Principles of combination of medicines taking into account the clinical course of diseases. Significance of pharmacokinetic parameters of drug in combination pharmacotherapy.
8. Interaction of medicinal products with food.
9. Features of the interaction of drugs that affect the different levels of regulatory systems of the body.
10. Side effects of drugs: locally irritant, toxic and metabolic exogenous and endogenous origin, weakening of immunity, neurogenic.
11. Drug dependence, medical and social aspects of combating it.
12. Features of pharmacotherapy in pregnant women.
13. Features of the use of drugs in women during lactation.
14. Features of pharmacotherapy in newborns. Pharmacokinetic characteristics of the drug.
15. Features of the course of diseases and principles of pharmacotherapy in the elderly. The significance of pharmacokinetic parameters of the drug in determining the dose and multiplicity of administration.
16. Prophylactic use of drugs in the elderly.

Control the level of knowledge

1. Fill in the table "Stages of pharmacokinetics of the drug in the body".

Pharmacokinetic characteristics of the drug	The content of the concept
Absorption Distribution Binding to proteins Biotransformation Breeding	

1. Fill in the table "Pharmacokinetic parameters characterizing the process of distribution of drugs".

Pharmacokinetic parameters	The content of the concept
1. Initial concentration of LS (Co) 2. The maximum concentration of MD in the blood (Cmax)	

3. Stationary (equilibrium) concentration (Css) 4. Distribution volume (Vd)	

3. Fill in the table "Pharmacokinetic parameters characterizing the process of drug delivery from an organism".

Pharmacokinetic parameters	**The content of the concept**
1. Constant output speed (Cel) 2. The half-life (t1 / 2) 3. Total clearance (Cl) 4. Constant rate of excretion (Crx)	

4. Fill in the table "Factors influencing the choice of dose of drugs":

Pharmacokinetic and other factors	**Effect on dose selection**
1. Type of dosage form 2. Hydrophilicity and hydrophobia of drugs 3. Volume of distribution of LR in the body 4. Binding to plasma proteins 5. pH value of the body fluids 6. Nature and content of auxiliary substances 7. Period of half-life of the drug 8. Condition of individual organs and systems 9. Therapeutic range of drugs 10. Concomitant diseases	

* Note: The effect of a factor on the choice of dose is marked with a "+" sign

5. Fill in the table "Principles of Dosage Depending on the Type of Pharmacotherapy":

Types of pharmacotherapy	**Principle of dosage**
1. Substitution therapy 2. Symptomatic therapy 3. Pathogenetic therapy 4. Etiotropic therapy 5. Antidote drug therapy	

6. Give definitions of terms and indicate drugs that determine the phenomena observed during re-administration, combined use and adverse effects of drugs. The answers are given in the form of a table:

Concept	Definition	Drugs
1. Addictive 2. Tachyphilacia 3. Drug addiction 4. Cumulation 5. Drug allergy 6. Synergism 7. Antagonism 8. Teratogenic and embryotoxic action 9. Mutagenic action 10. Idiosyncrazy 11. Carcinogenic action		

7. Explain what is the bioavailability of the drug? What is the clinical significance of bioavailability? What factors and how can they affect bioavailability? The answers are given in the form of a table:

Factors influencing bioavailability	Mechanism of influence
I. Related to the features of the medicinal product: 1. ..... 2. ..... 3.	
II. Peculiarities of the patient's body: 1. ..... 2. ..... 3.	

8. Fill in the table "Factors Affecting the efficiency of medicines at different types of input":

Input path	Beginning speed	Concentration in the blood	Biological filtering	Medicinal forms
1. **Example:** Inner-world venny	Instantly or in 1 1- 2 minutes	Missing	Missing	Only real solutions (unacceptable introduction of oil solutions, suspensions)
2. Intramuscular				

Input path	Beginning speed	Concentration in the blood	Biological filtering	Medicinal forms
3. Subcutaneous				
4.Ingational				
5. Inside				
6. Rectal				

9. Fill in the table "Effect of food on absorption of medicinal products":

Medicinal products	Absorption	
	Deceleration	Lack of influence
1. Amoxicillin 2. Acetylsalicylic acid 3. Acetaminophen 4. Glibenclamide 5. Digoxin 6. Nitrosorbide 7. Nitrazepam 8. Prednisolone 9. Chlorpropamide 10. Cephalosporins 11. Sulphanilamides 12. Phenobarbital 13. Furosemide 14. Theophylline		

Note: Give answers in the form of "+" or "-" characters.

10. Fill in the table "Physiological and pathological changes and their pharmacokinetic and therapeutic effects in geriatric patients":

Parameters	Physiological and pathological changes	Organic effects	Pharmacokinetic effects	Therapeutic effects
1. Weight of the body				

2. Secretion of the digestive aratus				
3. Heart and blood circulation				
4. Kidney				
5.Blocks of plasma				

11. To make a comparative assessment of pharmacokinetic processes depending on age. The answers are given in the form of a table:

Pharmacokinetic processes	**Children's age**	**Summer and aging age**
1. Absorption of the drug		
2. Binding of medicinal substances to plasma blood proteins		
3. Distribution of medicines		
4. The rate of metabolism		
5. Removal of drugs		

Test tasks

1. What processes do not study pharmacodynamics**?**
1. Drug withdrawal
2. Distribution of drugs in the body.
3. Biotransformation.
4. Mechanism of action of drugs.
5. Absorption of drugs.
6. Relationship of drugs with protein.

2. When choosing a dosage regimen based on the half-life, the drugs are determined.

1. Multiplicity of reception.
2. One dose.
3. Daily dose.
4. Intensity of hepatic blood flow.
5. Intensity of withdrawal of the drug.

3. The rate of withdrawal of drugs from the body characterizes:
1. Bioavailability.
2. Bioequivalence.
3. Period of half-life.
4. Equilibrium concentration.
5. Total clearance.

4. The bioavailability value is necessary to determine:
1. When taking a single dose internally.
2. Multiplicity of reception.
3. The rate of withdrawal of the drug.
4. The rate of absorption of the drug
5. Daily dose.

5. Pharmacodynamics studies:
1. Undesirable effects of drugs.
2. Interaction of medicinal products.
3. Biotransformation of drugs.
4. Mechanism of action and effects of drugs.
5. Distribution of medicines.

6. A factor that determines the appearance of an effect, its duration and intensity, are:
1. Plasma concentration of the drug.
2. Concentration of the drug for specific or non-specific tissue receptors.
3. Single dose of the drug.
4. Daily dose of medicinal substance.
5. Multiplicity of reception.

7. Refractory to the drug means:
1. Ricochet syndrome.
2. Initial insensitivity to the medicinal product.
3. The usual effect when taking large doses of the drug.
4. Tachyphilacia.
5. Reducing the duration and magnitude of the effect of prolonged use of the drug.

8. What does the paradoxical effect of a drug mean?
1. Formation of antibodies to a medicinal product.
2. The emergence of new symptoms after abrupt discontinuation of the drug.

3. Aggravation of the symptoms of the disease for which the medication was prescribed in the process of pharmacotherapy.
4. The patient's usual reaction to an extremely low dose of drugs.
5. Increased patient response to the usual dose of the drug.

9. Synthetic drug metabolism reactions include:
1. Oxidation.
2. Restoration.
3. Sulphate conjugation.
4. Hydrolysis.
5. Deamination**.**

10. What part of the drug is pharmacologically active?
1. Fraction of the medicinal substance associated with acidic alpha-glycoprotein.
2. Free fraction of medicinal substance.
3. Fraction of the drug associated with albumin plasma.
4. A part of the medicinal substance accumulated in the formed blood elements.
5. Fraction of drug substance associated with serum globulins..

11. What of the following can act as a mechanism of action of drugs?
1. Effect on specific receptors.
2. Direct chemical interaction.
3. Effect on selective ion flow through membranes.
4. Induction of glucuronyltransferase of the liver.
5. All of the above.

12. The term "presidential termination" means:
1. Metabolism of the first passage.
2. Binding to food components.
3. Biotransformation in the liver.
4. Biotransformation in the cells of the mucous membrane.
5. Complex of processes leading to inactivation
the drug before it enters the systemic circulation.

13. At what states is characterized by an increase in the half-life of medicinal substances:
1. Urolithiasis.
2. Myocardial infarction.
3. Shock.
4. Reception of barbiturates.
5. Summer age.

14. The displacement from the connection with plasma proteins of one drug by others is an example:
1. Pharmaceutical interactions.

2. Pharmacodynamic interaction.
3. Physiological interaction.
4. Pharmacokinetic interaction.

15. Receptor competition is an example:
1. Pharmacokinetic interaction.
2. Pharmacodynamic interaction.
3. Pharmaceutical interactions.

16. The basis of idiosyncrasy lies:
1. Immunopathological mechanism:
2. Anaphylactic reactions.
3. Superinfection.
4. Interaction of drugs.
5. An inherited defect of enzyme systems.

17. Pharmacokinetic interaction may be the result of:
1. Change of chemical reactions.
2. Change of physical reactions.
3. Increase in glucose in plasma.
4. Reduction of protein in plasma.
5. Change in receptor sensitivity.

18. Specify the types of side effects that are easily predictable.
1. From the sudden cessation of taking medication.
2. Damage (toxic).
3. Allergic and autoimmune.
4. Pharmacokinetic.
5. Mutagenic, teratogenic and embryotoxic.

19. The cause of side effects of drugs can be:
1. Reduced protein binding.
2. Acceleration of biotransformation of drugs.
3. Increased protein binding.
4. Increase the bound form of drugs.
5. Reducing the dose of drugs.

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TOPIC 4. Principal principles of pharmacotherapy of arterial hypertension and arterial hypotension.

Actuality of topic.

Arterial hypertension (AH) - one of the most common chronic diseases of a person. Based on data from the 2011–2012 NHANES survey, about one-third of adults in the United States are hypertensive. Hypertension is uncontrolled in almost half of these 71 million people, and of those with uncontrolled hypertension, about 36% or 13 million are unaware of the diagnosis. Even in patients in whom hypertension is diagnosed and treated, control is attained in only 60%. By convention, hypertension is categorized based on office measurements as stage 1 (140–159/90–99 mm Hg) and stage 2 (greater than 160/100 mm Hg). Cardiovascular morbidity and mortality increase as both systolic and diastolic blood pressures rise, but in individuals over age 50 years, the systolic pressure and pulse pressure are better predictors of complications than diastolic pressure. The prevalence of hypertension increases with age, and it is more common in blacks than in whites. Adequate blood pressure control reduces the incidence of acute coronary syndrome by 20–25%, stroke by 30–35%, and heart failure by 50%.

Purpose of the lesson: The student should know: etiology, pathogenesis of arterial hypertension; types of hypertension: primary, secondary; diagnostic methods; clinical symptoms; principles of pharmacotherapy AH; the concept of hypertensive crises, definitions, principles of providing urgent care. Arterial hypotension: concept, classification, etiology, pathogenesis, clinical symptoms, diagnostic methods, principles of pharmacotherapy. Concept about hypotensive states, principles of providing urgent care.

HOW IS BLOOD PRESSURE MEASURED & HYPERTENSION DIAGNOSED?

Blood pressure should be measured with a well-calibrated sphygmomanometer. The bladder width within the cuff should encircle at least 80% of the arm circumference. Readings should be taken after the patient has been resting comfortably, back supported in the sitting or supine position, for at least 5 minutes and at least 30 minutes after smoking or coffee ingestion. Office-based devices that permit multiple automated measurements after a pre-programmed rest period produce blood pressure readings that are independent of the “white coat” phenomenon (where blood pressure is elevated in the clinic but normal at home) and digit preference bias. Blood pressure measurements taken outside the office environment, either by intermittent self monitoring (home blood pressure) or with an automated device programmed to take measurements at regular intervals (ambulatory blood pressure) are more powerful predictors of outcomes and are increasingly advocated in clinical guidelines. Home measurements are also helpful in differentiating “white coat” hypertension from hypertension that is resistant to

treatment, and in diagnosis of “masked hypertension” (where blood pressure is normal in the clinic but elevated at home). The cardiovascular risk associated with masked hypertension is similar to that observed in sustained hypertension.

A single elevated blood pressure reading is not sufficient to establish the diagnosis of hypertension. The major exceptions to this rule are hypertensive presentations with unequivocal evidence of life-threatening end-organ damage, as seen in hypertensive emergency, or in hypertensive urgency where blood pressure is greater than 220/125 mm Hg but life-threatening end-organ damage is absent. In less severe cases, the diagnosis of hypertension depends on a series of measurements of blood pressure, since readings can vary and tend to regress toward the mean with time. Patients whose initial blood pressure is in the hypertensive range exhibit the greatest fall toward the normal range between the first and second encounters. However, the concern for diagnostic precision needs to be balanced by an appreciation of the importance of establishing the diagnosis of hypertension as quickly as possible, since a 3-month delay in treatment of hypertension in high-risk patients is associated with a twofold increase in cardiovascular morbidity and mortality. The Canadian Hypertension Education Program provides an algorithm designed to expedite the diagnosis of hypertension. To this end, these guidelines recommend short intervals between initial office visits and stress the importance of early identification of target organ damage or diabetes mellitus, which, if present, justifies pharmacologic intervention if blood pressure remains above 140/90 mm Hg after just two visits. The Canadian guidelines suggest the use of ambulatory and home blood pressure measurements as complements to office-based evaluations. Guidelines from the United Kingdom go further in suggesting that ambulatory or home BP measurements should be used in preference to office-based measurements in the diagnosis of hypertension. When measured by automated office devices, manual home cuffs, or daytime ambulatory equipment, stage 1 hypertension is diagnosed at an average blood pressure greater than 135/85 mm Hg; for 24-hour ambulatory measurement, the diagnostic threshold for stage 1 hypertension is still lower at 130/80 mm Hg.

Ambulatory blood pressure readings are normally lowest at night and the loss of this nocturnal dip is a dominant predictor of cardiovascular risk, particularly risk of thrombotic stroke. An accentuation of the normal morning increase in blood pressure is associated with increased likelihood of cerebral hemorrhage. Furthermore, variability of systolic blood pressure predicts cardiovascular events independently of mean systolic blood pressure. It is becoming increasingly clear that in diagnosing and monitoring hypertension, there should be a move away from isolated office readings and toward a more integrated view based on repeated measurements in a more “real world” environment. The diagnosis of hypertension does not automatically entail drug treatment; this decision depends on the clinical setting, as discussed below.

PREHYPERTENSION

Data from the Framingham cohort indicate that blood pressure bears a linear relationship with cardiovascular risk down to a systolic blood pressure of 115 mm

Hg; based on these data, it has been suggested that individuals with blood pressures in the gray area of 120–139/80–89 mm Hg be categorized as having "prehypertension." Because prehypertension often develops into hypertension (50% of affected individuals do so within 4 years), prehypertensive patients should be monitored annually.

APPROACH TO HYPERTENSION

Etiology & Classification

A. Primary Essential Hypertension

Essential hypertension is the term applied to the 95% of hypertensive patients in which elevated blood pressure results from complex interactions between multiple genetic and environmental factors. The proportion regarded as "essential" will diminish with improved detection of clearly defined secondary causes and with better understanding of pathophysiology. Essential hypertension occurs in 10–15% of white adults and 20–30% of black adults in the United States. The onset is usually between ages 25 and 50 years; it is uncommon before age 20 years. The best understood endogenous and environmental determinants of blood pressure include overactivation of the sympathetic nervous and renin-angiotensin-aldosterone systems, blunting of the pressure-natriuresis relationship, variation in cardiovascular and renal development, and elevated intracellular sodium and calcium levels

Exacerbating factors include obesity, sleep apnea, increased salt intake, excessive alcohol use, cigarette smoking, polycythemia, nonsteroidal anti-inflammatory (NSAID) therapy, and low potassium intake. **Obesity** is associated with an increase in intravascular volume, elevated cardiac output, activation of the renin-angiotensin system, and, probably, increased sympathetic outflow. Weight reduction lowers blood pressure modestly. In patients with **sleep apnea**, treatment with continuous positive airway pressure (CPAP) has been associated with improvements in blood pressure. **Increased salt intake** probably elevates blood pressure in some individuals so dietary salt restriction is recommended in patients with hypertension (see below).

Excessive use of **alcohol** also raises blood pressure, perhaps by increasing plasma catecholamines. Hypertension can be difficult to control in patients who consume more than 40 g of ethanol (two drinks) daily or drink in "binges." **Cigarette smoking** raises blood pressure by increasing plasma norepinephrine. Although the longterm effect of smoking on blood pressure is less clear, the synergistic effects of smoking and high blood pressure on cardiovascular risk are well documented. The relationship of exercise to hypertension is variable. Aerobic **exercise** lowers blood pressure in previously sedentary individuals, but increasingly strenuous exercise in already active subjects has less effect. The relationship between stress and hypertension is not established. **Polycythemia**, whether primary, drug-induced, or due to diminished plasma volume, increases blood viscosity and may raise blood pressure. **NSAIDs** produce increases in blood pressure averaging 5 mm Hg and are best avoided in patients with borderline or

elevated blood pressures. Low **potassium intake** is associated with higher blood pressure in some patients; an intake of 90 mmol/day is recommended.

The complex of abnormalities termed the "**metabolic syndrome**" (upper body obesity, insulin resistance, and hypertriglyceridemia) is associated with both the development of hypertension and an increased risk of adverse cardiovascular outcomes. Affected patients usually also have low high-density lipoprotein (HDL) cholesterol levels and elevated catecholamines and inflammatory markers such as C-reactive protein.

B. Secondary Hypertension

Approximately 5% of patients have hypertension secondary to identifiable specific causes. Secondary hypertension should be suspected in patients in whom hypertension develops at an early age or after the age of 50 years, and in those previously well controlled who become refractory to treatment. Hypertension resistant to three medications is another clue although multiple medications are usually required to control hypertension in persons with diabetes. Secondary causes include genetic syndromes; kidney disease; renal vascular disease; primary hyperaldosteronism; Cushing syndrome; pheochromocytoma; coarctation of the aorta and hypertension associated with pregnancy, estrogen use, hypercalcemia, and medications.

Identifiable causes of hypertension:

- Sleep apnea
- Drug-induced or drug-related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Long-term corticosteroid therapy and Cushing syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease

1. **Genetic causes**—Hypertension can be caused by mutations in single genes, inherited on a Mendelian basis. Although rare, these conditions provide important insight into blood pressure regulation and possibly the genetic basis of essential hypertension. **Glucocorticoid remediable aldosteronism** is an autosomal dominant cause of earlyonset hypertension with normal or high aldosterone and low renin levels. It is caused by the formation of a chimeric gene encoding both the enzyme responsible for the synthesis of aldosterone (transcriptionally regulated by angiotensin II) and an enzyme responsible for synthesis of cortisol (transcriptionally regulated by ACTH). As a consequence, aldosterone synthesis becomes driven by ACTH, which can be suppressed by exogenous cortisol. In the **syndrome of apparent mineralocorticoid excess**, early-onset hypertension with hypokalemic metabolic alkalosis is inherited on an autosomal recessive basis.

Although plasma renin is low and plasma aldosterone level is very low in these patients, aldosterone antagonists are effective in controlling hypertension. This disease is caused by loss of the enzyme, 11beta-hydroxysteroid dehydrogenase, which normally metabolizes cortisol and thus protects the otherwise “promiscuous” mineralocorticoid receptor in the distal nephron from inappropriate glucocorticoid activation. Similarly, glycyrrhetinic acid, found in licorice, causes increased blood pressure through inhibition of 11beta-hydroxysteroid dehydrogenase. The syndrome of **hypertension exacerbated** in pregnancy is inherited as an autosomal dominant trait. In these patients, a mutation in the mineralocorticoid receptor makes it abnormally responsive to progesterone and, paradoxically, to spironolactone. **Liddle syndrome** is an autosomal dominant condition characterized by earlyonset hypertension, hypokalemic alkalosis, low renin, and low aldosterone levels. This is caused by a mutation that results in constitutive activation of the epithelial sodium channel of the distal nephron, with resultant unregulated sodium reabsorption and volume expansion.

2. **Renal disease**—Renal parenchymal disease is the most common cause of secondary hypertension and is related to increased intravascular volume or increased activity of the renin–angiotensin–aldosterone system.

2. **Renal vascular hypertension**—Renal artery stenosis is present in 1–2% of hypertensive patients. Its cause in most younger individuals is fibromuscular dysplasia, particularly in women under 50 years of age. The remainder is due to atherosclerotic stenoses of the renal arteries. The mechanisms of hypertension relate to excessive renin release due to reduction in renal perfusion pressure and attenuation of pressure natriuresis with stenosis affecting a single kidney or with bilateral renal artery stenosis. Activation of the renal sympathetic nerves may also be important..

Renal vascular hypertension should be suspected in the following circumstances: (1) if the documented onset is before age 20 or after age 50 years, (2) hypertension is resistant to three or more drugs, (3) if there are epigastric or renal artery bruits, (4) if there is atherosclerotic disease of the aorta or peripheral arteries (15–25% of patients with symptomatic lower limb atherosclerotic vascular disease have renal artery stenosis), (5) if there is an abrupt increase (more than 25%) in the level of serum creatinine after administration of angiotensin-converting enzyme (ACE) inhibitors, or (6) if episodes of pulmonary edema are associated with abrupt surges in blood pressure. There is no ideal screening test for renal vascular hypertension. If suspicion is sufficiently high and endovascular intervention is a viable option, renal arteriography, the definitive diagnostic test, is the best approach. Renal arteriography is not recommended as a routine adjunct to coronary studies. Where suspicion is moderate to low, noninvasive angiography using magnetic resonance (MR) or CT are reasonable approaches. With improvements in technology and operator expertise, Doppler sonography may play an increasing role in detection of renal artery stenosis, providing physiologic indices of stenosis severity and ease of repeated examination to detect progression.

Gadolinium, a contrast agent used in MR angiography, is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min because it might precipitate nephrogenic systemic fibrosis in patients with advanced kidney disease. In young patients with fibromuscular disease, angioplasty is very effective, but there is controversy regarding the best approach to the treatment of atheromatous renal artery stenosis. Correction of the stenosis in selected patients might reduce the number of medications required to control blood pressure and could protect kidney function, but the extent of preexisting parenchymal damage to the affected and contralateral kidney has a significant influence on both blood pressure and kidney function outcomes following revascularization. Angioplasty and stenting may prove to be superior to medical therapy in a subset of patients, but identifying this group remains a challenge. A reasonable approach advocates medical therapy as long as hypertension can be well controlled and there is no progression of kidney disease. The addition of a statin should be considered. Endovascular intervention might be considered in patients with uncontrollable hypertension, progressive kidney disease, or episodic pulmonary edema attributable to the lesion. Angioplasty might also be warranted when progression of stenosis is either demonstrated or is predicted by a constellation of risk factors, including systolic blood pressure greater than 160 mm Hg, advanced age, diabetes mellitus, or high-grade stenosis (more than 60%) at the time of diagnosis. However, multiple studies have failed to identify an overall advantage of stenting over medical management in patients with atherosclerotic renal artery stenosis. The CORAL study utilized a distal capture device to prevent embolization into the kidney, but the conclusion was once again that stenting is not superior to medical therapy (incorporating a statin) in the management of atherosclerotic renal artery stenosis. Although drugs modulating the renin-angiotensin system have improved the success rate of medical therapy of hypertension due to renal artery stenosis, they may trigger hypotension and (usually reversible) kidney dysfunction in individuals with bilateral disease.

3. **Primary hyperaldosteronism**—Hyperaldosteronism is suggested when the plasma aldosterone concentration is elevated (normal: 1–16 ng/dL) in association with suppression of plasma renin activity (normal: 1–2.5 ng/mL/h). However, the plasma aldosterone/renin ratio (normal less than 30) is not highly specific as a screening test. This is because “bottoming out” of renin assays leads to exponential increases in the plasma aldosterone/renin ratio even when aldosterone levels are normal. Hence, an elevated plasma aldosterone/renin ratio should probably not be taken as evidence of hyperaldosteronism unless the aldosterone level is actually supranormal. The lesion responsible for hyperaldosteronism is an adrenal adenoma or bilateral adrenal hyperplasia. Approximately 50% of aldosterone-secreting adenomas arise as a consequence of somatic mutations in genes encoding glomerulosa cell membrane ion transporters, with resultant elevation of intracellular calcium concentration. Screening is appropriate in patients with resistant hypertension, (needing more than three drugs for control) and those

with spontaneous or thiazide-induced hypokalemia, incidentaloma, or family history of primary hyperaldosteronism.

During the workup for hyperaldosteronism, medications that alter renin and aldosterone levels, including ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics, beta-blockers, and clonidine, should be discontinued for 2 weeks before sampling; spironolactone and eplerenone should be held for 4 weeks. Calcium channel and alphareceptor blockers can be used to control blood pressure during this drug washout period. Patients with a plasma aldosterone level greater than 16 ng/dL and an aldosterone/ renin ratio of 30 or more might require further evaluation for primary hyperaldosteronism.

5. Cushing syndrome—Hypertension occurs in about 80% of patients with spontaneous Cushing syndrome. Excess glucocorticoid may act through salt and water retention (via mineralocorticoid effects), increased angiotensinogen levels, or permissive effects in the regulation of vascular tone.

6. Pheochromocytoma—Pheochromocytomas are uncommon; they are probably found in less than 0.1% of all patients with hypertension and in approximately two individuals per million population. However, autopsy studies indicate that pheochromocytomas are very often undiagnosed in life. The blood pressure elevation caused by the catecholamine excess results mainly from alpha-receptor– mediated vasoconstriction of arterioles, with a contribution from beta-1-receptor-mediated increases in cardiac output and renin release. Chronic vasoconstriction of the arterial and venous beds leads to a reduction in plasma volume and predisposes to postural hypotension. Glucose intolerance develops in some patients. Hypertensive crisis in pheochromocytoma may be precipitated by a variety of drugs, including tricyclic antidepressants, antidopaminergic agents, metoclopramide, and naloxone.

7. Coarctation of the aorta—Evidence of radial-femoral delay should be sought in all younger patients with hypertension.

8. Hypertension associated with pregnancy—Hypertension occurring de novo or worsening during pregnancy, including preeclampsia and eclampsia, is one of the most common causes of maternal and fetal morbidity and mortality. Autoantibodies with the potential to activate the angiotensin II type 1 receptor have been causally implicated in preeclampsia, in resistant hypertension, and in progressive systemic sclerosis.

9. Estrogen use—A small increase in blood pressure occurs in most women taking oral contraceptives. However, a more significant increase above 140/90 mm Hg is noted in about 5% of women, mostly in obese individuals older than age 35 who have been treated for more than 5 years. This is caused by increased hepatic synthesis of angiotensinogen. Postmenopausal estrogen does not generally cause hypertension but rather maintains endothelium-mediated vasodilation.

10. Other causes of secondary hypertension—Hypertension has also been associated with hypercalcemia, acromegaly, hyperthyroidism, hypothyroidism, baroreceptor denervation, compression of the rostral ventrolateral medulla, and increased intracranial pressure. A number of medications may cause or exacerbate hypertension—most importantly cyclosporine, tacrolimus, angiogenesis inhibitors, and erythrocyte-stimulating agents (such as erythropoietin, decongestants, and NSAIDs); cocaine and alcohol should also be considered. Over-the-counter products should also be considered, eg, a dietary supplement currently marketed to enhance libido contains yohimbine, an alpha-2–antagonist; it can produce severe rebound hypertension in patients taking clonidine.

When to Refer

Referral to a hypertension specialist should be considered in cases of severe, resistant or early-/late-onset hypertension or when secondary hypertension is suggested by screening.

Complications of Untreated Hypertension

Elevated blood pressure results in structural and functional changes in the vasculature and heart. Most of the adverse outcomes in hypertension are associated with thrombosis rather than bleeding, possibly because increased vascular shear stress converts the normally anticoagulant endothelium to a prothrombotic state. The excess morbidity and mortality related to hypertension approximately doubles for each 6 mm Hg increase in diastolic blood pressure. However, target-organ damage varies markedly between individuals with similar levels of office hypertension; home and ambulatory pressures are superior to office readings in the prediction of end-organ damage and variability in blood pressure from visit to visit predicts cardiovascular endpoints independently of mean office-based systolic blood pressure.

A. Hypertensive Cardiovascular Disease

Cardiac complications are the major causes of morbidity and mortality in primary (essential) hypertension. For any level of blood pressure, left ventricular hypertrophy is associated with incremental cardiovascular risk in association with heart failure (through systolic or diastolic dysfunction), ventricular arrhythmias, myocardial ischemia, and sudden death.

The occurrence of heart failure is reduced by 50% with antihypertensive therapy. Hypertensive left ventricular hypertrophy regresses with therapy and is most closely related to the degree of systolic blood pressure reduction. Diuretics have produced equal or greater reductions of left ventricular mass when compared with other drug classes. Conventional beta-blockers are less effective in reducing left ventricular hypertrophy but play a specific role in patients with established coronary artery disease or impaired left ventricular function.

B. Hypertensive Cerebrovascular Disease and Dementia

Hypertension is the major predisposing cause of hemorrhagic and ischemic stroke. Cerebrovascular complications are more closely correlated with systolic than diastolic blood pressure. The incidence of these complications is markedly reduced by antihypertensive therapy. Preceding hypertension is associated with a higher incidence of subsequent dementia of both vascular and Alzheimer types. Home and ambulatory blood pressure may be a better predictor of cognitive decline than office readings in older people. Effective blood pressure control may reduce the risk of development of cognitive dysfunction later in life, but once cerebral small-vessel disease is established, low blood pressure might exacerbate this problem.

C. Hypertensive Kidney Disease

Chronic hypertension is associated with nephrosclerosis, which accounts for about 25% of end-stage renal disease. Whether hypertension causes nephrosclerosis or results from kidney disease driven by other factors (such as diabetes mellitus, age, obesity, and smoking) remains uncertain. Nephrosclerosis is particularly prevalent in blacks, in whom susceptibility is linked to APOL1 mutations. One plausible hypothesis suggests that these mutations became prevalent in people of African descent because they also conferred resistance to trypanosomal infection.

D. Aortic Dissection

Hypertension is a contributing factor in many patients with dissection of the aorta.

E. Atherosclerotic Complications

Most Americans with hypertension die of complications of atherosclerosis, but antihypertensive therapy seems to have a lesser impact on atherosclerotic complications compared with the other effects of treatment outlined above. Prevention of cardiovascular outcomes related to atherosclerosis probably requires control of multiple risk factors, of which hypertension is only one.

Clinical Findings

The clinical and laboratory findings are mainly referable to involvement of the target organs: heart, brain, kidneys, eyes, and peripheral arteries.

A. Symptoms

Mild to moderate primary (essential) hypertension is largely asymptomatic for many years. The most frequent symptom, headache, is also very nonspecific. Accelerated hypertension is associated with somnolence, confusion, visual disturbances, and nausea and vomiting (hypertensive encephalopathy).

Hypertension in patients with pheochromocytomas that secrete predominantly norepinephrine is usually sustained but may be episodic. The typical attack lasts from minutes to hours and is associated with headache, anxiety, palpitation, profuse perspiration, pallor, tremor, and nausea and vomiting. Blood

pressure is markedly elevated, and angina or acute pulmonary edema may occur. In primary aldosteronism, patients may have muscular weakness, polyuria, and nocturia due to hypokalemia; malignant hypertension is rare. Chronic hypertension often leads to left ventricular hypertrophy and diastolic dysfunction, which can present with exertional and paroxysmal nocturnal dyspnea. Cerebral involvement causes stroke due to thrombosis or hemorrhage from microaneurysms of small penetrating intracranial arteries. Hypertensive encephalopathy is probably caused by acute capillary congestion and exudation with cerebral edema, which is reversible.

B. Signs

Like symptoms, physical findings depend on the cause of hypertension, its duration and severity, and the degree of effect on target organs.

1. Blood pressure—Blood pressure is taken in both arms and, if lower extremity pulses are diminished or delayed, in the legs to exclude coarctation of the aorta. An orthostatic drop of at least 20/10 mm Hg is often present in pheochromocytoma. Older patients may have falsely elevated readings by sphygmomanometry because of noncompressible vessels. This may be suspected in the presence of Osler sign—a palpable brachial or radial artery when the cuff is inflated above systolic pressure. Occasionally, it may be necessary to make direct measurements of intra-arterial pressure, especially in patients with apparent severe hypertension who do not tolerate therapy.

2. Retinas—Narrowing of arterial diameter to less than 50% of venous diameter, copper or silver wire appearance, exudates, hemorrhages, or hypertensive retinopathy are associated with a worse prognosis.

3. Heart—A left ventricular heave indicates severe or longstanding hypertrophy. Aortic regurgitation may be auscultated in up to 5% of patients, and hemodynamically insignificant aortic regurgitation can be detected by Doppler echocardiography in 10–20%. A presystolic (S4) gallop due to decreased compliance of the left ventricle is quite common in patients in sinus rhythm.

4. Pulses—Radial-femoral delay suggests coarctation of the aorta; loss of peripheral pulses occurs due to atherosclerosis, less commonly aortic dissection, and rarely Takayasu arteritis, all of which can involve the renal arteries.

C. Laboratory Findings

Recommended testing includes the following: hemoglobin; urinalysis and serum creatinine; fasting blood sugar level (hypertension is a risk factor for the development of diabetes, and hyperglycemia can be a presenting feature of pheochromocytoma); plasma lipids (necessary to calculate cardiovascular risk and as a modifiable risk factor); serum uric acid (hyperuricemia is a relative contraindication to diuretic therapy); and serum electrolytes.

D. Electrocardiography and Chest Radiographs

Electrocardiographic criteria are highly specific but not very sensitive for left ventricular hypertrophy. The “strain” pattern of ST–T wave changes is a sign of more advanced disease and is associated with a poor prognosis. A chest radiograph is not necessary in the workup for uncomplicated hypertension.

E. Echocardiography

The primary role of echocardiography should be to evaluate patients with clinical symptoms or signs of cardiac disease.

F. Diagnostic Studies

Additional diagnostic studies are indicated only if the clinical presentation or routine tests suggest secondary or complicated hypertension. These may include 24-hour urine free cortisol, urine or plasma metanephrines and plasma aldosterone and renin concentrations to screen for endocrine causes of hypertension. Renal ultrasound will detect structural changes (such as polycystic kidneys, asymmetry and hydronephrosis) as well as echogenicity and reduced cortical volume, which are reliable indicators of advanced chronic kidney disease. Evaluation for renal artery stenosis should be undertaken in concert with subspecialist consultation.

G. Summary

Since most hypertension is essential or primary, few studies are necessary beyond those listed above. If conventional therapy is unsuccessful or if secondary hypertension is suspected, further studies and perhaps referral to a hypertension specialist are indicated.

Nonpharmacologic Therapy

Lifestyle modification may have an impact on morbidity and mortality. A diet rich in fruits, vegetables, and low-fat dairy foods and low in saturated and total fats (DASH diet) has been shown to lower blood pressure. Additional measures, can prevent or mitigate hypertension or its cardiovascular consequences.

All patients with high-normal or elevated blood pressures, those who have a family history of cardiovascular complications of hypertension, and those who have multiple coronary risk factors should be counseled about nonpharmacologic approaches to lowering blood pressure. Approaches of proved but modest value include weight reduction, reduced alcohol consumption, and, in some patients, reduced salt intake (less than 5 g salt or 2 g sodium). Gradually increasing activity levels should be encouraged in previously sedentary patients, but strenuous exercise training programs in already active individuals may have less benefit. Alternative approaches that may be modestly effective include relaxation techniques and biofeedback. Calcium and potassium supplements have been advocated, but their ability to lower blood pressure is limited. Smoking cessation will reduce cardiovascular risk. Overall, the effects of lifestyle modification on blood pressure are modest.

Who Should Be Treated with Medications?

Treatment should ideally be offered to all persons in whom blood pressure reduction, irrespective of initial blood pressure levels, will appreciably reduce overall cardiovascular risk with an acceptably low rate of medication-associated adverse effects. Outcomes data indicate that patients with office-based blood pressure measurements that consistently exceed 160/100 mm Hg (stage 2 hypertension) will benefit from antihypertensive therapy irrespective of cardiovascular risk. Several international guidelines suggest that treatment thresholds evaluated by home-based measurements should be lower, perhaps 150/95 mm Hg using home blood pressure or daytime ambulatory measurements. However, prospective outcomes data for treatment based on measurements taken outside the clinic are lacking. Treatment should be offered at lower thresholds in those with elevated cardiovascular risk or in the presence of existing end-organ damage. The corollary of this is that treatment thresholds might reasonably be set higher for young people with extremely low cardiovascular risk; the Canadian guidelines suggest a threshold of greater than 160/100 mm Hg. However, since risk may be underestimated in this population, specialist referral should be considered in younger people with stage 1 hypertension to exclude end-organ damage and to screen for secondary causes.

Since evaluation of total cardiovascular risk is important in deciding who to treat with antihypertensive medications, risk calculators are becoming essential clinical tools. A reliable and regularly updated calculator is available at Qrisk.org. Free smart phone applications are also available to estimate coronary heart disease risk. In general, a 20% total cardiovascular risk (which includes stroke) is equivalent to a 15% coronary heart disease risk.

Cardiovascular risk factors

Major risk factors

- Hypertension
- Cigarette smoking
- Obesity (BMI ≥ 30)1
- Physical inactivity
- Dyslipidemia
- Diabetes mellitus
- Microalbuminuria or estimated GFR < 60 mL/min
- Age (> 55 years for men, > 65 years for women)
- Family history of premature cardiovascular disease (men < 55 years or women < 65 years)

Target-organ damage

<u>Heart</u>

- Left ventricular hypertrophy
- Angina or prior myocardial infarction

- Prior coronary revascularization
- Heart failure

Brain

- Stroke or transient ischemic attack
- Chronic kidney disease
- Peripheral arterial disease
- Retinopathy

Purposes of Treatment

The blood pressure target in most patients with hypertension is less than 140/90 mm Hg. Possible exceptions to this general rule are discussed below. Observational studies suggest that there does not seem to be a blood pressure level below which decrements in risk taper off. However, this may not be true with respect to pharmacologically modulated blood pressure. In fact, over-enthusiastic treatment may have adverse consequences in certain settings. There is an association between lower blood pressure and cognitive decline in elderly patients subjected to intensification of antihypertensive treatment later in life.

Antihypertensive treatment in those who are both very elderly and frail may paradoxically increase mortality. Excessive lowering of diastolic pressure, perhaps below 70 mm Hg, should be avoided in patients with coronary artery disease. In diabetic patients, treatment of systolic pressures to below 130–135 mm Hg significantly increases the risk of serious adverse effects with no additional gain in terms of cardiac, renal, or retinal disease. On the other hand, reducing systolic pressure below 130 mm Hg does seem to further lower the risk of stroke, so lower targets might be justified in patients at high risk for cerebrovascular events.

The SPS3 trial in patients recovering from a lacunar stroke indicated that treating the systolic blood pressure to less than 130 mm Hg (mean systolic blood pressure of 127 mm Hg among treated versus mean systolic blood pressure 138 mm Hg among untreated patients) probably reduced the risk of recurrent stroke (and with an acceptably low rate of adverse effects from treatment).

Large-scale trials in hypertension have focused on discrete end points occurring over relatively short intervals, thereby placing the emphasis on the prevention of catastrophic events in advanced disease. There is an ongoing shift in emphasis in viewing hypertension in the context of lifelong cardiovascular risk. Accordingly, treatment of persons with hypertension should focus on comprehensive risk reduction with more careful consideration of the possible long-term adverse effects of antihypertensive medications, which include the metabolic derangements linked to conventional beta-blockers and thiazide diuretics and possible modest elevations in the risk of malignancy associated with several antihypertensive drugs.

Statins should be more widely used. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed that statins can significantly improve outcomes in persons with hypertension (with modest background cardiovascular risk) whose total cholesterol is less than 250 mg/dL (6.5 mmol/L). Notably, the effect of statins

appeared to be synergistic with calcium channel blocker/ACE inhibitor regimens but not beta-blocker/diuretic regimens. The British Hypertension Society guidelines recommend that statins be offered as secondary prevention to patients whose total cholesterol exceeds 135 mg/dL (3.5 mmol/L) if they have documented coronary artery disease or a history of ischemic stroke. In addition, statins should be considered as primary prevention in patients with longstanding type 2 diabetes or in those with type 2 diabetes who are older than age 50 years, and perhaps in all persons with type 2 diabetes. Low-dose aspirin (81 mg/day) is likely to be beneficial in patients older than age 50 with either target-organ damage or elevated total cardiovascular risk (greater than 20–30%). Care should be taken to ensure that blood pressure is controlled to the recommended levels before starting aspirin to minimize the risk of intracranial hemorrhage.

DRUG THERAPY: CURRENT ANTIHYPERTENSIVE AGENTS

There are now many classes of antihypertensive drugs of which six (diuretics, beta-blockers, renin inhibitors, ACE inhibitors, calcium channel blockers, and ARBs) are suitable for initial therapy based on efficacy and tolerability. A number of considerations enter into the selection of the initial regimen for a given patient. These include the weight of evidence for beneficial effects on clinical outcomes, the safety and tolerability of the drug, its cost, demographic differences in response, concomitant medical conditions, and lifestyle issues. The specific classes of antihypertensive medications are discussed below, and guidelines for the choice of initial medications are offered.

A. Diurecs

Thiazide diuretics are the antihypertensives that have been most extensively studied and most consistently effective in clinical trials. They lower blood pressure initially by decreasing plasma volume, but during longterm therapy, their major hemodynamic effect is reduction of peripheral vascular resistance. Most of the antihypertensive effect of these agents is achieved at lower dosages than used previously (typically, 12.5 mg of hydrochlorothiazide or equivalent), but their biochemical and metabolic effects are dose related. Chlorthalidone has the advantage of better 24-hour blood pressure control than hydrochlorothiazide. Thiazides may be used at higher doses if plasma potassium is above 4.5 mmol/L. The loop diuretics (such as furosemide) may lead to electrolyte and volume depletion more readily than the thiazides and have short durations of action. Because of these adverse effects, loop diuretics should be reserved for use in patients with kidney dysfunction (serum creatinine greater than 2.5 mg/dL [208.3 mcmol/L]) in which case they are more effective than thiazides. Relative to beta-blockers and ACE inhibitors, diuretics are more potent in blacks, older individuals, the obese, and other subgroups with increased plasma volume or low plasma renin activity (or both). They are relatively more effective in smokers than in nonsmokers. Long-term thiazide administration also mitigates the loss of bone mineral content in older women at risk for osteoporosis.

Overall, diuretics administered alone control blood pressure in 50% of patients with mild to moderate hypertension and can be used effectively in combination with all other agents. They are also useful for lowering isolated or predominantly systolic hypertension.

B. Beta-Adrenergic Blocking Agents

These drugs are effective in hypertension because they decrease the heart rate and cardiac output. Even after continued use of beta-blockers, cardiac output remains lower and systemic vascular resistance higher with agents that do not have intrinsic sympathomimetic or alpha-blocking activity. The beta-blockers also decrease renin release and are more efficacious in populations with elevated plasma renin activity, such as younger white patients. They neutralize the reflex tachycardia caused by vasodilators and are especially useful in patients with associated conditions that benefit from the cardioprotective effects of these agents. These include individuals with angina pectoris, previous myocardial infarction, and stable heart failure as well as those with migraine headaches and somatic manifestations of anxiety.

Although all beta-blockers appear to be similar in antihypertensive potency, they differ in a number of pharmacologic properties, including specificity to the cardiac beta-1- receptors (cardioselectivity) and whether they also block the beta-2-receptors in the bronchi and vasculature; at higher dosages, however, all agents are nonselective. The beta-blockers also differ in their pharmacokinetics, lipid solubility—which determines whether they cross the blood-brain barrier and affects the incidence of central nervous system side effects—and route of metabolism. Unlike the traditional beta-blockers, carvedilol and nebivolol also diminish peripheral vascular resistance through concomitant alpha-blockade and increased nitric oxide release, respectively.

In treatment of pheochromocytoma, beta-blockers should not be administered until alpha-blockade has been established. Otherwise, blockade of vasodilatory beta- 2-adrenergic receptors will allow unopposed vasoconstrictor alpha-adrenergic receptor activation with worsening of hypertension. *For the same reason, betablockers should not be used to treat hypertension arising from cocaine use.*

Because of the lack of efficacy in primary prevention of myocardial infarction and inferiority compared with other drugs in prevention of stroke and left ventricular hypertrophy, traditional beta-blockers should not be regarded as ideal first-line agents in the treatment of hypertension without specific compelling indications (such as active coronary artery disease). It might be that vasodilating betablockers will emerge as alternative first-line antihypertensives, but this possibility has yet to be rigorously tested in outcomes studies.

Great care should be exercised if the decision is made, in the absence of compelling indications, to remove betablockers from the treatment regimen because abrupt withdrawal can precipitate acute coronary events and severe increases in blood pressure.

Beta-adrenergic blocking agents

Acebutolol (Sectral) 400 mg once daily
Atenolol (Tenormin) 25 mg once daily
Betaxolol (Kerlone) 10 mg once daily
Bisoprolol (Zebeta) 5 mg once daily
Carvedilol (Coreg) 6.25 mg twice daily, (Coreg CR) 20 mg ER once daily
Labetalol (Trandate) 100 mg twice daily
Metoprolol (Lopressor) 50 mg twice daily , Toprol-XL (SR preparation) 25 mg once daily
Nadolol (Corgard) 20 mg once daily
Nebivolol (Bystolic) 5 mg once daily
Pindolol (Visken) 5 mg twice daily
Propranolol (Inderal) 20 mg twice daily, InnoPran XL 80 mg ER once nightly
Timolol (generic) 5 mg twice daily

C. Renin Inhibitors

Since renin cleavage of angiotensinogen is the rate-limiting step in the renin-angiotensin cascade, the most efficient inactivation of this system would be expected with renin inhibition. Conventional ACE inhibitors and ARBs probably offer incomplete blockade, even in combination. Aliskiren (Tekturna 150 mg once daily), a renin inhibitor, binds the proteolytic site of renin, thereby preventing cleavage of angiotensinogen. As a consequence, levels of angiotensins I and II are reduced and renin concentration is increased. Aliskiren effectively lowers blood pressure, reduces albuminuria, and limits left ventricular hypertrophy but it has yet to be established as a first-line drug based on outcomes data. The combination of aliskiren with ACE inhibitors or ARBs in persons with type 2 diabetes mellitus certainly offers no advantage and might even increase the risk of adverse cardiac or renal consequences.

D. Angiotensin-Converting Enzyme

Inhibitors ACE inhibitors are being increasingly used as the initial medication in mild to moderate hypertension. Their primary mode of action is inhibition of the renin–angiotensin–aldosterone system, but they also inhibit bradykinin degradation, stimulate the synthesis of vasodilating prostaglandins, and can reduce sympathetic nervous system activity. These latter actions may explain why they exhibit some effect even in patients with low plasma renin activity. ACE inhibitors appear to be more effective in younger white patients. They are relatively less effective in blacks and older persons and in predominantly systolic hypertension. Although as single therapy they achieve adequate antihypertensive control in only about 40–50% of patients, the combination of an ACE inhibitor and a diuretic or calcium channel blocker is potent.

ACE inhibitors are the agents of choice in persons with type 1 diabetes with frank proteinuria or evidence of kidney dysfunction because they delay the progression to endstage kidney disease. Many authorities have expanded this indication to include persons with type 1 and type 2 diabetics with

microalbuminuria who do not meet the usual criteria for antihypertensive therapy. ACE inhibitors may also delay the progression of nondiabetic kidney disease. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that the ACE inhibitor ramipril reduced the number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes and also reduced the incidence of new-onset heart failure, kidney dysfunction, and new-onset diabetes in a population of patients at high risk for vascular events. Although this was not specifically a hypertensive population, the benefits were associated with a modest reduction in blood pressure, and the results inferentially support the use of ACE inhibitors in similar hypertensive patients. ACE inhibitors are a drug of choice (usually in conjunction with a diuretic and a beta-blocker) in patients with heart failure and are indicated also in asymptomatic patients with reduced ejection fraction.

ACE inhibitors

Benazepril (Lotensin) 10 mg once daily
Captopril (Capoten) 25 mg twice daily
Enalapril (Vasotec) 5 mg once daily
Moexipril (Univasc) 7.5 mg once daily
Perindopril (Aceon) 4 mg once daily
Quinapril (Accupril) 10 mg once daily
Ramipril (Altace) 2.5 mg once daily
Trandolapril (Mavik) 1 mg once daily 1–8 mg once daily

E. Angiotensin II Receptor Blockers

ARBs can improve cardiovascular outcomes in patients with hypertension as well as in patients with related conditions such as heart failure and type 2 diabetes with nephropathy. ARBs have not been compared with ACE inhibitors in randomized controlled trials in patients with hypertension, but two trials comparing losartan with captopril in heart failure and post-myocardial infarction left ventricular dysfunction showed trends toward worse outcomes in the losartan group. By contrast, valsartan seems as effective as ACE inhibitors in these settings, suggesting that ARBs may be heterogeneous with respect to effects beyond blood pressure control. The Losartan Intervention for Endpoints (LIFE) trial in nearly 9000 hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy—comparing losartan with the betablocker atenolol as initial therapy—demonstrated a significant reduction in stroke with losartan. Of note is that in diabetic patients, death and myocardial infarction were also reduced, and there was a lower occurrence of newonset diabetes. In this trial, as in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), blacks treated with renin-angiotensin-aldosterone system (RAAS) inhibitors exhibited less blood pressure reduction and less benefit with regard to clinical end points. In the treatment of hypertension, combination therapy with an ACE inhibitor and an ARB is not advised because it generally offers no advantage over monotherapy at maximum dose with addition of a complementary class where necessary.

Unlike ACE inhibitors, the ARBs do not cause cough and are less likely to be associated with skin rashes or angioedema.

Angiotensin II Receptor Blockers

Azilsartan Edarbi 40 mg once daily
Candesartan cilexitil Atacand 16 mg once daily
Eprosartan Teveten 600 mg once daily
Irbesartan Avapro 150 mg once daily
Losartan Cozaar 50 mg once daily
Olmesartan Benicar 20 mg once daily
Telmisartan Micardis 40 mg once daily
Valsartan Diovan 80 mg once daily

F. Aldosterone Receptor Antagonists

Spironolactone and eplerenone are natriuretic in sodiumretaining states, such as heart failure and cirrhosis, but only very weakly so in hypertension. These drugs have reemerged in the treatment of hypertension, particularly in resistant patients and are helpful additions to most other antihypertensive medications. Consistent with the increasingly appreciated importance of aldosterone in essential hypertension, the aldosterone receptor blockers are effective at lowering blood pressure in all hypertensive patients regardless of renin level, and are also effective in blacks. Aldosterone plays a central role in target-organ damage, including the development of ventricular and vascular hypertrophy and renal fibrosis. Aldosterone receptor antagonists ameliorate these consequences of hypertension, to some extent independently of effects on blood pressure. Spironolactone can cause breast pain and gynecomastia in men through activity at the progesterone receptor, an effect not seen with the more specific eplerenone. Hyperkalemia is a problem with both drugs, chiefly in patients with chronic kidney disease. Hyperkalemia is more likely if the pretreatment plasma potassium exceeds 4.5 mmol/L.

G. Calcium Channel Blocking Agents

These agents act by causing peripheral vasodilation but with less reflex tachycardia and fluid retention than other vasodilators. They are effective as single-drug therapy in approximately 60% of patients in all demographic groups and all grades of hypertension. For these reasons, they may be preferable to beta-blockers and ACE inhibitors in blacks and older persons. Verapamil and diltiazem should be combined cautiously with beta-blockers because of their potential for depressing AV conduction and sinus node automaticity as well as contractility.

The dihydropyridine agents—nifedipine, nicardipine, isradipine, felodipine, nisoldipine, and amlodipine—are more likely to produce symptoms of vasodilation, such as headache, flushing, palpitations, and peripheral edema. Edema is minimized by coadministration of an ACE inhibitor or ARB. Calcium channel blockers have negative inotropic effects and should be used cautiously in patients with cardiac dysfunction. Amlodipine is the only calcium channel blocker with established safety in patients with severe heart failure.

H. Alpha-Adrenoceptor Antagonists

Prazosin, terazosin, and doxazosin block postsynaptic alpha-receptors, relax smooth muscle, and reduce blood pressure by lowering peripheral vascular resistance.

These agents are effective as single-drug therapy in some individuals, but tachyphylaxis may appear during longterm therapy and side effects are relatively common. These include marked hypotension after the first dose which, therefore, should be small and given at bedtime. Post-dosing palpitations, headache, and nervousness may continue to occur during long-term therapy; these symptoms may be less frequent or severe with doxazosin because of its more gradual onset of action. Alpha-blockers should generally not be used as initial agents to treat hypertension— except perhaps in men with symptomatic prostatism or nightmares linked to posttraumatic stress disorder.

I. Drugs with Central Sympatholytic Action

Methyldopa, clonidine, guanabenz, and guanfacine lower blood pressure by stimulating alpha-adrenergic receptors in the central nervous system, thus reducing efferent peripheral sympathetic outflow. These agents are effective as single therapy in some patients, but they are usually used as second- or third-line agents because of the high frequency of drug intolerance, including sedation, fatigue, dry mouth, postural hypotension, and erectile dysfunction. An important concern is rebound hypertension following withdrawal. Methyldopa also causes hepatitis and hemolytic anemia and is avoided except in individuals who have already tolerated long-term therapy. There is considerable experience with methyldopa in pregnant women, and it is still used for this population. Clonidine is available in patches, which may have particular value in patients in whom compliance is a troublesome issue.

J. Arteriolar Dilators

Hydralazine and minoxidil relax vascular smooth muscle and produce peripheral vasodilation. When given alone, they stimulate reflex tachycardia, increase myocardial contractility, and cause headache, palpitations, and fluid retention. They are usually given in combination with diuretics and beta-blockers in resistant patients. Hydralazine produces frequent gastrointestinal disturbances and may induce a lupus-like syndrome. Minoxidil causes hirsutism and marked fluid retention; this agent is reserved for the most refractory of cases.

K. Peripheral Sympathetic Inhibitors

These agents are now used infrequently and usually in refractory hypertension. Reserpine remains a cost-effective antihypertensive agent. Its reputation for inducing mental depression and its other side effects— sedation, nasal stuffiness, sleep disturbances, and peptic ulcers—has made it unpopular, though these problems are uncommon at low dosages. Guanethidine and guanadrel inhibit catecholamine release from peripheral neurons but frequently cause

orthostatic hypotension (especially in the morning or after exercise), diarrhea, and fluid retention.

Developing an Antihypertensive Regimen

Historically, data from a number of large trials support the overall conclusion that antihypertensive therapy with diuretics and beta-blockers has a major beneficial effect on a broad spectrum of cardiovascular outcomes, reducing the incidence of stroke by 30–50% and of heart failure by 40–50%, and halting progression to accelerated hypertension syndromes. The decreases in fatal and nonfatal coronary heart disease and cardiovascular and total mortality were less dramatic, ranging from 10% to 15%. Similar placebo-controlled data pertaining to the newer agents are generally lacking, except for stroke reduction with the calcium channel blocker nitrendipine in the Systolic Hypertension in Europe trial. However, there is substantial evidence that ACE inhibitors, and to a lesser extent ARBs, reduce adverse cardiovascular outcomes in other related populations (eg, patients with diabetic nephropathy, heart failure, or postmyocardial infarction and individuals at high risk for cardiovascular events). Most large clinical trials that have compared outcomes in relatively unselected patients have failed to show a difference between newer agents—such as ACE inhibitors, calcium channel blockers, and ARBs—and the older diuretic-based regimens with regard to survival, myocardial infarction, and stroke. Where differences have been observed, they have mostly been attributable to subtle asymmetries in blood pressure control rather than to any inherent advantages of one agent over another. Recommendations for initial treatment identify ACE inhibitors, ARBs, and calcium channel blockers as valid choices. Because of their adverse metabolic profile, initial therapy with thiazides might best be restricted to older patients. Thiazides are acceptable as first-line therapy in blacks because of specific efficacy in this group.

As discussed above, beta-blockers should no longer be considered ideal first-line drugs in the treatment of hypertension without compelling indications for their use. Vasodilator beta-blockers (such as carvedilol and nebivolol) may produce better outcomes than traditional beta-blockers; however, this possibility remains a theoretical consideration.

The American Diabetes Association has advocated evening dosing of one or more antihypertensive medications to restore nocturnal blood pressure dipping. Outcomes data to support this proposal are limited. The Spanish MAPEC study of such nocturnal antihypertensive dosing showed a significant reduction in a range of major cardiovascular events in 2156 participants over 5.6 years. However, there are concerns that ischemic optic neuropathy may be triggered by profound nocturnal hypotension.

Thus, larger studies are necessary before this approach can be firmly recommended.

In sum, as a prelude to treatment, the patient should be informed of common side effects and the need for diligent compliance. In patients with mild or stage 1 hypertension (less than 160/90 mm Hg) in whom pharmacotherapy is indicated, treatment should start with a single agent at a low dose. Follow-up visits should

usually be at 4- to 6-week intervals to allow for full medication effects to be established (especially with diuretics) before further titration or adjustment. If, after titration to usual doses, the patient has shown a discernible but incomplete response and a good tolerance of the initial drug, a second medication should be added. As a rule of thumb, a blood pressure reduction of 10 mm Hg can be expected for each antihypertensive agent added to the regimen and titrated to the optimum dose. In those with more severe hypertension (stage 2), or with comorbidities (such as diabetes) that are likely to render them resistant to treatment, initiation with combination therapy is advised and more frequent follow-up is indicated. Patients who are compliant with their medications and who do not respond to conventional combination regimens should usually be evaluated for secondary hypertension before proceeding to more complex regimens.

Medication Nonadherence

Adherence to antihypertensive treatment is alarmingly poor. In one European study of patients' antihypertensive medication compliance, there was a 40% discontinuation rate at 1 year after initiation. Only 39% of patients were found to be taking their medications continuously over a 10-year period. Collaborative care, utilizing physicians, pharmacists, social workers, and nurses, to encourage compliance has had a variable and often rather modest effect on blood pressure control. Adherence is enhanced by patient education and by use of home blood pressure measurement. The choice of antihypertensive medication is important. Better compliance has been reported for patients whose medications could be taken once daily or as combination pills; poorer adherence was reported among patients given beta-blockers and diuretics.

Special Considerations in the Treatment of Diabetic Hypertensive Patients

Hypertensive patients with diabetes are at particularly high risk for cardiovascular events. Data from the ACCORD study of diabetics demonstrated that most of the benefits of blood pressure lowering were seen with a systolic target of less than 140 mm Hg; in fact, except for a reduction in stroke risk, there was an increased risk of serious adverse events in diabetics with a systolic target of less than 120/70 mm Hg. Thus, most recent US and international guidelines suggest a therapeutic blood pressure goal of less than 140/90 mm Hg in the diabetic population. Because of the beneficial effects of ACE inhibitors in diabetic nephropathy, they should be part of the initial treatment regimen. ARBs or perhaps renin inhibitors may be substituted in those intolerant of ACE inhibitors. While the ONTARGET study showed that combinations of ACE inhibitors and ARBs in persons with atherosclerosis or type 2 diabetes with end-organ damage appeared to minimize proteinuria, this strategy slightly increased the risks of progression to dialysis and of death; thus, it is not recommended. Most diabetic patients require combinations of three to five agents to achieve target blood pressure, usually including a diuretic and a calcium channel blocker or beta-blocker. In addition to

rigorous blood pressure control, treatment of persons with diabetes should include aggressive treatment of other risk factors.

Treatment of Hypertension in Chronic Kidney Disease

Hypertension is present in 40% of patients with a GFR of 60–90 mL/min, and 75% of patients with a GFR less than 30 mL/min. It is likely that inhibition of the renin-angiotensin system protects kidney function in kidney disease associated with significant proteinuria.

The blood pressure target in treating patients with hypertension and chronic kidney disease should generally be less than 140/90 mm Hg. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines advocate a lower target of less than 130/80 mm Hg in patients with significant proteinuria. Drugs that interrupt the reninangiotensin cascade are preferred for initial therapy. Transition from thiazide to loop diuretic is often necessary to control volume expansion as kidney function worsens. Evidence has demonstrated that ACE inhibitors remain protective and safe in kidney disease associated with significant proteinuria and serum creatinine as high as 5 mg/dL (380 mcmol/L). However, in patients with significant renal artery stenosis, ACE inhibitor therapy would likely worsen kidney function; therefore, kidney function and electrolytes should be monitored carefully in such patients. Persistence with ACE inhibitor or ARB therapy in the face of hyperkalemia is probably not warranted, since other antihypertensive medications are renoprotective as long as goal blood pressures are maintained.

Hypertension Management in Blacks

Substantial evidence indicates that blacks are not only more likely to become hypertensive and more susceptible to the cardiovascular and renal complications of hypertension— they also respond differently to many antihypertensive medications. The REGARDS study illustrates these disparities. At systolic blood pressures less than 120 mm Hg, black and white participants between 45 and 64 years of age had equal risk of stroke. For a 10 mm Hg increase in systolic blood pressure, the risk of stroke was threefold higher in black participants. At the level of stage 1 hypertension, the hazard ratio for stroke in black compared to white participants between 45 and 64 years of age was 2.35. This increased susceptibility may reflect genetic differences in the cause of hypertension or the subsequent responses to it, differences in occurrence of comorbid conditions such as diabetes or obesity, or environmental factors such as diet, activity, stress, or access to health care services. In any case, as in all persons with hypertension, a multifaceted program of education and lifestyle modification is warranted. Early introduction of combination therapy has been advocated, but there is no clinical trial data to support a lower than usual blood pressure goal in blacks. Because it appears that ACE inhibitors and ARBs—in the absence of concomitant diuretics—are less effective in blacks than in whites, initial therapy should generally be a diuretic or a diuretic in combination with a calcium channel blocker.

Treating Hypertension in the Elderly

Several studies in persons over 60 years of age have confirmed that antihypertensive therapy prevents fatal and nonfatal myocardial infarction and reduces overall cardiovascular mortality. These trials placed the focus on control of systolic blood pressure (the hypertension affecting the majority of those over age 60 is predominantly systolic)—in contrast to the historical emphasis on diastolic blood pressure. The most recent US Joint National Committee Panel Report (JNC8) adopted a rigorous outcomes-based position in recommending a treatment goal of less than 150/90 mm Hg in persons older than 60 years of age. However, most clinical guidelines suggest that treatment targets for older people (age 60–80 years) should be the same as those for younger individuals (less than 140/90 mm Hg). In initiating therapy in older patients, pressure should be reduced more gradually with a safe intermediate systolic blood pressure goal of 160 mm Hg. In the very elderly, over age 80 years, the HYVET study indicated that a reasonable ultimate systolic blood pressure goal would be 150/80 mm Hg, reflected by the Canadian and European guidelines target of less than 150/90 mm Hg in this population. The same medications are used in older patients, but at 50% lower doses. As treatment is initiated, older patients should be carefully monitored for orthostasis, altered cognition, and electrolyte disturbances. The HYVET trial recruited individuals who were relatively well; by contrast, there appears to be a loss of the usual relationship between blood pressure and morbidity/mortality in the very elderly who are also frail (as defined by a walking speed of less than 0.8 m/sec over 6 m). In the very frail (those unable to walk 6 m), higher blood pressures were paradoxically associated with better outcomes. A less aggressive approach to the treatment of hypertension would therefore seem appropriate in the very elderly who are also frail.

Follow-Up of Patients Receiving Hypertension Therapy

Once blood pressure is controlled on a well-tolerated regimen, follow-up visits can be infrequent and laboratory testing limited to those appropriate for the patient and the medications used. Yearly monitoring of blood lipids is recommended, and an electrocardiogram should be repeated at 2- to 4-year intervals depending on whether initial abnormalities are present, the presence of coronary risk factors, and age. Patients who have had excellent blood pressure control for several years, especially if they have lost weight and initiated favorable lifestyle modifications, might be considered for a trial of reduced antihypertensive medications.

HYPERTENSIVE URGENCIES & EMERGENCIES

Hypertensive emergencies have become less frequent in recent years but still require prompt recognition and aggressive but careful management. A spectrum of urgent presentations exists, and the appropriate therapeutic approach varies accordingly

Hypertensive urgencies are situations in which blood pressure must be reduced within a few hours. These include patients with asymptomatic severe hypertension (systolic blood pressure greater than 220 mm Hg or diastolic pressure greater than 125 mm Hg that persists after a period of observation) and those with optic disk edema, progressive target-organ complications, and severe perioperative hypertension. Elevated blood pressure levels alone—in the absence of symptoms or new or progressive target-organ damage—rarely require emergency therapy. Parenteral drug therapy is not usually required, and partial reduction of blood pressure with relief of symptoms is the goal.

Hypertensive emergencies require substantial reduction of blood pressure within 1 hour to avoid the risk of serious morbidity or death. Although blood pressure is usually strikingly elevated (diastolic pressure greater than 130 mm Hg), the correlation between pressure and endorgan damage is often poor. It is the latter that determines the seriousness of the emergency and the approach to treatment. Emergencies include hypertensive encephalopathy (headache, irritability, confusion, and altered mental status due to cerebrovascular spasm), hypertensive nephropathy (hematuria, proteinuria, and progressive kidney dysfunction due to arteriolar necrosis and intimal hyperplasia of the interlobular arteries), intracranial hemorrhage, aortic dissection, preeclampsia-eclampsia, pulmonary edema, unstable angina, or myocardial infarction. **Malignant hypertension** is by historical definition characterized by encephalopathy or nephropathy with accompanying hypertensive retinopathy. Progressive kidney disease usually ensues if treatment is not provided. The therapeutic approach is identical to that used with other antihypertensive emergencies.

Parenteral therapy is indicated in most hypertensive emergencies, especially if encephalopathy is present. The initial goal in hypertensive emergencies is to reduce the pressure by no more than 25% (within minutes to 1 or 2 hours) and then toward a level of 160/100 mm Hg within 2–6 hours. Excessive reductions in pressure may precipitate coronary, cerebral, or renal ischemia. To avoid such declines, the use of agents that have a predictable, dosedependent, transient, and progressive antihypertensive effect is preferable. In that regard, the use of sublingual or oral fast-acting nifedipine preparations is best avoided.

Acute ischemic stroke is often associated with marked elevation of blood pressure, which will usually fall spontaneously. In such cases, antihypertensives should only be used if the systolic blood pressure exceeds 180–200 mm Hg, and blood pressure should be reduced cautiously by 10–15%. If thrombolytics are to be given, blood pressure should be maintained at less than 185/110 mm Hg during treatment and for 24 hours following treatment.

In hemorrhagic stroke, the aim is to minimize bleeding with a target mean arterial pressure of less than 130 mm Hg. In acute subarachnoid hemorrhage, as long as the bleeding source remains uncorrected, a compromise must be struck between preventing further bleeding and maintaining cerebral perfusion in the face of cerebral vasospasm. In this situation, blood pressure goals depend on the patient’s usual blood pressure. In normotensive patients, the target should be a systolic blood pressure of 110–120 mm Hg; in hypertensive patients, blood pressure

should be treated to 20% below baseline pressure. In the treatment of hypertensive emergencies complicated by (or precipitated by) central nervous system injury, labetalol or nicardipine are good choices, since they are nonsedating and do not appear to cause significant increases in cerebral blood flow or intracranial pressure in this setting. In hypertensive emergencies arising from catecholaminergic mechanisms, such as pheochromocytoma or cocaine use, beta-blockers can worsen the hypertension because of unopposed peripheral vasoconstriction; nicardipine, clevidipine, or phentolamine are better choices. Labetalol is useful in these patients if the heart rate must be controlled.

Pharmacologic Management

A. Parenteral Agents

A growing number of agents are available for management of acute hypertensive problems.

Sodium nitroprusside is no longer the treatment of choice; in most situations, appropriate control of blood pressure is best achieved using combinations of nicardipine or clevidipine plus labetalol or esmolol.

1. Nicardipine—Intravenous nicardipine is the most potent and the longest acting of the parenteral calcium channel blockers. As a primarily arterial vasodilator, it has the potential to precipitate reflex tachycardia, and for that reason it should not be used without a beta-blocker in patients with coronary artery disease.

2. Clevidipine—Intravenous clevidipine is an L-type calcium channel blocker with a 1-minute half-life, which facilitates swift and tight control of severe hypertension. It acts on arterial resistance vessels and is devoid of venodilatory or cardiodepressant effects.

3. Labetalol—This combined beta- and alpha-blocking agent is the most potent adrenergic blocker for rapid blood pressure reduction. Other beta-blockers are far less potent. Excessive blood pressure drops are unusual. Experience with this agent in hypertensive syndromes associated with pregnancy has been favorable.

4. Esmolol—This rapidly acting beta-blocker is approved only for treatment of supraventricular tachycardia but is often used for lowering blood pressure. It is less potent than labetalol and should be reserved for patients in whom there is particular concern about serious adverse events related to beta-blockers.

5. Fenoldopam—Fenoldopam is a peripheral dopamine-1 (DA1) receptor agonist that causes a dose-dependent reduction in arterial pressure without evidence of tolerance, rebound, or withdrawal or deterioration of kidney function. In higher dosage ranges, tachycardia may occur. This drug is natriuretic, which may simplify volume management in acute kidney injury.

6. Enalaprilat—This is the active form of the oral ACE inhibitor enalapril. The onset of action is usually within 15 minutes, but the peak effect may be delayed for up to 6 hours. Thus, enalaprilat is used primarily as an adjunctive agent.

7. Diuretics—Intravenous loop diuretics can be very helpful when the patient has signs of heart failure or fluid retention, but the onset of their hypotensive response is slow, making them an adjunct rather than a primary agent for hypertensive emergencies. Low dosages should be used initially (furosemide, 20 mg, or bumetanide, 0.5 mg). They facilitate the response to vasodilators, which often stimulate fluid retention.

8. Hydralazine—Hydralazine can be given intravenously or intramuscularly, but its effect is less predictable than that of other drugs in this group. It produces reflex tachycardia and should not be given without beta-blockers in patients with possible coronary disease or aortic dissection. Hydralazine is now used primarily in pregnancy and in children, but even in these situations, it is not a first-line drug.

9. Nitroglycerin, intravenous—This agent should be reserved for patients with accompanying acute coronary ischemic syndromes.

10. Nitroprusside sodium—This agent is given by controlled intravenous infusion gradually titrated to the desired effect. It lowers the blood pressure within seconds by direct arteriolar and venous dilation. Monitoring with an intra-arterial line avoids hypotension. Nitroprusside— in combination with a beta-blocker—is useful in patients with aortic dissection.

B. Oral Agents

Patients with less severe acute hypertensive syndromes can often be treated with oral therapy. Suitable drugs will reduce the blood pressure over a period of hours. In those presenting as a consequence of noncompliance, it is usually sufficient to restore the patient's previously established oral regimen.

1. Clonidine—Clonidine, 0.2 mg orally initially, followed by 0.1 mg every hour to a total of 0.8 mg, will usually lower blood pressure over a period of several hours. Sedation is frequent, and rebound hypertension may occur if the drug is stopped.

2. Captopril—Captopril, 12.5–25 mg orally, will also lower blood pressure in 15–30 minutes. The response is variable and may be excessive. Captopril is the drug of choice in the management of scleroderma hypertensive crisis.

3. Nifedipine—The effect of fast-acting nifedipine capsules is unpredictable and may be excessive, resulting in hypotension and reflex tachycardia. Because myocardial infarction and stroke have been reported in this setting, the use of

sublingual nifedipine is not advised. Nifedipine retard, 20 mg orally, appears to be safe and effective.

D. Subsequent Therapy

When the blood pressure has been brought under control, combinations of oral antihypertensive agents can be added as parenteral drugs are tapered off over a period of 2–3 days.

ARTERIAL HYPOTENSION

The venous side of the circulation accommodates ~ 85% of the total blood volume; because of the low venous pressure (mean ~ 15 mmHg), it is referred to as the low-pressure system. The arterial vascular beds, representing the high-pressure system (mean pressure ~ 100 mm Hg), contain ~ 15%. The arterial pressure generates the driving force for perfusion of tissues and organs. Blood draining from these collects in the low-pressure system and is pumped back by the heart into the high-pressure system.

The arterial blood pressure (ABP) depends on: (1) the volume of blood per unit of time that is forced by the heart into the highpressure system—cardiac output corresponding to the product of stroke volume and heart rate (beats/min), stroke volume being determined by, inter alia, venous filling pressure; (2) the counterforce opposing the flow of blood, i. e., peripheral resistance, which is a function of arteriolar caliber.

Chronic hypotension (recumbent systolic BP < 105 mm Hg). Primary idiopathic hypotension generally has no clinical importance. If symptoms such as lassitude and dizziness occur, a program of physical exercise instead of drugs is advisable.

Secondary hypotension is a sign of an underlying disease that should be treated first. If stroke volume is too low, as in heart failure, a cardiac glycoside can be given to increase myocardial contractility and stroke volume. When stroke volume is decreased owing to insuf cient blood volume, plasma substitutes will be helpful in treating blood loss, whereas aldosterone deficiency requires administration of a mineralocorticoid (e. g., fludrocortisone). The latter is the drug of choice for orthostatic hypotension due to autonomic failure. A parasympatholytic (or electrical pacemaker) can restore cardiac rate in bradycardia.

Acute hypotension. Failure of orthostatic regulation. A change from the recumbent to the erect position (orthostasis) will cause blood within the low-pressure system to sink toward the feet because the veins in body parts below the heart will be distended, despite a reflex venoconstriction, by the weight of the column of blood in the blood vessels. The fall in stroke volume is partly compensated by a rise in heart rate. The remaining reduction of cardiac output can be countered by elevating the peripheral resistance, enabling blood pressure and organ perfusion to be maintained. An orthostatic malfunction is present when counterregulation fails and cerebral blood flow falls, with resultant symptoms, such

as dizziness, “black-out,” or even loss of consciousness. In the sympathotonic form, sympatheticallymediated circulatory reflexes are intensified (more pronounced tachycardia and rise in peripheral resistance, i. e., diastolic pressure); however, there is failure to compensate for the reduction in venous return. Prophylactic treatment with sympathomimetics would therefore hold little promise. Instead, cardiovascular fitness training would appear more important. An increase in venous return may be achieved in two ways. Increasing NaCl intake augments salt and fluid reserves and, hence, the blood volume (contraindications: hypertension, heart failure). Constriction of venous capacitance vessels might be produced by dihydroergotamine. Whether this effect could also be achieved by an α-sympathomimetic, remains debatable. In the very rare asympathotonic form, use of sympathomimetics would certainly be reasonable.

Classification of hypertensive drugs

1. Adrenomimetics - epinephrine (adrenalin), phenylephrine (mesaton), ephedrine, noradrenaline, midodrine;
2. Dofaminomimetics – dopamine, dobutamine;
3. Glucocorticosteroids - hydrocortisone, prednisolone, triamcinolone, dexamethasone;
4. Mineralocorticoids - Doxa, fludrocortisone acetate;
5. Analeptics – caffeine, cordiamin, camphor, sulfocamfokaine;
6. Drugs affecting angiotensin system - angiotensinamide;
7. Adaptogen - Eleutherococcus, ginseng, Rhaponticum, Rhodiola rosea, echinacea, aralia, magnolia vine;
8. Colloid and crystalloid solutions – drugs for rehydration (isotonic solution, glucose, and other).

Control questions

1. The main complaints, symptoms in diseases of the circulatory system and their significance in the choice of pharmacotherapy.
2. Instrumental methods of examination of circulatory organs and their clinical significance for pharmacotherapy.
3. Arterial hypertension, classification, etiology.
4. Pathogenetic approaches to medical treatment of arterial hypertension.
5. Diagnostic criteria for hypertension.
6. Arterial hypotension, classification, pathogenetic approaches to medical treatment.
7. Pharmacotherapeutic approaches to the treatment of hypertensive crises.
8. Principles of pharmacotherapy of acute hypotensive states.
9. Principles of pharmacotherapy of chronic hypotensive states.

List of practical works:

A. Homework.

1. To study the etiology, pathogenesis of hypertension.
2. To study the classification, clinical picture of hypertension.
3. Pay attention to the types of complications of hypertensive crises, to study their clinical picture.

B. Independent work at the lesson:

1. A curse of the thematic patient in the ward.
2. To study the working history of the disease (data laboratory-instrumental studies, conclusions of consultants) and a letter of medical appointments.
3. To distinguish signs in the subjective and objective study of the patient, characterizing a violation of vascular tone, leading clinical syndromes - AH, to write a clinical diagnosis of the disease.
4. Determine the group of drugs needed by the patient.
5. On the basis of theoretical data of pharmacodynamics and own observations, choose a drug for the control of the patient.
6. Make a prognosis of the side effects of drugs intended for the patient, and design a plan to detect them at an early stage.
7. To draw up a plan of urgent medical help in: a hypertensive crisis complicated and uncomplicated.

Control the level of knowledge.

1. Fill in the table "Emergency help with acute vascular insufficiency (hypotension)".

Acute vascular insufficiency	Symptom	Emergency aid
1. Collapse 2. Shock 3. Dizziness		

2. Fill in the table "Pharmacotherapy of a hypertensive crisis".

Preparation	Method of administration, dose	Action		
		beginning	maximum	duration

1. Nifedipine 2.Kaptopril 3.Nitroglycerin 4.Nysoldipine 5.Dibazol 6.Furosemide 7.Labetalol				

3. Formulate urgent medical therapy of anaphylactic, infectious-toxic, cardiogenic, hypoglycemic shock, collapse.

4. Fill in the table "Basic pathogenetic signs of shock states".

The main pathogenetic signs of shock	**Hemorrhagic**	**Traumatic**	**Dehydration**	**Cardiogenic**	**Anaphylactic**
1. Hypovolemia 2. Pain syndrome 3. Reduced tone of resistive vessels and B/P 4. Heart failure 5. Acidosis					

5. Make a list of the drugs needed to form an anti-shock kit in the case of anaphylactic shock.

6. Fill in the table "Characteristics of the arterial pulse".

Pulse properties	**Concept and characteristic**	**Variations of violation of the properties of the pulse**
1. Symmetry 2. Rhythm of the pulse 3. Pulse rate 4. Tension of the pulse 5. Fill the pulse 6. The size of the pulse 7. Pulse shape		

Solution of situational tasks

1. A man, 33 years old, complains of heartbeat, ineffective breath, heaviness in the area of the heart of moderate intensity, headache of pulsating nature, hot flush to the face, tremor in the gel, sweating, nervous tension. The state deteriorated sharply after psycho-emotional stress. In the history of: hypertonic disease in stage I. Medicinal therapy is episodic. Objectively, the skin of the face is hyperemic. Normostenik, somewhat elevated food. Pulse - 94 beats for 1 min, rhythmic, AT - 198/96 mm Hg. Art. The left heart line is displaced externally by 1.5 cm. The second tone accent is pulled over the pulmonary artery.

Clarify the nature of the crisis. Take a medication for his treatment.

2. A man, 58 years old, two days later arose and grow headaches, nausea, thrombosis was vomiting, did not relieve. Worrying is weakness, instability of walking, dizziness, periodic difficulty of speech. The state got worse after a nervous strain. In anamnesis: He has been suffering from arterial hypertension for the past 25 years. Regularly, during the last 2 years, accepts 1 tabl. (0.000075 g) of clonidine before going to bed. Maximum AT - 230/130 mm Hg. Art., working - 170/100 mm Hg. Art. Mother suffered from hypertension, died due to cerebral vascular stroke. Objectively: the patient is sleepy, sluggish. Hyperstress Obesity II st. Xanthelasms in the upper eyelid of the right eye. Pulse - 54 watts. for 1 min, rhythmic. AT - 220/154 mm Hg. Art. Left ventricular hypertrophy. Accent II tone over the aorta.

Formulate the diagnosis. Specify the drugs needed to treat this painful process.

3. A woman, 44, complains of a sharp headache, visual impairment, nausea, repeated vomiting, weakness in the right arm and leg, and periodic blurring of consciousness. The state deteriorated sharply 50 minutes ago. In anamnesis: for 10 years suffers from hypertension. Maximum AT - 220/130 mm Hg. Art., working - 170 / 110-115 mm Hg. Art. The last 1.5 years often causes ambulance doctors due to an increase in blood pressure. Objectively: the general condition is heavy. Consciousness is periodically clouded. Sudden stroke in the limbs. Pulse - 82 watts. for 1 min, rhythmic. AT - 240/140 mm Hg. Art. Left ventricular hypertrophy. Accent II tone and systolic noise over the aorta.

Formulate the diagnosis. Refine the nature of the attack. Justify the choice of drug for treatment of existing disorders.

4. A patient, 44 years old, suffering from hypertension, had a headache, "internal" tremor, palpitations, and a sense of fear. Objectively: the pulse is 100 oz. in 1 min, AT - 200/100 mm Hg. Art., the left limit of cardiac dullness is 1.5 cm shifted to the left of the left mid-clavicular line, the tones of the heart are sonorous, vesicular breathing. ECG: sinus tachycardia, signs of left ventricular hypertrophy.

Formulate the diagnosis. Make a combination therapy program.

5. A woman, 42 years old, complains of a severe headache pulsating in the frontal-parietal region, a feeling of heartbeat. He suffers from hypertension for 3 years. A significant increase in blood pressure is noted 2-3 times a month, with a duration of 3-8 hours. The attack ends with abundant urination. The left ventricle is enlarged, tons of heart are clean, pulse - 105 aU for 1 min, AT - 225/115 mm Hg. Art. Impact and minute volume of heart are enlarged. The overall peripheral vascular resistance is moderately elevated. ECG: signs of left ventricular hypertrophy. On the eyelid: the symptom of the Salus-Gouna.

Formulate the diagnosis. Make a combination therapy program.

6. A patient, 62 years old, suffers from hypertension for 10 years. 2 years ago, chronic obstructive bronchitis was diagnosed. Objectively: pulse - 64 beats per minute, blood pressure - 210/130 mm Hg. Art., the left border of the relative cardiac dullness is displaced to the left 2.5 cm from the middle-line line, I tone above the tip is weakened, the accent II tone over the aorta. On ECG: left ventricular hypertrophy.

Formulate the diagnosis. Specify the LS necessary for the treatment of this painful process, justify their choice, taking into account concomitant pathology.

7. A patient, 52 years old, suffers from hypertension in the II. Smoke Regularly not treated. Objectively: AT - 175/105 mm Hg. Art., heart rate - 92 beats for 1 min, in the lungs scattered dry wheezing against the background of weakened vesicular respiration. The liver protrudes 2 cm from the edge of the cranial arc, edema in the ankle joints.

State the main and concomitant diagnosis. Make a combination therapy program taking into account the concomitant illness.

8. A patient, 56 years old, is in a hospital for hypertension. Accepted medications: capoten 25 mg three times a day, advertizen - 1 mg 3 times a day. After 30 minutes after taking the drugs, the patient fell and for a few seconds, lost consciousness. Objectively: the skin is pale, moist. Pulse - 100 for 1 min, rhythmic. Blood pressure 60/20 mm hg Art.

What complication did the patient have? Specify the drugs needed to treat this painful process.

9. In a woman 34 years of age, bronchopneumonia, after an intradermal penicillin test, after 5 minutes, sudden cough, shortness of breath, fear, anxiety, headache, dizziness, tinnitus, nausea, vomiting, abdominal pain arose. Objectively: the general condition is heavy. Consciousness is blurred. Foam, convulsions, involuntary bowel movements and urination. Skin coats are pale with a cyanotic shade. Pulse 120 az. in 1 min, rhythmic, small filling, filiform. AT - 60/20 mm Hg. Art. The tones of the heart are deaf. In the lungs there is rigid vesicular respiration, scattered dry wheezing. Formulate the diagnosis.

Make a program of intensive care, substantiate its purpose.

10. In a woman, 32 years old, after an eating bite an attack of suffocation has developed. Objectively: the state is heavy. BH - 30 per minute Heart rate - 102 for 1 min., AT 100/70 mm Hg. Art. In the lungs there are dry wheezing that can be heard at a distance. The tones of the heart are muffled, the rhythm is correct.

What drug is most appropriate to appoint in the first place?

11. A man, 60 years old, complains about headaches, dizziness, head noise, the absence of night sleep, nausea in the morning, vision impairment, pain in the heart of a stenocardic nature through a 50-100 m walk, with a rise to the 2 nd floor, shortness of breath at physical activity, interruptions in the activity of the heart. Anamnesis suffers from hypertension for 30 years. Maximum blood pressure - 200/140 mm Hg. Art., working - 160/120 mm Hg. Art. Five years ago, suffered a myocardial infarction, two years ago - a sharp violation of cerebral circulation in the basin of the middle cerebral artery. Objectively: a general condition of moderate severity. Cyanosis of the lips. Left-side pyramidal insufficiency Pulse 84 beats per minute, arrhythmic type of extrasystolic arrhythmia (6-10 for 1 min), solid. AT - 84/136 mm Hg. Art. Left ventricular hypertrophy. Accent II tone and systolic noise over the aorta. Above the lungs is vesicular breathing, crepitation. Abdomen is soft, painless. The liver is 2 cm protruding from the edge of the edge arc on the right midlectric line. No edema.
Formulate the diagnosis. Conduct a selection of drugs. Make a combination therapy program.

Test tasks

1. In a patient T., 42 years old, during the hypertensive crisis left ventricular insufficiency developed in the form of pulmonary edema. Which drug and how should I appoint it immediately?
A. Manitol intravenously.
B. Furosemide intramuscularly.
C. Furosemide intravenously.
D. Propranolol intravenous.
E. Verapamil intravenously.

2. Headache in the neck, accompanied by dizziness, blinking of "flies" in front of the eyes, suggests that the cause of the pain:
A. Viral infection.
B. Inflammatory process of the brain.
C. Migren.
D. Increased blood pressure.
E. Brain tumor.

3. Which of the antihypertensives should be chosen for initial treatment of the patient with arterial hypertension (AT 190/100 mm Hg, heart rate 56 w / min)

suffering from gouty arthritis and receiving allopurinol (concentration of uric acid 0.57 mmol/l)
A. Triampur
B. Amlodipin
C. Hypothiazide.
D. Propranolol.
E. Verapamil.

4. In the treatment of hypertension medication therapy in the stabilization of blood pressure can:
A. Cancel after 1 year.
B. Cancel after 1 week.
C. Continue continuously.
D. Cancel after 1 month.
E. Cancel after 6 months.

5. Choose not a typical symptom for a hypertensive crisis:
A. Sore urination.
B. Nausea
C. Vomiting
D. Blowing flies in front of the eyes.
E. Headache.

6. Emergency treatment of anaphylactic shock involves the use of the following groups of drugs:
A. Antihistamines, adrenoblockers.
B. Antihistamines, non-hormonal immunosuppressants.
C. Antihistamines, glucocorticosteroids, adrenaline.
D. Stabilizers of cell membranes, glucocorticosteroids.
E. Ganglion blockers, antihistamines.

7. A pregnant woman (term of 10 weeks) with a hypertension complained to the doctor. Which tool is the most secure in this situation?
A. Metdylda.
B. Lozartan
C. Hydralazine.
D. Propranolol.
E. Captopril.

8. From the groups listed below, select those that are not used in the treatment of hypertension.
1. Diuretics.
2. Beta-adrenoblockers.
3. Blockers of angiotensin receptors.
4. ACE inhibitors.

5. Heart glycosides.

9. Indicate antihypertensive drugs that affect the renin-angiotensin system:
1. Propranolol.
2. Enalapril.
3. Prazosin
4. Furosemide.
5.Dibazol

10. To treat a hypertensive crisis, it is advisable to use the following drugs:
1. No-shpa inside.
2. Papaverine inside.
3. Hypothiazide inside.
4. Nifedipine under the tongue.
5.Validol under the tongue

11. The upper limit of arterial pressure in norm is (mm Hg):
1.120/80.
2.130/80.
3.140/80
4.140/90.
5.150/95.

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TOPIC 5. The basic principles of pharmacotherapy of coronary heart disease.

Actuality of topic.

Coronary heart disease, or atherosclerotic CAD, is the number one killer in the United States and worldwide. Every minute, an American dies of coronary heart disease. About 37% of people who experience an acute coronary event, either angina or myocardial infarction, will die of it in the same year. Death rates of coronary heart disease have declined every year since 1968, with about half of the decline from 1980 to 2000 due to treatments and half due to improved risk factors. Coronary heart disease is still responsible for approximately one of five deaths and over 600,000 deaths per year in the United States. Coronary heart disease afflicts nearly 16 million Americans and the prevalence rises steadily with age; thus, the aging of the US population promises to increase the overall burden of coronary heart disease. In Europe, 10% of the adult population and more than 20% of the elderly suffer from coronary artery disease; in 2000, there were 5.9 million patients registered with this disease in Ukraine. IBS ranks first among the causes of death in European countries and is over 21%.

Purpose of the lesson: The student must learn the etiopathogenetic factors of coronary heart disease, classification, clinic and the requirements offered for antianginal drugs. Know the general principles of pharmacotherapy for coronary heart disease and modern medical forms of antianginal drugs (aerosols, transdermal, transbuccal).

Lipid Disorders

For patients with known cardiovascular disease (secondary prevention), cholesterol lowering leads to a consistent reduction in total mortality and recurrent cardiovascular events in men and women and in middle-aged and older patients. Among patients without cardiovascular disease (primary prevention), the data are less conclusive, with rates of cardiovascular events, heart disease mortality, and all-cause mortality differing among studies. Nonetheless, treatment algorithms have been designed to assist clinicians in selecting patients for cholesterol-lowering therapy based on their overall risk of developing cardiovascular disease.

LIPID FRACTIONS & THE RISK OF CORONARY HEART DISEASE

In fasting serum, cholesterol is carried primarily on three different lipoproteins—the VLDL, LDL, and HDL molecules. Total cholesterol equals the sum of these three components:

Total cholesterol = HDL cholesterol + VLDL cholesterol + LDL cholesterol

Most clinical laboratories measure the total cholesterol, the total triglycerides, and the amount of cholesterol found in the HDL fraction, which is easily precipitated from serum. Most triglyceride is found in VLDL particles, which contain five times as much triglyceride by weight as cholesterol.

The total cholesterol is reasonably stable over time; however, measurements of HDL and especially triglycerides may vary considerably because of analytic error in the laboratory and biologic variation in a patient's lipid level. Thus, the LDL should always be estimated as the mean of at least two determinations; if those two estimates differ by more than 10%, a third lipid profile is obtained.

Some authorities use the ratio of the total to HDL cholesterol as an indicator of lipid-related coronary risk: the lower this ratio is, the better. Although ratios are useful predictors within populations of patients, they may obscure important information in individual patients. (A total cholesterol of 300 mg/dL [7.76 mmol/L] and an HDL of 60 mg/dL [1.56 mmol/L] result in the same ratio as a total cholesterol of 150 mg/dL [3.88 mmol/L] with an HDL of 30 mg/dL [0.78 mmol/L].) Moreover, the total cholesterol-to-HDL cholesterol ratio will magnify the importance of variations in HDL measurement.

There is no true "normal" range for serum lipids. In Western populations, cholesterol values are about 20% higher than in Asian populations and exceed 300 mg/dL (7.76 mmol/L) in nearly 5% of adults. About 10% of adults have LDL cholesterol levels above 200 mg/dL (5.17 mmol/L). Total and LDL cholesterol levels tend to rise with age in persons who are otherwise in good health.

Declines are seen in acute illness, and lipid studies in such patients are of little value with the exception of the serum triglyceride level in a patient with pancreatitis. Cholesterol levels (even when expressed as an age-matched percentile rank, such as the highest 20%) do not remain constant over time, especially from childhood through adolescence and young adulthood. Thus, children and young adults with relatively high cholesterol may have lower levels later in life, whereas those with low cholesterol may show increases.

THERAPEUTIC EFFECTS OF LOWERING CHOLESTEROL

Reducing cholesterol levels in healthy middle-aged men without CHD (primary prevention) reduces their risk in proportion to the reduction in LDL cholesterol. Treated adults have statistically significant and clinically important reductions in the rates of myocardial infarctions, new cases of angina, and need for coronary artery bypass procedures. The West of Scotland Study showed a 31% decrease in myocardial infarctions in middle-aged men treated with pravastatin compared with placebo. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) study showed similar results with lovastatin. As with any primary prevention interventions, large numbers of healthy patients need to be treated to prevent a single event. The numbers of patients needed to treat (NNT) to prevent a nonfatal myocardial infarction or a coronary artery disease death in these two studies were 46 and 50, respectively. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study of atorvastatin in persons with hypertension and

other risk factors but without CHD demonstrated a 36% reduction in CHD events. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) showed a 44% reduction in a combined end point of myocardial infarction, stroke, revascularization, hospitalization for unstable angina, or death from cardiovascular causes in both men and women. The NNT for 1 year to prevent one event was 169.

Primary prevention studies have found a less consistent effect on total mortality. The West of Scotland study found a 20% decrease in total mortality, tending toward statistical significance. The AFCAPS/TexCAPS study with lovastatin showed no difference in total mortality. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) also showed no reduction either in all-cause mortality or in CHD events when pravastatin was compared with usual care. Subjects treated with atorvastatin in the ASCOT study had a 13% reduction in mortality, but the result was not statistically significant. This study, however, was stopped early due to the marked reduction in CHD events. The JUPITER trial demonstrated a statistically significant 20% reduction in death from any cause. The NNT for 1 year was 400.

In patients with CHD, the benefits of cholesterol lowering are clearer. Major studies with statins have shown significant reductions in cardiovascular events, cardiovascular deaths, and all-cause mortality in men and women with coronary artery disease. The NNT to prevent a nonfatal myocardial infarction or a coronary artery disease death in these studies was between 12 and 34. Aggressive cholesterol lowering with these agents causes regression of atherosclerotic plaques in some patients, reduces the progression of atherosclerosis in saphenous vein grafts, and can slow or reverse carotid artery atherosclerosis. Results with other classes of medications have been less consistent. For example, patients treated with gemfibrozil had fewer cardiovascular events, but there was no benefit in all-cause mortality when compared with placebo.

The disparities in results between primary and secondary prevention studies highlight several important points. The benefits and adverse effects of cholesterol lowering may be specific to each type of drug; the clinician cannot assume that the effects will generalize to other classes of medication. Second, the net benefits from cholesterol lowering depend on the underlying risk of CHD and of other disease. In patients with atherosclerosis, morbidity and mortality rates associated with CHD are high, and measures that reduce it are more likely to be beneficial even if they have no effect—or even slightly harmful effects—on other diseases.

SECONDARY CONDITIONS THAT AFFECT LIPID METABOLISM

Several factors, including drugs, can influence serum lipids. These are important for two reasons: abnormal lipid levels (or changes in lipid levels) may be the presenting sign of some of these conditions, and correction of the underlying condition may obviate the need to treat an apparent lipid disorder. Diabetes and alcohol use, in particular, are commonly associated with high triglyceride levels that decline with improvements in glycemic control or reduction in alcohol use, respectively. Thus, secondary causes of high blood lipids should be considered in

each patient with a lipid disorder before lipid-lowering therapy is started. In most instances, special testing is not needed: a history and physical examination are sufficient. However, screening for hypothyroidism in patients with hyperlipidemia is cost effective.

CLINICAL PRESENTATIONS

Most patients with high cholesterol levels have no specific symptoms or signs. The vast majority of patients with lipid abnormalities are detected by the laboratory, either as part of the workup of a patient with cardiovascular disease or as part of a preventive screening strategy. Extremely high levels of chylomicrons or VLDL particles (triglyceride level above 1000 mg/dL or 10 mmol/L) result in the formation of ***eruptive xanthomas*** (red-yellow papules, especially on the buttocks). High LDL concentrations result in ***tendinous xanthomas*** on certain tendons (Achilles, patella, back of the hand. Such xanthomas usually indicate one of the underlying genetic hyperlipidemias. ***Lipemia retinalis*** (cream-colored blood vessels in the fundus) is seen with extremely high triglyceride levels (above 2000 mg/dL or 20 mmol/L).

SCREENING & TREATMENT OF HIGH BLOOD CHOLESTEROL

All patients with cardiovascular disease and diabetes should have their lipids measured. The only exceptions are patients in whom lipid lowering is not indicated for other reasons. Patients who already have evidence of atherosclerosis are the group at highest risk for suffering additional manifestations in the near term and thus have the most to gain from lipid lowering. Lipid lowering should be just one aspect of a program to reduce the progression and effects of the disease.

In patients with cardiovascular disease, a complete lipid profile (total cholesterol, HDL cholesterol, and triglyceride levels) after an overnight fast should be obtained. According to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, however, such patients are treated with statins independent of their lipid levels. Similarly, patients aged 40–75 with diabetes should also have a complete lipid profile. Those with diabetes and LDL greater than or equal to 70 mg/dL (1.81 mmol/L) should be treated with statins.

The best screening and treatment strategy for adults who do not have atherosclerotic cardiovascular disease is less clear. Several algorithms have been developed to guide the clinician in treatment decisions, but management decisions are individualized based on the patient’s risk.

Although the 2013 ACC/AHA guidelines recommend screening of all adults aged 21 years or older for high blood cholesterol, the United States Preventive Services Task Force (USPSTF) suggests beginning at age 20 years only if there are other cardiovascular risk factors such as tobacco use, diabetes, hypertension, obesity, or a family history of premature cardiovascular disease. For men without other risk factors, screening is recommended beginning at age 35 years. For women and for men aged 20 to 35 without increased risk, the USPSTF makes no recommendation for or against routine screening for lipid disorders. Although there is no established interval for screening, screening can be repeated every 5 years for

those with average or low risk and more often for those whose levels are close to therapeutic thresholds.

Individuals without cardiovascular disease should have their 10-year risk of CHD calculated. Although those with LDL cholesterol greater than 190 mg/dL (4.91 mmol/L) are recommended for treatment independent of their 10-year risk of cardiovascular disease, all other patients are recommended for treatment based on their overall cardiovascular risk. The best method for estimating 10-year risk is controversial. The 2013 ACC/AHA guidelines include a risk calculator that measures cardiovascular risk. It can be downloaded at myamericanheart.org under Statements & Guidelines and then Prevention Guidelines. It has been criticized by some authors as overestimating risk. The older Framingham 10-year calculator includes CHD but not stroke risk. One approach is to use both risk calculators until better data are available.

Numerous other risk factors have been studied in an attempt to better predict future CHD events. These include high-sensitivity C-reactive protein (hs-CRP), electron beam computed tomography (EBCT), homocysteine, fibrinogen, lipoprotein (a), LDL subfractions, anklebrachial index, and others. Several of these, particularly hs-CRP and EBCT, may add additional prognostic ability after accounting for traditional risk factors, but no clinical trials have adequately examined the effect of these on health outcomes. Clinical guidelines suggest limiting the use of additional risk factors such as hs-CRP to selected patients if additional data are likely to change a therapeutic decision.

Several strategies for obtaining the initial cholesterol measurement have been proposed, including: (1) measuring total cholesterol alone, (2) measuring total cholesterol and HDL cholesterol, or (3) measuring LDL cholesterol. Initial measurement of the LDL cholesterol is least likely to lead to patient misinformation and misclassification and is the strategy recommended by the 2013 ACC/AHA guidelines.

Treatment decisions are based on the presence of clinical cardiovascular disease or diabetes, patient age, LDL cholesterol greater than 190 mg/dL (4.91 mmol/L), and the estimated 10-year risk of developing cardiovascular disease. The 2013 ACC/AHA guidelines define four groups of patients who benefit from statin medications: (1) individuals with clinical atherosclerotic cardiovascular disease; (2) individuals with primary elevation of LDL cholesterol greater than190 mg/dL (4.91 mmol/L); (3) individuals aged 40–75 with diabetes and LDL greater than or equal to 70 mg/dL (1.81 mmol/L); and (4) individuals aged 40–75 without clinical atherosclerotic cardiovascular disease or diabetes, with LDL 70–189 mg/dL (1.81–4.91 mmol/L), and estimated 10-year CVD risk of 7.5% or higher.

Screening & Treatment in Women

The foregoing screening and treatment guidelines are designed for both men and women. Yet several observational studies suggest that a low HDL cholesterol is a more important risk factor for CHD in women than a high LDL cholesterol. Meta-analysis of studies including women with known heart disease, however, has found that statins prevent recurrent myocardial infarctions in women. There is insufficient

evidence to be certain of a similar effect from statins in women without evidence of CHD. Although most experts recommend application of the same primary prevention guidelines for women as for men, clinicians should be aware of the uncertainty in this area. Estimating the 10-year cardiovascular risk is particularly important in women since a larger percentage of women than men will have estimated 10-year cardiovascular risks below 7.5% per year and be advised not to take statins unless their LDL is very high (greater than 190 mg/dL [4.91 mmol/L]).

Screening & Treatment in Older Patients

Meta-analysis of evidence relating cholesterol to CHD in the elderly suggests that cholesterol is not a risk factor for CHD for persons over age 75 years. Clinical trials have rarely included such individuals. One exception is the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). In this study, elderly patients with cardiovascular disease (secondary prevention) benefited from statin therapy, whereas those without cardiovascular disease (primary prevention) did not. The 2013 ACC/AHA guidelines suggest continuing statin treatment in patients over age 75 who have cardiovascular disease. The guidelines, however, suggest not screening or treating patients over the age of 75 who do not have evidence of cardiovascular disease. Individual patient decisions to discontinue statin therapy should be based on overall functional status and life expectancy, comorbidities, and patient preference and should be made in context with overall therapeutic goals and end-of-life decisions.

TREATMENT OF HIGH LDL CHOLESTEROL

Reduction of LDL cholesterol with statins is just one part of a program to reduce the risk of cardiovascular disease. Other measures—including smoking cessation, hypertension control, and aspirin—are also of central importance. Less well studied but of potential value is raising the HDL cholesterol level. Quitting smoking reduces the effect of other cardiovascular risk factors (such as a high cholesterol level); it may also increase the HDL cholesterol level. Exercise (and weight loss) may reduce the LDL cholesterol and increase the HDL. Modest alcohol use (1–2 ounces a day) also raises HDL levels and appears to have a salutary effect on CHD rates. The use of medications to raise the HDL cholesterol has not been demonstrated to provide additional benefit. For example, cholesteryl ester transfer protein inhibitors are a class of medicines being investigated to raise HDL levels. Agents in this class, however, have not been shown to be effective. The use of niacin in addition to statins has also been carefully studied in the AIM-HIGH study and the HPS2-THRIVE study and shown not to be effective.

Diet Therapy

Studies of nonhospitalized adults have reported only modest cholesterol-lowering benefits of dietary therapy, typically in the range of a 5–10% decrease in LDL cholesterol, with even less in the long term. The effect of diet therapy, however, varies considerably among individuals, as some patients will have striking reductions in LDL cholesterol— up to a 25–30% decrease—whereas others will

have clinically important increases. Thus, the results of diet therapy should be assessed about 4 weeks after initiation.

Cholesterol-lowering diets may also have a variable effect on lipid fractions. Diets very low in total fat or in saturated fat may lower HDL cholesterol as much as LDL cholesterol. It is not known how these diet-induced changes affect coronary risk.

Several nutritional approaches to diet therapy are available. Most Americans currently eat over 35% of calories as fat, of which 15% is saturated fat. Dietary cholesterol intake averages 400 mg/day. A traditional cholesterol-lowering diet recommends reducing total fat to 25–30% and saturated fat to less than 7% of calories. Dietary cholesterol should be limited to less than 200 mg/day. These diets replace fat, particularly saturated fat, with carbohydrate. In most instances, this approach will also result in fewer total calories consumed and will facilitate weight loss in overweight patients. Other diet plans, including the Dean Ornish Diet, the Pritikin Diet, and most vegetarian diets, restrict fat even further. Low-fat, high-carbohydrate diets may, however, result in reductions in HDL cholesterol.

An alternative strategy is the Mediterranean diet, which maintains total fat at approximately 35–40% of total calories but replaces saturated fat with monounsaturated fat such as that found in canola oil and in olives, peanuts, avocados, and their oils. This diet is equally effective at lowering LDL cholesterol but is less likely to lead to reductions in HDL cholesterol. Several studies have suggested that this approach may also be associated with reductions in endothelial dysfunction, insulin resistance, and markers of vascular inflammation and may result in better resolution of the metabolic syndrome than traditional cholesterol-lowering diets. A clinical trial demonstrated reduced cardiovascular events in persons on a Mediterranean diet supplemented with additional nuts or extra-virgin olive oil compared to persons on a less intensive Mediterranean diet.

Other dietary changes may also result in beneficial changes in blood lipids. Soluble fiber, such as that found in oat bran or psyllium, may reduce LDL cholesterol by 5–10%. Garlic, soy protein, vitamin C, pecans, and plant sterols may also result in reduction of LDL cholesterol. Because oxidation of LDL cholesterol is a potential initiating event in atherogenesis, diets rich in antioxidants, found primarily in fruits and vegetables, may be helpful. Studies have suggested that when all of these elements are combined into a single dietary prescription, the impact of diet on LDL cholesterol may approach that of statin medications, lowering LDL cholesterol by close to 30%.

Pharmacologic Therapy

Most patients whose risk from CHD is considered high enough to warrant pharmacologic therapy of an elevated LDL cholesterol should be given aspirin prophylaxis at a dose of 81 mg/day unless there are contraindications such as aspirin sensitivity, bleeding diatheses, or active peptic ulcer disease. Other CHD risk factors, such as hypertension and smoking, should also be controlled.

The 2013 ACC/AHA guidelines suggest treatment with statins for all patients who require drug treatment. As discussed above, the guidelines define four groups of patients who benefit from statin medications.

A. Hydroxymethylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors (Statins)

The HMG-CoA reductase inhibitors (statins) work by inhibiting the rate-limiting enzyme in the formation of cholesterol. They reduce myocardial infarctions and total mortality in secondary prevention, as well as in older middle-aged men free of CHD. A meta-analysis has demonstrated significant reduction in risk of stroke. Cholesterol synthesis in the liver is reduced, with a compensatory increase in hepatic LDL receptors (presumably so that the liver can take more of the cholesterol that it needs from the blood) and a reduction in the circulating LDL cholesterol level by up to 35%. There are also modest increases in HDL levels and decreases in triglyceride levels.

The 2013 ACC/AHA guidelines divide statins into high-intensity and moderate-intensity statin therapy. High intensity statins lower LDL cholesterol by approximately 50%. Examples include atorvastatin 40–80 mg and rosuvastatin 20–40 mg/day. Moderate intensity statins lower LDL cholesterol by approximately 30–50%. Examples include atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, and lovastatin 40 mg. All statins are given once daily in the morning or evening. The most common side effects are muscle aches, occurring in up to 10% of patients, and mild gastrointestinal effects. Statins are associated with a 10% increase in the risk of diabetes. Other serious, but extremely uncommon, side effects include liver failure and muscle disease including myositis and rhabdomyolysis. Some patients experience muscle pain even when the serum creatine kinase levels are normal. Liver disease is more common in patients who are also taking fibrates or niacin. Manufacturers of HMG-CoA reductase inhibitors recommend monitoring liver enzymes before initiating therapy and as clinically indicated thereafter. Muscle disease is more common with statins and fibrates and niacin as well as with erythromycin, antifungal medications, nefazadone, and cyclosporine. Simvastatin at the highest approved dose—80 mg—is associated with a higher risk of muscle injury or myopathy. This dose should only be used in those who have been taking the medication for longer than 1 year without muscle toxicity

B. Niacin (Nicotinic Acid)

Niacin was the first lipid-lowering agent that was associated with a reduction in total mortality. Long-term followup of a secondary prevention trial of middle-aged men with previous myocardial infarction disclosed that about half of those who had been previously treated with niacin had died, compared with nearly 60% of the placebo group. This favorable effect on mortality was not seen during the trial itself, though there was a reduction in the incidence of recurrent coronary events. A meta-analysis of 10 randomized trials using niacin has also shown a 27% reduction in cardiovascular events.

Niacin reduces the production of VLDL particles, with secondary reduction in LDL and increases in HDL cholesterol levels. The average effect of full-dose niacin therapy, 3–4.5 g/day, is a 15–25% reduction in LDL cholesterol and a 25–35% increase in HDL cholesterol. Full doses are required to obtain the LDL effect, but the HDL effect is observed at lower doses, eg, 1 g/day. Niacin will also reduce triglycerides by half and will lower lipoprotein(a) (Lp[a]) levels and will increase plasma homocysteine levels. Intolerance to niacin is common; only 50–60% of patients can take full doses. Niacin causes a prostaglandin-mediated flushing that patients may describe as "hot flashes" or pruritus and that can be decreased with aspirin (81–325 mg/day) or other nonsteroidal anti-inflammatory agents taken during the same day. Flushing may also be decreased by initiating niacin therapy with a very small dose, eg, 100 mg with the evening meal. The dose can be doubled each week until 1.5 g/day is tolerated. After rechecking blood lipids, the dose is increased and divided over three meals until the goal of 3–4.5 g/day is reached (eg, 1 g with each meal). Extendedrelease niacin is better tolerated by most patients. It is not known whether routine monitoring of liver enzymes results in early detection and thus reduced severity of hepatocellular hepatitis with jaundice. Niacin can also exacerbate gout and peptic ulcer disease. Although niacin may increase blood sugar in some patients, clinical trials have shown that niacin can be safely used in diabetic patients.

C. Bile Acid–Binding Resins

The bile acid–binding resins include cholestyramine, colesevelam, and colestipol. Treatment with these agents reduces the incidence of coronary events in middle-aged men by about 20%, with no significant effect on total mortality. The resins work by binding bile acids in the intestine. The resultant reduction in the enterohepatic circulation causes the liver to increase its production of bile acids, using hepatic cholesterol to do so. Thus, hepatic LDL receptor activity increases, with a decline in plasma LDL levels. The triglyceride level tends to increase slightly in some patients treated with bile acid–binding resins; they should be used with caution in those with elevated triglycerides and probably not at all in patients who have triglyceride levels above 500 mg/dL. The clinician can anticipate a reduction of 15–25% in the LDL cholesterol level, with insignificant effects on the HDL level.

The usual dose of cholestyramine is 12–36 g of resin per day in divided doses with meals, mixed in water or, more palatably, juice. Doses of colestipol are 20% higher (each packet contains 5 g of resin). The dose of colesevelam is 625 mg, 6–7 tablets per day.

These agents often cause gastrointestinal symptoms, such as constipation and gas. They may interfere with the absorption of fat-soluble vitamins (thereby complicating the management of patients receiving warfarin) and may bind other drugs in the intestine. Concurrent use of psyllium may ameliorate the gastrointestinal side effects.

D. Fibric Acid Derivatives

The fibrates are peroxisome proliferative-activated receptoralpha (PPAR-alpha) agonists that result in potent reductions of plasma triglycerides and increases in HDL cholesterol. They reduce LDL levels by about 10–15%, although the result is quite variable, and triglyceride levels by about 40% and raise HDL levels by about 15–20%. The fibric acid derivatives or fibrates approved for use in the United States are gemfibrozil and fenofibrate. Ciprofibrate and bezafibrate are also available for use internationally.

Gemfibrozil reduced CHD rates in hypercholesterolemic middle-aged men free of coronary disease in the Helsinki Heart Study. The effect was observed only among those who also had lower HDL cholesterol levels and high triglyceride levels. In a VA study, gemfibrozil was also shown to reduce cardiovascular events in men with existing CHD whose primary lipid abnormality was a low HDL cholesterol. There was no effect on all-cause mortality.

The usual dose of gemfibrozil is 600 mg once or twice a day. Side effects include cholelithiasis, hepatitis, and myositis. The incidence of the latter two conditions may be higher among patients also taking other lipid-lowering agents. In the largest clinical trial that used clofibrate, there were significantly more deaths—especially due to cancer— in the treatment group; it should not be used.

E. Ezetimibe

Ezetimibe is a lipid-lowering drug that inhibits the intestinal absorption of dietary and biliary cholesterol by blocking passage across the intestinal wall by inhibiting a cholesterol transporter. The usual dose of ezetimibe is 10 mg/day orally. Ezetimibe reduces LDL cholesterol between 15% and 20% when used as monotherapy and can further reduce LDL in patients taking statins who are not yet at therapeutic goal.

However, the effects of ezetimide on CHD and its longterm safety are not yet known. Results from one small clinical trial, ENHANCE (a study of 720 persons with heterozygous familial hypercholesterolemia), showed no significant difference of intimal media thickness with ezetimibe plus an HMG-CoA reductase inhibitor compared with an HMG-CoA reductase inhibitor alone. A second study compared a statin plus ezetimibe with a statin plus extended-release niacin. The statin plus niacin caused a significant regression of carotid intima-media thickness and was superior to the statin plus ezetimibe combination.

Initial Selection of Medication

For patients who require a lipid-modifying medication, an HMG-CoA reductase inhibitor is recommended. Although other medications will also have beneficial effects on lipids, there is little evidence demonstrating the desired effects on cardiovascular disease and all-cause mortality. Resins are the only lipid-modifying medication considered safe in pregnancy.

Combination therapy is rarely indicated. Despite improvements in the lipid profile, there are few data demonstrating improved clinical outcomes of combination therapy when compared with HMG-CoA reductase inhibitors alone.

The AIM-High Study of niacin added to simvastatin, for example, was stopped early due to a lack of efficacy. The use of extended-release niacin with laropiprant (a prostaglandin antagonist) in high-risk patients taking a statin also did not reduce the risk of cardiovascular events.

Combinations may also increase the risk of complications of drug therapy. The combination of gemfibrozil and HMG-CoA reductase inhibitors increases the risk of muscle and liver disease more than either drug alone. An increase in adverse events was also seen when niacin plus laropiprant was added to statins.

HIGH BLOOD TRIGLYCERIDES

Patients with very high levels of serum triglycerides (greater than 1000 mg/dL) are at risk for pancreatitis. The pathophysiology is not certain, since pancreatitis never develops in some patients with very high triglyceride levels. Most patients with congenital abnormalities in triglyceride metabolism present in childhood; hypertriglyceridemiainduced pancreatitis first presenting in adults is more commonly due to an acquired problem in lipid metabolism.

Although there are no clear triglyceride levels that predict pancreatitis, most clinicians treat fasting levels above 500 mg/dL (5 mmol/L). The risk of pancreatitis may be more related to the triglyceride level following consumption of a fatty meal. Because postprandial increases in triglyceride are inevitable if fat-containing foods are eaten, fasting triglyceride levels in persons prone to pancreatitis should be kept well below that level.

The primary therapy for high triglyceride levels is dietary, avoiding alcohol, simple sugars, refined starches, saturated and trans fatty acids, and restricting total calories. Control of secondary causes of high triglyceride levels may also be helpful. In patients with fasting triglycerides greater than or equal to 500 mg/dL (5 mmol/L) despite adequate dietary compliance—and certainly in those with a previous episode of pancreatitis—therapy with a triglyceride-lowering drug (eg, niacin, a fibric acid derivative, omega-3-acid ethyl esters, or an HMG-CoA reductase inhibitor) is indicated. Combinations of these medications may also be used.

Whether patients with triglycerides greater than 150 mg/dL (1.5 mmol/L) should be treated to prevent CHD is not known. Meta-analysis of 17 observational studies suggests that after adjustment for other risk factors, elevated triglycerides increased CHD risk in men by 14% and in women by 37%. Elevated triglycerides are also an important feature of the metabolic syndrome, found in an estimated 25% of Americans—defined by three or more of the following five abnormalities: waist circumference greater than 102 cm in men or greater than 88 cm in women, serum triglyceride level of at least 150 mg/dL, HDL level of less than 40 mg/dL in men or less than 50 mg/dL in women, blood pressure of at least 130/85 mm Hg, and serum glucose level of at least 110 mg/dL. Other data, however, suggest that triglyceride measurements do not improve discrimination between those with and without CHD events, and clinical trial data are not available to support the routine treatment of high triglycerides in all patients.

CORONARY HEART DISEASE
(ATHEROSCLEROTIC CAD, ISCHEMIC HEART DISEASE)

Risk Factors for CAD

Most patients with coronary heart disease have some identifiable risk factor. These include a positive family history (the younger the onset in a first-degree relative, the greater the risk), male sex, blood lipid abnormalities, diabetes mellitus, hypertension, physical inactivity, abdominal obesity, and cigarette smoking, psychosocial factors, consumption of too few fruits and vegetables, and too much alcohol. Smoking remains the number one preventable cause of death and illness. According to the World Health Organization, 1 year after quitting, the risk of coronary heart disease decreases by 50%. Various interventions have been shown to increase the likelihood of successful smoking cessation.

Hypercholesterolemia is an important modifiable risk factor for coronary heart disease. Risk increases progressively with higher levels of low-density lipoprotein (LDL) cholesterol and declines with higher levels of high-density lipoprotein (HDL) cholesterol. Composite risk scores, such as the Framingham score and the 10-year atherosclerotic cardiovascular disease risk calculator (http://my.americanheart.org/cvriskcalculator), provide estimates of the 10-year probability of development of coronary heart disease that can guide primary prevention strategies. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults suggests statin therapy in four populations: patients with (1) clinical atherosclerotic disease, (2) LDL cholesterol 190 mg/dL or higher, (3) diabetes who are aged 40–75 years, and (4) an estimated 10-year atherosclotic risk of 7.5% or more aged 40–75 years. Importantly, the updated guidelines do not recommend treating to a target LDL cholesterol, an approach that has never been shown to be effective in randomized trials. Patients in these categories should be treated with moderate or high intensity statin, with high intensity statin for the higher risk populations. The ACC/ AHA atherosclerotic cardiovascular disease risk estimator allows clinicians to determine the 10-year coronary heart disease risk to determine treatment decisions. The predominant therapy recommended based on patient risk is either moderate- or high-intensity statin therapy.

The metabolic syndrome is defined as a constellation of three or more of the following: abdominal obesity, triglycerides 150 mg/dL or higher, HDL cholesterol less than 40 mg/dL for men and less than 50 mg/dL for women, fasting glucose 110 mg/dL or higher, and hypertension. This syndrome is increasing in prevalence at an alarming rate. Related to the metabolic syndrome, the epidemic of obesity is likewise a major factor contributing to coronary heart disease risk.

Myocardial Hibernation & Stunning

Areas of myocardium that are persistently underperfused but still viable may develop sustained contractile dysfunction. This phenomenon, which is termed “myocardial hibernation,” appears to represent an adaptive response that maybe

associated with depressed LV function. It is important to recognize this phenomenon, since this form of dysfunction is reversible following coronary revascularization. Hibernating myocardium can be identified by radionuclide testing, positron emission tomography (PET), contrast-enhanced MRI, or its retained response to inotropic stimulation with dobutamine. A related phenomenon, termed “myocardial stunning,” is the occurrence of persistent contractile dysfunction following prolonged or repetitive episodes of myocardial ischemia. Clinically, myocardial stunning is often seen after reperfusion of acute myocardial infarction and is defined with improvement following revascularization.

Primary & Secondary Prevention of Coronary Heart Disease

Although many risk factors for CAD are not modifiable, it is now clear that interventions, such as smoking cessation, treatment of dyslipidemia, and lowering of BP can both prevent coronary disease and delay its progression and complications after it is manifest. Treatment of lipid abnormalities delays the progression of atherosclerosis and in some cases may produce regression. Even in the absence of regression, fewer new lesions develop, endothelial function may be restored, and coronary event rates are markedly reduced in patients with clinical evidence of vascular disease.

A series of clinical trials has demonstrated the efficacy of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in preventing death, coronary events, and strokes. Beneficial results have been found in patients who have already experienced coronary events (secondary prevention), in those at particularly high risk for events (patients with diabetes and patients with peripheral artery disease), and those with elevated cholesterol without multiple risk factors, and those without vascular disease or diabetes with elevated hsCRP with normal LDL levels. The benfits of statin therapy at moderate and high doses are recommended by the cholesterol treatment guidelines. An early report of the IMPROVE-IT research showed that ezetimibe, 10 mg daily, combined with simvastatin was superior to simvastatin alone in reducing LDL cholesterol and in reducing the risk of myocardial infarction and ischemic stroke, but not mortality, in stabilized patients following an acute coronary syndrome.

Treatment to raise HDL levels has not shown consistent benefit. The AIM High trial found no benefit from the addition of niacin in patients with vascular disease and a serum LDL near 70 mg/dL who were receiving statin therapy. The HPS2-THRIVE trial found no benefit but rather substantial harm of extended-release niacin (2 g) plus laropiprant (an antiflushing agent) for preventing vascular events in a population of over 25,000 patients with vascular disease who were taking simvastatin.

The HOPE and the EUROPA trials demonstrated that ACE inhibitors (ramipril 10 mg/day and perindopril 8 mg/day, respectively) reduced fatal and nonfatal vascular events (cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes) by 20–25% in patients at high risk, including patients with diabetes with additional risk factors or patients with clinical coronary, cerebral, or peripheral arterial atherosclerotic disease.

CHRONIC STABLE ANGINA PECTORIS
ESSENTIALS OF DIAGNOSIS

- Precordial chest pain, usually precipitated by stress or exertion, relieved rapidly by rest or nitrates.
- ECG or scintigraphic evidence of ischemia during pain or stress testing.
- Angiographic demonstration of significant obstruction of major coronary vessels.

General Considerations

Angina pectoris is usually due to atherosclerotic heart disease. Coronary vasospasm may occur at the site of a lesion or, less frequently, in apparently normal vessels. Other unusual causes of coronary artery obstruction, such as congenital anomalies, emboli, arteritis, or dissection may cause ischemia or infarction. Angina may also occur in the absence of coronary artery obstruction as a result of severe myocardial hypertrophy, severe aortic stenosis or regurgitation, or in response to increased metabolic demands, as in hyperthyroidism, marked anemia, or paroxysmal tachycardias with rapid ventricular rates.

Clinical Findings

A. Symptoms

The diagnosis of angina pectoris depends principally upon the history, which should specifically include the following information: circumstances that precipitate and relieve angina, characteristics of the discomfort, location and radiation, duration of attacks, and effect of nitroglycerin.

1. Circumstances that precipitate and relieve angina— Angina occurs most commonly during activity and is relieved by resting. Patients may prefer to remain upright rather than lie down, as increased preload in recumbency increases myocardial work. The amount of activity required to produce angina may be relatively consistent under comparable physical and emotional circumstances or may vary from day to day. The threshold for angina is usually lower after meals, during excitement, or on exposure to cold. It is often lower in the morning or after strong emotion; the latter can provoke attacks in the absence of exertion. In addition, discomfort may occur during sexual activity, at rest, or at night as a result of coronary spasm.

2. Characteristics of the discomfort—Patients often do not refer to angina as “pain” but as a sensation of tightness, squeezing, burning, pressing, choking, aching, bursting, “gas,” indigestion, or an ill-characterized discomfort. It is often characterized by clenching a fist over the mid chest. The distress of angina is rarely sharply localized and is not spasmodic.

3. Location and radiation—The distribution of the distress may vary widely in different patients but is usually the same for each patient unless unstable angina or myocardial infarction supervenes. In most cases, the discomfort is felt behind or slightly to the left of the mid sternum. When it begins farther to the left or, uncommonly, on the right, it characteristically moves centrally substernally. Although angina may radiate to any dermatome from C8 to T4, it radiates most often to the left shoulder and upper arm, frequently moving down the inner volar aspect of the arm to the elbow, forearm, wrist, or fourth and fifth fingers. It may also radiate to the right shoulder or arm, the lower jaw, the neck, or even the back.

4. Duration of attacks—Angina is generally of short duration and subsides completely without residual discomfort. If the attack is precipitated by exertion and the patient promptly stops to rest, it usually lasts under 3 minutes. Attacks following a heavy meal or brought on by anger often last 15–20 minutes. Attacks lasting more than 30 minutes are unusual and suggest the development of an acute coronary syndrome with unstable angina, myocardial infarction, or an alternative diagnosis.

5. Effect of nitroglycerin—The diagnosis of angina pectoris is supported if sublingual nitroglycerin promptly and invariably shortens an attack and if prophylactic nitrates permit greater exertion or prevent angina entirely.

B. Signs

Examination during angina frequently reveals a significant elevation in systolic and diastolic BP, although hypotension may also occur, and may reflect more severe ischemia or inferior ischemia (especially with bradycardia) due to a Bezold-Jarisch reflex. Occasionally, a gallop rhythm and an apical systolic murmur due to transient mitral regurgitation from papillary muscle dysfunction are present during pain only. Supraventricular or ventricular arrhythmias may be present, either as the precipitating factor or as a result of ischemia.

It is important to detect signs of diseases that may contribute to or accompany atherosclerotic heart disease, eg, diabetes mellitus (retinopathy or neuropathy), xanthelasma tendinous xanthomas, hypertension, thyrotoxicosis, myxedema, or peripheral artery disease. Aortic stenosis or regurgitation, hypertrophic cardiomyopathy, and mitral valve prolapse should be sought, since they may produce angina or other forms of chest pain.

C. Laboratory Findings

Other than standard laboratory tests to evaluate for acute coronary syndrome (troponin and CK-MB), factors contributing to ischemia (such as anemia), and to screen for risk factors that may increase the probability of true coronary heart disease (such as hyperlipidemia and diabetes mellitus), blood tests are not helpful to diagnose chronic angina.

D. ECG

The resting ECG is often normal in patients with angina. In the remainder, abnormalities include old myocardial infarction, nonspecific ST–T changes, and changes of LVH. During anginal episodes, as well as during asymptomatic ischemia, the characteristic ECG change is horizontal or downsloping ST-segment depression that reverses after the ischemia disappears. T wave flattening or inversion may also occur. Less frequently, transient ST-segment elevation is observed; this finding suggests severe (transmural) ischemia from coronary occlusion, and it can occur with coronary spasm.

E. Pretest Probability

The history as detailed above, the physical examination findings, and laboratory and ECG findings are used to develop a pretest probability of CAD as the cause of the clinical symptoms. Other important factors to include in calculating the pretest probability of CAD are patient age, sex, and clinical symptoms. Patients with low to intermediate pretest probability for CAD should undergo noninvasive stress testing whereas patients with high pretest probability are generally referred for cardiac catheterization.

F. Exercise ECG

Exercise ECG testing is the most commonly used noninvasive procedure for evaluating for inducible ischemia in the patient with angina. Exercise ECG testing is often combined with imaging studies (nuclear or echocardiography), but in low-risk patients without baseline ST segment abnormalities or in whom anatomic localization is not necessary, the exercise ECG remains the recommended initial procedure because of considerations of cost, convenience, and longstanding prognostic data.

Exercise testing can be done on a motorized treadmill or with a bicycle ergometer. A variety of exercise protocols are utilized, the most common being the Bruce protocol, which increases the treadmill speed and elevation every 3 minutes until limited by symptoms. At least two ECG leads should be monitored continuously.

1. Precautions and risks—The risk of exercise testing is about one infarction or death per 1000 tests, but individuals who have pain at rest or minimal activity are at higher risk and should not be tested. Many of the traditional exclusions, such as recent myocardial infarction or heart failure, are no longer used if the patient is stable and ambulatory, but symptomatic aortic stenosis remains a relative contraindication.

2. Indications—Exercise testing is used (1) to confirm the diagnosis of angina; (2) to determine the severity of limitation of activity due to angina; (3) to assess prognosis in patients with known coronary disease, including those recovering from myocardial infarction, by detecting groups at high or low risk; and (4) to evaluate responses to therapy. Because false-positive tests often exceed true positives, leading to much patient anxiety and self-imposed or mandated disability, exercise testing of asymptomatic individuals should be done only for those whose

occupations place them or others at special risk (eg, airline pilots) and older individuals commencing strenuous activity.

3. Interpretation—The usual ECG criterion for a positive test is 1 mm (0.1 mV) horizontal or downsloping ST-segment depression (beyond baseline) measured 80 msec after the J point. By this criterion, 60–80% of patients with anatomically significant coronary disease will have a positive test, but 10–30% of those without significant disease will also be positive. False positives are uncommon when a 2-mm depression is present. Additional information is inferred from the time of onset and duration of the ECG changes, their magnitude and configuration, BP and heart rate changes, the duration of exercise, and the presence of associated symptoms. In general, patients exhibiting more severe ST-segment depression (more than 2 mm) at low workloads (less than 6 minutes on the Bruce protocol) or heart rates (less than 70% of age-predicted maximum)— especially when the duration of exercise and rise in BP are limited or when hypotension occurs during the test—have more severe disease and a poorer prognosis. Depending on symptom status, age, and other factors, such patients should be referred for coronary arteriography and possible revascularization. On the other hand, less impressive positive tests in asymptomatic patients are often "false positives." Therefore, exercise testing results that do not conform to the clinical suspicion should be confirmed by stress imaging.

G. Myocardial Stress Imaging

Myocardial stress imaging (scintigraphy, echocardiography, or MRI) is indicated (1) when the resting ECG makes an exercise ECG difficult to interpret (eg, left bundle branch block, baseline ST–T changes, low voltage); (2) for confirmation of the results of the exercise ECG when they are contrary to the clinical impression (eg, a positive test in an asymptomatic patient); (3) to localize the region of ischemia; (4) to distinguish ischemic from infarcted myocardium; (5) to assess the completeness of revascularization following bypass surgery or coronary angioplasty; or (6) as a prognostic indicator in patients with known coronary disease. Published criteria summarize these indications for stress testing.

1. Myocardial perfusion scintigraphy—This test, also known as radionuclide imaging, provides images in which radionuclide uptake is proportionate to blood flow at the time of injection.

Stress imaging is positive in about 75–90% of patients with anatomically significant coronary disease and in 20–30% of those without it. Occasionally, other conditions, including infiltrative diseases (sarcoidosis, amyloidosis), left bundle branch block, and dilated cardiomyopathy, may produce resting or persistent perfusion defects. False-positive radionuclide tests may occur as a result of diaphragmatic attenuation or, in women, attenuation through breast tissue. Tomographic imaging (single-photon emission computed tomography, SPECT) can reduce the severity of artifacts.

2. Radionuclide angiography—This procedure, also known as Multi Gated Acquisition Scan, or MUGA scan, uses radionuclide tracers to image the LV and measures its EF and wall motion. In coronary disease, resting abnormalities usually

represent infarction, and those that occur only with exercise usually indicate stress-induced ischemia. Exercise radionuclide angiography has approximately the same sensitivity as myocardial perfusion scintigraphy, but it is less specific in older individuals and those with other forms of heart disease. In addition, because of the precision around LVEF, the test is also used for monitoring patients exposed to cardiotoxic therapies (such as chemotherapeutic agents).

3. Stress echocardiography—Echocardiograms performed during supine exercise or immediately following upright exercise may demonstrate exercise-induced segmental wall motion abnormalities as an indicator of ischemia. In experienced laboratories, the test accuracy is comparable to that obtained with scintigraphy—though a higher proportion of tests is technically inadequate. While exercise is the preferred stress because of other information derived, pharmacologic stress with high-dose dobutamine (20–40 mcg/kg/min) can be used as an alternative to exercise.

H. Other Imaging

1. Positron emission tomography—PET and SPECT scanning can accurately distinguish transiently dysfunctional ("stunned") myocardium from scar tissue.

2. CT and MRI scanning—CT scanning can image the heart and, with contrast medium and multislice technology, the coronary arteries. Multislice CT angiography may be useful in evaluating patients with low likelihood of significant CAD to rule out disease. CT angiography may also be useful for evaluating chest pain and suspected acute coronary syndrome. However, the role of CT angiography in routine practice is yet to be established, since it currently requires both radiation exposure and contrast load. Radionuclide SPECT imaging also has similar radiation exposure. CT angiography is being studied and compared to routine stress testing in the large PROMISE Trial. CT angiography with noninvasive functional assessment of coronary stenosis (fractional flow reserve), termed "CTFFR," is also being evaluated in patients with low-intermediate likelihood of CAD.

Electron beam CT (EBCT) can quantify coronary artery calcification, which is highly correlated with atheromatous plaque and has high sensitivity, but low specificity, for obstructive coronary disease. Thus, although this test can stratify patients into lower and higher risk groups, the appropriate management of individual patients with asymptomatic coronary artery calcification—beyond aggressive risk factor modification—is unclear. This test has not traditionally been used in symptomatic patients. According to the American Heart Association, persons who are at low risk (less than 10% 10-year risk) or at high risk (greater than 20% 10-year risk) for obstructive coronary disease do not benefit from coronary calcium assessment (class III, level of evidence: B). However, in clinically selected, intermediate-risk patients, it may be reasonable to determine the atherosclerosis burden using EBCT in order to refine clinical risk prediction and to select patients for more aggressive target values for lipid-lowering therapies (class IIb, level of evidence: B).

Cardiac MRI using gadolinium provides high-resolution images of the heart and great vessels without radiation exposure or use of iodinated contrast media. Gadolinium has been associated with a rare but fatal complication in patients with severe kidney disease, called necrotizing systemic fibrosis. Gadolinium can demonstrate perfusion using dobutamine or adenosine to produce pharmacologic stress. Advances have been made in imaging the proximal coronary arteries, but this application remains investigational. Perhaps the most clinically used indication of cardiac MRI is for identification of myocardial fibrosis, either from myocardial infarction or infiltration. This allows high resolution imaging of myocardial viability.

I. Ambulatory ECG Monitoring

Ambulatory ECG recorders can monitor for ischemic STsegment depression but this modality is rarely used for ischemia detection.

J. Coronary Angiography

Selective coronary arteriography is the definitive diagnostic procedure for CAD. It can be performed with low mortality (about 0.1%) and morbidity (1–5%), but due to the invasive nature and cost, it is currently recommended only in patients with a high pretest probability of CAD.

Coronary arteriography should be performed in the following circumstances if percutaneous transluminal coronary angioplasty or bypass surgery is a consideration:

1. Life-limiting stable angina despite an adequate medical regimen.
2. Clinical presentation (unstable angina, postinfarction angina, etc) or noninvasive testing suggests high-risk disease .
3. Concomitant aortic valve disease and angina pectoris, to determine whether the angina is due to accompanying coronary disease.
4. Asymptomatic older patients undergoing valve surgery so that concomitant bypass may be done if the anatomy is propitious.
5. Recurrence of symptoms after coronary revascularization to determine whether bypass grafts or native vessels are occluded.
6. Cardiac failure where a surgically correctable lesion, such as LV aneurysm, mitral regurgitation, or reversible ischemic dysfunction, is suspected.
7. Survivors of sudden death, symptomatic, or lifethreatening arrhythmias when CAD may be a correctable cause.
8. Chest pain of uncertain cause or cardiomyopathy of unknown cause.
9. Emergently performed cardiac catheterization with intention to perform primary PCI in patients with suspected acute myocardial infarction.

A narrowing of more than 50% of the luminal diameter is considered hemodynamically (and clinically) significant, although most lesions producing ischemia are associated with narrowing in excess of 70%. In those with strongly positive exercise ECGs or scintigraphic studies, threevessel or left main disease may be present in 75–95% depending on the criteria used. **Intravascular ultrasound** (IVUS) is useful when the angiogram is equivocal as well as for

assessing the results of angioplasty or stenting. In addition, IVUS is the invasive diagnostic method of choice for ostial left main lesions and coronary dissections. In fractional flow reserve (FFR), a pressure wire is used to measure the relative change in pressure across a coronary lesion after adenosine-induced hyperemia. Revascularization based on abnormal FFR improves clinical outcomes compared to revascularization of all angiographically stenotic lesions. FFR is an important invasive tool to aid with ischemia-driven revascularization and has become the standard tool to evaluate borderline lesions in cases in which the clinical team is evaluating the clinical and hemodynamic significance of a coronary stenosis.

LV angiography is usually performed at the same time as coronary arteriography. Global and regional LV function are visualized, as well as mitral regurgitation if present. LV function is a major determinant of prognosis in coronary heart disease.

Differential Diagnosis

When atypical features are present—such as prolonged duration (hours or days) or darting, or knifelike pains at the apex or over the precordium—ischemia is less likely.

Anterior chest wall syndrome is characterized by a sharply localized tenderness of the intercostal muscles. Inflammation of the chondrocostal junctions may result in diffuse chest pain that is also reproduced by local pressure (Tietze syndrome). Intercostal neuritis (due to herpes zoster or diabetes mellitus, for example) also mimics angina.

Cervical or thoracic spine disease involving the dorsal roots produces sudden sharp, severe chest pain suggesting angina in location and “radiation” but related to specific movements of the neck or spine, recumbency, and straining or lifting. Pain due to cervical or thoracic disk disease involves the outer or dorsal aspect of the arm and the thumb and index fingers rather than the ring and little fingers.

Reflux esophagitis, peptic ulcer, chronic cholecystitis, esophageal spasm, and functional gastrointestinal disease may produce pain suggestive of angina pectoris. The picture may be especially confusing because ischemic pain may also be associated with upper gastrointestinal symptoms, and esophageal motility disorders may be improved by nitrates and calcium channel blockers. Assessment of esophageal motility may be helpful.

Degenerative and inflammatory lesions of the left shoulder and thoracic outlet syndromes may cause chest pain due to nerve irritation or muscular compression; the symptoms are usually precipitated by movement of the arm and shoulder and are associated with paresthesias.

Pneumonia, pulmonary embolism, and spontaneous pneumothorax may cause chest pain as well as dyspnea. Dissection of the thoracic aorta can cause severe chest pain that is commonly felt in the back; it is sudden in onset, reaches maximum intensity immediately, and may be associated with changes in pulses. Other cardiac disorders, such as mitral valve prolapse, hypertrophic cardiomyopathy, myocarditis, pericarditis, aortic valve disease, or RVH may cause atypical chest pain or even myocardial ischemia.

Treatment

Sublingual nitroglycerin is the drug of choice for acute management; it acts in about 1–2 minutes. As soon as the attack begins, one fresh tablet is placed under the tongue. This may be repeated at 3- to 5-minute intervals, but current recommendations are that if pain is not relieved or improving after 5 minutes, the patient should call the doctor; pain not responding to three tablets or lasting more than 20 minutes may represent evolving infarction. The dosage (0.3, 0.4, or 0.6 mg) and the number of tablets to be used before seeking further medical attention must be individualized. Nitroglycerin buccal spray is also available as a metered (0.4 mg) delivery system. It has the advantage of being more convenient for patients who have difficulty handling the pills and of being more stable.

Prevention of Further Attacks

A. Aggravating Factors

Angina may be aggravated by hypertension, LV failure, arrhythmia (usually tachycardias), strenuous activity, cold temperatures, and emotional states. These factors should be identified and treated when possible.

B. Nitroglycerin

Nitroglycerin, 0.3–0.6 mg sublingually or 0.4–0.8 mg translingually by spray, should be taken 5 minutes before any activity likely to precipitate angina. Sublingual isosorbide dinitrate (2.5–5 mg) is only slightly longer-acting than sublingual nitroglycerin.

C. Long-Acting Nitrates

Longer-acting nitrate preparations include isosorbide dinitrate, 10–40 mg orally three times daily; isosorbide mononitrate, 10–40 mg orally twice daily or 60–120 mg once daily in a sustained-release preparation; oral sustainedrelease nitroglycerin preparations, 6.25–12.5 mg two to four times daily; nitroglycerin ointment, ointment 2%, 0.5 to 2 inches (7.5 to 30 mg in the morning and six hours later); and transdermal nitroglycerin patches that deliver nitroglycerin at rates of 0.2, 0.4, and 0.6 mg/h rate (0.1–0.8 mg/h), and should be taken off after 12–14 hours of use for a 10–12 hour patch-free interval daily. The main limitation to long-term nitrate therapy is tolerance, which can be limited by using a regimen that includes a minimum 8- to 10-hour period per day without nitrates. Isosorbide dinitrate can be given three times daily, with the last dose after dinner, or longer-acting isosorbide mononitrate once daily. Transdermal nitrate preparations should be removed overnight in most patients.

Nitrate therapy is often limited by headache. Other side effects include nausea, light-headedness, and hypotension.

D. Beta-Blockers

Beta-blockers are the only antianginal agents that have been demonstrated to prolong life in patients with coronary disease (post-myocardial infarction). Beta-

blockers should be considered for first-line therapy in most patients with chronic angina and are recommened as such by the Stable Ischemic Heart disease guidelines. Beta-blockers with intrinsic sympathomimetic activity, such as pindolol, are less desirable because they may exacerbate angina in some individuals and have not been effective in secondary prevention trials. The dosages of all these drugs when given for angina are similar. The major contraindications are severe bronchospastic disease, bradyarrhythmias, and decompensated heart failure.

E. Ranolazine

Ranolazine is indicated as first-line use for chronic angina. Ranolazine has no effect on heart rate and BP, and it has been shown in clinical trials to prolong exercise duration and time to angina, both as monotherapy and when administered with conventional antianginal therapy. It is safe to use with erectile dysfunction drugs. The usual dose is 500 mg orally twice a day. Because it can cause QT prolongation, it is contraindicated in patients with existing QT prolongation; in patients taking QT prolonging drugs, such as class I or III antiarrhythmics (eg, quinidine, dofetilide, sotalol); and in those taking potent and moderate CYP450 3A inhibitors (eg, clarithromycin and rifampin). Of interest, in spite of the QT prolongation, there is a significantly lower rate of ventricular arrhythmias with its use following acute coronary syndromes, as shown in the MERLIN trial. It also decreases occurrence of atrial fibrillation and results in a small decrease in HbA1c. It is contraindicated in patients with significant liver and kidney disease. Ranolazine is not to be used for treatment of acute anginal episodes.

F. Calcium Channel Blocking Agents

Unlike the beta-blockers, calcium channel blockers have not been shown to reduce mortality postinfarction and in some cases have increased ischemia and mortality rates. This appears to be the case with some dihydropyridines (eg, nifedipine) and with diltiazem and verapamil in patients with clinical heart failure or moderate to severe LV dysfunction. Meta-analyses have suggested that shortacting nifedipine in moderate to high doses causes an increase in mortality. It is uncertain whether these findings are relevant to longer-acting dihydropyridines. Nevertheless, considering the uncertainties and the lack of demonstrated favorable effect on outcomes, calcium channel blockers should be considered third-line anti-ischemic drugs in the postinfarction patient. Similarly, these agents, with the exception of amlodipine (which proved safe in patients with heart failure in the PRAISE-2 trial), should be avoided in patients with heart failure or low Efs.

Diltiazem, amlodipine, and verapamil are preferable because they produce less reflex tachycardia and because the former, at least, may cause fewer side effects. Nifedipine, nicardipine, and amlodipine are also approved agents for angina. Isradipine, felodipine, and nisoldipine are not approved for angina but probably are as effective as the other dihydropyridines.

G. Ivabradine

Ivabradine selectively blocks the If current and specifically lowers heart rate. It has been shown to reduce angina in patients with chronic stable angina and is approved in Europe. However, the SIGNIFY trial found that there may have been harm for patients with significant angina with regard to hard outcomes of cardiovascular death and myocardial infarction, thus raising concerns regarding its use for this indication.

H. Alternative and Combination Therapies

Patients who do not respond to one class of antianginal medication often respond to another. It may, therefore, be worthwhile to use an alternative agent before progressing to combinations. The stable ischemic heart disease guidelines recommend starting with a beta-blocker as initial therapy, followed by calcium channel blockers, long-acting nitrates, or ranolazine. A few patients will have further response to a regimen including all four agents.

I. Platelet-Inhibiting Agents

Several studies have demonstrated the benefit of antiplatelet drugs for patients with stable and unstable vascular disease. Therefore, unless contraindicated, aspirin (81–325 mg orally daily) should be prescribed for all patients with angina. Clopidogrel, 75 mg orally daily, reduces vascular events in patients with stable vascular disease (as an alternative to aspirin) and in patients with acute coronary syndromes (in addition to aspirin). Thus, it is also a good alternative in aspirin-intolerant patients. Clopidogrel in addition to aspirin did not reduce myocardial infarction, stroke, or cardiovascular death in the CHARISMA trial of patients with cardiovascular disease or multiple risk factors, with about a 50% increase in bleeding. However, it might be reasonable to use combination clopidogrel and aspirin for certain high-risk patients with established coronary disease. Specifically, prolonged used of dual antiplatelet therapy with aspirin and clopidogrel may be beneficial in patients post-percutenous stenting with drug-eluting stents.

The latest antiplatelet agent to be approved by the FDA, vorapaxar, is an inhibitor of the protease-activated receptor-1. It was shown to reduce cardiovascular events for patients with stable atherosclerosis with a history of myocardial infarction or peripheral artery disease in the TRA 2P trial. It is contraindicated for patients with a history of stroke or transient ischemic attack due to increased risk of intracranial hemorrhage.

J. Risk Reduction

Patients with coronary disease should undergo aggressive risk factor modification. This approach, with a particular focus on statin treatment, treating hypertension, stopping smoking, and exercise and weight control (especially for patients with metabolic syndrome or at risk for diabetes), may markedly improve outcome. For patients with diabetes and cardiovascular disease, there is uncertainty about the optimal target blood sugar control. The ADVANCE trial suggested some benefit for tight blood sugar control with target HbA1C of 6.5% or less but the

ACCORD trial found that routine aggressive targeting for blood sugar control to HbA1C to less than 6.0% in patients with diabetes and coronary disease was associated with increased mortality. Therefore, tight blood sugar control should be avoided particularly in patients with a history of severe hypoglycemia, longstanding diabetes, and advanced vascular disease. Aggressive BP control (target systolic BP less than 120 mm Hg) in the ACCORD trial was not associated with reduction in coronary heart disease events, although stroke was reduced.

K. Revascularization

1. Indications—There is general agreement that otherwise healthy patients in the following groups should undergo revascularization: (1) Patients with unacceptable symptoms despite medical therapy to its tolerable limits. (2) Patients with left main coronary artery stenosis greater than 50% with or without symptoms. (3) Patients with three-vessel disease with LV dysfunction (EF less than 50% or previous transmural infarction). (4) Patients with unstable angina who after symptom control by medical therapy continue to exhibit ischemia on exercise testing or monitoring. (5) Post-myocardial infarction patients with continuing angina or severe ischemia on noninvasive testing. The use of revascularization for patients with acute coronary syndromes and acute ST elevation myocardial infarction is discussed below.

Data from the COURAGE trial have shown that for patients with chronic angina and disease suitable for PCI, PCI in addition to stringent guideline-directed medical therapy aimed at both risk reduction and anti-anginal care offers no mortality benefit beyond excellent medical therapy alone, and relatively moderate long-term symptomatic improvement. Therefore, for patients with mild to moderate CAD and limited symptoms, revascularization may not provide significant functional status quality-of-life benefit. For patients with moderate to significant coronary stenosis, such as those who have two-vessel disease associated with underlying LV dysfunction, anatomically critical lesions (greater than 90% proximal stenoses, especially of the proximal left anterior descending artery), or physiologic evidence of severe ischemia (early positive exercise tests, large exercise-induced thallium scintigraphic defects, or frequent episodes of ischemia on ambulatory monitoring), a heart team consisting of revascularization physicians (interventional cardiologists and surgeons) may be required to review and provide patients with the best revascularization options.

2. Type of procedure

A. Percutaneous coronary intervention including stenting—PCI, including balloon angioplasty and coronary stenting, can effectively open stenotic coronary arteries. Coronary stenting, with either bare metal stents or drug-eluting stents, has substantially reduced restenosis. Stenting can also be used selectively for left main coronary stenosis, particularly when CABG is contraindicated or deemed high risk.

PCI is possible but often less successful in bypass graft stenoses. Experienced operators are able to successfully dilate more than 90% of lesions attempted. The

major early complication is intimal dissection with vessel occlusion, although this is rare with coronary stenting. The use of intravenous platelet glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) substantially reduces the rate of periprocedural myocardial infarction, and placement of intracoronary stents markedly improves initial and long-term angiographic results, especially with complex and long lesions. After percutaneous coronary intervention, all patients should have CK-MB and troponin measured. The definition of a periprocedural infarction is still under debate with many experts advocating for a clinical definition that incorporates different enzyme cutpoints, angiographic findings, and electrocardiographic evidence. Acute thrombosis after stent placement can largely be prevented by aggressive antithrombotic therapy (long-term aspirin, 81–325 mg, plus clopidogrel, 300–600 mg loading dose followed by 75 mg daily, for between 30 days and 1 year, and with acute use of platelet glycoprotein IIb/IIIa inhibitors).

A major limitation with PCI has been restenosis, which occurs in the first 6 months in less than 10% of vessels treated with drug-eluting stents, 15–30% of vessels treated with bare metal stents, and 30–40% of vessels without stenting. Factors associated with higher restenosis rates include diabetes, small luminal diameter, longer and more complex lesions, and lesions at coronary ostia or in the left anterior descending coronary artery. Drug-eluting stents that elute antiproliferative agents, such as sirolimus, everolimus, zotarolimus, or paclitaxel, have substantially reduced restenosis. In-stent restenosis is often treated with restenting with drug-eluting stents, and rarely with brachytherapy. The nearly 2 million PCIs performed worldwide per year far exceed the number of CABG operations, but the rationale for many of the procedures performed in patients with stable angina should be for angina symptom reduction. The COURAGE trial has confirmed earlier studies in showing that even for patients with moderate anginal symptoms and positive stress tests PCI provides no benefit over medical therapy with respect to death or myocardial infarction. PCI was more effective at relieving angina, although most patients in the medical group had improvement in symptoms. Thus, in patients with mild or moderate stable symptoms, aggressive lipid-lowering and antianginal therapy may be a preferable initial strategy, reserving PCI for patients with significant and refractory symptoms or for those who are unable to take the prescribed medicines.

Several studies of PCI, including those with drugeluting stents, versus CABG in patients with multivessel disease have been reported. The SYNTAX trial as well as previously performed trials with drug-eluting stent use in PCI patients show comparable mortality and infarction rates over follow-up periods of 1–3 years but a high rate (approximately 40%) of repeat procedures following PCI. Stroke rates are higher with CABG. As a result, the choice of revascularization procedure may depend on details of coronary anatomy and is often a matter of patient preference. However, it should be noted that less than 20% of patients with multivessel disease meet the entry criteria for the clinical trials, so these results cannot be generalized to all multivessel disease patients. Outcomes with percutaneous revascularization in patients with diabetes have generally been inferior to those with CABG. The FREEDOM trial demonstrated that CABG surgery was superior to PCI with regards

to death, myocardial infarction, and stroke for patients with diabetes and multivessel coronary disease at 5 years across all subgroups of SYNTAX score anatomy.

B. Coronary artery bypass grafting—CABG can be accomplished with a very low mortality rate (1–3%) in otherwise healthy patients with preserved cardiac function. However, the mortality rate of this procedure rises to 4–8% in older individuals and in patients who have had a prior CABG.

Grafts using one or both internal mammary arteries (usually to the left anterior descending artery or its branches) provide the best long-term results in terms of patency and flow. Segments of the saphenous vein (or, less optimally, other veins) or the radial artery interposed between the aorta and the coronary arteries distal to the obstructions are also used. One to five distal anastomoses are commonly performed.

Minimally invasive surgical techniques may involve a limited sternotomy, lateral thoracotomy (MIDCAB), or thoracoscopy (port-access). They are more technically demanding, usually not suitable for more than two grafts, and do not have established durability. Bypass surgery can be performed both on circulatory support (on-pump) and without direct circulatory support (off-pump). Randomized trial data have not shown a benefit with off-pump bypass surgery but minimally invasive surgical techniques allow earlier postoperative mobilization and discharge.

The operative mortality rate is increased in patients with poor LV function (LVEF less than 35%) or those requiring additional procedures (valve replacement or ventricular aneurysmectomy). Patients over 70 years of age, patients undergoing repeat procedures, or those with important noncardiac disease (especially chronic kidney disease and diabetes) or poor general health also have higher operative mortality and morbidity rates, and full recovery is slow. Thus, CABG should be reserved for more severely symptomatic patients in this group. Early (1–6 months) graft patency rates average 85–90% (higher for internal mammary grafts), and subsequent graft closure rates are about 4% annually. Early graft failure is common in vessels with poor distal flow, while late closure is more frequent in patients who continue smoking and those with untreated hyperlipidemia. Antiplatelet therapy with aspirin improves graft patency rates. Smoking cessation and vigorous treatment of blood lipid abnormalities (particularly with statins) are necessary. Repeat revascularization (see below) may be necessitated because of recurrent symptoms due to progressive native vessel disease and graft occlusions. Reoperation is technically demanding and less often fully successful than the initial operation. In addition, in patients with ischemic mitral regurgitation, mitral repair at the time of a CABG does not offer any clinical benefit.

L. Mechanical Extracorporeal Counterpulsation

Extracorporeal counterpulsation entails repetitive inflation of a high-pressure chamber surrounding the lower half of the body during the diastolic phase of the cardiac cycle for daily 1-hour sessions over a period of 7 weeks. Randomized trials

have shown that extracorporeal counterpulsation reduces angina thus it may be considered for relief of refractory angina in patients with stable coronary disease.

M. Neuromodulation

Spinal cord stimulation can be used to relieve chronic refractory angina. Spinal cord stimulators are subcutaneously implantable via a minimally invasive procedure under local anesthesia.

Prognosis

The prognosis of angina pectoris has improved with development of therapies aimed at secondary prevention. Mortality rates vary depending on the number of vessels diseased, the severity of obstruction, the status of LV function, and the presence of complex arrhythmias. Mortality rates are progressively higher in patients with one-, two-, and three-vessel disease and those with left main coronary artery obstruction (ranging from 1% per year to 25% per year). The outlook in individual patients is unpredictable, and nearly half of the deaths are sudden. Therefore, risk stratification is attempted. Patients with accelerating symptoms have a poorer outlook. Among stable patients, those whose exercise tolerance is severely limited by ischemia (less than 6 minutes on the Bruce treadmill protocol) and those with extensive ischemia by exercise ECG or scintigraphy have more severe anatomic disease and a poorer prognosis. The Duke Treadmill Score, based on a standard Bruce protocol exercise treadmill test, provides an estimate of risk of death at 1 year.

When to Refer

All patients with new or worsening symptoms believed to represent progressive angina or a positive stress test for myocardial ischemia with continued angina despite medical therapy (or both) should be referred to a cardiologist.

When to Admit

• Patients with elevated cardiac biomarkers, ischemic ECG findings, or hemodynamic instability.

• Patients with new or worsened symptoms, possibly thought to be ischemic, but who lack high-risk features can be observed with serial ECGs and biomarkers, and discharged if stress testing shows low-risk findings.

CORONARY VASOSPASM & ANGINA WITH NORMAL CORONARY ARTERIOGRAMS

Prinzmetal (variant) angina

ESSENTIALS OF DIAGNOSIS

- Precordial chest pain, often occurring at rest during stress or without known precipitant, relieved rapidly by nitrates.
- ECG evidence of ischemia during pain, sometimes with ST-segment elevation.

- Angiographic demonstration of: – No significant obstruction of major coronary vessels. – Coronary spasm that responds to intra-coronary nitroglycerin or calcium channel blockers.

General Considerations

Although most symptoms of myocardial ischemia result from fixed stenosis of the coronary arteries, intraplaque hemorrhage, or thrombosis at the site of lesions, some ischemic events may be precipitated or exacerbated by coronary vasoconstriction.

Spasm of the large coronary arteries with resulting decreased coronary blood flow may occur spontaneously or may be induced by exposure to cold, emotional stress, or vasoconstricting medications, such as ergot-derivative drugs. Spasm may occur both in normal and in stenosed coronary arteries. Even myocardial infarction may occur as a result of spasm in the absence of visible obstructive coronary heart disease, although most instances of such coronary spasm occur in the presence of coronary stenosis.

Cocaine can induce myocardial ischemia and infarction by causing coronary artery vasoconstriction or by increasing myocardial energy requirements. It also may contribute to accelerated atherosclerosis and thrombosis. The ischemia in **Prinzmetal (variant) angina** usually results from coronary vasoconstriction. It tends to involve the right coronary artery and there may be no fixed stenoses. Myocardial ischemia may also occur in patients with normal coronary arteries as a result of disease of the coronary microcirculation or abnormal vascular reactivity. This has been termed "**syndrome X**."

Clinical Findings

Ischemia may be silent or result in angina pectoris.

Prinzmetal (variant) angina is a clinical syndrome in which chest pain occurs without the usual precipitating factors and is associated with ST-segment elevation rather than depression. It often affects women under 50 years of age. It characteristically occurs in the early morning, awakening patients from sleep, and is apt to be associated with arrhythmias or conduction defects. It may be diagnosed by challenge with ergonovine (a vasoconstrictor), although the results of such provocation are not specific and it entails risk.

Treatment

Patients with chest pain associated with ST-segment elevation should undergo coronary arteriography to determine whether fixed stenotic lesions are present. If they are, aggressive medical therapy or revascularization is indicated, since this may represent an unstable phase of the disease. If significant lesions are not seen and spasm is suspected, avoidance of precipitants, such as cigarette smoking and cocaine, is the top priority. Episodes of coronary spasm generally respond well to nitrates, and both nitrates and calcium channel blockers (including longacting nifedipine, diltiazem, or amlopidine) are effective prophylactically. By allowing unopposed alpha-1-mediated vasoconstriction, beta-blockers have

exacerbated coronary vasospasm, but they may have a role in management of patients in whom spasm is associated with fixed stenoses.

When to Refer

All patients with persistent symptoms of chest pain that may represent spasm should be referred to a cardiologist.

ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

ESSENTIALS OF DIAGNOSIS

- Distinction in acute coronary syndrome between patients with and without ST-segment elevation at presentation is essential to determine need for reperfusion therapy.
- Fibrinolytic therapy is harmful in acute coronary syndrome without ST-segment elevation, unlike with ST-segment elevation, where acute reperfusion saves lives.
- Antiplatelet and anticoagulation therapies and coronary intervention are mainstays of treatment.

General Considerations

Acute coronary syndromes comprise the spectrum of unstable cardiac ischemia from unstable angina to acute myocardial infarction. Acute coronary syndromes are classified based on the presenting ECG as either "STsegment elevation" (STEMI) or "non–ST-segment elevation" (NSTEMI). This allows for immediate classification and guides determination of whether patients should be considered for acute reperfusion therapy. The evolution of cardiac biomarkers then allows determination of whether myocardial infarction has occurred.

Acute coronary syndromes represent a dynamic state in which patients frequently shift from one category to another, as new ST elevation can develop after presentation and cardiac biomarkers can become abnormal with recurrent ischemic episodes.

Clinical Findings

A. Symptoms and Signs

Patients with acute coronary syndromes generally have symptoms and signs of myocardial ischemia either at rest or with minimal exertion. These symptoms and signs are similar to the chronic angina symptoms described above, consisting of substernal chest pain or discomfort that may radiate to the jaw, left shoulder or arm. Dyspnea, nausea, diaphoresis, or syncope may either accompany the chest discomfort or may be the only symptom of acute coronary syndrome. About one-third of patients with myocardial infarction have no chest pain per se—these patients tend to be older, female, have diabetes, and be at higher risk for subsequent mortality. Patients with acute coronary syndromes have signs of heart failure in about 10% of cases, and this is also associated with higher risk of death.

Many hospitals have developed **chest pain observation units** to provide a systematic approach toward serial risk stratification to improve the triage process. In many cases, those who have not experienced new chest pain and have insignificant ECG changes and no cardiac biomarker elevation undergo treadmill exercise tests or imaging procedures to exclude ischemia at the end of an 8- to 24-hour period and are discharged directly from the emergency department if these tests are negative.

B. Laboratory Findings

Depending on the time from symptom onset to presentation, initial laboratory findings may be normal. The markers of cardiac myocyte necrosis, myoglobin, CK-MB, and troponin I and T may all be used to identify acute myocardial infarction. These markers have a well-described pattern of release over time in patients with myocardial infarction (see Laboratory Findings, Acute Myocardial Infarction with ST-Segment Elevation, below). In patients with STEMI, these initial markers are often within normal limits as the patient is being rushed to immediate reperfusion. In patients without ST-segment elevation, it is the presence of abnormal CK-MB or troponin values that are associated with myocyte necrosis and the diagnosis of myocardial infarction. **The universal definition of myocardial infarction** is a rise of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes of new ischemia, new Q waves, or imaging evidence of new loss of viable myocardium or new wall motion abnormality.

Serum creatinine is an important determinant of risk, and estimated creatinine clearance is important to guide dosing of certain antithrombotics, including eptifibatide and enoxaparin.

C. ECG

Many patients with acute coronary syndromes will exhibit ECG changes during pain—either ST-segment elevation, ST-segment depression, or T wave flattening or inversion. Dynamic ST segment shift is the most specific for acute coronary syndrome. ST-segment elevation in lead AVR suggests left main or three vessel disease.

Treatment

General Measures

Treatment of acute coronary syndromes without ST elevation should be multifaceted. Patients who are at medium or high risk should be hospitalized, maintained at bed rest or at very limited activity for the first 24 hours, monitored, and given supplemental oxygen. Sedation with a benzodiazepine agent may help if anxiety is present.

Antiplatelet and Anticoagulation Therapy

Patients should receive a combination of antiplatelet and anticoagulant agents on presentation. *Fibrinolytic therapy should be avoided in patients without ST-segment elevation since they generally do not have an acute coronary occlusion, and the risk of such therapy appears to outweigh the benefit.*

1. Antiplatelet therapy

A. Aspirin—Aspirin, 162–325 mg loading dose, then 81–325 mg daily, should be commenced immediately and continued for the first month. The 2012 ACC/AHA guidelines for longer-term aspirin treatment recommend aspirin 75–162 mg/day as preferable to higher doses with or without coronary stenting.

B. P2Y12 Inhibitors—ACC/AHA guidelines call for either a P2Y12 inhibitor (**clopidogrel, prasugrel** [at the time of PCI], or ticagrelor) as a class I recommendation. The European Society of Cardiology guidelines provide a stronger recommendation for a P2Y12 inhibitor up-front, as a class IA recommendation for all patients. Both sets of guidelines recommend postponing elective CABG surgery for at least 5 days after the last dose of clopidogrel or **ticagrelor** and at least 7 days after the last dose of prasugrel, due to risk of bleeding.

The European Society of Cardiology guidelines recommend ticagrelor for all patients at moderate to high risk for acute coronary syndrome (class 1 recommendation). **Prasugrel** is recommended for patients who have not yet received another P2Y12 inhibitor, for whom a PCI is planned, and who are not at high risk for life-threatening bleeding. Clopidogrel is reserved for patients who cannot receive either ticagrelor or prasugrel. Some studies have shown an association between assays of residual platelet function and thrombotic risk during P2Y12 inhibitor therapy, and both the European and the US guidelines do not recommend routine platelet function testing to guide therapy (class IIb recommendation).

Prasugrel is both more potent and has a faster onset of action than clopidogrel. The TRITON trial compared prasugrel with clopidogrel in patients with STEMI or NSTEMI in whom PCI was planned; prasugrel resulted in a 19% relative reduction in death from cardiovascular causes, myocardial infarction, or stroke, at the expense of an increase in serious bleeding (including fatal bleeding). Stent thrombosis was reduced by half. Because patients with prior stroke or transient ischemic attack had higher risk of intracranial hemorrhage, prasugrel is contraindicated in such patients. Bleeding was also higher in patients with low body weight (less than 60 kg) and age 75 years or older, and caution should be used in these populations. For patients with STEMI treated with PCI, prasugrel appears to be especially effective without a substantial increase in bleeding. For patients who will not receive revascularization, prasugrel, when compared to clopidogrel, had no overall benefit in the TRILOGY trial (the dose of prasugrel was lowered for the elderly).

Ticagrelor has a faster onset of action than clopidogrel and a more consistent and potent effect. The PLATO trial showed that when ticagrelor was started at the time of presentation in acute coronary syndrome patients (UA/NSTEMI and

STEMI), it reduced cardiovascular death, myocardial infarction, and stroke by 16% when compared with clopidogrel. In addition, there was a 22% relative risk reduction in mortality with ticagrelor. The overall rates of bleeding were similar between ticagrelor and clopidogrel, although nonCABG related bleeding was modestly higher. The finding of a lesser treatment effect in the United States may have been related to use of higher-dose aspirin, and thus when using ticagrelor, low-dose aspirin (81 mg/day) is recommended.

C. Glycoprotein IIb/IIIa inhibitors—Small-molecule inhibitors of the platelet glycoprotein IIb/IIIa receptor are useful adjuncts in high-risk patients (usually defined by fluctuating ST-segment depression or positive biomarkers) with acute coronary syndromes, particularly when they are undergoing PCI. **Tirofiban**, 25 mcg/kg over 3 minutes, followed by 0.15 mcg/kg/min, and **eptifibatide**, 180 mcg/kg bolus followed by a continuous infusion of 2 mcg/kg/min, have both been shown to be effective. Downward dose adjustments of the infusions are required in patients with reduced kidney function. The bolus or loading dose remains unadjusted. For example, if the estimated creatinine clearance is below 50 mL/min, the eptifibatide infusion should be cut in half to 1 mcg/kg/min. The ISAR-REACT 2 trial showed that for patients undergoing PCI with high-risk acute coronary syndrome, especially with elevated troponin, intravenous **abciximab** (added to a 600-mg loading dose of clopidogrel) reduces ischemic events by about 25%. The EARLY-ACS trial in over 10,000 patients with high-risk acute coronary syndrome found no benefit from eptifibatide started at the time of admission and higher rates of bleeding compared with eptifibatide treatment started at the time of invasive coronary angiography.

2. Anticoagulant therapy

A. Heparin—Several trials have shown that LMWH (enoxaparin 1 mg/kg subcutaneously every 12 hours) is somewhat more effective than unfractionated heparin in preventing recurrent ischemic events in the setting of acute coronary syndromes. However, the SYNERGY trial showed that unfractionated heparin and enoxaparin had similar rates of death or (re)infarction in the setting of frequent early coronary intervention.

B. Fondaparinux—Fondaparinux, a specific factor Xa inhibitor given in a dose of 2.5 mg subcutaneously once a day, was found in the OASIS-5 trial to be equally effective as enoxaparin among 20,000 patients at preventing early death, myocardial infarction, and refractory ischemia, and resulted in a 50% reduction in major bleeding. This reduction in major bleeding translated into a significant reduction in mortality (and in death or myocardial infarction) at 30 days. While catheter-related thrombosis was more common during coronary intervention procedures with fondaparinux, the FUTURA trial found that it can be controlled by adding unfractionated heparin (in a dose of 85 units/kg without glycoprotein IIb/IIIa inhibitors, and 60 units/kg with glycoprotein IIb/IIIa inhibitors) during the procedure. Guidelines recommend fondaparinux, describing it as especially favorable for patients who are initially treated medically and who are at high risk for bleeding, such as the elderly.

C. Direct thrombin inhibitors—The ACUITY trial showed that **bivalirudin** appears to be a reasonable alternative to heparin (unfractionated heparin or enoxaparin) plus a glycoprotein IIb/IIIa antagonist for many patients with acute coronary syndromes who are undergoing early coronary intervention. Bivalirudin (without routine glycoprotein IIb/IIIa inhibitor) is associated with substantially less bleeding than heparin plus glycoprotein IIb/IIIa inhibitor. The ISAR REACT-4 trial showed that bivalirudin has similar efficacy compared to abciximab but better bleeding outcomes in NSTEMI patients. Bivalrudin does not currently have an FDA-approved indication for NSTEMI care.

Temporary Discontinuation of Antiplatelet Therapy for Procedures

Patients who have had recent coronary stents are at risk for thrombotic events, including stent thrombosis, if P2Y12 inhibitors are discontinued for procedures (eg, dental procedures or colonoscopy). If possible, these procedures should be delayed until the end of the necessary treatment period with P2Y12 inhibitors, which generally is at least 1 month with bare metal stents and 3–6 months with drug-eluting stents. Before that time, if a procedure is necessary, risk and benefit of continuing the antiplatelet therapy through the time of the procedure should be assessed. Aspirin should generally be continued throughout the period of the procedure. A cardiologist should be consulted before temporary discontinuation of these agents.

Nitroglycerin

Nitrates are first-line therapy for patients with acute coronary syndromes presenting with chest pain. Nonparenteral therapy with sublingual or oral agents or nitroglycerin ointment is usually sufficient. If pain persists or recurs, intravenous nitroglycerin should be started. The usual initial dosage is 10 mcg/min. The dosage should be titrated upward by 10–20 mcg/min (to a maximum of 200 mcg/min) until angina disappears or mean arterial pressure drops by 10%. Careful — usually continuous — BP monitoring is required when intravenous nitroglycerin is used. Avoid hypotension (systolic BP less than 100 mm Hg). Tolerance to continuous nitrate infusion is common.

Beta-Blockers

Beta-blockers are an important part of the initial treatment of unstable angina unless otherwise contraindicated. Use of agents with intrinsic sympathomimetic activity should be avoided in this setting. Oral medication is adequate in most patients, but intravenous treatment with metoprolol, given as three 5-mg doses 5 minutes apart as tolerated and in the absence of heart failure, achieves a more rapid effect. Oral therapy should be titrated upward as BP permits.

Calcium Channel Blockers

Calcium channel blockers have not been shown to favorably affect outcome in unstable angina, and they should be used primarily as third-line therapy in patients with continuing symptoms on nitrates and beta-blockers or those who are

not candidates for these drugs. In the presence of nitrates and without accompanying beta-blockers, diltiazem or verapamil is preferred, since nifedipine and the other dihydropyridines are more likely to cause reflex tachycardia or hypotension. The initial dosage should be low, but upward titration should proceed steadily.

Statins

The PROVE-IT trial provides evidence for starting a statin in the days immediately following an acute coronary syndrome. In this trial, more intensive therapy with **atorvastatin** 80 mg/day, regardless of total or LDL cholesterol level, improved outcome compared to **pravastatin** 40 mg/day, with the curves of death or major cardiovascular event separating as early as 3 months after starting therapy. Highdose statins are recommended for all patients with acute coronary syndromes.

Indications for Coronary Angiography

For patients with acute coronary syndrome, including non–ST-segment elevation myocardial infarction, risk stratification is important for determining intensity of care. Several therapies, including glycoprotein IIb/IIIa inhibitors, LMWH heparin, and early invasive catheterization, have been shown to have the greatest benefit in higher-risk patients with acute coronary syndrome. As outlined in the ACC/AHA guidelines, patients with any high-risk feature generally warrant an early invasive strategy with catheterization and revascularization. For patients without these high-risk features, either an invasive or noninvasive approach, using exercise (or pharmacologic stress for patients unable to exercise) stress testing to identify patients who have residual ischemia and/or high risk, can be used. Moreover, based on the ICTUS trial, a strategy based on selective coronary angiography and revascularization for instability or inducible ischemia, or both, even for patients with positive troponin, is acceptable (ACC/ AHA class IIb recommendation).

Two risk-stratification tools are available that can be used at the bedside, the GRACE Risk Score (http://www .outcomes-umassmed.org/grace) and the TIMI Risk Score (available for PDA download at http://www.timi.org). The GRACE risk score, which applies to patients with or without ST elevation, was developed in a more generalizable registry population and includes Killip class, BP, STsegment deviation, cardiac arrest at presentation, serum creatinine, elevated creatine kinase (CK)-MB or troponin, and heart rate. The TIMI Risk Score includes seven variables: age 65 years or older, three or more cardiac risk factors, prior coronary stenosis 50% or more, ST-segment deviation, two anginal events in prior 24 hours, aspirin in prior 7 days, and elevated cardiac markers.

When to Refer

• All patients with acute myocardial infarction should be referred to a cardiologist.

• Patients who are taking a P2Y12 inhibitor following coronary stenting should consult a cardiologist before discontinuing treatment for nonemergency procedures.

ACUTE MYOCARDIAL INFARCTION WITH ST-SEGMENT ELEVATION

ESSENTIALS OF DIAGNOSIS

- Sudden but not instantaneous development of prolonged (more than 30 minutes) anterior chest discomfort (sometimes felt as "gas" or pressure).
- Sometimes painless, masquerading as acute heart failure, syncope, stroke, or shock.
- ECG: ST-segment elevation or left bundle branch block.
- Immediate reperfusion treatment is warranted.
- Primary PCI within 90 minutes of first medical contact is the goal and is superior to fibrinolytic therapy.
- Fibrinolytic therapy within 30 minutes of hospital presentation is the goal, and reduces mortality if given within 12 hours of onset of symptoms.

General Considerations

STEMI results, in most cases, from an occlusive coronary thrombus at the site of a preexisting (though not necessarily severe) atherosclerotic plaque. More rarely, infarction may result from prolonged vasospasm, inadequate myocardial blood flow (eg, hypotension), or excessive metabolic demand. Very rarely, myocardial infarction may be caused by embolic occlusion, vasculitis, aortic root or coronary artery dissection, or aortitis. Cocaine, a cause of infarction, should be considered in young individuals without risk factors. A condition that may mimic STEMI is stress cardiomyopathy (also referred to as Tako-Tsubo or apical ballooning syndrome).

ST elevation connotes an acute coronary occlusion and warrants immediate reperfusion therapy.

Clinical Findings

A. Symptoms

1. Premonitory pain—There is usually a worsening in the pattern of angina preceding the onset of symptoms of myocardial infarction; classically the onset of angina occurs with minimal exertion or at rest.

2. Pain of infarction—Unlike anginal episodes, most infarctions occur at rest, and more commonly in the early morning. The pain is similar to angina in

location and radiation but it may be more severe, and it builds up rapidly or in waves to maximum intensity over a few minutes or longer. Nitroglycerin has little effect; even opioids may not relieve the pain.

3**. Associated symptoms**—Patients may break out in a cold sweat, feel weak and apprehensive, and move about, seeking a position of comfort. They prefer not to lie quietly. Light-headedness, syncope, dyspnea, orthopnea, cough, wheezing, nausea and vomiting, or abdominal bloating may be present singly or in any combination.

4. Painless infarction—One-third of patients with acute myocardial infarction present without chest pain, and these patients tend to be undertreated and have poor outcomes. Older patients, women, and patients with diabetes mellitus are more likely to present without chest pain. As many as 25% of infarctions are detected on routine ECG without any recallable acute episode.

5. Sudden death and early arrhythmias—Of all deaths from myocardial infarction, about 50% occur before the patients arrive at the hospital, with death presumably caused by ventricular fibrillation.

B. Signs

1. General—Patients may appear anxious and sometimes are sweating profusely. The heart rate may range from marked bradycardia (most commonly in inferior infarction) to tachycardia, low cardiac output, or arrhythmia. The BP may be high, especially in former hypertensive patients, or low in patients with shock. Respiratory distress usually indicates heart failure. Fever, usually low grade, may appear after 12 hours and persist for several days.

2. Chest—The Killip classification is the standard way to classify heart failure in patients with acute myocardial infarction and has powerful prognostic value. Killip class I is absence of rales and S3 , class II is rales that do not clear with coughing over one-third or less of the lung fields or presence of an S3 , class III is rales that do not clear with coughing over more than one-third of the lung fields, and class IV is cardiogenic shock (rales, hypotension, and signs of hypoperfusion).

3. Heart—The cardiac examination may be unimpressive or very abnormal. Jugular venous distention reflects RA hypertension, and a Kussmaul sign (failure of decrease of jugular venous pressure with inspiration) is suggestive of RV infarction. Soft heart sounds may indicate LV dysfunction. Atrial gallops (S4) are the rule, whereas ventricular gallops (S3) are less common and indicate significant LV dysfunction. Mitral regurgitation murmurs are not uncommon and may indicate papillary muscle dysfunction or, rarely, rupture. Pericardial friction rubs are uncommon in the first 24 hours but may appear later.

4. Extremities—Edema is usually not present. Cyanosis and cold temperature indicate low output. The peripheral pulses should be noted, since later shock or emboli may alter the examination.

C. Laboratory Findings

Cardiac-specific markers of myocardial damage include quantitative determinations of CK-MB, highly sensitive and conventional troponin I, and troponin T. Each of these tests may become positive as early as 4–6 hours after the onset of a myocardial infarction and should be abnormal by 8–12 hours. Troponins are more sensitive and specific than CK-MB. "Highly sensitive" or "fourth-generation" troponin assays, which are not yet widely used in the United States but are the standard assays in most of Europe, have a 10- to 100-fold lower limit of detection, allowing myocardial infarction to be detected earlier, using the change in value over 3 hours.

Circulating levels of troponins may remain elevated for 5–7 days or longer and therefore are generally not useful for evaluating suspected early reinfarction. Elevated CK-MB generally normalizes within 24 hours, thus being more helpful for evaluation of reinfarction. Low level elevations of troponin in patients with severe chronic kidney disease may not be related to acute coronary disease but rather a function of the physiologic washout of the marker. While many conditions including chronic heart failure are associated with elevated levels of the high-sensitivity troponin assays, these assays may be especially useful when negative to exclude myocardial infarction in patients complaining of chest pain.

D. ECG

The extent of the ECG abnormalities, especially the sum of the total amount of ST-segment deviation, is a good indicator of the extent of acute infarction and risk of subsequent adverse events. The classic evolution of changes is from peaked ("hyperacute") T waves, to ST-segment elevation, to Q wave development, to T wave inversion. This may occur over a few hours to several days. The evolution of new Q waves (longer than 30 msec in duration and 25% of the R wave amplitude) is diagnostic, but Q waves do not occur in 30–50% of acute infarctions (non-Q wave infarctions). Left bundle branch block, especially when new (or not known to be old), in a patient with symptoms of an acute myocardial infarction, is considered to be a "STEMI equivalent"; reperfusion therapy is indicated for the affected patient. Concordant ST elevation (ie, ST elevation in leads with an overall positive QRS complex) with left bundle branch block is a specific finding indicating STEMI.

E. Chest Radiography

The chest radiograph may demonstrate signs of heart failure, but these changes often lag behind the clinical findings. Signs of aortic dissection, including mediastinal widening, should be sought as a possible alternative diagnosis.

F. Echocardiography

Echocardiography provides convenient bedside assessment of LV global and regional function. This can help with the diagnosis and management of infarction; echocardiography has been used successfully to make judgments about admission and management of patients with suspected infarction, including in patients with ST-segment elevation or left bundle branch block of uncertain significance, since

normal wall motion makes an infarction unlikely. Doppler echocardiography is generally the most convenient procedure for diagnosing postinfarction mitral regurgitation or VSD.

G. Other

Noninvasive Studies Diagnosis of myocardial infarction and extent of myocardial infarction can be assessed by various imaging studies in addition to echocardiography. **MRI** with gadolinium contrast enhancement is the most sensitive test to detect and quantitate extent of infarction, with the ability to detect as little as 2 g of myocardial infarction. **Technetium99m pyrophosphate scintigraphy**, when injected at least 18 hours postinfarction, complexes with calcium in necrotic myocardium to provide a "hot spot" image of the infarction. This test is insensitive to small infarctions, and false-positive studies occur, so its use is limited to patients in whom the diagnosis by ECG and enzymes is not possible— principally those who present several days after the event or have intraoperative infarctions. **Scintigraphy with thallium-201** or technetium-based perfusion tracers will demonstrate "cold spots" in regions of diminished perfusion, which usually represent infarction when the radiotracer is administered at rest, but abnormalities do not distinguish recent from old damage. All of these tests may be considered after the patient has had revascularization.

H. Hemodynamic Measurements

These can be helpful in managing the patient with suspected cardiogenic shock. Use of PA catheters, however, has generally not been associated with better outcomes and should be limited to patients with severe hemodynamic compromise for whom the information would be anticipated to change management.

Treatment

A. Aspirin, P2Y12 Inhibitors (Prasugrel, Ticagrelor, and Clopidogrel)

All patients with definite or suspected acute myocardial infarction should receive aspirin at a dose of 162 mg or 325 mg at once regardless of whether fibrinolytic therapy is being considered or the patient has been taking aspirin. Chewable aspirin provides more rapid blood levels. Patients with a definite aspirin allergy should be treated with a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor).

P2Y12 inhibitors, in combination with aspirin, have been shown to provide important benefits in patients with acute STEMI. Thus, guidelines call for a P2Y12 inhibitor to be added to aspirin for all patients with STEMI, regardless of whether reperfusion is given, and continued for at least 14 days, and generally for 1 year. The preferred P2Y12 inhibitors are prasugrel (60 mg orally on day 1, then 10 mg daily) or ticagrelor (180 mg orally on day 1, then 90 mg twice daily). Both of these drugs demonstrated superior outcomes to clopidogrel in clinical studies of primary PCI. Clopidogrel should be administered as a loading dose of 300–600 mg orally for faster onset of action than the 75 mg maintenance dose. With fibrinolytic therapy, there are no randomized trial data regarding when the early use of

prasugrel or ticagrelor and clopidogrel is indicated (with a 300-mg loading dose for patients younger than 75 years and no loading dose for patients older than 75 years). Prasugrel is contraindicated in patients with history of stroke or who are older than 75 years.

B. Reperfusion Therapy

The current recommendation is to treat patients with STEMI who seek medical attention within 12 hours of the onset of symptoms with reperfusion therapy, either primary PCI or fibrinolytic therapy. Patients without ST-segment elevation (previously labeled "non-Q wave" infarctions) do not benefit, and may derive harm, from thrombolysis.

1. Primary percutaneous coronary intervention—Immediate coronary angiography and primary PCI (including stenting) of the infarct-related artery have been shown to be superior to thrombolysis when done by experienced operators in high-volume centers with rapid time from first medical contact to intervention ("door-to-balloon"). US and European guidelines call for first medical contact or "door-to-balloon" times of 90 minutes or less. Several trials have shown that if efficient transfer systems are in place, transfer of patients with acute myocardial infarction from hospitals without primary PCI capability to hospitals with primary PCI capability with first door-to-device times of 120 minutes or less can improve outcome compared with fibrinolytic therapy at the presenting hospital, although this requires sophisticated systems to ensure rapid identification, transfer, and expertise in PCI. Because PCI also carries a lower risk of hemorrhagic complications, including intracranial hemorrhage, it may be the preferred strategy in many older patients and others with contraindications to fibrinolytic therapy.

A. Stenting—Percutaneous coronary intervention (PCI) with stenting is standard for patients with acute myocardial infarction. Primary PCI stenting is done with bivalirudin, a direct thrombin inhibitor, or unfractionated heparin with or without glycoprotein IIb/IIIa inhibitors. Although randomized trials have shown a benefit with regard to fewer repeat interventions for restenosis with the use of drugeluting stents in STEMI patients, bare metal stents are still used for patients without the ability to obtain and comply with P2Y12 inhibitor therapy, which is often not known at the time of PCI. In the subgroup of patients with cardiogenic shock, early catheterization and percutaneous or surgical revascularization are the preferred management and have been shown to reduce mortality.

Heat primary PCI also showed increased stent thrombosis and more adverse cardiovascular events with bivalirudin compared to unfractionated heparin.

"Facilitated" PCI, whereby a combination of medications (full- or reduced-dose fibrinolytic agents, with or without glycoprotein IIb/IIIa inhibitors) is given followed by immediate PCI is not recommended. Patients should be treated either with primary PCI or with fibrinolytic agents (and immediate rescue PCI for reperfusion failure), if it can be done promptly as outlined in the ACC/AHA and European guidelines. Timely access to most appropriate reperfusion, including primary PCI, can be expanded with development of regional systems of care,

including emergency medical systems and networks of hospitals. Patients treated with fibrinolytic therapy appear to have improved outcomes if transferred for routine coronary angiography and PCI within 24 hours.

B. Antiplatelet therapy after drug-eluting or bare metal stents—In patients with an acute coronary syndrome, dual antiplatelet therapy is indicated for 1 year in all patients (including those with medical therapy and those patients undergoing revascularization irrespective of stent type). For patients undergoing elective or stable PCI, the duration of dual antiplatelet therapy is recommended for at least 1 month for patients receiving bare metal stents. For patients receiving drug-eluting stents, dual antiplatelet therapy is recommended for at least 1 year by the ACC/AHA PCI guidelines. These recommendations are based both on the durations of therapies during the studies evaluating the stents, and the pathophysiologic understanding of the timing of endothelialization following bare metal versus drugeluting stent implantation. The DAPT (dual antiplatelet therapy) study showed fewer death, myocardial infarction, and stroke events with longer (up to 30 months) dual antiplatelet therapy for patients who had received drug-eluting stents, but it also showed more bleeding and a tendency for higher mortality. Treatment with clopidogrel for longer than 1 year after drug-eluting stents, therefore, should be individualized based on thrombotic and bleeding risks.

2. Fibrinolytic therapy

A. Benefit—Fibrinolytic therapy reduces mortality and limits infarct size in patients with STEMI (defined as 0.1 mV or more in two inferior or lateral leads or two contiguous precordial leads), or with left bundle branch block (not known to be old). The greatest benefit occurs if treatment is initiated within the first 3 hours after the onset of presentation, when up to a 50% reduction in mortality rate can be achieved. The magnitude of benefit declines rapidly thereafter, but a 10% relative mortality reduction can be achieved up to 12 hours after the onset of chest pain. The survival benefit is greatest in patients with large—usually anterior— infarctions. Primary PCI (including stenting) of the infarctrelated artery, however, is superior to thrombolysis when done by experienced operators with rapid time from first medical contact to intervention (“door-to-balloon”).

B. Contraindications—Major bleeding complications occur in 0.5–5% of patients, the most serious of which is intracranial hemorrhage. The major risk factors for intracranial bleeding are age 75 years or older, hypertension at presentation (especially over 180/110 mm Hg), low body weight (less than 70 kg), and the use of fibrin-specific fibrinolytic agents (alteplase, reteplase, tenecteplase). Although patients over age 75 years have a much higher mortality rate with acute myocardial infarction and therefore may derive greater benefit, the risk of severe bleeding is also higher, particularly among patients with risk factors for intracranial hemorrhage, such as severe hypertension or recent stroke. Patients presenting more than 12 hours after the onset of chest pain may also derive a small benefit, particularly if pain and ST-segment elevation persist, but rarely does this benefit outweigh the attendant risk

Absolute contraindications to fibrinolytic therapy include previous hemorrhagic stroke, other strokes or cerebrovascular events within 1 year, known intracranial neoplasm, recent head trauma (including minor trauma), active internal bleeding (excluding menstruation), or suspected aortic dissection. **Relative contraindications** are BP greater than 180/110 mm Hg at presentation, other intracerebral pathology not listed above as a contraindication, known bleeding diathesis, trauma within 2–4 weeks, major surgery within 3 weeks, prolonged (more than 10 minutes) or traumatic cardiopulmonary resuscitation, recent (within 2–4 weeks) internal bleeding, noncompressible vascular punctures, active diabetic retinopathy, pregnancy, active peptic ulcer disease, a history of severe hypertension, current use of anticoagulants (INR greater than 2.0–3.0), and (for streptokinase) prior allergic reaction or exposure to streptokinase or anistreplase within 2 years.

C. Fibrinolytic agents

Alteplase (recombinant tissue plasminogen activator; t-PA) results in about a 50% reduction in circulating fibrinogen. In the first GUSTO trial, which compared a 90-minute dosing of t-PA (with unfractionated heparin) with streptokinase, the 30-day mortality rate with t-PA was one absolute percentage point lower (one additional life saved per 100 patients treated), though there was also a small increase in the rate of intracranial hemorrhage. An angiographic substudy confirmed a higher 90-minute patency rate and a higher rate of normal (TIMI grade 3) flow in patients.

Reteplase is a recombinant deletion mutant of t-PA that is slightly less fibrin specific. In comparative trials, it appeared to have efficacy similar to that of alteplase, but it has a longer duration of action and can be administered as two boluses 30 minutes apart.

Tenecteplase (TNK-t-PA) is a genetically engineered substitution mutant of native t-PA that has reduced plasma clearance, increased fibrin sensitivity, and increased resistance to plasminogen activator inhibitor-1. It can be given as a single weight-adjusted bolus. In the ASSENT 2 trial, this agent was equivalent to t-PA with regard to efficacy and resulted in significantly less noncerebral bleeding. **Streptokinase**, commonly used outside of the United States, is somewhat less effective at opening occluded arteries and less effective at reducing mortality. It is non–fibrin-specific, causes depletion of circulating fibrinogen, and has a tendency to induce hypotension, particularly if infused rapidly. This can be managed by slowing or interrupting the infusion and administering fluids. There is controversy as to whether adjunctive heparin is beneficial in patients given streptokinase, unlike its administration with the more clotspecific agents. Allergic reactions, including anaphylaxis, occur in 1–2% of patients, and this agent should generally not be administered to patients with prior exposure.

(1) Selection of a fibrinolytic agent—In the United States, most patients are treated with alteplase, reteplase, or tenecteplase. The differences in efficacy between them are small compared with the potential benefit of treating a greater proportion of appropriate candidates in a more prompt manner. The principal

objective should be to administer a thrombolytic agent within 30 minutes of presentation—or even during transport. The ability to administer tenecteplase as a single bolus is an attractive feature that may facilitate earlier treatment. The combination of a reduced-dose thrombolytic given with a platelet glycoprotein IIb/IIIa inhibitor does not reduce mortality but does cause a modest increase in bleeding complications.

(2) Postfibrinolytic management—After completion of the fibrinolytic infusion, aspirin (81–325 mg/day) and anticoagulation should be continued until revascularization or for the duration of the hospital stay (or up to 8 days). Anticoagulation with LMWH (enoxaparin or fondaparinux) is preferable to unfractionated heparin.

(a) Low-molecular-weight heparin—In the EXTRACT trial, enoxaparin significantly reduced death and myocardial infarction at day 30 (compared with unfractionated heparin), at the expense of a modest increase in bleeding. In patients younger than age 75, enoxaparin was given as a 30-mg intravenous bolus and 1 mg/kg subcutaneously every 12 hours; in patients age 75 years and older, it was given with no bolus and 0.75 mg/kg subcutaneously every 12 hours. This appeared to attenuate the risk of intracranial hemorrhage in the elderly that had been seen with full-dose enoxaparin. Another antithrombotic option is fondaparinux, given at a dose of 2.5 mg subcutaneously once a day. There is no benefit of fondaparinux among patients undergoing primary PCI, and fondaparinux is not recommended as a sole anticoagulant during PCI due to risk of catheter thrombosis.

(b) Unfractionated heparin—Anticoagulation with intravenous heparin (initial dose of 60 units/kg bolus to a maximum of 4000 units, followed by an infusion of 12 units/kg/h to a maximum of 1000 units/hour, then adjusted to maintain an aPTT of 50–75 seconds beginning with an aPTT drawn 3 hours after thrombolytic) is continued for at least 48 hours after alteplase, reteplase, or tenecteplase, and with continuation of an anticoagulant until revascularization (if performed) or until hospital discharge (or day 8).

(c) Prophylactic therapy against gastrointestinal bleeding—For all patients with STEMI treated with intensive antithrombotic therapy, prophylactic treatment with proton pump inhibitors, or antacids and an H2-blocker, is advisable, although certain proton pump inhibitors, such as omeprazole and esomeprazole, decrease the effect of clopidogrel.

3. Assessment of myocardial reperfusion, recurrent ischemic pain, reinfarction—Myocardial reperfusion can be recognized clinically by the early cessation of pain and the resolution of ST-segment elevation. Although at least 50% resolution of ST-segment elevation by 90 minutes may occur without coronary reperfusion, ST resolution is a strong predictor of better outcome. Even with anticoagulation, 10–20% of reperfused vessels will reocclude during hospitalization, although reocclusion and reinfarction appear to be reduced following intervention. Reinfarction, indicated by recurrence of pain and ST-segment elevation, can be treated by readministration of a thrombolytic agent or immediate angiography and PCI.

C. General Measures

Cardiac care unit monitoring should be instituted as soon as possible. Patients without complications can be transferred to a telemetry unit after 24 hours. Activity should initially be limited to bed rest but can be advanced within 24 hours. Progressive ambulation should be started after 24–72 hours if tolerated. For patients without complications, discharge by day 4 appears to be appropriate. Lowflow oxygen therapy (2–4 L/min) should be given if oxygen saturation is reduced.

D. Analgesia

An initial attempt should be made to relieve pain with sublingual nitroglycerin. However, if no response occurs after two or three tablets, intravenous opioids provide the most rapid and effective analgesia and may also reduce pulmonary congestion. Morphine sulfate, 4–8 mg, or meperidine, 50–75 mg, should be given. Subsequent small doses can be given every 15 minutes until pain abates. Nonsteroidal anti-inflammatory agents, other than aspirin, should be avoided during hospitalization for STEMI due to increased risk of mortality, myocardial rupture, hypertension, heart failure, and kidney injury with their use.

E. Beta-Adrenergic Blocking Agents

Trials have shown modest short-term benefit from betablockers started during the first 24 hours after acute myocardial infarction if there are no contraindications (metoprolol 25–50 mg orally twice daily). Aggressive betablockade can increase shock, with overall harm in patients with heart failure. Thus, early beta-blockade should be avoided in patients with any degree of heart failure, evidence of low output state, increased risk of cardiogenic shock, or other relative contraindications to beta-blockade. Carvedilol (beginning at 6.25 mg twice a day, titrated to 25 mg twice a day) was shown to be beneficial in the CAPRICORN trial following the acute phase of large myocardial infarction.

F. Nitrates

Nitroglycerin is the agent of choice for continued or recurrent ischemic pain and is useful in lowering BP or relieving pulmonary congestion. However, routine nitrate administration is not recommended, since no improvement in outcome has been observed in the ISIS-4 or GISSI-3 trials. Nitrates should be avoided in patients who received phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafil) in the prior 24 hours.

G. Angiotensin-Converting Enzyme (ACE)

Inhibitors A series of trials (SAVE, AIRE, SMILE, TRACE, GISSI-III, and ISIS-4) have shown both short- and long-term improvement in survival with ACE inhibitor therapy. The benefits are greatest in patients with an EF of 40% or less, large infarctions, or clinical evidence of heart failure. Because substantial amounts of the survival benefit occur on the first day, ACE inhibitor treatment should be commenced early in patients without hypotension, especially patients with large or

anterior myocardial infarction. Given the benefits of ACE inhibitors for patients with vascular disease, it is reasonable to use ACE inhibitors for all patients following STEMI who do not have contraindications.

H. Angiotensin Receptor Blockers

Although there has been inconsistency in the effects of different ARBs on mortality for patients post-myocardial infarction with heart failure and/or LV dysfunction, the VALIANT trial showed that valsartan 160 mg orally twice a day is equivalent to captopril in reducing mortality. Thus, valsartan should be used for all patients with ACE inhibitor intolerance, and is a reasonable, albeit more expensive, alternative to captopril. The combination of captopril and valsartan (at a reduced dose) was no better than either agent alone and resulted in more side effects.

I. Aldosterone Antagonists

The RALES trial showed that 25 mg spironolactone can reduce the mortality rate of patients with advanced heart failure, and the EPHESUS trial showed a 15% relative risk reduction in mortality with eplerenone 25 mg daily for patients post-myocardial infarction with LV dysfunction (LVEF of 40% or less) and either clinical heart failure or diabetes. Kidney dysfunction or hyperkalemia are contraindications, and patients must be monitored carefully for development of hyperkalemia.

J. Calcium Channel Blockers

There are no studies to support the routine use of calcium channel blockers in most patients with acute myocardial infarction—and indeed, they *have the potential to exacerbate ischemia* and *cause death* from reflex tachycardia or myocardial depression. Long-acting calcium channel blockers should generally be reserved for management of hypertension or ischemia as second- or third-line drugs after beta-blockers and nitrates.

K. Long-Term Antithrombotic

Therapy Discharge on aspirin, 81–325 mg/day, since it is highly effective, inexpensive, and well tolerated, is a key quality indicator of myocardial infarction care. Patients who received a coronary stent should also receive a P2Y12 inhibitor (see Antiplatelet therapy after drug-eluting or bare metal stents, above).

Patients who have received a coronary stent and who require warfarin anticoagulation present a particular challenge, since “triple therapy” with aspirin, clopidogrel, and warfarin has a high risk of bleeding. Triple therapy should be (1) limited to patients with a clear indication for warfarin (such as *CHADS2* score of 2 or more or a mechanical prosthetic valve), (2) used for the shortest period of time (such as 1 month after placement of bare metal stent; drugeluting stents that would require longer clopidogrel duration should be avoided if possible), (3) used with low-dose aspirin and with strategies to reduce risk of bleeding (eg, proton pump inhibitors for patients with a history of gastrointestinal bleeding), and (4) used with consideration of a lower target anticoagulation intensity (INR 2.0 to 2.5, at least for

the indication of atrial fibrillation) during the period of concomitant treatment with aspirin and P2Y12 therapy. Several ongoing studies are evaluating the NOACs in this area.

L. Coronary Angiography

For patients who do not reperfuse based on lack of at least 50% resolution of ST elevation, rescue angioplasty should be performed and has been shown to reduce the composite risk of death, reinfarction, stroke, or severe heart failure. According to the evidence in the 2012 European and ACC/ AHA guidelines, patients treated with coronary angiography and PCI 3–24 hours after fibrinolytic therapy showed improved outcomes. Patients with recurrent ischemic pain prior to discharge should undergo catheterization and, if indicated, revascularization. PCI of a totally occluded infarct-related artery more than 24 hours after STEMI should generally not be performed in asymptomatic patients with one or two vessel disease without evidence of severe ischemia.

When to Refer

All patients with acute myocardial infarction should be referred to a cardiologist.

Complications

A variety of complications can occur after myocardial infarction even when treatment is initiated promptly.

Postinfarction Ischemia

In clinical trials of thrombolysis, recurrent ischemia occurred in about one-third of patients, was more common following non–ST elevation myocardial infarction than after STEMI, and had important short- and long-term prognostic implications. Vigorous medical therapy should be instituted, including nitrates and beta-blockers as well as aspirin 81–325 mg/day, anticoagulant therapy (unfractionated heparin, enoxaparin, or fondaparinux) and clopidogrel (75 mg orally daily). Most patients with postinfarction angina—and all who are refractory to medical therapy—should undergo early catheterization and revascularization by PCI or CABG.

Arrhythmias:

- Abnormalities of rhythm and conduction are common
- Sinus bradycardia
- Supraventricular tachyarrhythmias
- Ventricular arrhythmias
- Conduction disturbances

Myocardial Dysfunction

- ***Acute LV failure***
- ***Hypotension and shock***

RV Infarction

Mechanical Defects

Myocardial Rupture
LV Aneurysm
Pericarditis
Mural Thrombus

Postinfarction Management

After the first 24 hours, the focus of patient management is to prevent recurrent ischemia, improve infarct healing and prevent remodeling, and prevent recurrent vascular events. Patients with hemodynamic compromise, who are at high risk for death, need careful monitoring and management of volume status.

A. Risk Stratification

Risk stratification is important for the management of STEMI. GRACE and TIMI risk scores can be helpful tools. The GRACE risk score is available for web access and/or PDA download at http://gracescore.org, and the TIMI Risk Score is available at http://www.timi.org. Patients with recurrent ischemia (spontaneous or provoked), hemodynamic instability, impaired LV function, heart failure, or serious ventricular arrhythmias should undergo cardiac catheterization. ACE inhibitor (or ARB) therapy is indicated in patients with clinical heart failure or LVEF of 40% or less. Aldosterone blockade is indicated for patients with an LVEF of 40% or less and either heart failure or diabetes mellitus.

For patients not undergoing cardiac catheterization, submaximal exercise (or pharmacologic stress testing for patients unable to exercise) before discharge or a maximal test after 3–6 weeks (the latter being more sensitive for ischemia) helps patients and clinicians plan the return to normal activity. Imaging in conjunction with stress testing adds additional sensitivity for ischemia and provides localizing information. Both exercise and pharmacologic stress imaging have successfully predicted subsequent outcome. One of these tests should be used prior to discharge in patients who have received thrombolytic therapy as a means of selecting appropriate candidates for coronary angiography

B. Secondary Prevention

Postinfarction management should begin with identification and modification of risk factors. Treatment of hyperlipidemia and smoking cessation both prevent recurrent infarction and death. Statin therapy should be started before the patient is discharged from the hospital to reduce recurrent atherothrombotic events. BP control and cardiac rehabilitation or exercise are also recommended. Beta-blockers improve survival rates, primarily by reducing the incidence of sudden death in high-risk subsets of patients, though their value may be less in patients without complications with small infarctions and normal exercise tests. While a variety of beta-blockers have been shown to be beneficial, for patients with LV dysfunction managed with contemporary treatment, carvedilol titrated to 25 mg orally twice a day has been shown to reduce mortality. Beta-blockers with intrinsic sympathomimetic activity have not proved beneficial in postinfarction patients. Antiplatelet agents are beneficial; aspirin (81–325 mg daily, with 81 mg daily the

preferred long-term dose) is recommended, and adding clopidogrel (75 mg daily) has been shown to provide additional short-term benefit after STEMI. Prasugrel provides further reduction in thrombotic outcomes compared with clopidogrel, at the cost of more bleeding. Likewise, ticagrelor provides benefit over clopidogrel but should be used with low-dose aspirin (81 mg/day). Warfarin anticoagulation for 3 months reduces the incidence of arterial emboli after large anterior infarctions and, according to the results of at least one study, it improves long-term prognosis; however, these studies were done before the routine use of aspirin and clopidogrel. An advantage to combining low-dose aspirin and warfarin has not been demonstrated, except perhaps in patients with atrial fibrillation. Calcium channel blockers have not been shown to improve prognoses overall and should not be prescribed purely for secondary prevention. Antiarrhythmic therapy other than with beta-blockers has not been shown to be effective except in patients with symptomatic arrhythmias. Amiodarone has been studied in several trials of postinfarct patients with either LV dysfunction or frequent ventricular ectopy. Although survival was not improved, amiodarone was not harmful—unlike other agents in this setting. Therefore, it is the agent of choice for individuals with symptomatic postinfarction supraventricular arrhythmias. While implantable defibrillators improve survival for patients with postinfarction LV dysfunction and heart failure, the DINAMIT trial found no benefit to implantable defibrillators implanted in the 40 days following acute myocardial infarction. Cardiac rehabilitation programs and exercise training can be of considerable psychological benefit and appear to improve prognosis.

C. ACE Inhibitors and ARBs in Patients with LV Dysfunction

Patients who sustain substantial myocardial damage often experience subsequent progressive LV dilation and dysfunction, leading to clinical heart failure and reduced long-term survival. In patients with EFs less than 40%, long-term ACE inhibitor (or ARB) therapy prevents LV dilation and the onset of heart failure and prolongs survival. The HOPE trial, as well as an overview of trials of ACE inhibitors for secondary prevention, also demonstrated a reduction of approximately 20% in mortality rates and the occurrence of nonfatal myocardial infarction and stroke with ramipril treatment of patients with coronary or peripheral vascular disease and without confirmed LV systolic dysfunction. Therefore, ACE inhibitor therapy should be strongly considered in this broader group of patients—and especially in patients with diabetes and those with even mild systolic hypertension, in whom the greatest benefit was observed.

D. Revascularization

Postinfarction patients not treated with primary PCI who appear likely to benefit from early revascularization with CABG if the anatomy is appropriate are (1) those who have undergone fibrinolytic therapy, especially if they have highrisk features (including systolic BP of less than 100 mm Hg, heart rate of greater than 100 bpm, Killip class II or III, and ST-segment depression of 2 mm or more in the

anterior leads); (2) patients with LV dysfunction (EF less than 30–40%); (3) patients with NSTEMI and high-risk features; and (4) patients with markedly positive exercise tests and multi-vessel disease. The value of revascularization in patients not treated with acute reperfusion therapy with preserved LV function who have mild ischemia and are not symptom limited is less clear. In general, patients without high-risk features who survive infarctions without complications, have preserved LV function (EF greater than 50%), and have no exercise-induced ischemia have an excellent prognosis and do not require invasive evaluation.

Control questions

1. Anatomical and physiological features of the heart.
2. Etiology of ischemic heart disease.
3. Major complaints, symptoms and research in CHD.
4. Basic pathogetic factors of development of coronary artery disease.
5. Classification and pharmacotherapy of coronary artery disease.
6. Etiology and pathogenesis of angina pectoris.
7. Clinical picture of angina pectoris.
8. Etiology, pathogenesis of stable and unstable (progressive) angina.
9. Principles of complex therapy of myocardial infarction ..
10. Etiology and pathogenesis of atherosclerosis. The notion of dislipoproteinemia.
11. Directions of pharmacotherapy of atherosclerosis. Major groups of hypolipidemic drugs.
12. Write in the recipes and write testimony to the use of such drugs: acetylsalicylic acid, nitroglycerin, cardiot, nifedipine, verapamil, amlodipine, propranolol, sinodofarm, heparin, atenolol, fraxiparin, thiotriazolin, atorvastatin, phenofibrate, captopril, enalapril, hydrochlorothiazide, furosemide .

List of practical works

A. Homework.

1. To study the etiology, pathogenesis of coronary heart disease.
2. To know the classification of CHD and clinical picture.
3. Be able to provide first aid with pain attacks in the area of the heart.
4. To study the main areas of treatment of coronary artery disease.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the working history of the disease (data laboratory-instrumental studies, conclusions of consultants) and a letter of medical appointments.
3. To write a protocol of independent work on the selection and selection of the examined patient of the basic drug and justify the appointment of combined

medical therapy.
4. To distinguish signs in the subjective and objective study of the patient, characterizing the leading clinical syndromes of angina, to write a clinical diagnosis of the disease.
5. Define a group of drugs required by the patient.
6. On the basis of theoretical data of pharmacodynamics and own observations, choose the drug of the examined patient.
7. To substantiate duration of basic and maintenance therapy.
8. Make a plan for urgent medical assistance in the case of an attack of angina pectoris.

Control the level of knowledge

1. Fill in the table "Basic areas of pharmacotherapy of coronary heart disease".

Directions of pharmacotherapy	Pharmacotherapeutic groups of medicines	Medicines
1. Increase the delivery of oxygen to the heart muscle 2. Reduce the need for myocardium in oxygen 3. Improve the rheological properties of the blood 4. Reduce lipid peroxide oxidation processes		

2. Fill in the table "Pharmacotherapy of Dislipoproteinemia".

Pharmacotherapeutic groups of medicines	The mechanism of action	Medicines
Statins Fibrate Sequestrants of bile acids Nicotinic acid Omega-3		

3. Fill in the table " Medicines for the treatment of coronary heart disease".

Pharmacotherapeutic groups of medicines	Medicines, route of administration, dose	Possible replacements medicines

Antianginal drugs: 1) Nitrates: to treat an attack to prevent an attack buccal form transdermal form aerosol form 2) Calcium channel blockers: phenylalkylamine, benzothiazepine, dihydropyridine 3) beta-blockers: - noncardioselectomy - cardioselective 4) Antiagregants 5) Means of metabolic correction		

Solution of situational tasks

1. In a man 65 years of age, suffering from coronary artery disease, stable angina pectoris III functional class, extrasystolic arrhythmia, CH I - a strong, burning nature of pain in the sternum, suffocation, loss of consciousness arose. Objectively, the general condition is heavy. The skin is pale, covered with abundant cold sweat, pronounced acrocyanosis. Pulse -140 ud for 1 min by type of flashing tachyarrhythmia, AT- 70/40 mm Hg. Art. The tones of the heart are deaf. Anury.

Formulate a diagnosis and an emergency treatment program. Justify the choice of drugs

2. A man, 48 years old, is concerned about the compressive nature of the pain behind the sternum, which occurs when walking on a flat terrain through 500 - 800 m, with a rise to 2 -3, after nervous loads. The indicated attacks are observed within 3 months. I resorted to sublingual administration of nitroglycerin, but refused to further use, since it caused a severe headache. Objectively, hypertensin increased eating. Pulse - 76 beats per minute, rhythmic, periodic extrasystoles - 2-4 per 1 min., AT - 136/84. mm Hg Art. Left ventricular hypertrophy. Weak accent II tone and systolic noise above the aorta. On the ECG signs of myocardial hypoxia in the periosterotomy of the left ventricle. The doctor prescribed the following treatment: isodinitis (20 mg) by 1 tabl. 3 times a day, finetine (80 mg) per 1 tablet. 3 times a day and anaprilin (40 mg) by 0.5 tabl. 3 times a day.

Formulate the diagnosis. Check the correctness of the recommended treatment.

3. The patient, 62 years old, was hospitalized with complaints of severe pain for the sternum, which lasted for 1 hour and was not removed by nitroglycerin. He suffers from angina, the previous treatment was treated with nitrates. There are no

concomitant diseases. Objectively: cyanosis of the lips. Tons of heart are deaf, rhythmic activity. ECG: Acute phase of transmural infarction of the anterior wall of the left ventricle.

Your actions?

4. A man, 62 years old, was hospitalized in an intensive care unit with a long onset of relapsing pain, which is not withdrawn by the administration of nitroglycerin. Objectively: AT - 80/60 mm Hg. st., heart rate - 106 for 1 min, MD - 22 for 1 min. During auscultation, the tones of the heart are deaf, the rhythm of the gallop.

What is the decrease in blood pressure?

5. A man, 60 years old, complains of angina attacks while walking, ascending to the second floor. Many years suffering from coronary heart disease. Objectively in the lungs vesicular respiration, BD - 18 per min. Heart tones are muffled. Heart rate - coincides with the size of the pulse and is 90 for 1 min, blood pressure - 140/70 mm Hg. st., legs pastos. On ECG: left ventricular hypertrophy.

Formulate the diagnosis. Make a plan of treatment.

6. A man, 52, complains of angina attacks that occur when walking at a distance of 500 meters, heart failure. Ill sick about a year. Objectively: BH 16 for 1 min. The borders of the heart are displaced by 1 cm to the left, the tones are muffled, heart rate - 84 for 1 min, single extrasystoles, pulse - 78 per min, AT - 150/70 mm Hg. Art.

Formulate the diagnosis. Make a plan of treatment. Which drugs are shown to improve the long-term outlook?

7. A man, 47 years old, in the pre-war time, there are angina pectoris attacks. At the time of Holter monitoring, the arcuate shift of the ST segment upwards in the chest leads, which is stored for 15 minutes. Objectively: tones of the heart muffled, heart rate - 64 per min, AT - 140/80 mm Hg. Art.

Formulate the diagnosis. Which drug is appropriate to appoint?

8. A patient, 48 years old, is disturbed by compressive pain in the area of the heart and behind the sternum, which occurs when walking at a distance of 150-200 m and ascents to the 2nd floor and disappears in a state of rest. Pulse and heart rate constant 50-52 per minute, AT - 120/70 mm Hg. Art. On ECG sinus rhythm is correct. On veloergometry - ischemic changes on the ECG at a voltage of 40 W.

Which drug should be prescribed to the patient in the first place?

9. A patient, 62 years old, felt severe pain in the sternum, shortness of breath. Objectively: the patient is pale, wet, acrocyanosis. BH - 28 for 1 min, orthopneum. AT - 100/60 mm Hg. Art. In the lungs on both sides, moist rattles. At ECG: heart rate - 240 per min, the tooth P is not determined, R-R is the same and is 0.25 s, QRS - 0.18 s, in leads V5 - V6 arcuate depression of segment ST up to 3 mm.

Formulate the diagnosis. Suggest the most effective tactics for the management of this patient.

10. A patient, aged 50, complains of an unbearable pain in the sternum that appeared 5 minutes ago. The pain appears 1-2 times a month, more often between 5 and 6 o'clock in the morning, lasts 15-20 minutes. During the day it feels healthy. Objectively: pulse - 78 beats per minute, AT - 120/80 mm Hg. Art. The limits of the heart are not changed. Tones are rhythmic. No ECG changes recorded at rest and after loading. At night, during the attack, a short-term increase in the ST segment in leads I, aVL, V2-V6 was recorded.

What drug should be prescribed to treat an attack?

11. A man, 60 years old, complains about headaches, dizziness, head noise, the absence of night sleep, nausea in the morning, vision impairment, pain in the area of the heart of angina pectoris after 50-100 m walking, with a rise to the 2 nd floor, shortness of breath at physical activity, interruptions in the activity of the heart. Anamnesis suffers from hypertension for 30 years. Maximum blood pressure - 200/140 mm Hg. Art., working - 160/120 mm Hg. Art. Five years ago, suffered a myocardial infarction, two years ago - a sharp violation of cerebral circulation in the basin of the middle cerebral artery. Objectively: a general condition of moderate severity. Cyanosis of the lips. Left-side pyramidal insufficiency Pulse 84 beats per minute, arrhythmic type of extrasystolic arrhythmia (6-10 for 1 min), solid. AT - 84/136 mm Hg. Art. Left ventricular hypertrophy. Accent II tone and systolic noise over the aorta. Above the breath is vesicular, crepitation. Abdomen is soft, painless. The liver is 2 cm protruding from below the edge of the articular region along the right midlectric line. No edema.

Formulate the diagnosis. Conduct a selection of drugs. Make a combination therapy program. Give her a clinical and pharmacological justification.

Test decisions

1. A patient 52 years old, suffering from coronary heart disease, stable angina pectoris. What is recommended to appoint in order to interrupt angina attacks, if from nitroglycerin there is an unbearable headache?

A. Corvaton (molsidomin).
B. Isosorbite 5-mononitrate.
C. Anaprilin.
D. Apresin.
E. Nifedipine

2. In the clinical examination of a patient suffering from hypertension in the course of 20 years, found: dyspnea, palpitation, cyanosis, wheezing in the lungs. These symptoms indicate:

A. On the development of heart failure.
B. About the development of hypertensive crisis.
C. About the development of myocardial infarction.
D. About the development of concomitant pneumonia.
E. About the development of heart rhythm abnormalities.

3. The patient suffers from coronary heart disease and arterial hypertension. Which of the following drug groups is most appropriate in this case?

A. Alpha-blockers.
B. Nitrates.
C. Diuretics.
D. Myotropic antispasmodics.
E. Beta-adrenoblockers.

4. For the appointment of a regular doctor to the patient for 25 years in order to treat the attack of angina was injected intramuscularly solution 50% analginin 2 ml, after which the patient developed anaphylactic shock, resulting in the patient died. What should a doctor do to prevent the side effects of the drug?

A. Carry out a patient's review.
B. To measure arterial pressure.
C. Specify patient complaints.
D. Assemble a medical (allergic) anamnesis.
E. Ask about concomitant diseases.

5. Patient Yu., Who suffered a myocardial infarction, was discharged to outpatient supervision. What dose of acetylsalicylic acid should be prescribed to the patient in order to prevent thrombosis?

A. 2000 mg per day.
B. 100 mg.
C. 3000 mg per day.
D. 1000 mg per day.
E 500 mg per day.

6. **The upper limit of the norm of the total cholesterol content in blood plasma is:**

1. 3.2 mmol/l.
2. 4.2 mmol/L.
3. 5.2 mmol/L.
4. 6.2 mmol L.

5. 7.2 mmol/L

7. For the treatment of coronary artery disease, different groups of drugs are used. Among them are the main and auxiliary. From the list below, select the main (basic) anti-anginal medications:

1. Hypolipidemic means.
2. Myotropic antispasmodics.
3. Beta-adrenoblockers.
4. Anticoagulants.
5. Antiagregants.

8. A 62-year-old man appealed to the pharmacy with complaints of an overloaded pain of compression with irradiation under the left shoulder blade. The patient can be recommended:

1. Nitrogranulong internally.
2. Nitroglycerin sublingual.
3. Analgin inside.
4. Sustack-forte internally.
5. No-shpa inside.

9. Features of inhalation forms of nitroglycerin are:

1. A faster hemodynamic effect.
2. Less bioavailability of the drug.
3. High bioavailability of the drug.
4. Fewer side effects.
5. Most of the side effects.

10. Patients with high levels of total cholesterol and low density lipoprotein have the most appropriate recommendation:

1.Probukol.
2. Cholesterol.
3. Lipanor.
4. Lovostatin.
5.Aspirin.

11. Patients with high levels of triglycerides in blood should be advised most:

1.Probukol.
2. Cholesterol.
3. Lipanor.
4.Atorivastatin

5.Aspirin.

12. Antianginal drugs include:

1.Papaverin
2. Dipyridamol.
3.Enalapril.
4.Validol.
5.Nitrosorbide.

13. Factors for the development of coronary artery disease are all of the following, except:

1. Hypercholesterolemia.
2. Arterial hypertension.
3. Smoking
4. Female sex.
5. Diabetes mellitus.

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TOPIC 6. Types of violations of heart rate and conduction, principles of pharmacotherapy. Acute and chronic heart failure, principles of pharmacotherapy.

Actuality of the topic: To learn the etiopathogenetic factors of chronic and acute heart failure, requirements for drugs used for the treatment of acute and chronic heart failure. The student should have the concept of mechanical functions of the heart, the main etiopathogenetic mechanisms of the formation and progression of heart failure; diagnostic methods, clinical symptoms, principles of pharmacotherapy.

Cardiac arrhythmias are abnormalities in the frequency, rhythm and sequence of abnormalities in the cardiac organs, which can lead to a reduction in the duration and quality of life. Arrhythmias arise as a result of noticeable structural changes in the conduction system in any heart disease and (or) under the influence of diseases of the nervous, endocrine, and others. systems. For the treatment of arrhythmias, antiarrhythmic drugs are used.

Purpose of the lesson. The student should know the etiopathogenetic factors of cardiac arrhythmias, the lectophysiological functions of the heart, types of cardiac rhythm and conduction disorders; pathogenesis, diagnostic methods, clinical manifestations of the most common cardiac arrhythmias; principles of pharmacotherapy.

Know the drugs used to treat acute and chronic heart failure. Circulatory insufficiency is a pathological condition in which the cardiovascular system is not able to deliver the necessary amount of blood to organs and tissues for their normal activity in rest or in physical and emotional stresses. To date, tactics of such patients have changed in many respects. There were cardiotonics of non-glycoside structure, new classes of cardiotropic drugs.

DISORDERS OF RATE & RHYTHM

Abnormalities of cardiac rhythm and conduction can be symptomatic (syncope, near syncope, dizziness, fatigue, or palpitations), or asymptomatic. In addition, they can be lethal (sudden cardiac death) or dangerous to the extent that they reduce cardiac output so that perfusion of the brain and myocardium is impaired. Stable supraventricular tachycardia is generally well tolerated in patients without underlying heart disease but may lead to myocardial ischemia or heart failure in patients with coronary disease, valvular abnormalities, and systolic or diastolic myocardial dysfunction. Ventricular tachycardia, if prolonged (lasting more than 10–30 seconds), often results in hemodynamic compromise and may deteriorate into ventricular fibrillation if left untreated.

Whether slow heart rates produce symptoms at rest or with exertion depends

on whether cerebral and peripheral perfusion can be maintained, which is generally a function of whether the patient is upright or supine and whether LV function is adequate to maintain stroke volume. If the heart rate abruptly slows, as with the onset of complete heart block or sinus arrest, syncope or convulsions (or both) may result.

Arrhythmias are detected either because they produce symptoms or because they are detected during the course of monitoring. Arrhythmias causing sudden death, syncope, or near syncope require further evaluation and treatment unless they are related to conditions that are reversible or immediately treatable (eg, electrolyte abnormalities or acute myocardial infarction). In contrast, there is controversy over when and how to evaluate and treat rhythm disturbances that are not symptomatic but are possible markers for more serious abnormalities (eg, nonsustained ventricular tachycardia [NSVT]). This uncertainty reflects two issues: (1) the difficulty of reliably stratifying patients into high-risk and low-risk groups; and (2) the lack of treatments that are both effective and safe. Thus, screening patients for these so-called "premonitory" abnormalities is often not productive.

A number of procedures are used to evaluate patients with symptoms who are believed to be at risk for lifethreatening arrhythmias, including in-hospital and ambulatory ECG monitoring, event recorders (instruments that can be used for prolonged periods to record or transmit rhythm tracings when infrequent episodes occur), exercise testing, catheter-based electrophysiologic studies (to assess sinus node function, AV conduction, and inducibility of arrhythmias), and tests of autonomic nervous system function (tilt-table testing).

Treatment of arrhythmias varies and can include modalities such as antiarrhythmic drugs and more invasive techniques, such as catheter ablation.

Antiarrhythmic Drugs

Antiarrhythmic drugs are frequently used to treat arrhythmias, but they have variable efficacy and produce frequent side effects. They are often divided into classes based on their electropharmacologic actions, and many of these drugs have multiple actions. The most frequently used ***classification scheme*** is the Vaughan-Williams, which consists of four ***classes***.

Class I agents block membrane sodium channels. Three subclasses are further defined by the effect of the agents on the Purkinje fiber action potential.

Class Ia drugs (ie, quinidine, procainamide, disopyramide) slow the rate of rise of the action potential (Vmax) and prolong its duration, thus slowing conduction and increasing refractoriness (moderate depression of phase 0 upstroke of the action potential).

Class Ib agents (ie, lidocaine, mexiletine) shorten action potential duration; they do not affect conduction or refractoriness (minimal depression of phase 0 upstroke of the action potential).

Class Ic agents (ie, flecainide, propafenone) prolong Vmax and slow repolarization, thus slowing conduction and prolonging refractoriness, but more so than class Ia drugs (maximal depression of phase 0 upstroke of the action potential).

Class II agents are the beta-blockers, which decrease automaticity, prolong AV conduction, and prolong refractoriness.

Class III agents (ie, amiodarone, dronedarone, sotalol, dofetilide, ibutilide) block potassium channels and prolong repolarization, widening the QRS and prolonging the QT interval. They decrease automaticity and conduction and prolong refractoriness. Dronedarone has been shown to reduce cardiovascular hospitalizations when used in patients with paroxysmal atrial fibrillation in the absence of heart failure; however, the PALLAS trial found an increase in cardiovascular events when dronedarone was used in patients with permanent atrial fibrillation.

Class IV agents are the calcium channel blockers, which decrease automaticity and AV conduction.

There are some antiarrhythmic agents that do not fall into one of these categories. The most frequently used are digoxin and adenosine. Digoxin inhibits the Na+, K+- ATPase pump. Digoxin prolongs AV nodal conduction and the AV nodal refractory period, but it shortens the action potential and decreases the refractoriness of the ventricular myocardium and Purkinje fibers. Adenosine can block AV nodal conduction and shortens atrial refractoriness.

Although the in vitro electrophysiologic effects of most of these agents have been defined, their use remains largely empiric. All can exacerbate arrhythmias (proarrhythmic effect), and many depress LV function.

The risk of antiarrhythmic agents has been highlighted by many studies, most notably the Coronary Arrhythmia Suppression Trial (CAST), in which two class Ic agents (flecainide, encainide) and a class Ia agent (moricizine) increased mortality rates in patients with asymptomatic ventricular ectopy after myocardial infarction. A similar result has been reported in the Mortality in the Survival With Oral D-sotalol (SWORD) study with d-sotalol, a class III agent without the beta-blocking activity of the currently marketed formulation d,l-sotalol. Class 1c antiarrhythmic agents should therefore not be used in patients with prior myocardial infarction or structural heart disease.

The use of antiarrhythmic agents for specific arrhythmias is discussed below.

Catheter Ablation for Cardiac Arrhythmias

Catheter ablation has become the primary modality of therapy for many symptomatic supraventricular arrhythmias, including AV nodal reentrant tachycardia, tachycardias involving accessory pathways, paroxysmal atrial tachycardia, and atrial flutter. Catheter ablation of atrial fibrillation is more complex and usually involves complete electrical isolation of the pulmonary veins (which are often the sites of initiation of atrial fibrillation) or placing linear lesions within the atria to prevent propagation throughout the atrial chamber. This technique is currently considered a reasonable second-line therapy (after pharmacologic treatment) for certain patients with symptomatic drug-refractory atrial fibrillation. Catheter ablation of ventricular arrhythmias has proved more difficult, but experienced centers have demonstrated reasonable success with all types of ventricular tachycardias including bundlebranch reentry, tachycardia

originating in the ventricular outflow tract or papillary muscles, tachycardias originating in the specialized conduction system (fascicular ventricular tachycardia), and ventricular tachycardias occurring in patients with ischemic or dilated cardiomyopathy. Ablation of many of these arrhythmias can be performed from the endocardial surface via endovascular catheter placement or on the epicardial surface of the heart via a percutaneous subxiphoid approach.

Catheter ablation has also been successfully performed for the treatment of ventricular fibrillation when a uniform premature ventricular contraction (PVC) can be identified. In addition, patients with symptomatic PVCs or PVCs occurring at a high enough burden to result in a cardiomyopathy (usually more than 10,000/day) are often referred for catheter ablation as well.

Catheter ablation procedures are generally safe, with an overall major complication rate ranging from 1% to 5%. Major vascular damage during catheter insertion occurs in less than 2% of patients. There is a low incidence of perforation of the myocardial wall resulting in pericardial tamponade. Sufficient damage to the AV node to require permanent cardiac pacing occurs in less than 1% of patients. When transseptal access through the interatrial septum or retrograde LV catheterization is required, additional potential complications include damage to the heart valves, damage to a coronary artery, or systemic emboli. A rare but potentially fatal complication after catheter ablation of atrial fibrillation is the development of an atrioesophageal fistula resulting from ablation on the posterior wall of the LA just overlying the esophagus, estimated to occur in less than 0.1% of procedures.

SINUS ARRHYTHMIA, BRADYCARDIA, & TACHYCARDIA

Sinus arrhythmia is a cyclic increase in normal heart rate with inspiration and decrease with expiration. It results from reflex changes in vagal influence on the normal pacemaker and disappears with breath holding or increase of heart rate. It is common in both the young and the elderly and is not a pathologic arrhythmia.

Sinus bradycardia is a heart rate slower than 60 beats/min due to increased vagal influence on the normal pacemaker or organic disease of the sinus node. The rate usually increases during exercise or administration of atropine. In healthy individuals, and especially in patients who are in excellent physical condition, sinus bradycardia to rates of 50 beats/min or even lower is a normal finding. However, severe sinus bradycardia (less than 45 beats/min) may be an indication of sinus node pathology (see below), especially in elderly patients and individuals with heart disease. It may cause weakness, confusion, or syncope if cerebral perfusion is impaired. Atrial, junctional, and ventricular ectopic rhythms are more apt to occur with slow sinus rates. Pacing may be required if symptoms correlate with the bradycardia.

Sinus tachycardia is defined as a heart rate faster than 100 beats/min that is caused by rapid impulse formation from the sinoatrial node; it occurs with fever, exercise, emotion, pain, anemia, heart failure, shock, thyrotoxicosis, or in response to many drugs. Alcohol and alcohol withdrawal are common causes of sinus tachycardia and other supraventricular arrhythmias. The onset and termination are

usually gradual, in contrast to paroxysmal supraventricular tachycardia due to reentry. The rate infrequently exceeds 160 beats/min but may reach 180 beats/min in young persons. The rhythm is generally regular, but serial 1-minute counts of the heart rate indicate that it varies five or more beats per minute with changes in position, with breath holding, or with sedation. In rare instances, otherwise healthy individuals may present with “inappropriate” sinus tachycardia where persistently elevated basal heart rates are not in-line with physiologic demands. Long-term consequences of this disorder are few. While the exact mechanism underlying “inappropriate” sinus tachycardia is unclear, pharmacologic agents, such as beta-blockers or ivabradine (which selectively blocks the If current within the sinus node), have been shown to have varying success in improving symptoms. Catheter ablation aimed at modifying the sinus node to lower mean heart rate has been reported; however, recurrence rates are high.

When to Refer

Patients with symptoms related to bradycardia or tachycardia when reversible etiologies have been excluded.

When to Admit

Patients with bradycardia and recent or recurrent syncope.

ATRIAL PREMATURE BEATS (Atrial Extrasystoles)

ESSENTIALS OF DIAGNOSIS

- Usually asymptomatic.
- Isolated interruption in regular rhythm.
- P-wave morphology on ECG usually differs from sinus P-wave morphology.
- Can be harbinger of future development of atrial fibrillation.

Atrial premature beats occur when an ectopic focus in the atria fires before the next sinus node impulse. The contour of the P wave usually differs from the patient’s normal complex, unless the ectopic focus is near the sinus node. Such premature beats occur frequently in normal hearts. Acceleration of the heart rate by any means usually abolishes most premature beats. Early atrial premature beats may cause aberrant QRS complexes (left or right bundle branch block) or may not be conducted to the ventricles because the AV node or ventricles are still refractory.

The distinction between aberrantly conducted supraventricular beats from ventricular beats is difficult in patients with a wide QRS complex; it is important because of the differing prognostic and therapeutic implications of each type. Findings favoring a ventricular origin include (1) AV dissociation; (2) a QRS duration exceeding 0.14 second; (3) capture or fusion beats (infrequent); (4) left axis deviation with right bundle branch block morphology; (5) monophasic (R) or biphasic (qR, QR, or RS) complexes in V1 ; and (6) a qR or QS complex in V6 . Supraventricular origin is favored by (1) a triphasic QRS complex, especially with initial negativity in leads I and V6 ; (2) ventricular rates exceeding 170 beats/min;

(3) QRS duration longer than 0.12 second but not longer than 0.14 second; and (4) the presence of preexcitation syndrome.

The relationship of the P waves to the tachycardia complex is helpful. A 1:1 relationship usually means a supraventricular origin, except in the case of ventricular tachycardia with retrograde atrial activation. Treatment of this arrhythmia is rarely indicated.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Frequently associated with palpitations.
- Abrupt onset/offset.
- Rapid, regular rhythm.
- Most commonly seen in young adults.
- Rarely causes syncope.
- Usually have a narrow QRS complex on ECG.
- Often responsive to vagal maneuvers, AV nodal blockers, or adenosine.

General Considerations

This is a common paroxysmal tachycardia and often occurs in patients without structural heart disease. The most common mechanism for paroxysmal supraventricular tachycardia is reentry, which may be initiated or terminated by a fortuitously timed atrial or ventricular premature beat. The reentrant circuit most commonly involves dual pathways (a slow and a fast pathway) within the AV node. This is referred to as AV nodal reentrant tachycardia (AVNRT). Less commonly, reentry is due to an accessory pathway between the atria and ventricles, referred to as atrioventricular reciprocating tachycardia (AVRT). Approximately one-third of patients with supraventricular tachycardia have accessory pathways to the ventricles. The pathophysiology and management of arrhythmias due to accessory pathways differ in important ways and are discussed separately below.

Clinical Findings

A. Symptoms and Signs

Patients may be asymptomatic except for awareness of rapid heart action, but some experience mild chest pain, shortness of breath, diaphoresis, or lightheadedness, especially when episodes are prolonged, even in the absence of associated cardiac abnormalities. Episodes begin and end abruptly and may last a few seconds to several hours or longer.

B. ECG

The heart rate may be 140–240 beats/min (usually 160–220 beats/min) and is regular (despite exercise or change in position). The P wave usually differs in contour from sinus beats and is often buried in the QRS complex.

Treatment

In the absence of structural heart disease, serious effects are rare, and most episodes resolve spontaneously. Particular effort should be made to terminate the episode quickly if cardiac failure, syncope, or anginal pain develops or if there is underlying cardiac or (particularly) coronary disease. Because reentry is the most common mechanism for paroxysmal supraventricular tachycardia, effective therapy requires that conduction be interrupted at some point in the reentry circuit and the vast majority of these circuits involve the AV node.

A. Mechanical Measures

A variety of maneuvers have been used to interrupt episodes, and patients may learn to perform these themselves. These maneuvers result in an acute increase in vagal tone and include the Valsalva maneuver, lowering the head between the knees, coughing, splashing cold water on the face, and breath holding. The Valsalva maneuver is most effective when performed with the patient supine, exerting around 40 mm Hg of intrathoracic pressure (by blowing through a 10 mL syringe) for at least 15 seconds. Maximum vagal response occurs upon release of intrathoracic pressure. Carotid sinus massage is another technique often performed by physicians but should be avoided if the patient has carotid bruits or a history of transient cerebral ischemic attacks. Firm but gentle pressure and massage are applied first over the right carotid sinus for 10–20 seconds and, if unsuccessful, then over the left carotid sinus. Pressure should not be exerted on both sides at the same time. These maneuvers stimulate a vagal outpouring, delay AV conduction, and block the reentry mechanism at the level of the AV node. They result in abrupt termination of the arrhythmia in 20–50% of cases.

B. Drug Therapy

If mechanical measures fail, two rapidly acting intravenous agents will terminate more than 90% of episodes. Intravenous ***adenosine*** has a very brief duration of action and minimal negative inotropic activity. Because the half-life of adenosine is less than 10 seconds, the drug must be given rapidly (in 1–2 seconds from a peripheral intravenous line); use half the dose if given through a central line. Adenosine causes a block of electrical conduction through the AV node. Adenosine is very well tolerated, but nearly 20% of patients will experience transient flushing, and some patients will experience severe chest discomfort. Caution must be taken when adenosine is given to elderly patients because the resulting pause can be prolonged. Adenosine must also be used with caution in patients with reactive airways disease because it can promote bronchospasm.

Calcium channel blockers also rapidly induce AV block and break many episodes of reentrant supraventricular tachycardia. These agents should be used with caution in patients with heart failure due to their negative inotropic effects. These agents include ***verapamil*** and ***diltiazem***. Diltiazem may cause less hypotension and myocardial depression than verapamil.

Intravenous beta-blockers include ***esmolol*** (a very short-acting beta-blocker), propranolol, and metoprolol. All may be effective for virtually any type of supraventricular tachycardia and cause less myocardial depression than the calcium

channel blockers. If the tachycardia is believed to be mediated by an accessory pathway, intravenous ***procainamide*** may terminate the tachycardia by prolonging refractoriness in the accessory pathway; however, because it facilitates AV conduction and an initial increase in rate may occur, it is usually not given until after a calcium channel blocker or a beta-blocker has been administered. Although intravenous amiodarone is safe, it is usually not required and often ineffective for the treatment of these arrhythmias.

C. Cardioversion

If the patient is hemodynamically unstable or if adenosine, beta-blockers, and calcium channel blockers are contraindicated or ineffective, synchronized electrical cardioversion (beginning at 100 J) is almost universally successful. If digitalis toxicity is present or strongly suspected, as in the case of paroxysmal tachycardia with block, electrical cardioversion should be avoided.

Prevention

A. Catheter Ablation

Because of concerns about the safety and the intolerability of antiarrhythmic medications, radiofrequency ablation is the preferred approach to patients with recurrent symptomatic reentrant supraventricular tachycardia, whether it is due to dual pathways within the AV node or to accessory pathways.

B. Drugs

AV nodal blocking agents are the drugs of choice as firstline medical therapy. Beta-blockers or nondihydropyridine calcium channel blockers, such as diltiazem and verapamil, are typically used first. Patients who do not respond to agents that increase the refractoriness of the AV node may be treated with antiarrhythmics. The class Ic agents (flecainide, propafenone) can be used in patients without underlying structural heart disease. In patients with evidence of structural heart disease, class III agents, such as sotalol or amiodarone, are a better choice because of the lower incidence of ventricular proarrhythmia during long-term therapy.

SUPRAVENTRICULAR TACHYCARDIAS DUE TO ACCESSORY AV PATHWAYS
(Preexcitation Syndromes)
ESSENTIALS OF DIAGNOSIS

- Frequently associated with palpitations.
- Can be associated with syncope.
- Rapid, regular rhythm.
- May have narrow or wide QRS complex on ECG.
- Often have preexcitation (delta wave) on baseline ECG.

General Considerations

Accessory pathways or bypass tracts between the atrium and the ventricle bypass the compact AV node and can predispose to reentrant arrhythmias, such as AV reciprocating tachycardia (AVRT) and atrial fibrillation. These may be wholly or partly within the node (eg, Mahaim fibers), yielding a short PR interval and normal QRS morphology. More commonly, they make direct connections between the atrium and ventricle through Kent bundles (**Wolff-ParkinsonWhite syndrome**). This often produces a short PR interval with a delta wave (preexcitation) at the onset of the wide, slurred QRS complex owing to early ventricular depolarization of the region adjacent to the pathway. Although the morphology and polarity of the delta wave can suggest the location of the pathway, mapping by intracardiac recordings is required for precise anatomic localization.

Accessory pathways occur in 0.1–0.3% of the population and facilitate reentrant arrhythmias owing to the disparity in refractory periods of the AV node and accessory pathway. Whether the tachycardia is associated with a narrow or wide QRS complex is frequently determined by whether antegrade conduction is through the node (narrow) or the bypass tract (wide). Some bypass tracts conduct only in a retrograde direction. In these cases, the bypass tract is termed “concealed” because it is not readily apparent on a baseline (sinus) ECG. Orthodromic reentrant tachycardia is a reentrant rhythm that conducts antegrade down the AV node and retrograde up the accessory pathway, resulting in a narrow QRS complex unless an underlying bundle branch block or interventricular conduction delay is present. Antidromic reentrant tachycardia conducts antegrade down the accessory pathway and retrograde through the AV node, resulting in a wide and often bizarre-appearing QRS complex, which may be mistaken for ventricular tachycardia. Accessory pathways often have shorter refractory periods than specialized conduction tissue, and thus tachycardias involving accessory pathways have the potential to be more rapid. Up to 30% of patients with Wolff-Parkinson-White syndrome will develop atrial fibrillation or flutter with antegrade conduction down the accessory pathway and a rapid ventricular response. If this conduction is very rapid, it can potentially degenerate to ventricular fibrillation.

Clinical Findings & Treatment

Some patients have a delta wave found incidentally on ECG (Wolff-Parkinson-White pattern). Even in the absence of palpitations, light-headedness, or syncope, these patients are at higher risk for sudden cardiac death than the general population. Risk factors include age younger than 30, male sex, history of atrial fibrillation and associated congenital heart disease. Multiple risk stratification strategies have been proposed to identify asymptomatic patients with Wolff-Parkinson-White pattern ECG who may be at higher risk for lethal cardiac arrhythmias. A sudden loss of preexcitation during exercise testing likely indicates an accessory pathway with poor conduction properties and therefore low risk for rapid anterograde conduction. In the absence of this finding or other signs of weak anterograde properties (intermittent preexcitation on resting ECG or Holter monitoring), patients may be referred for invasive electrophysiology testing. During the study, patients found to have the shortest preexcited R-R interval (SPERRI)

during atrial fibrillation of 250 msec or less or inducible supraventricular tachycardia are at increased risk for sudden cardiac death and should undergo catheter ablation.

A. Catheter Ablation

As with AVNRT, radiofrequency catheter ablation has become the procedure of choice in patients with accessory pathways and recurrent symptoms or asymptomatic patients with Wolff-Parkinson-White pattern ECG and high risk features at baseline or during electrophysiology study. Success rates for ablation of accessory pathways with radiofrequency catheters exceed 95% in appropriate patients. Major complications from catheter ablation are rare but include AV block, cardiac tamponade, and thromboembolic events. Minor complications, including hematoma at the catheter access site, occurs in 1–2% of procedures.

B. Pharmacologic Treatment

Narrow-complex reentrant rhythms involving a bypass tract can be managed as discussed for AVNRT. Atrial fibrillation and flutter with a concomitant antegrade conducting bypass tract must be managed differently, since agents such as digoxin, calcium channel blockers, and even beta-blockers may increase the refractoriness of the AV node with minimal or no effect on the accessory pathway, often leading to faster ventricular rates. Therefore, these agents should be avoided. The class Ia, class Ic, and class III antiarrhythmic agents will increase the refractoriness of the bypass tract and are the drugs of choice for wide-complex tachycardias involving accessory pathways. If hemodynamic compromise is present, electrical cardioversion is warranted.

Long-term therapy often involves a combination of agents that increase refractoriness in the bypass tract (class Ia or Ic agents) and in the AV node (calcium channel blockers and beta-blockers), provided that atrial fibrillation or flutter with short RR cycle lengths is not present. The class III agent, amiodarone, can be effective in refractory cases. Patients who are difficult to manage should undergo electrophysiologic evaluation.

When to Refer

• Patients with an incidental finding of Wolff-ParkinsonWhite pattern on ECG without evidence of loss of preexcitation spontaneously or during exercise testing.

• Patients with recurrent symptoms or episodes despite treatment with AV nodal blocking agents.

• Patients with preexcitation and a history of atrial fibrillation.

When to Admit

• Patients with paroxysmal supraventricular tachycardia and syncope.

• Patients with a history of syncope and preexcitation identified on an ECG.

ATRIAL FIBRILLATION

ESSENTIALS OF DIAGNOSIS

- Irregularly irregular heart rhythm.
- Usually tachycardic.
- Often associated with palpitations (acute onset) or fatigue (chronic).
- ECG shows erratic atrial activity with irregular ventricular response.
- High risk for thromboembolism: common cause of stroke.
- High incidence and prevalence in the elderly population.

General Considerations

Atrial fibrillation is the most common chronic arrhythmia, with an incidence and prevalence that rise with age, so that it affects approximately 9% of individuals over age 80 years. It occurs in rheumatic and other forms of VHD, dilated cardiomyopathy, ASD, hypertension, and coronary heart disease as well as in patients with no apparent cardiac disease; it may be the initial presenting sign in thyrotoxicosis, and this condition should be excluded with the initial episode. The atrial activity may be very fine and difficult to detect on the ECG, or quite coarse and often mistaken for atrial flutter. Atrial fibrillation often appears in a paroxysmal fashion before becoming the established rhythm. Pericarditis, chest trauma, thoracic or cardiac surgery, thyroid disorders, obstructive sleep apnea, or pulmonary disease (as well as medications such as theophylline and betaadrenergic agonists) may cause paroxysmal episodes in patients with normal hearts. Acute alcohol excess and alcohol withdrawal—and, in predisposed individuals, even consumption of small amounts of alcohol—may precipitate atrial fibrillation. This latter presentation, which is often termed “holiday heart,” is usually transient and self-limited. Short-term rate control usually suffices as treatment. Perhaps the most serious consequence of atrial fibrillation is the propensity for thrombus formation due to stasis in the atria (particularly the left atrial appendage) and consequent embolization, most devastatingly to the cerebral circulation. Overall, the rate of stroke is approximately 5% per year. However, patients with significant obstructive mitral stenosis, chronic heart failure or LV dysfunction, diabetes mellitus, hypertension, female sex (when present with other risk factors), vascular disease, or age 65 years or older (and particularly 75 years or older), and those with a history of prior stroke or other embolic events are at substantially higher risk (up to nearly 20% per year in patients with multiple risk factors). A substantial portion of the aging population with hypertension has asymptomatic or “subclinical” atrial fibrillation that is also associated with increased risk of stroke.

Clinical Findings

A. Symptoms and Signs

Atrial fibrillation itself is rarely life-threatening; however, it can have serious consequences if the ventricular rate is sufficiently rapid to precipitate hypotension, myocardial ischemia, or tachycardia-induced myocardial dysfunction. Moreover, particularly in patients with risk factors, atrial fibrillation is a major preventable

cause of stroke. Although many patients—particularly older or inactive individuals— have relatively few symptoms if the rate is controlled, some patients are aware of the irregular rhythm and may find it very uncomfortable. Most patients will complain of fatigue whether they experience other symptoms or not. The heart rate may range from quite slow to extremely rapid, but is uniformly irregular unless underlying complete heart block with junctional escape rhythm or a permanent ventricular pacemaker is in place. Atrial fibrillation is the only common arrhythmia in which the ventricular rate is rapid and the rhythm very irregular. Because of the varying stroke volumes resulting from fluctuating periods of diastolic filling, not all ventricular beats produce a palpable peripheral pulse. The difference between the apical rate and the pulse rate is the "pulse deficit"; this deficit is greater when the ventricular rate is high.

B. ECG

The surface ECG typically demonstrates erratic, disorganized atrial activity between discrete QRS complexes occurring in an irregular pattern. The atrial activity may be very fine and difficult to detect on the ECG, or quite coarse and often mistaken for atrial flutter.

Treatment

A. Newly Diagnosed Atrial Fibrillation

1. Initial management

A. Hemodyanmicaliy *unstable* patient—If the patient is hemodynamically unstable—usually as a result of a rapid ventricular rate or associated cardiac or noncardiac conditions—hospitalization and immediate treatment of atrial fibrillation are required. Urgent cardioversion is usually indicated in patients with shock or severe hypotension, pulmonary edema, or ongoing myocardial infarction or ischemia. There is a potential risk of thromboembolism in patients undergoing cardioversion who have not received anticoagulation therapy if atrial fibrillation has been present for more than 48 hours; however, in hemodynamically unstable patients the need for immediate rate control outweighs that risk. Electrical cardioversion is usually preferred in unstable patients. An initial shock with 100–200 J is administered in synchrony with the R wave. If sinus rhythm is not restored, an additional attempt with 360 J is indicated. If this fails, cardioversion may be successful after loading with intravenous **ibutilide** (1 mg over 10 minutes, repeated in 10 minutes if necessary).

B. Hemodynamicaliy *stable* patient — If, as is often the case—particularly in older individuals—the patient has no symptoms, hemodynamic instability, or evidence of important precipitating conditions (such as silent myocardial infarction or ischemia, decompensated heart failure, pulmonary embolism, or hemodynamically significant valvular disease), hospitalization is usually not necessary. In most of these cases, atrial fibrillation is an unrecognized chronic or paroxysmal condition and should be managed. For new onset atrial fibrillation, thyroid function tests and echocardiography to assesss for occult valvular or

myocardial disease should be performed.

In hemodynamically stable patients with controlled symptoms, a strategy of rate control and anticoagulation is appropriate. This is also true when the conditions that precipitated atrial fibrillation are likely to persist for some time (such as following cardiac or noncardiac surgery, with respiratory failure, or with pericarditis). Rate control and anticoagulation are also appropriate even when the conditions causing the atrial fibrillation might resolve spontaneously over a period of hours to days (such as atrial fibrillation due to excessive alcohol intake, electrolyte imbalance or atrial fibrillation due to exposure to excessive theophylline or sympathomimetic agents). The choice of agent is guided by the hemodynamic status of the patient, associated conditions, and the urgency of achieving rate control. Although both hypotension and heart failure may improve when the ventricular rate is slowed, calcium channel blockers and beta-blockers may themselves precipitate hemodynamic deterioration. Digoxin is less risky. The total digoxin loading dose is 0.75 to 1.5 mg, which can be given intravenously or orally; half of the total loading dose is given initially, then one-quarter of the loading dose, then the final quarter of the loading dose at 8–12 hour intervals. The initial intravenous digoxin loading dose is 0.5 mg intravenously over 30 minutes and the initial oral digoxin loading dose is 0.5 mg. The loading dose is generally reduced by 50% if the CrCl < 10 mL/min, and the total digitalization dose is 0.5 to 1 mg if the CrCl is 10 to 50 mL/min.

Despite rapid digitalization, rate control is rather slow and may be inadequate, particularly in patients with sympathetic activation.

In the setting of myocardial infarction or ischemia, betablockers are the preferred agent. The most frequently used agents are either metoprolol (administered as a 5-mg intravenous bolus, repeated twice at intervals of 5 minutes and then given as needed by repeat boluses or orally at total daily doses of 50–400 mg) or, in very unstable patients, esmolol (0.5 mg/kg intravenously, repeated once if necessary, followed by a titrated infusion of 0.05–0.2 mg/kg/min). If betablockers are contraindicated, calcium channel blockers are immediately effective. Diltiazem (20 mg bolus, repeated after 15 minutes if necessary, followed by a maintenance infusion of 5–15 mg/h) is the preferred calcium blocker if hypotension or LV dysfunction is present. Otherwise, verapamil (5–10 mg intravenously over 2–3 minutes, repeated after 30 minutes if necessary) may be used. Amiodarone, even when administered intravenously, has a relatively slow onset but is often a useful adjunct when rate control with the previously cited agents is incomplete or contraindicated or when cardioversion is planned in the near future. However, amiodarone should not be used in this setting if long-term therapy is planned with other antiarrhythmic agents.

If the onset of atrial fibrillation was more than 48 hours prior to presentation (or unknown) and early cardioversion is considered necessary due to the inability to adequately control rate, a transesophageal echocardiogram should be performed prior to cardioversion to exclude left atrial thrombus. If thrombus is present, the cardioversion is delayed until after a 4-week period of therapeutic anticoagulation. In any case, because atrial contractile activity may not recover for several weeks

after restoration of sinus rhythm in patients who have been in atrial fibrillation for more than several days, cardioversion should be followed by anticoagulation for at least 1 month unless there is a strong contraindication.

2. Subsequent management — Up to two-thirds of patients experiencing a first episode of atrial fibrillation will spontaneously revert to sinus rhythm within 24 hours. In the absence of VHD, diabetes, hypertension, or other risk factors for stroke, these patients may not require longterm anticoagulation beyond aspirin. If atrial fibrillation persists or has been present for more than a week, spontaneous conversion is unlikely. In most cases, immediate cardioversion is not required, and management consists of rate control and anticoagulation whether or not the patient has been admitted to the hospital. Rate control is usually relatively easy to achieve with beta-blockers, rate-slowing calcium blockers and, occasionally, digoxin, used as single agents or more often in combination. In older patients, who often have diminished AV nodal function and relatively limited activity, modest rate control can often be achieved with a single agent. Many younger or more active individuals require a combination of two agents. Choice of the initial medication is best based on the presence of accompanying conditions: hypertensive patients should be given beta-blockers or calcium blockers; coronary patients should usually receive a betablocker; and patients with heart failure should be given a beta-blocker with consideration of adding digoxin. Adequacy of rate control should be evaluated by recording the apical pulse rate both at rest and with an appropriate level of activity (such as after brisk walking around the corridor or climbing stairs).

A. Anticoagulation — For patients with atrial fibrillation, even when it is paroxysmal or occurs rarely, the need for oral anticoagulation should be evaluated and treatment initiated for those without strong contraindication. Patients with "**lone atrial fibrillation**" (eg, no evidence of associated heart disease, hypertension, atherosclerotic vascular disease, diabetes mellitus, or history of stroke or transient ischemic attack) under age 65 years need no antithrombotic treatment. Patients with **transient atrial fibrillation**, such as in the setting of acute myocardial infarction or pneumonia, but no prior history of arrhythmia, are at high risk for future development of atrial fibrillation and appropriate anticoagulation should be initiated based on risk factors. If the cause is **reversible**, such as after coronary artery bypass surgery or associated with hyperthyroidism, then long-term anticoagulation is not necessary.

In addition to the traditional five risk factors that comprise the ***CHADS2 score*** (heart failure, hypertension, age 75 years or older, diabetes mellitus, and [2 points for] history of stroke or transient ischemic attack), the European and American guidelines recommend that three additional factors included in the ***CHA2 DS2 -VASc score*** be considered: age 65–74 years, female gender, and presence of vascular be used, with a preference for oral anticoagulation, taking into account risk, benefit, and patient preferences. Unfortunately, studies show that only about half of patients with atrial fibrillation and an indication for oral anticoagulation are receiving it, and even when treated with warfarin, they are out of the target INR

range nearly half the time. Cardioversion, if planned, should be performed after at least 3–4 weeks of anticoagulation at a therapeutic level (or after exclusion of left atrial appendage thrombus by transesophageal echocardiogram as discussed above). Anticoagulation clinics with systematic management of warfarin dosing and adjustment have been shown to result in better maintenance of target anticoagulation.

Four **NOACs**—***dabigatran, rivaroxaban, apixaban,*** and ***edoxaban***—have been shown to be at least as effective as warfarin for stroke prevention in patients with atrial fibrillation and have been approved by the FDA for this indication. These drugs have not been studied in patients with moderate or severe mitral stenosis (called "valvular atrial fibrillation"), and they should not be used for patients with mechanical prosthetic valves.

Dabigatran was compared with warfarin (in the RELY trial) for prevention of stroke and systemic embolism for patients with atrial fibrillation and at least one additional risk factor for stroke. The lower dabigatran dose (110 mg orally twice daily, not approved in the United States) was noninferior to warfarin in stroke prevention and caused significantly less bleeding, and a second higher dose (150 mg orally twice daily) resulted in significantly fewer strokes with similar bleeding rates. Both doses of dabigatran caused substantially less intracerebral hemorrhage than warfarin. There is a higher incidence of gastrointestinal bleeding with dabigatran. The higher dose (150 mg twice a day) should generally be avoided in patients over 80 years of age due to higher rates of bleeding. There is no readily available reversal agent for any of the NOACs. In spite of this, when oral anticoagulation with either dabigatran or warfarin was stopped for elective or emergency procedures or surgery in the RELY trial, the risk of bleeding was numerically lower with dabigatran than with warfarin. Patients may be converted from warfarin to dabigatran by stopping the warfarin and beginning dabigatran once the INR is 2.0 or less, and this is a reasonable approach for transition from warfarin to any of the NOACs. Neither dabigatran nor any of the NOACs should be used in patients with mechanical prosthetic heart valves where the drugs are less effective and riskier.

Rivaroxaban is approved by the FDA for stroke prevention in nonvalvular atrial fibrillation. Rivaroxaban, which should be be taken with a high-calorie meal (usually dinner) to increase absorption, is dosed at 20 mg once daily, with a reduced dose (15 mg/day) for patients with creatinine clearances between 30 mL/min and 50 mL/min. Similar to dabigatran, there is substantially less intracranial hemorrhage with rivaroxaban than warfarin

Apixaban is more effective than warfarin at stroke prevention while having a substantially lower risk of major bleeding (in the ARISOTLE trial) and a lower risk of allcause mortality. The apixaban dosage is 5 mg twice daily or 2.5 mg twice daily for patients with two of three high-risk criteria (age 80 years or older, body weight 60 kg or less, and serum creatinine of 1.5 mg/dL or more). Apixaban is associated with less intracranial hemorrhage and is well tolerated. Apixaban was also shown to be superior to aspirin (and better tolerated) in the AVERROES trial of patients deemed not suitable for warfarin. These NOACs have important

advantages over warfarin, and therefore they are recommended preferentially over VKAs in the European Guidelines.

Edoxaban was tested in two doses against warfarin (in the ENGAGE-AF trial), and the higher dose (60 mg once a day) was as effective as warfarin at preventing stroke or systemic embolism and had similar rates of major bleeding and lower rates of hemorrhagic stroke. The 60-mg dose was approved by the FDA but with a box warning that it is less effective in patients whose creatinine clearance is more than 95 mL/min. The dose is decreased to 30 mg/day for patients whose creatinine clearance is less than 50 mL/min.

Each of the NOACs to be safe and effective around the time of electrical cardioversion. In each of these trials, and in one modest-sized prospective randomized trial of rivaroxaban that specifically addressed cardioversion, the rates of stroke were low (and similar to warfarin) with the NOACs when given for at least 3–4 weeks prior to cardioversion. An advantage of the NOACs is that when stable anticoagulation is desired before elective cardioversion, it is achieved faster than with warfarin.

B. Rate control or elective cardioversion — Two large randomized controlled trials (the 4060-patient Atrial Fibrillation Follow-up Investigation of Rhythm Management, or AFFIRM trial; and the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation, or RACE trial) compared strategies of rate control and rhythm control. In both, a strategy of rate control and long-term anticoagulation was associated with no higher rates of death or stroke—both, if anything, favored rate control— and only a modestly increased risk of hemorrhagic events than a strategy of restoring sinus rhythm and maintaining it with antiarrhythmic drug therapy. Of note is that exercise tolerance and quality of life were not significantly better in the rhythm control group. Nonetheless, the decision of whether to attempt to restore sinus rhythm following the initial episode remains controversial. Elective cardioversion following an appropriate period of anticoagulation is generally recommended for the initial episode in patients in whom atrial fibrillation is thought to be of recent onset and when there is an identifiable precipitating factor. Similarly, cardioversion is appropriate in patients who remain symptomatic from the rhythm despite aggressive efforts to achieve rate control.

In cases in which elective cardioversion is required, it may be accomplished electrically or pharmacologically. **Intravenous ibutilide** may be used as described above in a setting in which the patient can undergo continuous ECG monitoring for at least 4–6 hours following administration. Treatment with intravenous magnesium (usually 2g pretreatment only but up to 5 mg pretreatment and posttreatment) may prevent rare episodes of torsades de pointes associated with ibutilide administration. In patients in whom a decision has been made to continue antiarrhythmic therapy to maintain sinus rhythm (see next paragraph), cardioversion can be attempted with an agent that is being considered for long-term use. For instance, after therapeutic anticoagulation has been established, amiodarone can be initiated on an outpatient basis (400 mg twice daily for 2 weeks, followed by 200 mg twice daily for at least

2–4 weeks and then a maintenance dose of 200 mg daily). Because amiodarone increases the prothrombin time in patients taking warfarin and increases digoxin levels, careful monitoring of anticoagulation and drug levels is required.

Other agents that may be used for both cardioversion and maintenance therapy include dofetilide, propafenone, flecainide, and sotalol. **Dofetilide** (125–500 mcg orally twice daily) must be initiated in hospital due to the potential risk of torsades de pointes and the downward dose adjustment that is required for patients with renal impairment. **Propafenone** (150–300 mg orally every 8 hours) should be avoided in patients with structural heart disease (CAD, systolic dysfunction, or significant LVH). **Flecainide** (50–150 mg orally twice daily) should be used in conjunction with an AV nodal blocking drug if there is a history of atrial flutter and should be avoided in patients with structural heart disease. **Sotalol** (80–160 mg orally twice daily) should be initiated in the hospital in patients with structural heart disease due to a risk of torsades de pointes; it is not very effective for converting atrial fibrillation but can be used to maintain sinus rhythm following cardioversion.

In patients treated long-term with an antiarrhythmic agent, sinus rhythm will persist in approximately 50%. The most commonly used medications are amiodarone, dronedarone, sotalol, propafenone, flecainide, and dofetilide, but the latter four agents are associated with a clear risk of proarrhythmia in certain populations; dronedarone has less efficacy than amiodarone, and amiodarone frequently causes other adverse effects. Therefore, after an initial presentation of atrial fibrillation, it may be prudent to determine whether atrial fibrillation recurs during a period of 6 months without antiarrhythmic drugs (during which anticoagulation is maintained). If it does recur, the decision to restore sinus rhythm and initiate long-term antiarrhythmic therapy can be based on how well the patient tolerates atrial fibrillation. The decision to maintain long-term anticoagulation should be based on risk factors (CHADS2 or CHA2 DS2 -VASc score) and not on the perceived presence or absence of atrial fibrillation as future episodes may be asymptomatic.

B. Paroxysmal and Refractory Atrial Fibrillation

1. Recurrent paroxysmal atrial fibrillation — Patients with recurrent paroxysmal atrial fibrillation are at similar (or slightly lower) stroke risk as those who are in atrial fibrillation chronically. Although these episodes may be apparent to the patient, many are not recognized and may be totally asymptomatic. Thus, ambulatory ECG monitoring or event recorders are indicated in those in whom paroxysmal atrial fibrillation is suspected. Antiarrhythmic agents are usually not successful in preventing all paroxysmal atrial fibrillation episodes. However, dofetilide has been shown to be as effective as amiodarone in maintaining sinus rhythm in certain patients and does not have as many untoward longterm effects. Long-term anticoagulation should be considered for all patients except in those who are under 65 years of age and have no additional stroke risk factors.

2. Refractory atrial fibrillation —

Because of trial results indicating that important adverse clinical outcomes

(death, stroke, hemorrhage, heart failure) are no more common with rate control than rhythm control, atrial fibrillation should generally be considered refractory if it causes persistent symptoms or limits activity. This is much more likely in younger individuals and those who are active or engage in strenuous exercise. Even in such individuals, two-drug or three-drug combinations of a beta-blocker, rate-slowing calcium blocker, and digoxin usually can prevent excessive ventricular rates, though in some cases they are associated with excessive bradycardia during sedentary periods.

If antiarrhythmic or rate-control medications fail to improve the symptoms of atrial fibrillation, catheter ablation of foci in and around the pulmonary veins that initiate atrial fibrillation may be considered. Pulmonary vein isolation is a reasonable second-line therapy for individuals with symptomatic atrial fibrillation that is refractory to pharmacologic therapy. Ablation is successful about 70% of the time in the short term, but more than one procedure may be required, and eventually atrial fibrillation is likely to recur. Therefore, for patients with risk factors for stroke, anticoagulation should be continued indefinitely after ablation. The procedure is routinely performed in the electrophysiology laboratory using a catheter-based approach and can also be performed via a subxiphoid approach thorascopically, via thoracotomy, or via median sternotomy in the operating room by experienced surgeons. In symptomatic patients with poor rate control who are deemed inappropriate for pulmonary vein isolation, radiofrequency ablation of the AV node and permanent pacing ensure rate control and may facilitate a more physiologic rate response to activity, but this is used only as a last resort.

When to Refer

• Symptomatic atrial fibrillation with or without rate control.

• Asymptomatic atrial fibrillation with poor rate control despite AV nodal blockers.

When to Admit

• Atrial fibrillation with rapid ventricular response resulting in hemodynamic compromise.

• Atrial fibrillation resulting in acute heart failure.

ATRIAL FLUTTER

ESSENTIALS OF DIAGNOSIS

- Usually regular heart rhythm.
- Often tachycardic (100–150 beats/min).
- Often associated with palpitations (acute onset) or fatigue (chronic).
- shows “sawtooth” pattern of atrial activity in leads II, III, and AVF.
- Often seen in conjunction with structural heart disease or chronic obstructive pulmonary disease (COPD).

Atrial flutter is less common than fibrillation. It may occur in patients with structurally normal hearts but is more commonly seen in patients with COPD, rheumatic or coronary heart disease, heart failure, ASD, or surgically repaired congenital heart disease. The reentrant circuit generates atrial rates of 250–350 beats/min, usually with transmission of every second, third, or fourth impulse through the AV node to the ventricles. The ECG typically demonstrates a "sawtooth" pattern of atrial activity in the inferior leads (II, III, and AVF).

Treatment

Ventricular rate control is accomplished using the same agents used in atrial fibrillation, but it is much more difficult with atrial flutter than with atrial fibrillation. Conversion of atrial flutter to sinus rhythm with class I antiarrhythmic agents is also difficult to achieve, and administration of these drugs has been associated with slowing of the atrial flutter rate to the point at which 1:1 AV conduction can occur at rates in excess of 200 beats/min, with subsequent hemodynamic collapse. The intravenous class III antiarrhythmic agent ibutilide has been significantly more successful in converting atrial flutter. About 50–70% of patients return to sinus rhythm within 60–90 minutes following the infusion of 1–2 mg of this agent. Electrical cardioversion is also very effective for atrial flutter, with approximately 90% of patients converting following synchronized shocks of as little as 25–50 J.

Although the organization of atrial contractile function in this arrhythmia may provide some protection against thrombus formation, the risk of thromboembolism should be considered equivalent to atrial fibrillation due to the common coexistence of these arrhythmias. Precardioversion anticoagulation is not necessary for atrial flutter of less than 48 hours, duration except in the setting of mitral valve disease. As with atrial fibrillation, anticoagulation should be continued for at least 4 weeks after electrical or chemical cardioversion and long-term in patients with risk factors for thromboembolism.

Chronic atrial flutter is often a difficult management problem, as rate control is difficult. If pharmacologic therapy is chosen, amiodarone and dofetilide are the antiarrhythmics of choice. Dofetilide is often given in conjunction with an AV nodal blocker (other than verapamil). Atrial flutter can follow a typical or atypical reentry circuit around the atrium. The anatomy of the typical circuit has been well defined and allows for catheter ablation within the atrium to interrupt the circuit and eliminate atrial flutter. Catheter ablation is a highly successful treatment that has become the preferred approach for recurrent typical atrial flutter. Atrial flutter and atrial fibrillation frequently coexist, and patients may require catheter ablation of both arrhythmias.

When to Refer

• Symptomatic atrial flutter with or without rate control.

• Asymptomatic atrial flutter with poor rate control despite AV nodal blockers.

When to Admit

• Atrial flutter with 1:1 conduction resulting in hemodynamic compromise.
• Atrial flutter resulting in acute heart failure.

MULTIFOCAL ATRIAL TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- ECG reveals three or more distinct P-wave morphologies. Often associated with palpitations.
- Associated with severe COPD.
- Treatment of the underlying lung disease is the most effective therapy.

This is a rhythm characterized by varying P-wave morphology (by definition, three or more foci) and markedly irregular PP intervals. The rate is usually between 100 and 140 beats/min. Most patients have concomitant severe COPD. Treatment of the underlying condition is the most effective approach; verapamil, 240–480 mg orally daily in divided doses is also of value in some patients. This arrhythmia may progress to atrial fibrillation in some patients.

AV JUNCTIONAL RHYTHM

ESSENTIALS OF DIAGNOSIS

- Regular heart rhythm.
- Can have wide or narrow QRS complex.
- Often seen in digitalis toxicity.

The atrial-nodal junction or the nodal-His bundle junction may assume pacemaker activity for the heart, usually at a rate of 35–60 beats/min. This may occur in patients with myocarditis, CAD, and digitalis toxicity as well as in individuals with normal hearts. The rate responds normally to exercise, and the diagnosis is often an incidental finding on ECG monitoring, but it can be suspected if the jugular venous pulse shows cannon a waves. Junctional rhythm is often an escape rhythm because of depressed sinus node function with sinoatrial block or delayed conduction in the AV node.

Nonparoxysmal junctional tachycardia results from increased automaticity of the junctional tissues in digitalis toxicity or ischemia and is associated with a narrow QRS complex and a rate usually less than 120–130 beats/min. It is usually considered benign when it occurs in acute myocardial infarction, but the ischemia that induces it may also cause ventricular tachycardia and ventricular fibrillation.

VENTRICULAR PREMATURE BEATS
(Ventricular Extrasystoles)

Ventricular premature beats, also called PVCs, are typically isolated beats originating from ventricular tissue. Sudden death occurs more frequently (presumably as a result of ventricular fibrillation) when ventricular premature beats

occur in the presence of organic heart disease but not in individuals with no known cardiac disease.

Clinical Findings

The patient may or may not sense the irregular beat, usually as a skipped beat. Exercise generally abolishes premature beats in normal hearts, and the rhythm becomes regular. Ventricular premature beats are characterized by wide QRS complexes that differ in morphology from the patient's normal beats. They are usually not preceded by a P wave, although retrograde ventriculoatrial conduction may occur. Bigeminy and trigeminy are arrhythmias in which every second or third beat is premature; these patterns confirm a reentry mechanism for the ectopic beat. Ambulatory ECG monitoring or monitoring during graded exercise may reveal more frequent and complex ventricular premature beats than occur in a single routine ECG. An increased frequency of ventricular premature beats during exercise is associated with a higher risk of cardiovascular mortality and should be investigated further.

Treatment

If no associated cardiac disease is present and if the ectopic beats are asymptomatic, no therapy is indicated. Patients with mild symptoms or anxiety from palpitations can be reassured about the benign nature of this arrhythmia. If PVCs are frequent, electrolyte abnormalities (especially hypokalemia or hyperkalemia and hypomagnesemia), hyperthyroidism, and occult heart disease should be excluded. In addition, an echocardiogram should be performed in patients in whom a burden of PVCs of more than 10,000 per day has been documented by Holter monitoring. Pharmacologic treatment is indicated only for patients who are symptomatic or in whom cardiomyopathy thought to be due to the high burden of PVCs (generally greater than 10% of daily heart beats) develops. Betablockers and non-dihydropyridine calcium channel blockers are appropriate as first-line therapy. The class I and III agents may be effective in reducing ventricular premature beats but are often poorly tolerated and can be proarrhythmic in up to 5% of patients. Catheter ablation is a well-established therapy for symptomatic individuals who do not respond to medication or for those patients whose burden of ectopic beats has resulted in a tachycardia-induced cardiomyopathy.

VENTRICULAR TACHYCARDIA

ESSENTIALS OF DIAGNOSIS

- Fast, wide QRS complex on ECG.
- Often associated with structural heart disease.
- Frequently associated with syncope.
- n the absence of reversible cause, implantable cardioverter defibrillator (ICD) is recommended.

General Considerations

Ventricular tachycardia is defined as three or more consecutive ventricular premature beats. The usual rate is 160–240 beats/min and is moderately regular but less so than atrial tachycardia. The usual mechanism is reentry, but abnormally triggered rhythms occur.

Ventricular tachycardia is a frequent complication of acute myocardial infarction and dilated cardiomyopathy but may occur in chronic coronary disease, hypertrophic cardiomyopathy, mitral valve prolapse, myocarditis, and in most other forms of myocardial disease. It can also be a consequence of atypical forms of cardiomyopathies, such as arrhythmogenic right ventricular cardiomyopathy However, ventricular tachycardia can also occur in patients with structurally normal hearts. **Torsades de pointes**, a form of ventricular tachycardia in which QRS morphology twists around the baseline, may occur in the setting of severe hypokalemia, hypomagnesemia, or after administration of a drug that prolongs the QT interval. In nonacute settings, most patients with ventricular tachycardia have known or easily detectable cardiac disease, and the finding of ventricular tachycardia is an unfavorable prognostic sign.

Clinical Findings

A. Symptoms and Signs

Patients may be asymptomatic or experience syncope or milder symptoms of impaired cerebral perfusion.

B. Laboratory Findings

Ventricular tachycardia can occur in the setting of hypokalemia and hypomagnesemia. Cardiac markers may be elevated when ventricular tachycardia presents in the setting of acute myocardial infarction or as a consequence of underlying coronary disease and demand ischemia.

C. Differentiation of Aberrantly

Conducted Supraventricular Beats from Ventricular Beats Ventricular tachycardia is either nonsustained (three or more consecutive beats lasting less than 30 seconds and terminating spontaneously) or sustained. The distinction from aberrant conduction of supraventricular tachycardia may be difficult in patients with a wide QRS complex; however, it is important because of the differing prognostic and therapeutic implications of each type. Findings favoring a ventricular origin include (1) AV dissociation; (2) a QRS duration exceeding 0.14 second; (3) capture or fusion beats (infrequent); (4) left axis deviation with right bundle branch block morphology; (5) monophasic (R) or biphasic (qR, QR, or RS) complexes in V1 ; and (6) a qR or QS complex in V6 . Supraventricular origin is favored by (1) a triphasic QRS complex, especially if there was initial negativity in leads I and V6 ; (2) ventricular rates exceeding 170 beats/min; (3) QRS duration longer than 0.12 second but not longer than 0.14 second; and (4) the presence of preexcitation syndrome.

Treatment

A. Acute Ventricular Tachycardia

The treatment of acute ventricular tachycardia is determined by the degree of hemodynamic compromise and the duration of the arrhythmia. In patients with structurally normal hearts, the prognosis is generally benign and syncope is uncommon. The etiology is often triggered activity from the right or left ventricular outflow tract and immediate treatment with a short-acting intravenous beta-blocker may terminate the episode. The management of ventricular tachycardia in acute myocardial infarction is discussed in the Complications section of Acute Myocardial Infarction with ST-Segment Elevation, above. In other patients, if ventricular tachycardia causes hypotension, heart failure, or myocardial ischemia, synchronized DC cardioversion with 100–360 J should be performed immediately. If the patient is tolerating the rhythm, amiodarone 150 mg as a slow intravenous bolus over 10 minutes, followed by an infusion of 1 mg/min for 6 hours and then a maintenance infusion of 0.5 mg/min for an additional 18–42 hours can be used. Significant hypotension can occur with rapid infusions of amiodarone. Lidocaine, 1 mg/kg as an intravenous bolus injection, can also be used. If the ventricular tachycardia recurs, supplemental amiodarone infusions of 150 mg over 10 minutes can be given. If the patient is stable, intravenous procainamide, 20 mg/min intravenously (up to 1000 mg), followed by an infusion of 20–80 mcg/kg/min could also be tried. Empiric magnesium replacement (1–2 g intravenously) may help especially for polymorphic ventricular tachycardia. If polymorphic ventricular tachycardia recurs, increasing the heart rate with isoproterenol infusion (2–10 mcg/min) or atrial pacing with a temporary pacemaker (at 90–120 bpm) will effectively shorten the QT interval to prevent further episodes.

B. Chronic Recurrent Ventricular Tachycardia

1. Sustained ventricular tachycardia —

Patients with symptomatic or sustained ventricular tachycardia in the absence of a reversible precipitating cause (acute myocardial infarction or ischemia, electrolyte imbalance, drug toxicity, etc) are at high risk for recurrence. In patients with structurally normal hearts and ventricular tachycardia with typical outflow tract (left bundle branch block with inferior axis) or left posterior fascicle (right bundle branch block with superior axis) appearance on ECG, treatment with a beta-blocker or a non-dihydropyridine calcium channel blocker may be tried. Catheter ablation has a high success rate in patients who do not respond to initial medical treatment. In patients with significant LV dysfunction, subsequent sudden death is common and ICD implantation is recommended. Beta-blockers are the mainstay for medical treatment of ventricular tachycardia in patients with structural heart disease. Antiarrhythmic drugs have not been shown to lower mortality in these patients but may decrease subsequent episodes and reduce the number of ICD shocks. Amiodarone is generally preferred in patients with structural heart disease but sotalol may be considered as well. Catheter ablation can be used as a palliative therapy for those patients with recurrent tachycardia who receive ICD shocks despite antiarrhythmic therapy; however, recurrence rates are high.

2. Nonsustained ventricular tachycardia (NSVT)

NSVT is defined as runs of three or more ventricular beats lasting less than 30 seconds and terminating spontaneously. These may be symptomatic (usually experienced as light-headedness) or asymptomatic. In individuals without heart disease, NSVT is generally associated with a benign prognosis. In patients with structural heart disease, NSVT is associated with an increased risk of subsequent symptomatic ventricular tachycardia and sudden death, especially when seen more than 48 hours after myocardial infarction. Betablockers reduce these risks in patients with significant LV systolic dysfunction, but the role of antiarrhythmic drug in this situation is less clear. In general, antiarrhythmic therapy may be considered in patients with structural heart disease with symptomatic NSVT when treatment of reversible factors or optimization of the beta-blocker dosage fails to suppress the arrhythmia. In patients with chronic heart failure and reduced EF who do not otherwise meet indication for ICD implantation (EF less than 35%), the presence of NSVT may prompt electrophysiology study. Inducibility of sustained ventricular tachycardia in this situation warrants ICD implantation.

When to Admit

Any sustained ventricular tachycardia

VENTRICULAR FIBRILLATION & DEATH

Sudden cardiac death is defined as unexpected nontraumatic death in clinically well or stable patients who die within 1 hour after onset of symptoms. The causative rhythm in most cases is ventricular fibrillation, which is usually preceded by ventricular tachycardia except in the setting of acute ischemia or infarction. Complete heart block and sinus node arrest may also cause sudden death. A disproportionate number of sudden deaths occur in the early morning hours and this suggests that there is a strong interplay with the autonomic nervous system. Over 75% of victims of sudden cardiac death have severe CAD. Many have old myocardial infarctions. Sudden death may be the initial manifestation of coronary disease in up to 20% of patients and accounts for approximately 50% of deaths from coronary disease. Other conditions that predispose to sudden death include severe LVH, hypertrophic cardiomyopathy, congestive cardiomyopathy, aortic stenosis, pulmonic stenosis, primary pulmonary hypertension, cyanotic congenital heart disease, atrial myxoma, mitral valve prolapse, hypoxia, electrolyte abnormalities, prolonged QT interval syndrome, the Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, and conduction system disease.

Treatment

Unless ventricular fibrillation occurs shortly after myocardial infarction, is associated with ischemia, or is seen with an unusual correctable process (such as an electrolyte abnormality, drug toxicity, or aortic stenosis), surviving patients require evaluation and intervention since recurrences are frequent. Coronary arteriography

should be performed to exclude coronary disease as the underlying cause (even in the presence of aortic stenosis), since revascularization may prevent recurrence. When ventricular fibrillation occurs in the initial 24 hours after infarction, long-term management is no different from that of other patients with acute infarction. Conduction disturbances should be managed as described in the next section. Survivors of ventricular fibrillation or cardiac arrest have improved long-term outcomes if a hypothermia protocol is rapidly initiated and continued for 24–36 hours after cardiac arrest.

The current consensus is that if myocardial infarction or ischemia, bradyarrhythmias and conduction disturbances or other identifiable and correctable precipitating causes of ventricular fibrillation are not found to be the cause of the sudden death episode, an ICD is the treatment of choice. In addition, evidence from the MADIT II study and Sudden Cardiac Death in Heart Failure Trial (SCDHeFT) suggest that patients with severe LV dysfunction— whether due to an ischemic cause, such as a remote myocardial infarction, or a nonischemic cause of advanced heart failure—have a reduced risk of death with the prophylactic implantation of an ICD. However, the DINAMIT study demonstrated that implanting prophylactic ICDs in patients early after myocardial infarction is associated with a trend toward worse outcomes. These patients may be managed with a wearable defibrillator vest until recovery of ventricular function can be assessed by echocardiogram at a later date.

ACCELERATED IDIOVENTRICULAR RHYTHM

Accelerated idioventricular rhythm is a regular wide complex rhythm with a rate of 60–120 beats/min, usually with a gradual onset. Because the rate is often similar to the sinus rate, fusion beats and alternating rhythms are common. Two mechanisms have been invoked: (1) an escape rhythm due to suppression of higher pacemakers resulting from sinoatrial and AV block or from depressed sinus node function; and (2) slow ventricular tachycardia due to increased automaticity or, less frequently, reentry. It occurs commonly in acute infarction and following reperfusion with thrombolytic drugs. The incidence of associated ventricular fibrillation is much less than that of ventricular tachycardia with a rapid rate, and treatment is not indicated unless there is hemodynamic compromise or more serious arrhythmias. This rhythm also is common in digitalis toxicity.

Accelerated idioventricular rhythm must be distinguished from the idioventricular or junctional rhythm with rates less than 40–45 beats/min that occurs in the presence of complete AV block. AV dissociation—where ventricular rate exceeds sinus—but not AV block, occurs in most cases of accelerated idioventricular rhythm.

LONG QT SYNDROME

Congenital long QT syndrome is an uncommon disease that is characterized by recurrent syncope, a long QT interval (usually 0.5–0.7 second), documented

ventricular arrhythmias, and sudden death. It may occur in the presence (Jervell-Lange-Nielsen syndrome) or absence (Romano-Ward syndrome) of congenital deafness. Inheritance may be autosomal recessive or autosomal dominant (Romano-Ward). Specific genetic mutations affecting membrane potassium and sodium channels have been identified and help delineate the mechanisms and susceptibility to arrhythmia.

Because this is a primary electrical disorder usually with no evidence of structural heart disease or LV dysfunction, the long-term prognosis is excellent if arrhythmia is controlled. Long-term treatment with beta-blockers (particularly nadolol) has been shown to be effective. ICD implantation is recommended for patients in whom recurrent syncope, sustained ventricular arrhythmias, or sudden cardiac death occurs despite drug therapy. An ICD should be considered as primary therapy in certain patients, such as those in whom aborted sudden cardiac death is the initial presentation of the long-QT syndrome, when there is a strong family history of sudden cardiac death, or when compliance or intolerance to drugs is a concern.

Acquired long QT interval secondary to the use of antiarrhythmic agents, methadone, antidepressant drugs, or certain antibiotics; electrolyte abnormalities; myocardial ischemia; or significant bradycardia may result in ventricular tachycardia (particularly torsades de pointes). Notably, many antiarrhythmic drugs that are effective for the treatment of atrial and ventricular arrhythmias may significantly prolong the QT interval (sotalol, dofetilide). If a drug therapy is found to prolong the QT interval beyond 500 ms or 15% longer than the baseline QT, it should be discontinued.

The management of torsades de pointes differs from that of other forms of ventricular tachycardia. Class Ia, Ic, or III antiarrhythmics, which prolong the QT interval, should be avoided—or withdrawn immediately if being used. Intravenous beta-blockers may be effective, especially in congenital forms of long QT syndrome; intravenous magnesium should be given acutely. Increasing the heart rate, whether by infusion of beta-agonist (dopamine or isoproterenol) or temporary atrial or ventricular pacing, is an effective approach that can both break and prevent the rhythm.

BRADYCARDIAS & CONDUCTION DISTURBANCES SICK SINUS SYNDROME ESSENTIALS OF DIAGNOSIS

- Most patients are asymptomatic.
- More common in elderly population.
- May have recurrent supraventricular arrhythmia and bradyarrhythmia.
- Frequently seen in patients with concomitant atrial fibrillation.
- Often chronotropically incompetent.
- May be caused by drug therapy.

General Considerations

This broad diagnosis is applied to patients with sinus arrest, sinoatrial exit block (recognized by a pause equal to a multiple of the underlying PP interval or

progressive shortening of the PP interval prior to a pause), or persistent sinus bradycardia. These rhythms are often caused or exacerbated by drug therapy (digitalis, calcium channel blockers, beta-blockers, sympatholytic agents, antiarrhythmics), and agents that may be responsible should be withdrawn prior to making the diagnosis. Another presentation is of recurrent supraventricular tachycardias (paroxysmal reentry tachycardias, atrial flutter, and atrial fibrillation), associated with bradyarrhythmias ("tachy-brady syndrome"). The long pauses that often follow the termination of tachycardia cause the associated symptoms.

Sick sinus syndrome occurs most commonly in elderly patients and is frequently seen in patients with concomitant atrial fibrillation. The pathologic changes are usually nonspecific, characterized by patchy fibrosis of the sinus node and cardiac conduction system. Sick sinus syndrome may rarely be caused by other conditions, including sarcoidosis, amyloidosis, Chagas disease, and various cardiomyopathies. Coronary disease is an uncommon cause.

Clinical Findings

Most patients with ECG evidence of sick sinus syndrome are asymptomatic, but rare individuals may experience syncope, dizziness, confusion, palpitations, heart failure, or angina. Because these symptoms are either nonspecific or are due to other causes, it is essential that they be demonstrated to coincide temporally with arrhythmias. This may require prolonged ambulatory monitoring or the use of an event recorder.

Treatment

Most symptomatic patients will require permanent pacing (see AV Block, below). Dual-chamber pacemaker implantation is preferred because atrial-only pacing is associated with a higher incidence of subsequent atrial fibrillation, and subsequent AV block occurs at a rate of 2% per year, necessitating reoperation in patients without a ventricular lead. Treatment of associated tachyarrhythmias is often difficult without first instituting pacing, since beta-blockers, calcium-channel blockers, digoxin, and other antiarrhythmic agents may exacerbate the bradycardia. Unfortunately, symptomatic relief following pacing has not been consistent, largely because of inadequate documentation of the etiologic role of bradyarrhythmias in producing the symptom. Furthermore, many of these patients may have associated ventricular arrhythmias that may require treatment. Permanent pacing does not reduce mortality but may alleviate symptoms and improve quality of life in carefully selected patients.

AV BLOCK

AV block is categorized as first-degree (PR interval greater than 0.21 second with all atrial impulses conducted), second-degree (intermittent blocked beats), or thirddegree (complete heart block, in which no supraventricular impulses are conducted to the ventricles).

Second-degree block is further subclassified. In **Mobitz type I**

(Wenckebach) AV block, the AV conduction time (PR interval) progressively lengthens, with the RR interval shortening before the blocked beat; this phenomenon is almost always due to abnormal conduction within the AV node. In **Mobitz type II AV block**, there are intermittently nonconducted atrial beats not preceded by lengthening AV conduction. It is usually due to block within the His bundle system. The classification as Mobitz type I or Mobitz type II is difficult when only 2:1 AV block is present on the ECG. If the width of the QRS complex is narrow (less than 0.12 second), the block is usually nodal; if the QRS complex is wide (0.12 second or more), the block is more likely infranodal. In addition, the presence of PR prolongation (greater than 0.21 second) during 2:1 AV block suggests nodal disease and therefore Mobitz type I AV block. Electrophysiologic studies may be necessary for accurate localization. Management of AV block in acute myocardial infarction has already been discussed.

First-degree and **Mobitz type I block** may occur in normal individuals with heightened vagal tone. They may also occur as a drug effect (especially digitalis, calcium channel blockers, beta-blockers, or other sympatholytic agents), often superimposed on organic disease. These disturbances also occur transiently or chronically due to ischemia, infarction, inflammatory processes (including Lyme disease), fibrosis, calcification, or infiltration. The prognosis is usually good, since reliable alternative pacemakers arise from the AV junction below the level of block if higher degrees of block occur.

Mobitz type II block is almost always due to organic disease involving the infranodal conduction system. In the event of progression to complete heart block, alternative pacemakers are not reliable. Thus, prophylactic ventricular pacing is usually required.

Complete (third-degree) heart block is a more advanced form of block often due to a lesion distal to the His bundle and associated with bilateral bundle branch block. The QRS is wide and the ventricular rate is slower, usually less than 50 beats/min. Transmission of atrial impulses through the AV node is completely blocked, and a ventricular pacemaker maintains a slow, regular ventricular rate, usually less than 45 beats/min. Exercise does not increase the rate. Patients may be asymptomatic or may complain of weakness or dyspnea if the rate is less than 35 beats/min; symptoms may occur at higher rates if the left ventricle cannot increase its stroke output. During periods of transition from partial to complete heart block, some patients have ventricular asystole that lasts several seconds or longer. Syncope occurs abruptly.

Patients with episodic or chronic infranodal complete heart block require permanent pacing, and temporary pacing is indicated if implantation of a permanent pacemaker is delayed.

Treatment

The indications for **permanent pacing** are symptomatic bradyarrhythmias, asymptomatic Mobitz II AV block, or complete heart block. A standardized nomenclature for pacemaker generators is used, usually consisting of four letters. The first letter refers to the chamber that is stimulated (A = atrium, V = ventricle, D

= dual, for both). The second letter refers to the chamber in which sensing occurs (also A, V, or D). The third letter refers to the sensory mode (I = inhibition by a sensed impulse, T = triggering by a sensed impulse, D = dual modes of response). The fourth letter refers to the programmability or rate modulation capacity (usually P for programming for two functions, M for programming more than two, and R for rate modulation).

A dual-chamber multiple programmable pacemaker that senses and paces in both chambers is the most physiologic approach to pacing patients who remain in sinus rhythm. AV synchrony is particularly important in patients in whom atrial contraction produces a substantial increment in stroke volume and in those in whom sensing the atrial rate to provide rate-responsive ventricular pacing is useful. In patients with single-chamber ventricular pacemakers, the lack of an atrial kick may lead to the so-called pacemaker syndrome, in which the patient experiences signs of low cardiac output while upright. In patients with complete heart block with left ventricular systolic dysfunction, implantation of a pacemaker capable of simultaneous left and right ventricular pacing (CRT-P) may be indicated.

Pulse generators are also available that can increase their rate in response to motion or respiratory rate when the intrinsic atrial rate is inappropriately low. These are most useful in active individuals. Follow-up after pacemaker implantation, usually by telephonic monitoring, is essential. All pulse generators and lead systems have an early failure rate that is now well below 1% and an expected battery life varying from 6 years to 10 years.

AV DISSOCIATION

When a ventricular pacemaker is firing at a rate faster than or close to the sinus rate (accelerated idioventricular rhythm, ventricular premature beats, or ventricular tachycardia), atrial impulses arriving at the AV node when it is refractory may not be conducted. This phenomenon is AV dissociation but does not necessarily indicate AV block. No treatment is required aside from management of the causative arrhythmia.

INTRAVENTRICULAR CONDUCTION DEFECTS

Intraventricular conduction defects, including bundle branch block, are common in individuals with otherwise normal hearts and in many disease processes, including ischemic heart disease, inflammatory disease, infiltrative disease, cardiomyopathy, and postcardiotomy. Bifascicular block is present when two of these—right bundle, left anterior, and left posterior fascicle—are involved. Trifascicular block is defined as right bundle branch block with alternating left hemiblock, alternating right and left bundle branch block, or bifascicular block with documented prolonged infranodal conduction (long His-ventricular interval).

The prognosis of intraventricular block is generally related to the underlying myocardial process. Patients with no apparent heart disease have an overall survival rate similar to that of matched controls. However, left bundle branch block—but

not right—is associated with a higher risk of development of overt cardiac disease and cardiac mortality. In patients with underlying coronary heart disease, both right and left bundle branch block are associated with higher cardiovascular and all-cause mortality.

In asymptomatic patients with bifascicular block, the incidence of occult complete heart block or progression to it is low and pacing is not usually warranted. However, when syncope is present in patients with bifascicular block and no other readily identifiable cause is found, early pacemaker implantation has been shown to reduce further episodes.

Control questions

1. Anatomical and physiological features of the structure of the conducting system of the heart.
2. Characteristics of the main functions of the heart: electrophysiological - automatism, excitability, conductivity, refractoriness; mechanical - contractility, tonicity.
3. Major complaints, symptoms and research in various types of arrhythmias.
4. Pathogenesis and electrophysiological mechanisms of heart rhythm and conduction disorders.
5. Classification of violations of heart rate and conduction. Clinical and electrocardiographic manifestations.
6. Sinus tachycardia - etiology, clinical picture, principles of pharmacotherapy.
7. Sinus bradycardia - etiology, clinical picture, principles of pharmacotherapy.
8. Syndrome of weakness of the sinus-atrium node - etiology, clinical picture, principles of pharmacotherapy.
9. Vaginal tachycardia - etiology, clinical picture, principles of pharmacotherapy.
10. Oncological extrasystoles - etiology, clinical picture, principles of pharmacotherapy.
11. Ventricular extrasystoles - etiology, clinical picture, principles of pharmacotherapy.
12. Ventricular paroxysmal tachycardia - etiology, clinical picture, pharmacotherapy.
13. Flushing arrhythmia (atrial fibrillation) - etiology, clinical picture, pharmacotherapy.
14. Blockade of the heart - etiology, clinical picture, pharmacotherapy.
15. Fibrillation of the ventricles - etiology, clinical picture, pharmacotherapy.
16. Modern approaches to pharmacotherapy of arrhythmias and requirements for antiarrhythmic drugs.
17. Classification of antiarrhythmic drugs.

List of practical works

A. Homework.

1. To know the classification, the clinic of arrhythmias.
2. Be able to provide first aid with tachyarrhythmias and bradiarrhythmias.
3. To study the main directions of treatment of various types of arrhythmias.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data of laboratory and instrumental studies, examination of consultants, records of the attending physician) and the letter of medical appointments.
3. At examination of the patient to allocate subjective, physical, laboratory-instrumental signs of violation of heart rhythm and conductivity.
4. Write a clinical diagnosis:
a) the underlying disease; complications of the underlying disease;
b) concomitant diseases.
5. Define a group of LS necessary to correct the existing violations.
6. On the basis of theoretical data and own observations, to make a choice of the specific drug of the examined patient.

Control the level of knowledge

1. Fill in the table "Medicines for the treatment of arrhythmias that are life-threatening".

Type of arrhythmias	Medicine	Way of administration, dose
1. Prednisolucular paroxysmal tachycardia 2.Paroxysm of atrial fibrillation 3. Atrial flutter 4. Throat and fibrillation of the ventricles		

2. Fill in the table "Medications for long-term treatment of arrhythmias".

Type of arrhythmias	Medicine	Way of administration, dose

1. Sinus tachycardia 2. Synovial bradycardia 3.Extracystolarya of the atria 4. Vestibular ecstasy 5.Permanent form of atrial fibrillation 6.Internal heart block		

Solution of situational tasks

1. The cardiologic department is delivered to a patient with acute myocardial infarction, complicated by an attack of paroxysmal tachycardia. The attack was shot by intravenous drip administration of lidocaine. After the attack: pulse - 80-88 ace. for 1 min, rhythmic, AT - 100/70 mm Hg, tons of hearts are deaf. In the lungs there is a small amount of wet wheezing on both sides. A few hours after the termination of the administration of lidocaine, the attack was repeated, it was taken by Novocaine, but it was repeated.

Explain the cause of the ineffectiveness of typical antiarrhythmics. Take correction of treatment. Make a list of drugs that can not be used in conjunction with strophanthin.

2. A man, 47 years old, complains of periodic headaches, palpitations and heart rhythm disorders, Objectively: tone of the heart muffled, heart rate - 90 for 1 min, blood pressure - 170/100 mm Hg. Art. ECG: left ventricular hypertrophy, ventricular extrasystoles with a frequency of 10-15 for 1 min. Diagnosis is established: hypertension and CHD.

What drugs should be prescribed for treating a rhythm disorder in this patient?

3. A patient, 70 years old, with CHD and postinfarction cardiosclerosis suddenly appeared heart attack. Pulse - 140 per minute, weak. AT - 100/60 mm Hg Art. On ECG - expansion of the complex QRS (0.13 pp.) And negative tones of T in classical leads. The reflexive methods used to relieve heart attacks have not yielded an effect.

Formulate a clinical diagnosis. What drugs should be used in this case?

4. Due to the persistent stenocardiac pains of the patient, 56 years old, they were admitted to a hospital where the ST segment was increased by 5 mm with the formation of a QR tooth in the leads V1-V4. In the first day there was a state of clinical death, in the future - frequent episodes of extrasystoles.

What is the tactic of further treatment of this patient?

5. A patient, 45 years old, with a small-centered myocardial infarction complains of a feeling of interruptions in the area of the heart. On ECG: absence of teeth P, waves f in leads II, III, aVF, V1 V2, nerve ventricular complexes, heart rate - 220 for 1 min, AT - 100/70 mm Hg. For the treatment of an attack, obidin, verapamil, novocaineamid, cordaron, hylouritmal, but without a positive effect during 2 days were used.

Appoint a treatment and justify it.

Test tasks

1. What is the normal heart rate in an adult?

1.40-60 ah. per minute
2.50-70 ah. per minute
3.60-80 ah. per minute
4.70-90 ah. per minute
5.80-90 ah. per minute

2. Specify the drug of choice for the treatment of ventricular rhythm disturbances hearts in patients with acute myocardial infarction:

1.Lidokain.
2.Verapamil.
3.Diltiasem.
4.Hinidine.
5.Fenigidin.

3. For violations of intracardiac conduction use:

1.Anaprilin
2.Isoptin.
3.Izadrin
4.Novokainamid.
5.Amiodarone

4. A patient with chronic CHN, a tachysystolic form, has been diagnosed with 68 years flashing arrhythmia. He is shown:

1.Gerlic glycosides
2.Blocator calcium channels.
3.Beta-adrenoblockers.
4.Myogenic antispasmodics.
5.Nitrates.

HEART FAILURE

ESSENTIALS OF DIAGNOSIS

- LV failure: Either due to systolic or diastolic dysfunction. Predominant symptoms are those of low cardiac output and congestion, including dyspnea.
- RV failure: Symptoms of fluid overload predominate; usually RV failure is secondary to LV failure.
- Assessment of LV function is a crucial part of diagnosis and management.
- Optimal management of chronic heart failure includes combination medical therapies, such as ACE inhibitors, aldosterone antagonists, and beta-blockers.

General Considerations

Heart failure is a common syndrome that is increasing in incidence and prevalence. Approximately 5 million patients in the United States have heart failure, and there are around 800,000 new cases each year. Each year in the United States, over 1 million patients are discharged from the hospital with a diagnosis of heart failure. It is primarily a disease of aging, with over 75% of existing and new cases occurring in individuals over 65 years of age. Seventy-five percent of heart failure patients have antecedent hypertension. The prevalence of heart failure rises from less than 1% in individuals below 60 years to nearly 10% in those over 80 years of age.

Heart failure may be right sided or left sided (or both). Patients with **left heart failure** may have symptoms of low cardiac output and elevated pulmonary venous pressure; dyspnea is the predominant feature. Signs of fluid retention predominate in **right heart failure**. Most patients exhibit symptoms or signs of both right- and left-sided failure, and LV dysfunction is the primary cause of RV failure. Approximately half of patients with heart failure have **preserved LV systolic function** and usually have some degree of diastolic dysfunction. Patients with reduced or preserved systolic function may have similar symptoms and it may be difficult to distinguish clinically between the two based on signs and symptoms. In developed countries, CAD with resulting myocardial infarction and loss of functioning myocardium (ischemic cardiomyopathy) is the most common cause of **systolic heart failure**. Systemic hypertension remains an important cause of heart failure and, even more commonly in the United States, an exacerbating factor in patients with cardiac dysfunction due to other causes, such as CAD. Several processes may present with dilated or congestive cardiomyopathy, which is characterized by LV or biventricular dilation and generalized systolic dysfunction. These are discussed elsewhere in this chapter, but the most common are alcoholic cardiomyopathy, viral myocarditis (including infections by HIV), and dilated cardiomyopathies with no obvious underlying cause (idiopathic cardiomyopathy). Rare causes of dilated cardiomyopathy include infiltrative diseases (hemochromatosis, sarcoidosis, amyloidosis, etc), other infectious agents, metabolic disorders, cardiotoxins, and drug toxicity. VHDs—particularly degenerative aortic stenosis and chronic aortic or mitral regurgitation—are not infrequent causes of heart failure. Persistent tachycardia, often related to atrial arrhythmias, can cause systolic dysfunction that may be reversible with controlling the rate. **Diastolic**

cardiac dysfunction is associated with aging and related myocardial stiffening, as well as LVH, commonly resulting from hypertension. Conditions such as hypertrophic or restrictive cardiomyopathy, diabetes, and pericardial disease can produce the same clinical picture. Atrial fibrillation with or without rapid ventricular response may contribute to impaired left ventricular filling.

Heart failure is often preventable by early detection of patients at risk and by early intervention. The importance of these approaches is emphasized by US guidelines that have incorporated a classification of heart failure that includes four stages. Stage A includes patients at risk for developing heart failure (such as patients with hypertension). In the majority of these patients, development of heart failure can be prevented with interventions such as the aggressive treatment of hypertension, modification of coronary risk factors, and reduction of excessive alcohol intake. Stage B includes patients who have structural heart disease but no current or previously recognized symptoms of heart failure. Examples include patients with previous myocardial infarction, other causes of reduced systolic function, LVH, or asymptomatic valvular disease. Both ACE inhibitors and beta-blockers prevent heart failure in the first two of these conditions, and more aggressive treatment of hypertension and early surgical intervention are effective in the latter two. Stages C and D include patients with clinical heart failure and the relatively small group of patients that has become refractory to the usual therapies, respectively.

Clinical Findings

A. Symptoms

The most common symptom of patients with **left heart failure** is shortness of breath, chiefly exertional dyspnea at first and then progressing to orthopnea, paroxysmal nocturnal dyspnea, and rest dyspnea. Chronic nonproductive cough, which is often worse in the recumbent position, may occur. Nocturia due to excretion of fluid retained during the day and increased renal perfusion in the recumbent position is a common nonspecific symptom of heart failure, as is fatigue and exercise intolerance. These symptoms correlate poorly with the degree of cardiac dysfunction. Patients with **right heart failure** have predominate signs of fluid retention, with the patient exhibiting edema, hepatic congestion and, on occasion, loss of appetite and nausea due to edema of the gut or impaired gastrointestinal perfusion and ascites. Surprisingly, some individuals with severe LV dysfunction will display few signs of left heart failure and appear to have isolated right heart failure. Indeed, they may be clinically indistinguishable from patients with cor pulmonale, who have right heart failure secondary to pulmonary disease.

Patients with **acute heart failure** from myocardial infarction, myocarditis, and acute valvular regurgitation due to endocarditis or other conditions usually present with pulmonary edema. Patients with episodic symptoms may be having LV dysfunction due to intermittent ischemia. Patients may also present with acute exacerbations of chronic, stable heart failure. Exacerbations are usually caused by alterations in therapy (or patient noncompliance), excessive salt and fluid intake,

arrhythmias, excessive activity, pulmonary emboli, intercurrent infection, or progression of the underlying disease.

Patients with **heart failure** are often categorized by the NYHA **classification as class I (asymptomatic), class II (symptomatic with moderate activity), class III (symptomatic with mild activity), or class IV (symptomatic at rest)**. This classification is important since some of the treatments are indicated based on NYHA classification.

B. Signs

Many patients with heart failure, including some with severe symptoms, appear comfortable at rest. Others will be dyspneic during conversation or minor activity, and those with long-standing severe heart failure may appear cachectic or cyanotic. The vital signs may be normal, but tachycardia, hypotension, and reduced pulse pressure may be present. Patients often show signs of increased sympathetic nervous system activity, including cold extremities and diaphoresis. Important peripheral signs of heart failure can be detected by examination of the neck, the lungs, the abdomen, and the extremities. RA pressure may be estimated through the height of the pulsations in the jugular venous system. In addition to the height of the venous pressure, abnormal pulsations, such as regurgitant v waves, should be sought. Examination of the carotid pulse may allow estimation of pulse pressure as well as detection of aortic stenosis. Thyroid examination may reveal occult hyperthyroidism or hypothyroidism, which are readily treatable causes of heart failure. Crackles at the lung bases reflect transudation of fluid into the alveoli. Pleural effusions may cause bibasilar dullness to percussion. Expiratory wheezing and rhonchi may be signs of heart failure. Patients with severe right heart failure may have hepatic enlargement—tender or nontender—due to passive congestion. Systolic pulsations may be felt in tricuspid regurgitation. Sustained moderate pressure on the liver may increase jugular venous pressure (a positive hepatojugular reflux is an increase of greater than 1 cm). Ascites may also be present. Peripheral pitting edema is a common sign in patients with right heart failure and may extend into the thighs and abdominal wall.

Cardinal cardiac examination signs are a parasternal lift, indicating pulmonary hypertension; an enlarged and sustained LV impulse, indicating LV dilation and hypertrophy; a diminished first heart sound, suggesting impaired contractility; and an S3 gallop originating in the LV and sometimes the RV. An S4 is usually present in diastolic heart failure. Murmurs should be sought to exclude primary valvular disease; secondary mitral regurgitation and tricuspid regurgitation murmurs are common in patients with dilated ventricles. In chronic heart failure, many of the expected signs of heart failure may be absent despite markedly abnormal cardiac function and hemodynamic measurements.

C. Laboratory Findings

A blood count may reveal anemia and a high red-cell distribution width (RDW), both of which are associated with poor prognosis in chronic heart failure through poorly understood mechanisms. Kidney function tests can determine

whether cardiac failure is associated with impaired kidney function that may reflect poor kidney perfusion. Chronic kidney disease is another poor prognostic factor in heart failure and may limit certain treatment options. Serum electrolytes may disclose hypokalemia, which increases the risk of arrhythmias; hyperkalemia, which may limit the use of inhibitors of the renin–angiotensin system; or hyponatremia, an indicator of marked activation of the renin–angiotensin system and a poor prognostic sign. Thyroid function should be assessed to detect occult thyrotoxicosis or myxedema, and iron studies should be checked to test for hemochromatosis. In unexplained cases, appropriate biopsies may lead to a diagnosis of amyloidosis. Myocardial biopsy may exclude specific causes of dilated cardiomyopathy but rarely reveals specific reversible diagnoses.

Serum BNP is a powerful prognostic marker that adds to clinical assessment in differentiating dyspnea due to heart failure from noncardiac causes. Two markers—BNP and NT-proBNP—provide similar diagnostic and prognostic information. BNP is expressed primarily in the ventricles and is elevated when ventricular filling pressures are high. It is quite sensitive in patients with symptomatic heart failure—whether due to systolic or to diastolic dysfunction—but less specific in older patients, women, and patients with COPD. Studies have shown that BNP can help in emergency department triage in the diagnosis of acute decompensated heart failure, such that an NT-proBNP less than 300 pg/mL or BNP less than 100 pg/ mL, combined with a normal ECG, makes heart failure unlikely. BNP is less sensitive and specific to diagnose heart failure in the chronic setting. BNP may be helpful in guiding the intensity of diuretic and a more consistent use of disease-modifying therapies, such as ACE inhibitors and beta-blockers, for the management of chronic heart failure. Worsening breathlessness or weight associated with a rising BNP (or both) might prompt increasing the dose of diuretics. However, to date, in spite of evidence from a meta-analysis of randomized trials showing benefit from using BNP to guide therapy, particularly for patients younger than 75 years, practice guidelines have not yet recommended this strategy. Elevation of serum troponin, and especially of high-sensitivity troponin, is common in both chronic and acute heart failure, and it is associated with higher risk of adverse outcomes.

D. ECG and Chest Radiography

ECG may indicate an underlying or secondary arrhythmia, myocardial infarction, or nonspecific changes that often include low voltage, intraventricular conduction defects, LVH, and nonspecific repolarization changes. Chest radiographs provide information about the size and shape of the cardiac silhouette. Cardiomegaly is an important finding and is a poor prognostic sign. Evidence of pulmonary venous hypertension includes relative dilation of the upper lobe veins, perivascular edema (haziness of vessel outlines), interstitial edema, and alveolar fluid. In **acute heart failure**, these findings correlate moderately well with pulmonary venous pressure. However, patients with **chronic heart failure** may show relatively normal pulmonary vasculature despite markedly elevated pressures. Pleural effusions are common and tend to be bilateral or right-sided.

E. Additional Studies

Many studies have indicated that the clinical diagnosis of systolic myocardial dysfunction is often inaccurate. The primary confounding conditions are diastolic dysfunction of the heart with decreased relaxation and filling of the LV (particularly in hypertension and in hypertrophic states) and pulmonary disease. Because patients with heart failure usually have significant resting ECG abnormalities, stress imaging procedures, such as perfusion scintigraphy or dobutamine echocardiography, are often indicated.

The most useful test is the echocardiogram because it can differentiate heart failure with and without preserved LV systolic function. The echocardiogram can define the size and function of both ventricles and of the atria. It will also allow detection of pericardial effusion, valvular abnormalities, intracardiac shunts, and segmental wall motion abnormalities suggestive of old myocardial infarction as opposed to more generalized forms of dilated cardiomyopathy.

Radionuclide angiography as well as cardiac MRI also measure LVEF and permit analysis of regional wall motion. These tests are especially useful when echocardiography is technically suboptimal, such as in patients with severe pulmonary disease. When myocardial ischemia is suspected as a cause of LV dysfunction, stress testing should be performed.

F. Cardiac Catheterization

In most patients with heart failure, clinical examination and noninvasive tests can determine LV size and function and valve function to confirm the diagnosis. Left heart catheterization may be helpful to define the presence and extent of CAD, although CT angiography may also be appropriate, especially when the likelihood of coronary disease is low. Evaluation for coronary disease is particularly important when LV dysfunction may be partially reversible by revascularization. The combination of angina or noninvasive evidence of significant myocardial ischemia with symptomatic heart failure is often an indication for coronary angiography if the patient is a potential candidate for revascularization. Right heart catheterization may be useful to select and monitor therapy in patients refractory to standard therapy.

Treatment:

Heart Failure with Reduced EF

The treatment of heart failure is aimed at relieving symptoms, improving functional status, and preventing death and hospitalizations. The evidence of clinical benefit, including reducing death and hospitalization, of most therapies is limited to patients with heart failure with reduced LVEF. Treatment of heart failure with preserved LV ejection is aimed at improving symptoms and treating comorbidities.

A. Correction of Reversible Causes

The major reversible causes of heart failure with reduced EF, also called chronic systolic heart failure, include valvular lesions, myocardial ischemia, uncontrolled hypertension, arrhythmias (especially persistent tachycardias), alcohol- or drug-induced myocardial depression, intracardiac shunts, and high-output states. Calcium channel blockers with negative inotropy (specifically verapamil or diltiazem), antiarrhythmic drugs, thiazolidinediones, and nonsteroidal anti-inflammatory agents may be important contributors to worsening heart failure. Some metabolic and infiltrative cardiomyopathies may be partially reversible, or their progression may be slowed; these include hemochromatosis, sarcoidosis, and amyloidosis. Once possible reversible components are being addressed, the measures outlined below are appropriate.

B. Pharmacologic Treatment

See also the following section on Acute Heart Failure & Pulmonary Edema.

1. Diuretic therapy—Diuretics are the most effective means of providing symptomatic relief to patients with moderate to severe heart failure with dyspnea and fluid overload, for heart failure with reduced and with preserved LVEF. Few patients with symptoms or signs of fluid retention can be optimally managed without a diuretic. However, excessive diuresis can lead to electrolyte imbalance and neurohormonal activation. *A combination of a diuretic and an ACE inhibitor should be the initial treatment in most symptomatic patients with heart failure and reduced LVEF, with the early addition of a beta-blocker.*

When fluid retention is mild, thiazide diuretics or a similar type of agent (hydrochlorothiazide, 25–100 mg; metolazone, 2.5–5 mg; chlorthalidone, 25–50 mg; etc) may be sufficient. Thiazide or related diuretics often provide better control of hypertension than short-acting loop agents. The thiazides are generally ineffective when the glomerular filtration rate falls below 30–40 mL/min, a not infrequent occurrence in patients with severe heart failure. Metolazone maintains its efficacy down to a glomerular filtration rate of approximately 20–30 mL/min.

Patients with more severe heart failure should be treated with one of the oral loop diuretics. These include furosemide (20–320 mg daily), bumetanide (1–8 mg daily), and torsemide (20–200 mg daily). These agents have a rapid onset and a relatively short duration of action. In patients with preserved kidney function, two or more daily doses are preferable to a single larger dose. In acute situations or when gastrointestinal absorption is in doubt, they should be given intravenously. Torsemide may be effective when furosemide is not, including related to better absorption and a longer half life. Larger doses (up to 500 mg of furosemide or equivalent) may be required with severe renal impairment.

The oral potassium-sparing agents are often useful in combination with the loop diuretics and thiazides. Triamterene (37.5–75 mg daily) and amiloride (5–10 mg daily) act on the distal tubule to reduce potassium secretion. Their diuretic potency is only mild and not adequate for most patients with heart failure, but they may minimize the hypokalemia induced by more potent agents.

Spironolactone (12.5–100 mg daily) and eplerenone (25–100 mg daily) are specific inhibitors of aldosterone, which is often increased in heart failure. These

drugs spare loss of potassium, they have some diuretic effect (especially at higher doses), and they also improve clinical outcomes, including survival (see below). Their onsets of action are slower than the other potassium-sparing agents, and spironolactone's side effects include gynecomastia. Combinations of potassium supplements or ACE inhibitors and potassium-sparing drugs can produce hyperkalemia but have been used with success in patients with persistent hypokalemia.

Patients with refractory edema may respond to combinations of a loop diuretic and thiazide-like agents. Metolazone, because of its maintained activity with chronic kidney disease, is the most useful agent for such a combination. Extreme caution must be observed with this approach, since massive diuresis and electrolyte imbalances often occur; 2.5 mg of metolazone orally should be added to the previous dosage of loop diuretic. In many cases this is necessary only once or twice a week, but dosages up to 10 mg daily have been used in some patients.

2. Inhibitors of the renin–angiotensin–aldosterone system—Inhibition of the renin–angiotensin–aldosterone system with ACE inhibitors should be part of the initial therapy of this syndrome based on their life-saving benefits.

A. Ace inhibitors—At least seven ACE inhibitors have been shown to be effective for the treatment of heart failure or the related indication of postinfarction LV dysfunction. ACE inhibitors reduce mortality by approximately 20% in patients with symptomatic heart failure and have also been shown to prevent hospitalizations, increase exercise tolerance, and reduce symptoms in these patients. As a result, ACE inhibitors should be part of first-line treatment of patients with symptomatic LV systolic dysfunction (EF less than 40%), usually in combination with a diuretic. They are also indicated for the management of patients with reduced EFs without symptoms because they prevent the progression to clinical heart failure.

Because ACE inhibitors may induce significant hypotension, particularly following the initial doses, they must be started with caution. Hypotension is most prominent in patients with already low BPs (systolic pressure less than 100 mm Hg), hypovolemia, prerenal azotemia (especially if it is diuretic induced), and hyponatremia (an indicator of activation of the renin–angiotensin system). These patients should generally be started at low dosages (captopril 6.25 mg orally three times daily, enalapril 2.5 mg orally daily, or the equivalent), but other patients may be started at twice these dosages. Within several days (for those with the markers of higher risk) or at most 2 weeks, patients should be questioned about symptoms of hypotension, and both kidney function and K+ levels should be monitored.

ACE inhibitors should be titrated to the dosages proved effective in clinical trials (captopril 50 mg three times daily, enalapril 10 mg twice daily, ramipril 10 mg daily, lisinopril 20 mg daily, or the equivalent) over a period of 1–3 months. Most patients will tolerate these doses. Asymptomatic hypotension is not a contraindication to up-titrating or continuing ACE inhibitors.

B. Angiotensin II receptor blockers—Another approach to inhibiting the renin–angiotensin–aldosterone system is the use of specific ARBs, which will decrease adverse effects of angiotensin II by blocking the AT1 receptor. In addition, because there are alternative pathways of angiotensin II production in many tissues, the receptor blockers may provide more complete blockade of the AT1 receptor. However, these agents do not share the effects of ACE inhibitors on other potentially important pathways that produce increases in bradykinin, prostaglandins, and nitric oxide in the heart, blood vessels, and other tissues. ARBs, specifically candesartan or valsartan, provide important benefits as an alternative to, and in addition to, ACE inhibitors in chronic heart failure with reduced LVEF. (A large trial of patients with chronic heart failure and preserved LVEF found no benefit from the ARB irbesartan.)

C. Spironolactione and eplerenone—Inhibiting aldosterone has become a mainstay of management of symptomatic heart failure with reduced LVEF. The RALES trial compared spironolactone 25 mg daily with placebo in patients with advanced heart failure (current or recent class IV) already receiving ACE inhibitors and diuretics and showed a 29% reduction in mortality as well as similar decreases in other clinical end points. Hyperkalemia was uncommon in this severe heart failure clinical trial population, which was maintained on high doses of diuretic, but hyperkalemia with spironolactone appears to be common in general practice. Potassium levels should be monitored closely during initiation of spironolactone (after 1 and 4 weeks of therapy), particularly for patients with even mild degrees of kidney injury, and in patients receiving ACE inhibitors. Based on the EMPHASIS-HF trial, the efficacy and safety of aldosterone antagonism—in the form of eplerenone, 25–50 mg orally daily—is established for patients with mild or moderate heart failure. *Careful monitoring of serum potassium levels, in particular for patients with any degree of kidney failure, is important to avoid lifethreatening hyperkalemia. Serum potassium should be checked within 1 week of initiating an aldosterone blocker and periodically thereafter.*

3. Beta-blockers—Beta-blockers are part of the foundation of care of chronic heart failure based on their lifesaving benefits. The mechanism of this benefit remains unclear, but it is likely that chronic elevations of catecholamines and sympathetic nervous system activity cause progressive myocardial damage, leading to worsening LV function and dilation. The primary evidence for this hypothesis is that over a period of 3–6 months, beta-blockers produce consistent substantial rises in EF (averaging 10% absolute increase) and reductions in LV size and mass.

Three drugs have strong evidence of reducing mortality: carvedilol (a nonselective beta-1- and beta-2-receptor blocker), the beta-1-selective extended-release agent metoprolol succinate (but not short-acting metoprolol tartrate), and bisoprolol (beta-1-selective agent). This has led to a strong recommendation that stable patients (defined as having no recent deterioration or evidence of volume overload) with mild, moderate, and even severe heart failure should be treated with

a beta-blocker unless there is a noncardiac contraindication. One trial comparing carvedilol and (short-acting) metoprolol tartrate (COMET) found significant reductions in allcause mortality and cardiovascular mortality with carvedilol. Thus, patients with chronic heart failure should be treated with extended-release metoprolol succinate, bisoprolol, or carvedilol, but not short-acting metoprolol tartrate.

Because even apparently stable patients may deteriorate when beta-blockers are initiated, initiation must be done gradually and with great care. Carvedilol is initiated at a dosage of 3.125 mg orally twice daily and may be increased to 6.25, 12.5, and 25 mg twice daily at intervals of approximately 2 weeks. The protocols for sustained-release metoprolol use were started at 12.5 or 25 mg orally daily and doubled at intervals of 2 weeks to a target dose of 200 mg daily (using the Toprol XL sustained-release preparation). Bisoprolol was administered at a dosage of 1.25, 2.5, 3.75, 5, 7.5, and 10 mg orally daily, with increments at 1- to 4-week intervals. More gradual up-titration is often more convenient and may be better tolerated. The SENIORS trial of 2135 patients found that nebivolol was effective in elderly patients (70 years and older) with chronic heart failure, although the evidence of degree of benefit was not as strong as with the three proven beta-blockers carvedilol, metoprolol succinate, or bisoprolol.

Patients should be instructed to monitor their weights at home as an indicator of fluid retention and to report any increase or change in symptoms immediately. Before each dose increase, patients should be seen and examined to ensure that there has not been fluid retention or worsening of symptoms. If heart failure worsens, this can usually be managed by increasing diuretic doses and delaying further increases in beta-blocker doses, though downward adjustments or discontinuation is sometimes required. Carvedilol, because of its beta-blocking activity, may cause dizziness or hypotension. This can usually be managed by reducing the doses of other vasodilators and by slowing the pace of dose increases.

4. Digitalis glycosides—The efficacy of digitalis glycosides in reducing the symptoms of heart failure has been established in at least four multicenter trials that have demonstrated that digoxin withdrawal is associated with worsening symptoms and signs of heart failure, more frequent hospitalizations for decompensation, and reduced exercise tolerance. Digoxin should be considered for patients who remain symptomatic when taking diuretics and ACE inhibitors as well as for patients with heart failure who are in atrial fibrillation and require rate control.

Digoxin has a half-life of 24–36 hours and is eliminated almost entirely by the kidneys. The oral maintenance dose may range from 0.125 mg three times weekly to 0.5 mg daily. It is lower in patients with kidney dysfunction, in older patients, and in those with smaller lean body mass. Although an oral loading dose of 0.75–1.25 mg (depending primarily on lean body size) over 24–48 hours may be given if an early effect is desired, in most patients with chronic heart failure it is sufficient to begin with the expected maintenance dose (usually 0.125–0.25 mg daily). Amiodarone, quinidine, propafenone, and verapamil are among the drugs that may increase digoxin levels up to 100%. It is prudent to measure a blood level

after 7–14 days (and at least 6 hours after the last dose was administered). Optimum serum digoxin levels are 0.7–1.2 ng/mL, though clinically evident toxicity is rare with levels less than 1.8 ng/mL. Digoxin may induce ventricular arrhythmias, especially when hypokalemia or myocardial ischemia is present. Once an appropriate maintenance dose is established, subsequent levels are usually not indicated unless there is a change in kidney function or medications that affects digoxin levels or a significant deterioration in cardiac status that may be associated with reduced clearance.

5. Nitrates and hydralazine—Although ACE inhibitors, which have vasodilating properties, improve prognosis, such a benefit is not established with the direct-acting vasodilators. The combination of hydralazine and isosorbide dinitrate has been shown to improve outcome in African Americans, but the effect is less clear than the well-established benefits of ACE inhibitors. The 2012 European guidelines give hydralazine and isosorbide dinitrate a modest class IIb recommendation for patients with reduced LVEF who are unable to tolerate ACE inhibitor and ARB therapy or who have persistent symptoms despite treatment with a beta-blocker, ACE inhibitor, and aldosterone antagonist.

A. Nitrates—Intravenous vasodilators (sodium nitroprusside or nitroglycerin) are used primarily for acute or severely decompensated chronic heart failure, especially when accompanied by hypertension or myocardial ischemia. If neither of the latter is present, therapy is best initiated and adjusted based on hemodynamic measurements. The starting dosage for nitroglycerin is generally about 10 mcg/min, which is titrated upward by 10–20 mcg/min (to a maximum of 200 mcg/min) until mean arterial pressure drops by 10%. Hypotension (BP less than 100 mm Hg systolic) should be avoided. For sodium nitroprusside, the starting dosage is 5–10 mcg/min, with upward titration to a maximum dose of 400 mcg/min.

Isosorbide dinitrate, 20–40 mg orally three times daily, and nitroglycerin ointment, 2%, 15–16 mg (1.4 inches; 1 inch = 15 mg) every 6–8 hours, appears to be equally effective, although the ointment is generally reserved for inpatient use only. The nitrates are moderately effective in relieving shortness of breath, especially in patients with mild to moderate symptoms, but less successful—probably because they have little effect on cardiac output—in advanced heart failure. Nitrate therapy is generally well tolerated, but headaches and hypotension may limit the dose of all agents. The development of tolerance to longterm nitrate therapy occurs. This is minimized by intermittent therapy, especially if a daily 8- to 12-hour nitrate-free interval is used, but probably develops to some extent in most patients receiving these agents. Transdermal nitroglycerin patches have no sustained effect in patients with heart failure and should not be used for this indication.

B. Hydralazine—Oral hydralazine is a potent arteriolar dilator; when used as a single agent, it has not been shown to improve symptoms or exercise tolerance

during longterm treatment. The combination of nitrates and oral hydralazine produces greater hemodynamic effects.

Hydralazine therapy is frequently limited by side effects. Approximately 30% of patients are unable to tolerate the relatively high doses required to produce hemodynamic improvement in heart failure (200–400 mg daily in divided doses).

6. Ivabradine—Ivabradine inhibits the If channel in the sinus node and has the specific effect of slowing sinus rate. Ivabradine is approved for use in the United States for stable patients with heart failure and heart rate of 70 beats per minute or more on maximally tolerated beta blockers. It is approved by the European Medicines Agency for use in patients with a heart rate of 75 beats per minute or more. The European guidelines give it a class IIa recommendation for patients in sinus rhythm with a heart rate of 70 beats per minute or more with an EF of 35% or less, and persisting symptoms despite treatment with an evidencebased dose of beta-blocker (or a maximum tolerated dose below that), ACE inhibitor (or ARB), and an aldosterone antagonist (or ARB). In a trial of patients with chronic angina, ivabradine did not reduce cardiovascular events, and there may have been more events with ivabradine (than placebo) in patients with symptomatic angina.

7. Combination of medical therapies—Optimal management of chronic heart failure involves using combinations of proven life-saving therapies. In addition to ACE inhibitors and beta-blockers, patients who remain symptomatic should be considered for additional therapy, in the form of ARBs (best proven in class II–III heart failure), mineralocorticoid (aldosterone) receptor antagonists, or hydralazine and isosorbide dinitrate (with some evidence of benefit in African Americans).

8. Treatments that may cause harm in heart failure with reduced LVEF—Several therapies should be avoided, when possible, in patients with systolic heart failure. These include thiazoladinediones (glitazones) that cause worsening heart failure, most calcium channel blockers (with the exception of amlodipine and felodipine), nonsteroidal antiinflammatory drugs, and cyclooxygenase-2 inhibitors that cause sodium and water retention and renal impairment, and the combination of an ACE inhibitor, ARB, and aldosterone blocker that increases the risk of hyperkalemia.

9. Anticoagulation—Patients with LV failure and reduced EF are at somewhat increased risk for developing intracardiac thrombi and systemic arterial emboli. However, this risk appears to be primarily in patients who are in atrial fibrillation, who have had thromboemboli, or who have had a large recent anterior myocardial infarction. In general, these patients should receive *warfarin* for 3 months following the myocardial infarction. Other patients with heart failure have embolic rates of approximately two per 100 patient-years of follow-up, which approximates the rate of major bleeding, and routine anticoagulation does not

appear warranted except in patients with prior embolic events or mobile LV thrombi.

10. Antiarrhythmic therapy—Patients with moderate to severe heart failure have a high incidence of both symptomatic and asymptomatic arrhythmias. Although less than 10% of patients have syncope or presyncope resulting from ventricular tachycardia, ambulatory monitoring reveals that up to 70% of patients have asymptomatic episodes of NSVT. These arrhythmias indicate a poor prognosis independent of the severity of LV dysfunction, but many of the deaths are probably not arrhythmia related. Beta-blockers, because of their marked favorable effect on prognosis in general and on the incidence of sudden death specifically, should be initiated in these as well as all other patients with heart failure. Empiric antiarrhythmic therapy with amiodarone did not improve outcome in the SCD-HeFT trial, and most other agents are contraindicated because of their proarrhythmic effects in this population and their adverse effect on cardiac function. For patients with systolic heart failure and atrial fibrillation, a rhythm control strategy has not been shown to improve outcome compared to a rate control strategy and thus should be reserved for patients with a reversible cause of atrial fibrillation or refractory symptoms. Then, amiodarone is the drug of choice.

11. Statin therapy — Even though vascular disease is present in many patients with chronic heart failure, the role of statins has not been well defined in the heart failure population. Two trials — the CORONA and the GISSI-HF trials— have failed to show benefits of statins in the chronic heart failure population.

C. Nonpharmacologic Treatment

1. Implantable cardioverter defibrillators — Randomized clinical trials have extended the indications for ICDs beyond patients with symptomatic or asymptomatic arrhythmias to the broad population of patients with chronic heart failure and LV systolic dysfunction who are receiving contemporary heart failure treatments, including beta-blockers. In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), 1232 patients with prior myocardial infarction and an EF less than 30% were randomized to an ICD or a control group. Mortality was 31% lower in the ICD group, which translated into nine lives saved for each 100 patients who received a device and were monitored for 3 years. The United States Centers for Medicare and Medicaid Services provides reimbursement coverage to include patients with chronic heart failure and ischemic or nonischemic cardiomyopathy with an EF of 35% or less.

2. Biventricular pacing (resynchronization) — Many patients with heart failure due to systolic dysfunction have abnormal intraventricular conduction that results in dyssynchronous and hence inefficient contractions. Several studies have evaluated the efficacy of “multisite” pacing, using leads that stimulate the RV from the apex and the LV from the lateral wall via the coronary sinus. Patients with wide QRS complexes (generally 120 msec or more), reduced EFs, and moderate to

severe symptoms have been evaluated. Results from trials with up to 2 years of followup have shown an increase in EF, improvement in symptoms and exercise tolerance, and reduction in death and hospitalization. The best responders to cardiac resynchronization therapy are patients with wider QRS, left bundle branch block, and nonischemic cardiomyopathy, and the lowest responders are those with narrow QRS and non–left bundle branch block pattern. Thus, as recommended in the 2013 European guidelines, resynchronization therapy is indicated for patients with class II, III, and ambulatory class IV heart failure, EF of 35% or less, and left bundle branch block pattern with QRS duration of 120 msec or more. Patients with non–left bundle branch block pattern and prolonged QRS duration may be considered for treatment.

3. Case management, diet, and exercise training

Thirty to 50 percent of heart failure patients who are hospitalized will be readmitted within 3–6 months. Strategies to prevent clinical deterioration, such as case management, home monitoring of weight and clinical status, and patient adjustment of diuretics, can prevent rehospitalizations and should be part of the treatment regimen of advanced heart failure. Involvement of a multidisciplinary team (rather than a single physician) and in-person (rather than telephonic) communication appear to be important features of successful programs.

Patients should routinely practice moderate salt restriction (2–2.5 g sodium or 5–6 g salt per day). More severe sodium restriction is usually difficult to achieve and unnecessary because of the availability of potent diuretic agents.

Exercise training improves activity tolerance in significant part by reversing the peripheral abnormalities associated with heart failure and deconditioning. In severe heart failure, restriction of activity may facilitate temporary recompensation. Thus, in stable patients, a prudent increase in activity or a regular exercise regimen can be encouraged. Indeed, a gradual exercise program is associated with diminished symptoms and substantial increases in exercise capacity.

4. Coronary revascularization — Since underlying CAD is the cause of heart failure in the majority of patients, coronary revascularization has been thought to be able to both improve symptoms and prevent progression. However, theSTITCH trial failed to show an overall survival benefit from CABG among patients with multivessel coronary disease who were candidates for CABG but who also had heart failure and an LVEF of 35% or less. Revascularization does appear warranted for some patients with heart failure, including those with more severe angina or left main coronary disease (excluded from the STITCH trial), or selected patients with less severe symptoms.

5. Cardiac transplantation — Because of the poor prognosis of patients with advanced heart failure, cardiac transplantation is widely used. Many centers have 1-year survival rates exceeding 80–90%, and 5-year survival rates above 70%. Infections, hypertension and kidney dysfunction caused by cyclosporine, rapidly progressive coronary atherosclerosis, and immunosuppressant-related cancers have

been the major complications. The high cost and limited number of donor organs require careful patient selection early in the course.

6. Other surgical treatment options — Externally powered and implantable ventricular assist devices can be used in patients who require ventricular support either to allow the heart to recover or as a bridge to transplantation. The latest generation devices are small enough to allow patients unrestricted mobility and even discharge from the hospital. Continuous flow devices appear to be more effective than pulsatile flow devices. However, complications are frequent, including bleeding, thromboembolism, and infection, and the cost is very high, exceeding in the initial 1–3 months. Although 1-year survival was improved in the REMATCH randomized trial, all 129 patients died by 26 months. Newer-generation continuous flow pump ventricular assist devices have been shown to result in better survival than the first-generation pulsatile flow device used in REMATCH.

7. Palliative care—Despite the technologic advances of recent years, it should be remembered that many patients with chronic heart failure are elderly and have multiple comorbidities. Many of them will not experience meaningful improvements in survival with aggressive therapy, and the goal of management should be symptomatic improvement and palliation.

Treatment:

Heart Failure with Preserved EF

Although half of all heart failure occurs among patients with normal LVEF, often with diastolic dysfunction, no therapies have been shown to improve survival in this population. The mainstay of management of patients with heart failure with preserved EF is to manage fluid overload with diuretic therapy and to treat comorbidities like hypertension.

A. Correction of Reversible Causes

Hypertension, pericardial disease, and atrial tachycardias are potentially reversible factors that can contribute to heart failure with preserved EF. Since tachycardia is associated with shorter overall diastolic filling time, controlling accelerated heart rate may be important.

B. Pharmacologic reatment

1. Diuretic therapy — Diuretics are important to control symptoms of fluid overload in patients with heart failure with preserved EF, similar to symptoms from systolic heart failure.

2. Inhibitors of the renin-angiotensin-aldosterone system—ACE inhibitors and ARBs have not been shown to improve outcome in patients with heart failure and preserved EF, despite being good therapies for the comorbidity of hypertension. Spironolactone has not shown to improve outcome in a large trial of patients with heart failure and preserved EF, but there may have been some benefit in patients

enrolled in the Americas who had more clearly defined heart failure. Spironolactone should remain a therapeutic option, especially for patients who also have hypertension.

C. Nonpharmacologic Treatment

Unlike in patients with heart failure and reduced EF, ICD and resynchronization device treatments do not have a role in patients with preserved EF. Revascularization for patients with heart failure and preserved EF should be guided by the same considerations as for patients with heart failure with reduced EF.

Prognosis

Once manifest, heart failure with reduced EF carries a poor prognosis. Even with modern treatment, the 5-year mortality is approximately 50%. Mortality rates vary from less than 5% per year in those with no or few symptoms to greater than 30% per year in those with severe and refractory symptoms. These figures emphasize the critical importance of early detection and intervention. Higher mortality is related to older age, lower LVEF, more severe symptoms, chronic kidney disease, and diabetes. The prognosis of heart failure has improved in the past two decades, probably at least in part because of the more widespread use of ACE inhibitors and beta-blockers, which markedly improve survival.

When to Refer

Patients with new symptoms of heart failure not explained by an obvious cause should be referred to a cardiologist. Patients with continued symptoms of heart failure and reduced LVEF (35% or less) should be referred to a cardiologist for consideration of placement of an ICD or cardiac resynchronization therapy (if QRS duration is 120 msec or more, especially with left bundle branch block pattern).

When to Admit

• Patients with unexplained new or worsened symptoms or positive cardiac biomarkers concerning for acute myocardial necrosis.

• Patients with hypoxia, fluid overload, or pulmonary edema not readily resolved in an outpatient setting.

ACUTE HEART FAILURE & PULMONARY EDEMA

ESSENTIALS OF DIAGNOSIS

- Acute onset or worsening of dyspnea at rest.
- Tachycardia, diaphoresis, cyanosis.
- Pulmonary rales, rhonchi; expiratory wheezing.
- Radiograph shows interstitial and alveolar edema with or without cardiomegaly.

- Arterial hypoxemia.

General Considerations

Typical causes of acute cardiogenic pulmonary edema include acute myocardial infarction or severe ischemia, exacerbation of chronic heart failure, acute severe hypertension, acute kidney injury, acute volume overload of the LV (valvular regurgitation), and mitral stenosis. By far the most common presentation in developed countries is one of acute or subacute deterioration of chronic heart failure, precipitated by discontinuation of medications, excessive salt intake, myocardial ischemia, tachyarrhythmias (especially rapid atrial fibrillation), or intercurrent infection. Often in the latter group, there is preceding volume overload with worsening edema and progressive shortness of breath for which earlier intervention can usually avoid the need for hospital admission.

Clinical Findings

Acute pulmonary edema presents with a characteristic clinical picture of severe dyspnea, the production of pink, frothy sputum, and diaphoresis and cyanosis. Rales are present in all lung fields, as are generalized wheezing and rhonchi. Pulmonary edema may appear acutely or subacutely in the setting of chronic heart failure or may be the first manifestation of cardiac disease, usually acute myocardial infarction, which may be painful or silent. Less severe decompensations usually present with dyspnea at rest, rales, and other evidence of fluid retention but without severe hypoxia.

Noncardiac causes of pulmonary edema include intravenous opioids, increased intracerebral pressure, high altitude, sepsis, several medications, inhaled toxins, transfusion reactions, shock, and disseminated intravascular coagulation. These are distinguished from cardiogenic pulmonary edema by the clinical setting, history, and physical examination. Conversely, in most patients with cardiogenic pulmonary edema, an underlying cardiac abnormality can usually be detected clinically or by ECG, chest radiograph, or echocardiogram.

The chest radiograph reveals signs of pulmonary vascular redistribution, blurriness of vascular outlines, increased interstitial markings, and, characteristically, the butterfly pattern of distribution of alveolar edema. The heart may be enlarged or normal in size depending on whether heart failure was previously present. Assessment of cardiac function by echocardiography is important, since a substantial proportion of patients has normal EFs with elevated atrial pressures due to diastolic dysfunction. In cardiogenic pulmonary edema, BNP is elevated, and the PCWP is invariably elevated, usually over 25 mm Hg. In noncardiogenic pulmonary edema, the wedge pressure may be normal or even low.

Treatment

In full-blown pulmonary edema, the patient should be placed in a sitting position with legs dangling over the side of the bed; this facilitates respiration and reduces venous return. Oxygen is delivered by mask to obtain an arterial Po2 greater than 60 mm Hg. Noninvasive pressure support ventilation may improve

oxygenation and prevent severe CO2 retention while pharmacologic interventions take effect. However, if respiratory distress remains severe, endotracheal intubation and mechanical ventilation may be necessary.

Morphine is highly effective in pulmonary edema and may be helpful in less severe decompensations when the patient is uncomfortable. The initial dosage is 2–8 mg intravenously (subcutaneous administration is effective in milder cases) and may be repeated after 2–4 hours. Morphine increases venous capacitance, lowering LA pressure, and relieves anxiety, which can reduce the efficiency of ventilation. However, morphine may lead to CO2 retention by reducing the ventilatory drive. It should be avoidedin patients with opioid-induced pulmonary edema, who may improve with opioid antagonists, and in those with neurogenic pulmonary edema.

Intravenous diuretic therapy (furosemide, 40 mg, or bumetanide, 1 mg—or higher doses if the patient has been receiving long-term diuretic therapy) is usually indicated even if the patient has not exhibited prior fluid retention. These agents produce venodilation prior to the onset of diuresis. The DOSE trial has shown that, for acute decompensated heart failure, bolus doses of furosemide are of similar efficacy as continuous intravenous infusion, and that higher-dose furosemide (2.5 times the prior daily dose) resulted in more rapid fluid removal without a substantially higher risk of kidney impairment.

Nitrate therapy accelerates clinical improvement by reducing both BP and LV filling pressures. Sublingual nitroglycerin or isosorbide dinitrate, topical nitroglycerin, or intravenous nitrates will ameliorate dyspnea rapidly prior to the onset of diuresis, and these agents are particularly valuable in patients with accompanying hypertension.

Intravenous nesiritide, a recombinant form of human BNP, is a potent vasodilator that reduces ventricular filling pressures and improves cardiac output. Its hemodynamic effects resemble those of intravenous nitroglycerin with a more predictable dose–response curve and a longer duration of action. In clinical studies, nesiritide (administered as 2 mcg/kg by intravenous bolus injection followed by an infusion of 0.01 mcg/kg/min, which may be up-titrated if needed) produced a rapid improvement in both dyspnea and hemodynamics. The primary adverse effect is hypotension, which may be symptomatic and sustained. Because most patients with acute heart failure respond well to conventional therapy, the role of nesiritide may be primarily in patients who continue to be symptomatic after initial treatment with diuretics and nitrates.

In some cases, dobutamine or milrinone may help maintain patients who are awaiting cardiac transplantation.

Bronchospasm may occur in response to pulmonary edema and may itself exacerbate hypoxemia and dyspnea. Treatment with inhaled beta-adrenergic agonists or intravenous aminophylline may be helpful, but both may also provoke tachycardia and supraventricular arrhythmias.

In most cases, pulmonary edema responds rapidly to therapy. When the patient has improved, the cause or precipitating factor should be ascertained. In patients without prior heart failure, evaluation should include echocardiography and, in many cases, cardiac catheterization and coronary angiography. Patients with

acute decompensation of chronic heart failure should be treated to achieve a euvolemic state and have their medical regimen optimized. Generally, an oral diuretic and an ACE inhibitor should be initiated, with efficacy and tolerability confirmed prior to discharge. In selected patients, early but careful initiation of beta-blockers in low doses should be considered.

Control questions

1. Anatomical and physiological features of the cardiovascular system.
2. Major complaints, symptoms and research in heart failure.
3. Chronic heart failure - etiology and pathogenesis.
4. Clinical picture of chronic HF.
5. Classification of chronic HF.
6. Acute heart failure: cardiac asthma - etiology, pathogenesis, clinical picture, principles of pharmacotherapy;
7. Swelling of the lungs - etiology, pathogenesis, clinical picture, principles of pharmacotherapy.
8. The main directions of pharmacotherapy HF.

List of practical works

A. Homework.

1. To study the etiology, pathogenesis of heart failure.
2. To know the classification, the clinic of acute and chronic heart failure.
3. Be able to provide first aid with acute heart failure.
4. To study the main directions of treatment of acute and chronic heart failure.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data of laboratory and instrumental studies, examination of consultants, records of the attending physician) and the letter of medical appointments.
3. At examination of the patient to allocate subjective, physical, laboratory-instrumental features: heart failure (acute, chronic).
4. Write a clinical diagnosis:
a) the underlying disease; complications of the underlying disease;
b) concomitant diseases.
5. Define a group of medicines necessary to correct the existing violations.
6. To write a protocol of independent work on the selection and selection of an insured patient, CG, and others. medicines , to justify appointment of combined medical therapy.

Control the level of knowledge

1. Fill in the table "Basic directions and means of pathogenetic therapy of chronic HF".

Directions of pharmacotherapy	Pharmacological groups	Medications
1. Reduction of pre- and post-load on the myocardium 2. Reduced myocardial remodeling 3. Reducing the volume of circulating blood 4. Strengthening the contractile function of the myocardium 5. Improvement of metabolic processes in the myocardium		

2. Fill in the table: "The main direction and preparations of pathogenetic therapy of HF".

HF pathogenesis	Ways of correction	Medicinal remedies
1. Activation of neurohumoral factors 2. Increased total peripheral vascular resistance 3.Saturia of sodium and fluid in the body 4. Decreased contractile function of the heart 5. Breast-feeding of myocardial metabolism		

3. List the characteristics that are characteristic of the various stages of HF:

Clinical signs	Stage I	Stage II-A	Stage II-Б	Stage III
1. Ascites 2.Hydrotoraks 3. Heart and palms at rest 4. Chicken in the lungs				

5. Heart and palms in normal physical activity 6. Constipation of the lower extremities in the evening 7. Permanent and pronounced peripheral edema 8. Difficulty breathing with fatigent arrhythmia 9. Expansion of heart size in all directions 10. Stem of hepatomegaly 11. Cyanous flush on cheeks, acrocyanosis				

Note: answers are marked with "+" or "-" characters.

Solution of situational tasks

1. A patient, 42 years old, is in a therapeutic hospital with a diagnosis: rheumatic heart disease, active phase, II st.aktivnosti, reverse carditis, failure of the aortic valve, CH-II B st. Within one month, digitoxin receives 1 tablet. (0,0001 g) 2 times a day. Heart rate decreased from 90 a. for 1 min to 50 auks. for 1 min However, during the last week, dyspnea, swelling on the legs, diarrhea decreased, liver increased. What caused the deterioration of the patient's condition?

Which AG should be prescribed to reduce the severity of decompensation?

2. A patient, 65 years old, complains of shortness of breath at rest, nerythemic heartbeat, edema on the legs, abdominal enlargement, heaviness in the right hypochondrium, daily diuresis - 0.6 l. In the history: suffered a major myocardial infarction 5 years ago. Periodic attacks of angina after nerve loading, lifting to II floor. Shortness of breath and swelling on legs are noted during the last 2 years. Periodically took digoxin (1 ton 2 times a day, 5 days a week) "courses" for 2 months with a 1-month break (according to the recommendation of the district therapist). The deterioration arose 3 weeks ago and progresses. Objectively: general condition of moderate severity, orthopnea. Cyanosis of the lips, acrocyanosis, swelling of the veins of the neck, pulse - 118 beats. for 1 min, arrhythmic type of flashing arrhythmia. Heart rate - 144 for 1 min AT - 120/90 mm Hg.. Hypertrophy of both ventricles. Accent II tone over the pulmonary artery, systolic noise over the aorta. BH - 26 for 1 min. Breathing is rigid, in the thoracic areas of wheezing. The tongue is dry. The abdomen is rounded, the free fluid is determined in the lateral portions. The liver protrudes 12 cm from the edge of the edge arc on the right median-buccal line, dense, smooth, painful. Edema of the legs, lumbar-sacral spine. ECG - flashing arrhythmia, tachysystolic form (heart rate - 156 for 1 min), hypertrophy of both ventricles. Cerebellar changes in the posterior margin of the left ventricle.

Formulate a clinical diagnosis. Justify the choice of SG, its dose, the rate of saturation in the period of initial digitization. Specify the clinical and electrocardiographic criteria for the effectiveness of this stage of glycosidotherapy.

3. Another physician is called to the department of the pathology of pregnancy to the patient, 27 years old. Diagnosis: Pregnancy 35 weeks. Rheumatic heart disease, inactive phase, mitral stenosis. Complaint with attacks of suffocation, can not lie. In the lungs, breathing is rigid, in the lower parts of the wet wheezing. No edema.

Your diagnosis? Your Urgent Destinations?

4. A patient, 52 years old, developed an attack of cardiac asthma. At examination of pulse 78 av. for 1 min, rhythmic. BP - 170/100 mm Hg. Heart tones are muffled. Increase in liver, moderate edema of the legs. The doctor prescribed intravenous administration of strophanthina.

Evaluate the tactics of patient management. Make a plan for correction of the patient's treatment.

5. In the cardiology department there is a patient who was delivered with a sharp, extensive myocardial infarction. Condition of the patient of moderate severity, pulse - 100 a. for 1 min, rhythmic. The tones of the heart are deaf. Breathing over the lungs is vesicular. The liver is not enlarged, no edema. The strophantine was prescribed to the patient. After the introduction of the minimum dose (0.25 ml - 0.05% r-n), there were single extrasystoles, after the second administration of the same dose developed bigemenia.

Evaluate the tactics of patient management. Explain the cause of the complication.

6. On the 3rd day of treatment with digoxin in the patient revealed: pulse - 50 uah. for 1 min, extrasystoles by type of bignement.

Formulate the diagnosis. Patient's treatment plan.

7. A male, 75 years old, with a diagnosis of CHD: cardiosclerosis, atherosclerotic, flashing arrhythmia, HF IIB stage and chronic pyelonephritis, is prescribed digoxin. In the first 6 days, the dose of digoxin was 0.25 mg twice daily, which resulted in decreased dyspnea, edema, cyanosis. However, at day 7 in the patient appeared nausea, bradycardia.

What is the cause of the complications? Tactics of treatment.

8. A man, 53 years old, is in a hospital for 1.5 months in a hospital about a myocardial infarction, which is complicated by a swelling of the lungs. Objectively: a patient with moderate nutrition, an unspecified cyanosis of the lips. Pulse - 80 UD for 1 min, BP 140/90 mm Hg., BH - 20 per 1 minute. In the lower parts of the lungs are wheezing. Heart tones are muffled. The liver is not enlarged. No edema.

Formulate the diagnosis. What treatment should be prescribed to the patient?

9. In the patient the attack of cardiac asthma BP - 140/80 mm Hg. The doctor gave the patient a tablet of nitroglycerin under the tongue, intravenously introduced lasix 4.0 ml, strophanthin - 0.05% - 0.5 ml per 10 ml of physiological saline sodium chloride, made oxygen inhalation

Are the doctor doing the right thing? Explain the pharmacodynamics of each drug in this situation.

Test tasks

1. Character of cyanosis in patients with cardiovascular insufficiency:
A. Diffuse.
B. On the face.
C. On separate parts of the body.
D. On the lower extremities.
E. Acrocyanosis.

2. The early signs of CHF include:
1. Edema of the legs.
2.Cashel.
3.Carticle
4. Ascites.
5.Acrocyanosis.

3. Select the groups of LS, shown for pathogenetic treatment of CHF:
1. Fibrinolytic.
2. Anticoagulants.
3. ACE inhibitors.
4. Glucocorticoids.
5. Sedative

4. With CHF, medical therapy should be used:
1. Only during hospitalization.
2. Constantly.
3. Only when deterioration of well-being.
4. In the spring-autumn period.
5. With pain in the heart area.

5. The drug of choice for combining AG with HF among these drugs is:
1.Korinfar
2.Prazosin
3. Propranolol.
4.Nitrosorbide.
5.Enalapril.

6. The main purpose of treatment for patients with CHF is:
1. Decreased edema.

2.Normalization of blood pressure.
3. Improving the quality of life.
4.Distension of shortness of breath.
5.Normalization of heart rate.

7. One of the reasons for the development of chronic heart failure is:
1. Proof of angina pectoris.
2. Haemodynamic overload of the myocardium.
3. Hypertensive crisis.
4. All of the above.
5. None of the above.

8. With the development of CHF increased activity:
1.Central nervous system.
2. Parasympathetic nervous system.
3. Renin-angiotensin system.

9. The use of diuretics in CHF in conjunction with hypertension allows:
1. Decrease intravascular volume of fluid.
2. Reduce pressure in the cavities of the heart.
3. Reduce pressure in peripheral vessels.
4. Reduce swelling of the vascular wall.
5. All of the above.

10. The most simple clinical indicator of the effectiveness of diuretic therapy in patients with CHF is:
1. Reduced blood pressure.
2. Decreased dyspnea and tachycardia.
3. Decrease the size of the liver.
4. Decrease in body weight.
5. Reduction of the amount of wet wheezing in the lungs.

11. The causes of chronic heart failure may be:
1. Pneumonia.
2.Angina
3. Hypertensive illness.
4. A sharp bronchitis.
5. Varicose veins of the lower extremities.

12. Specify the features that are characteristic of 2 functional classes of HF:
1. Normal exercise does not cause palpitations and shortness of breath.
2. The usual physical activity causes excessive fatigue, palpitations, shortness of breath.
3. Shortness of breath and palpitation at rest.
4. A small amount of physical activity causes excessive fatigue, palpitations,

shortness of breath, or an attack of angina pectoris.

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TOPIC 7. Pharmacotherapeutic principles of treatment of infectious inflammatory diseases of the upper and lower respiratory tract

Actuality of topic.

The level of morbidity, more than 40% is determined by diseases of the respiratory system. More than half of the initial appeals to doctors is due to respiratory diseases. Diseases of the upper and lower respiratory tracts are distinguished. As a rule, patients with mild upper respiratory tract diseases (acute respiratory disease, rhinitis, pharyngitis, etc.), patients turn to the pharmacy. In the practice of pharmacist it is extremely important to be able to distinguish safe symptoms from the symptoms of serious illness.

A rather high level of morbidity is determined by diseases of the respiratory system. More than half of the initial appeals to doctors is due to respiratory diseases. Diseases of the upper and lower (bronchitis, pneumonia, pleurisy, pulmonary tuberculosis) of the respiratory tract are distinguished. In the practice of pharmacist it is extremely important to be able to distinguish safe symptoms from the symptoms of serious illness.

Purpose of the lesson: The student must learn the anatomy and physiology of the respiratory system, the etiopathogenetic factors of the diseases of the upper respiratory tract (acute respiratory infections, flu, tonsillitis, pharyngitis, laryngitis). Know the requirements for medicines used to treat diseases of the respiratory system for rational pharmacotherapy.

The student should know and practice in practice the methods of examination of the patient with respiratory diseases (history, examination, palpation, percussion, auscultation), to know the diagnostic manipulations (sputum research, puncture of the pleural cavity, biopsy of the lungs, bronchoscopy), radiological diagnosis (radiography and radiography, tomography, bronchography, pneumoscintiography), microbiological methods of investigation. To study diseases of the lower respiratory tract: bronchitis, pneumonia, pleurisy - etiology, pathogenesis, clinic, diagnostic methods, principles of treatment; Know the pulmonary tuberculosis and extrapulmonary localization: etiology, clinic, diagnosis, principles of pharmacotherapy.

DISORDERS OF THE AIRWAYS

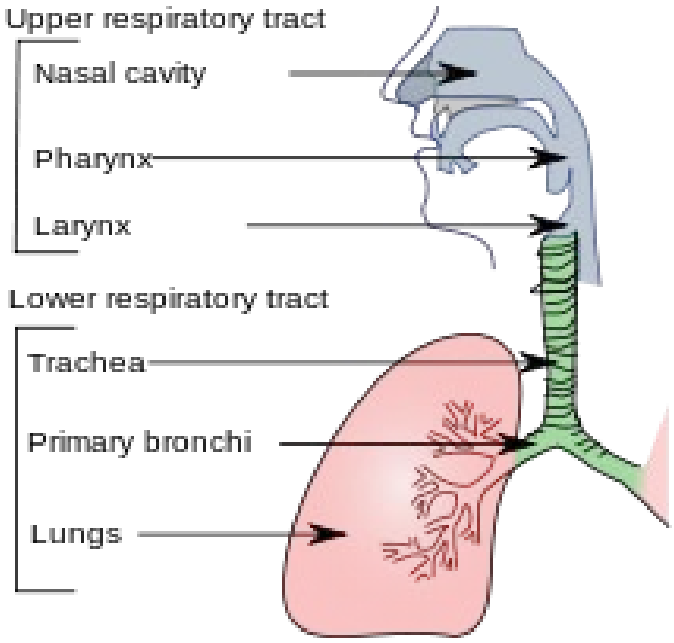
Airway disorders have diverse causes but share certain common pathophysiologic and clinical features. Airflow limitation is characteristic and frequently causes dyspnea and cough. Other symptoms are common and typically disease-specific. Disorders of the airways can be classified as those that involve the upper airways—loosely defined as those above and including the vocal folds—and those that involve the lower airways.

DISORDERS OF THE UPPER AIRWAYS

Acute upper airway obstruction can be immediately lifethreatening and must be relieved promptly to avoid asphyxia. Causes of acute upper airway obstruction include trauma to the larynx or pharynx, foreign body aspiration, laryngospasm, laryngeal edema from thermal injury or angioedema, infections (acute epiglottitis, Ludwig angina, pharyngeal or retropharyngeal abscess), and acute allergic laryngitis.

Chronic obstruction of the upper airway may be caused by carcinoma of the pharynx or larynx, laryngeal or subglottic stenosis, laryngeal granulomas or webs, or bilateral vocal fold paralysis. Laryngeal or subglottic stenosis may become evident weeks or months after translaryngeal endotracheal intubation. Inspiratory stridor, intercostal retractions on inspiration, a palpable inspiratory thrill over the larynx, and wheezing localized to the neck or trachea on auscultation are characteristic findings. Flow-volume loops may show flow limitations characteristic of obstruction. Soft-tissue radiographs of the neck may show supraglottic or infraglottic narrowing. CT and MRI scans can reveal exact sites of obstruction. Flexible endoscopy may be diagnostic, but caution is necessary to avoid exacerbating upper airway edema and precipitating critical airway narrowing.

Vocal fold dysfunction syndrome is characterized by paradoxical vocal fold adduction, resulting in both acute and chronic upper airway obstruction. It can cause dyspnea and wheezing that may be distinguished from asthma or exercise-induced asthma by the lack of response to bronchodilator therapy, normal spirometry immediately after an attack, spirometric evidence of upper airway obstruction, a negative bronchial provocation test, or direct visualization of adduction of the vocal folds on both inspiration and expiration. The condition appears to be psychogenic in nature. Bronchodilators are of no therapeutic benefit. Treatment consists of speech therapy, which uses breathing, voice, and neck relaxation exercises to abort the symptoms.



INFECTIONS OF THE NOSE & PARANASAL SINUSES

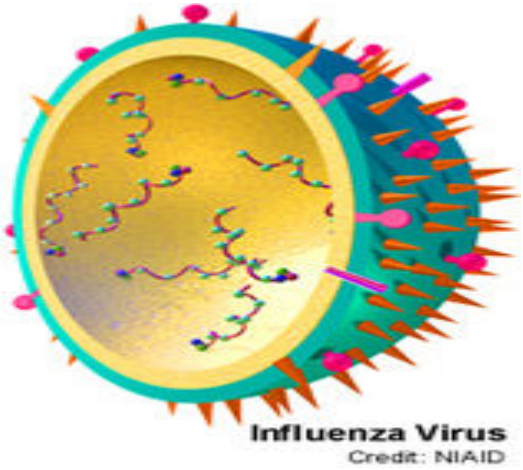
1. Acute Viral Rhinosinusitis (Common Cold)

ESSENTIALS OF DIAGNOSIS:

- Clear rhinorrhea, hyposmia, and nasal congestion.
- Associated symptoms, including malaise, headache, and cough.
- Erythematous, engorged nasal mucosa on examination without intranasal purulence.
- Symptoms last less than 4 weeks and typically less than 10 days. Symptoms are self-limited.

Clinical Findings

The nonspecific symptoms of the ubiquitous common cold are present in the early phases of many diseases that affect the upper aerodigestive tract. Because there are numerous serologic types of rhinoviruses, adenoviruses, and other viruses, patients remain susceptible throughout life. These infections, while generally quite benign and self-limited, have been implicated in the development or exacerbation of more serious conditions, such as acute bacterial sinusitis, acute otitis media, asthma and cystic fibrosis exacerbation, and bronchitis. Nasal congestion, decreased sense of smell, watery rhinorrhea, and sneezing, accompanied by general malaise, throat discomfort, and, occasionally, headache are typical in viral infections. Nasal examination usually shows erythematous, edematous mucosa and a watery discharge. The presence of purulent nasal discharge suggests bacterial rhinosinusitis.



Treatment

Even though there are no effective antiviral therapies for either the prevention or treatment of viral rhinitis, there is a common misperception among patients that antibiotics are helpful. Zinc for the treatment of viral rhinitis has been controversial. A 2011 meta-analysis of randomized controlled trials demonstrated no benefit in five studies that used less than 75 mg of zinc acetate daily, but significant reduction in duration of cold symptoms was noted in all three studies that used zinc acetate in daily doses of over 75 mg. The effect with zinc salts other than acetate was also significant at doses greater than 75 mg/day, but not as high as the zinc acetate lozenge studies (20% vs 42% reduction in cold duration). Buffered hypertonic saline (3–5%) nasal irrigation has been shown to improve symptoms and reduce the need for nonsteroidal anti-inflammatory drugs. Other supportive measures, such as oral decongestants (pseudoephedrine, 30–60 mg every 4–6 hours or 120 mg twice daily), may provide some relief of rhinorrhea and nasal obstruction. Nasal sprays, such as oxymetazoline or phenylephrine, are rapidly effective but should not be used for more than a few days to prevent rebound congestion. Withdrawal of the drug after prolonged use leads to rhinitis medicamentosa, an almost addictive need for continuous usage. Treatment of rhinitis medicamentosa requires mandatory cessation of the sprays, and this is often extremely frustrating for patients. Topical intranasal corticosteroids (eg, flunisolide, 2 sprays in each nostril twice daily), intranasal anticholinergic (ipratropium 0.06% nasal spray, 2–3 sprays every 8 hours as needed), or a short tapering course of oral prednisone may help during the process of withdrawal.

Complications

Other than mild eustachian tube dysfunction or transient middle ear effusion, complications of viral rhinitis are unusual. Secondary acute bacterial rhinosinusitis may occur and is suggested by persistence of symptoms beyond 10 days, accompanied both by purulent green or yellow nasal secretions and unilateral facial or tooth pain. (See Acute Bacterial Rhinosinusitis below.)

2. Acute Bacterial Rhinosinusitis (Sinusitis)

ESSENTIALS OF DIAGNOSIS:

- Purulent yellow-green nasal discharge or expectoration.
- Facial pain or pressure over the affected sinus or sinuses.
- Nasal obstruction.
- Acute onset of symptoms (between 1 and 4 weeks' duration). Associated symptoms, including cough, malaise, fever, and headache.

General Considerations

Acute sinus infections are uncommon compared with viral rhinitis, but they still affect nearly 20 million Americans annually, accounting for over 2 billion dollars in health care expenditures for sinusitis annually. Such infections are often associated with inflammation of the nasal cavity mucosa near the drainage pores of the sinuses. To acknowledge this inflammation as a major component of the disease and to differentiate it from such processes as allergic or acute viral rhinitis, otolaryngologists prefer the term "bacterial rhinosinusitis."

Acute bacterial rhinosinusitis usually is a result of impaired mucociliary clearance and obstruction of the osteomeatal complex, or sinus "pore." Edematous mucosa causes obstruction of the complex, resulting in the accumulation of mucous secretion in the sinus cavity that becomes secondarily infected by bacteria. The largest of these osteomeatal complexes is deep to the middle turbinate in the middle meatus. This complex is actually a confluence of complexes draining the maxillary, ethmoid, and frontal sinuses. The sphenoid drains from a separate complex between the septum and superior turbinate.

The typical pathogens of bacterial sinusitis are the same as those that cause acute otitis media: S pneumoniae, other streptococci, H influenzae, and less commonly, S aureus and Moraxella catarrhalis. Pathogens vary regionally in both prevalence and drug resistance; about 25% of healthy asymptomatic individuals may, if sinus aspirates are cultured, harbor such bacteria as well. Understanding of the anatomy, pathogenesis, and microbiology of acute bacterial rhinosinusitis can help the clinician make the most expeditious and cost-effective diagnosis and treatment while avoiding serious complications.

Clinical Findings

A. Symptoms and Signs

There are no agreed-upon criteria for the diagnosis of acute bacterial rhinosinusitis in adults. All study groups note a number of major symptoms, including purulent nasal drainage, nasal obstruction or congestion, facial pain/ pressure, altered smell, cough, and fever. Minor symptoms include headache, otalgia, halitosis, dental pain, and fatigue. Many of the more specific signs and symptoms may be related to the affected sinuses. It is important to note that studies have demonstrated no correlation between patient reports of "sinus headache" and presence of sinusitis on CT scan. Bacterial rhinosinusitis can be distinguished from viral rhinitis by persistence of symptoms more than 10 days after onset or worsening of symptoms within 10 days after initial improvement. Acute infections are defined as those lasting less than 4 weeks, with subacute infections lasting between 4 weeks and 12 weeks.

Acute maxillary sinusitis is the most common form of acute bacterial rhinosinusitis because the maxillary is the largest sinus with a single drainage pathway that is easily obstructed. Unilateral facial fullness, pressure, and tenderness over the cheek are common symptoms, but may not be present in many cases. Pain may refer to the upper incisor and canine teeth via branches of the trigeminal nerve, which traverse the floor of the sinus. Purulent nasal drainage should be noted with nasal airway obstruction or facial pain (pressure). Maxillary sinusitis may result from dental infection, and teeth that are tender should be carefully examined for signs of abscess. Removal of the diseased tooth or drainage of the periapical abscess typically resolves the sinus infection.

Acute ethmoiditis in adults is often accompanied by maxillary sinusitis, and symptoms are similar to those described above. Localized ethmoid sinusitis may present with pain and pressure over the high lateral wall of the nose between the eyes that may radiate to the orbit.

Sphenoid sinusitis is usually seen in the setting of pansinusitis or infection of all the paranasal sinuses on at least one side. The patient may complain of a headache “in the middle of the head” and often points to the vertex.

Acute frontal sinusitis may cause pain and tenderness of the forehead. This is most easily elicited by palpation of the orbital roof just below the medial end of the eyebrow.

Hospital-associated sinusitis is a form of acute bacterial rhinosinusitis that may present without any symptoms in the head and neck. It is a common source of fever in critically ill patients and is often associated with prolonged presence of a nasogastric or, rarely, nasotracheal tube causing inflammation of the nasal mucosa and osteomeatal complex obstruction. Pansinusitis on the side of the tube is common on imaging studies.

B. Imaging

It is usually possible to make the diagnosis of acute bacterial rhinosinusitis on clinical grounds alone. Although more sensitive than clinical examination, routine radiographs are not cost-effective and are not recommended by the Agency for Health Care Policy and Research or American Association of Otolaryngology Guidelines in the routine diagnosis of acute bacterial rhinosinusitis. Consensus guidelines report that imaging may be helpful when clinically based criteria are difficult to evaluate, when the patient does not respond to appropriate therapy, when patients have been treated repeatedly with antibiotics for presumed sinusitis, when intracranial involvement or cerebrospinal fluid rhinorrhea is suspected, when complicated dental infection is suspected, or when symptoms of more serious infection are noted.

When necessary, noncontrast, screening coronal CT scans are more cost-effective and provide more information than conventional sinus films. CT provides a rapid and effective means to assess all of the paranasal sinuses, identify areas of greater concern (such as bony dehiscence, periosteal elevation or maxillary tooth root exposure within the sinus), and speed appropriate therapy.

CT scans are reasonably sensitive but are not specific. Swollen soft tissue and

fluid may be difficult to distinguish when opacification of the sinus is present from other conditions, such as chronic rhinosinusitis, nasal polyposis, or mucus retention cysts. Sinus abnormalities can be seen in most patients with an upper respiratory infection, while bacterial rhinosinusitis develops in only 2%.

If malignancy, intracranial extension, or opportunistic infection is suspected, MRI with gadolinium should be ordered instead of, or in addition to, CT. MRI will distinguish tumor from fluid, inflammation, and inspissated mucus far better than CT, as well as better delineating tumor extent with respect to adjacent structures, such as the orbit, skull base, and palate. Bone destruction can be demonstrated as well by MRI as by CT.

Treatment

All patients with acute bacterial rhinosinusitis should have careful evaluation of pain. Nonsteroidal anti-inflammatory drugs are generally recommended. Sinus symptoms may be improved with oral or nasal decongestants (or both)—eg, oral pseudoephedrine, 30–120 mg per dose, up to 240 mg/day; nasal oxymetazoline, 0.05%, or xylometazoline, 0.05–0.1%, one or two sprays in each nostril every 6–8 hours for up to 3 days. All clinical practice guidelines recommend using intranasal corticosteroids from the initiation of symptoms that could be acute bacterial rhinosinusitis or acute viral rhinitis since meta-analysis demonstrates a small, but significant, reduction in facial pain and congestion scores with use. Recommendations also exist for high-dose mometasone furoate (200 mcg each nostril twice daily) for 21 days and are well supported in the literature.

Between 40% and 69% of patients with acute bacterial rhinosinusitis improve symptomatically within 2 weeks without antibiotic therapy. Antibiotic treatment is controversial in uncomplicated cases of clinically diagnosed acute bacterial rhinosinusitis because only 5% of patients will note a shorter duration of illness with treatment, and antibiotic treatment is associated with nearly twice the number of adverse events compared with placebo. Antibiotics may be considered when symptoms last more than 10 days or when symptoms (including fever, facial pain, and swelling of the face) are severe or when cases are complicated (such as immunodeficiency). In these patients, administration of antibiotics does reduce the incidence of clinical failure by 50% and represents the most cost-effective treatment strategy. Double-blinded studies exist to support numerous antibiotic choices. Selection of antibiotics is usually empiric and based on a number of factors, including regional patterns of antibiotic resistance, antibiotic allergy, cost, and patient tolerance. Unless the patient is allergic to penicillin, amoxicillin should be used as the first-line agent. Treatment is usually for 7–10 days, although longer courses are sometimes required to prevent relapses. Macrolide therapy has been recommended as first-line therapy in patients with penicillin allergy, and tetracyclines have also been used.

Multidrug-resistant S pneumoniae prevalence is growing in many urban areas of the United States, as are betalactamase beta-lactam inhibitor producing strains of H influenza and M catarrhalis. In such regions, guidelines call for empiric use of amoxicillin-clavulanate or second- or thirdgeneration cephalosporins.

Fluoroquinolones are reserved for treatment failures or for patients with a recent history of antibiotic therapy for another infection. Recurrent sinusitis or sinusitis that does not appear to respond clinically warrants CT imaging and evaluation by a specialist.

Hospital-associated infections in critically ill patients are treated differently from community-acquired infections. Broad-spectrum antibiotic coverage for bacteria, including P aeruginosa, S aureus (including methicillinresistant strains), and anaerobes must be considered. Removal of the nasogastric tube and improved nasal hygiene (nasal saline sprays, humidification of supplemental nasal oxygen, and nasal decongestants) are critical interventions and often curative in mild cases without aggressive antibiotic use. Endoscopic or transantral cultures may help direct medical therapy in complicated cases.

Oral antibiotic regimens for acute sinusitis

First-line therapy

Amoxicillin 1000 mg three times daily 7–10 days

Trimethoprim-sulfamethoxazole 160 mg–800 mg twice daily 7–10 days Suitable in penicillin allergy

Doxycycline 200 mg once daily × 1 day, 100 mg twice daily thereafter 7–10 days Suitable in penicillin allergy

Amoxicillin-clavulanate1 1000/62.5 mg ER 2 tablets twice daily 10 days

First-line therapy after recent antibiotic use (within 4–6 weeks) Levofloxacin 500 mg once daily 10 days

Amoxicillin-clavulanate 875/125 mg twice daily 10 days

Second-line therapy

Amoxicillin-clavulanate 1000/62.5 mg ER 2 tablets twice daily 10 days If no improvement after 3 days on first-line therapy Moxifloxacin 400 mg once daily 10 days If no improvement after 3 days on first-line therapy.

ALLERGIC RHINITIS

ESSENTIALS OF DIAGNOSIS

- Clear rhinorrhea, sneezing, tearing, eye irritation, and pruritus.
- Associated symptoms, including cough, bronchospasm, and eczematous dermatitis.
- Environmental allergen exposure with presence of allergen-specific IgE.

General Considerations

Allergic rhinitis is very common in the United States. Population studies have reported the prevalence as between 14% and 40% among Americans, with most consensus panels agreeing on 20%. Allergic rhinitis adversely affects school and work performance, costing about $6 billion annually in the United States. These costs may be underestimated as epidemiology studies consistently show an

association with asthma. Seasonal allergic rhinitis is most commonly caused by pollens and spores. Flowering shrub and tree pollens are most common in the spring, flowering plants and grasses in the summer, and ragweed and molds in the fall. Dust, household mites, air pollution, and pet dander may produce year-round symptoms, termed “perennial rhinitis.”

Clinical Findings

The symptoms of “hay fever” are similar to those of viral rhinitis but are usually persistent and may show seasonal variation. Nasal symptoms are often accompanied by eye irritation, pruritus, conjunctival erythema, and excessive tearing. Many patients will note a strong family history of atopy or allergy.

The clinician should be careful to distinguish allergic rhinitis from nonallergic or vasomotor rhinitis. **Vasomotor rhinitis** is caused by increased sensitivity of the vidian nerve and is a common cause of clear rhinorrhea in the elderly. Often patients will report that they have troubling rhinorrhea in response to numerous nasal stimuli, including warm or cold air, odors or scents, light, or particulate matter.

On physical examination, the mucosa of the turbinates is usually pale or violaceous because of venous engorgement. This is in contrast to the erythema of viral rhinitis. Nasal polyps, which are yellowish boggy masses of hypertrophic mucosa, are associated with long-standing allergic rhinitis.

Treatment

A. Intranasal Corticosteroids

Intranasal corticosteroid sprays have revolutionized the treatment of allergic rhinitis. Evidence-based literature reviews show that these are more effective—and frequently less expensive—than nonsedating antihistamines. Patients should be reminded that there may be a delay in onset of relief of 2 or more weeks. Corticosteroid sprays may also shrink hypertrophic nasal mucosa and nasal polyps, thereby providing an improved nasal airway and osteomeatal complex drainage. Because of this effect, intranasal corticosteroids are critical in treating allergy in patients prone to recurrent acute bacterial rhinosinusitis or chronic rhinosinusitis. There are many available preparations, including beclomethasone (42 mcg/spray twice daily per nostril), flunisolide (25 mcg/spray twice daily per nostril), mometasone furoate (200 mcg once daily per nostril), budesonide (100 mcg twice daily per nostril), and fluticasone propionate (200 mcg once daily per nostril). All intranasal corticosteroids are considered equally effective. Probably the most critical factors are compliance with regular use and proper introduction into the nasal cavity. In order to deliver medication to the region of the middle meatus, proper application involves holding the bottle straight up with the head tilted forward and pointing the bottle toward the ipsilateral ear when spraying. Side effects are limited and the most annoying is epistaxis. Some experts believe that this is related to incorrect delivery of the drug to the nasal septum.

B. Antihistamines

Treatment of allergic and perennial rhinitis has improved in recent years. Antihistamines offer temporary, but immediate, control of many of the most troubling symptoms of allergic rhinitis. Effective antihistamines include nonsedating loratadine (10 mg orally once daily), desloratadine (5 mg once daily), and fexofenadine (60 mg twice daily or 120 mg once daily), and minimally sedating cetirizine (10 mg orally once daily). Brompheniramine or chlorpheniramine (4 mg orally every 6–8 hours, or 8–12 mg orally every 8–12 hours as a sustained-release tablet) and clemastine (1.34–2.68 mg orally twice daily) may be less expensive although usually associated with some drowsiness. The H1-receptor antagonist nasal spray azelastine (1–2 sprays per nostril daily) has also been shown to be effective in a randomized trial, although many patients object to its bitter taste. Topical nasal sprays are particularly useful in patients who experience side effects, mostly xerostomia and sedation, of oral antihistamines. Many patients who find initial benefit from an antihistamine complain that allergy symptoms eventually return after several months of use. In such patients, typically with perennial allergy problems, antihistamine tolerance seems to develop, and alternating effective antihistamines periodically can control symptoms over the long term.

C. Adjunctive Treatment Measures

In addition to intranasal corticosteroid sprays and antihistamines, including H1-receptor antagonists, the literature supports the use of antileukotriene medications, such as montelukast (10 mg/day orally), alone or with cetirizine (10 mg/day orally), or loratadine (10 mg/day orally). Improved nasal rhinorrhea, sneezing, and congestion are seen with the use of leukotriene receptor antagonists, often in conjunction with antihistamines. Cromolyn sodium and sodium nedocromil are also useful adjunct agents for allergic rhinitis. They work by stabilizing mast cells and preventing proinflammatory mediator release. They are not absorbed by the gastrointestinal tract but do function topically and have very few side effects. The most useful form of cromolyn is probably the ophthalmologic preparation; the nasal preparation is not nearly as effective as inhaled corticosteroids. Intranasal cromolyn is cleared rapidly and must be administered four times daily for continued relief of symptoms.

Intranasal anticholinergic agents, such as ipratropium bromide 0.03% or 0.06% sprays (42–84 mcg per nostril three times daily), may be helpful adjuncts when rhinorrhea is a major symptom. Ipratropium nasal sprays are not as effective as intranasal corticosteroids for treating allergic rhinitis but are particularly useful for treating **vasomotor rhinitis.**

Avoiding or reducing exposure to airborne allergens is the most effective means of alleviating symptoms of allergic rhinitis. Depending on the allergen, this can be extremely difficult. Maintaining an allergen-free environment by covering pillows and mattresses with plastic covers, substituting synthetic materials (foam mattress, acrylics) for animal products (wool, horsehair), and removing dust-collecting household fixtures (carpets, drapes, bedspreads, wicker) is worth the attempt to help more troubled patients. Air purifiers and dust filters may also aid in maintaining an allergenfree environment. Nasal saline irrigations are a useful

adjunct in the treatment of allergic rhinitis to mechanically flush the allergens from the nasal cavity. Though debated, there is no clear benefit to hypertonic saline over commercially available normal saline preparations (eg, Ayr or Ocean Spray). When symptoms are extremely bothersome, a search for offending allergens may prove helpful. This can either be done by serum radioallergosorbent test (RAST) testing or skin testing by an allergist.

In some cases, allergic rhinitis symptoms are inadequately relieved by medication and avoidance measures. Often, such patients have a strong family history of atopy and may also have lower respiratory manifestations, such as allergic asthma. Referral to an allergist may be appropriate for consideration of immunotherapy. This treatment course is quite involved, with proper identification of offending allergens, progressively increasing doses of allergen(s), and eventual maintenance dose administration over a period of 3–5 years. Immunotherapy has been proven to reduce circulating IgE levels in patients with allergic rhinitis and reduce the need for allergy medications. Both subcutaneous and sublingual immunotherapy have been shown to be effective in the long-term treatment of refractory allergic rhinitis. Treatments are given at a suitable medical facility with monitoring following treatment because of the risk of anaphylaxis during dose escalation. Local reactions from injections are common and usually self-limited.

PHARYNGITIS & TONSILLITIS

ESSENTIALS OF DIAGNOSIS

- Sore throat.
- Fever.
- Anterior cervical adenopathy.
- Tonsillar exudate.
- Focus is to treat group A beta-hemolytic streptococcus infection to prevent rheumatic sequelae.

General Considerations

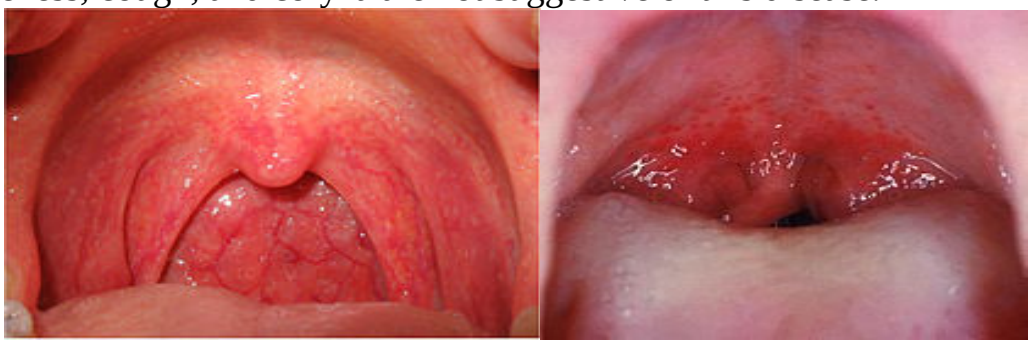
Pharyngitis and tonsillitis account for over 10% of all office visits to primary care clinicians and 50% of outpatient antibiotic use. The main concern is determining who is likely to have a group A beta-hemolytic streptococcal (GABHS) infection, as this can lead to subsequent complications, such as rheumatic fever and glomerulonephritis. A second public health policy concern is reducing the extraordinary cost (both in dollars and in the development of antibioticresistant S pneumoniae) in the United States associated with unnecessary antibiotic use. Questions being asked: Have the rapid antigen tests supplanted the need to culture a throat under most circumstances? Are clinical criteria alone a sufficient basis for decisions about which patients should be given antibiotics? Should any patient receive any antibiotic other than penicillin (or erythromycin if penicillin-allergic)? For how long should treatment be continued? Numerous well-done studies and experience with rapid laboratory tests for detection of streptococci (eliminating the

delay caused by culturing) informed a consensus experience.

Clinical Findings

A. Symptoms and Signs

The clinical features most suggestive of GABHS pharyngitis include fever over 38°C, tender anterior cervical adenopathy, lack of a cough, and a pharyngotonsillar exudate. These four features (the Centor criteria), when present, strongly suggest GABHS. When two or three of the four are present, there is an intermediate likelihood of GABHS. When only one criterion is present, GABHS is unlikely. Sore throat may be severe, with odynophagia, tender adenopathy, and a scarlatiniform rash. An elevated white count and left shift are also possible. Hoarseness, cough, and coryza are not suggestive of this disease.



Marked lymphadenopathy and a shaggy, white-purple tonsillar exudate, often extending into the nasopharynx, suggest mononucleosis, especially if present in a young adult. With about 90% sensitivity, lymphocyte-to-whiteblood-cell ratios of greater than 35% suggest EBV infection and not tonsillitis. Hepatosplenomegaly and a positive heterophil agglutination test or elevated anti-EBV titer are corroborative. However, about one-third of patients with infectious mononucleosis have secondary streptococcal tonsillitis, requiring treatment. Ampicillin should routinely be avoided if mononucleosis is suspected because it induces a rash that might be misinterpreted by the patient as a penicillin allergy. Diphtheria (extremely rare but described in the alcoholic population) presents with low-grade fever and an ill patient with a gray tonsillar pseudomembrane.

The most common pathogens other than GABHS in the differential diagnosis of “sore throat” are viruses, Neisseria gonorrhoeae, Mycoplasma, and Chlamydia trachomatis. Rhinorrhea and lack of exudate would suggest a virus, but in practice it is not possible to confidently distinguish viral upper respiratory infection from GABHS on clinical grounds alone. Infections with Corynebacterium diphtheria, anaerobic streptococci, and Corynebacterium haemolyticum (which responds better to erythromycin than penicillin) may also mimic pharyngitis due to GABHS.

B. Laboratory Findings

A single-swab throat culture is 90–95% sensitive and the rapid antigen detection testing (RADT) is 90–99% sensitive for GABHS. Results from the RADT are available in about 15 minutes, much sooner than from the throat culture.

Treatment

Given the availability of many well-documented studies in recent years, one would think that a consensus might develop as to the most appropriate way to treat a sore throat. The Infectious Diseases Society of America recommends laboratory confirmation of the clinical diagnosis by means of either throat culture or RADT of the throat swab. The American College of Physicians–American Society of Internal Medicine (ACP-ASIM), in collaboration with the Centers for Disease Control and Prevention, advocates use of a clinical algorithm alone—in lieu of microbiologic testing—for confirmation of the diagnosis in adults for whom the suspicion of streptococcal infection is high. Others examine the assumptions of the ACP-ASIM guideline for using a clinical algorithm alone and question whether those recommendations will achieve the stated objective of dramatically decreasing excess antibiotic use. A reasonable strategy to follow is that patients with zero or one Centor criteria are at very low risk for GABHS and therefore, do not need throat cultures or RADT of the throat swab and should not receive antibiotics. Patients with two or three Centor criteria need throat cultures or RADT of the throat swab, since positive results would warrant antibiotic treatment. Patients who have four Centor criteria are likely to have GABHS and can receive empiric therapy without throat culture or RADT.

Forty years ago, a single intramuscular injection of benzathine penicillin or procaine penicillin, 1.2 million units once, was the standard antibiotic treatment. This remains effective, but the injection is painful. It is now used for patients if compliance with an oral regimen is an issue. Currently, oral treatment is effective and preferred. Antibiotic choice aims to reduce the already low (10– 20%) incidence of treatment failures (positive culture after treatment despite symptomatic resolution) and recurrences. Penicillin V potassium (250 mg orally three times daily or 500 mg twice daily for 10 days) or cefuroxime axetil (250 mg orally twice daily for 5–10 days) are both effective. The efficacy of a 5-day regimen of penicillin V potassium appears to be similar to that of a 10-day course, with a 94% clinical response rate and an 84% streptococcal eradication rate. Erythromycin (also active against Mycoplasma and Chlamydia) is a reasonable alternative to penicillin in allergic patients. Cephalosporins are somewhat more effective than penicillin in producing bacteriologic cures; 5-day administration has been successful for cefpodoxime and cefuroxime. The macrolide antibiotics have also been reported to be successful in shorter-duration regimens. Azithromycin (500 mg once daily), because of its long half-life, need be taken for only 3 days.

Adequate antibiotic treatment usually avoids the streptococcal complications of scarlet fever, glomerulonephritis, rheumatic myocarditis, and local abscess formation.

Antibiotics for treatment failures are also somewhat controversial. Surprisingly, penicillin-tolerant strains are not isolated more frequently in those who fail treatment than in those treated successfully with penicillin. The reasons for failure appear to be complex, and a second course of treatment with the same drug is reasonable. Alternatives to penicillin include cefuroxime and other cephalosporins, dicloxacillin (which is beta-lactamase–resistant), and amoxicillin

with clavulanate. When there is a history of penicillin allergy, alternatives should be used, such as erythromycin. Erythromycin resistance—with failure rates of about 25%—is an increasing problem in many areas. In cases of severe penicillin allergy, cephalosporins should be avoided as the cross-reaction is common (8% or more).

Ancillary treatment of pharyngitis includes analgesics and anti-inflammatory agents, such as aspirin, acetaminophen, and corticosteroids. In meta-analysis, corticosteroids increased the likelihood of complete pain resolution at 24 hours by threefold without an increase in recurrence or adverse events. Some patients find that salt water gargling is soothing. In severe cases, anesthetic gargles and lozenges (eg, benzocaine) may provide additional symptomatic relief. Occasionally, odynophagia is so intense that hospitalization for intravenous hydration and antibiotics is necessary.

Patients who have had rheumatic fever should be treated with a continuous course of antimicrobial prophylaxis (erythromycin, 250 mg twice daily orally, or penicillin G, 500 mg once daily orally) for at least 5 years.

COMMON LARYNGEAL DISORDERS

Acute Laryngitis

Acute laryngitis is probably the most common cause of hoarseness, which may persist for a week or so after other symptoms of an upper respiratory infection have cleared. The patient should be warned to avoid vigorous use of the voice (singing, shouting) until their voice returns to normal, since persistent use may lead to the formation of traumatic vocal fold hemorrhage, polyps, and cysts. Although thought to be usually viral in origin, both M catarrhalis and H influenzae may be isolated from the nasopharynx at higher than expected frequencies. Despite this finding, a meta-analysis has failed to demonstrate any convincing evidence that antibiotics significantly alter the natural resolution of acute laryngitis. Erythromycin may speed subjective perception of hoarseness and cough. Oral or intramuscular corticosteroids may be used in highly selected cases of professional vocalists to speed recovery and allow scheduled performances. Examination of the vocal folds and assessment of vocal technique are mandatory prior to corticosteroid initiation, since inflamed vocal folds are at greater risk for hemorrhage and the subsequent development of traumatic vocal fold pathology.

Laryngopharyngeal Reflux

ESSENTIALS OF DIAGNOSIS

- Commonly associated with hoarseness, throat irritation, and chronic cough.
- Symptoms typically occur when upright and half of patients do not experience heartburn.
- Laryngoscopy is critical to exclude other causes of hoarseness.
- Diagnosis is made based on response to proton pump inhibitor therapy.
- Treatment failure with proton pump inhibitors is common and may suggest other etiologies.

Gastroesophageal reflux into the larynx (***laryngopharyngeal reflux***) is considered a cause of chronic hoarseness when other causes of abnormal vocal fold vibration (such as tumor or nodules) have been excluded by laryngoscopy. Gastroesophageal reflux disease (GERD) has also been suggested as a contributing factor to other symptoms, such as throat clearing, throat discomfort, chronic cough, a sensation of postnasal drip, esophageal spasm, and some cases of asthma. Since less than half of patients with laryngeal acid exposure have typical symptoms of heartburn and regurgitation, the lack of such symptoms should not be construed as eliminating this cause. Indeed, most patients with symptomatic laryngopharyngeal reflux, as it is now called, do not meet criteria for GERD by pH probe testing and these entities must be considered separately. The prevalence of this condition is hotly debated in the literature, and laryngopharyngeal reflux may not be as common as once thought.

Evaluation should initially exclude other causes of dysphonia through laryngoscopy; consultation with an otolaryngologist is advisable. Many clinicians opt for an empiric trial of a proton pump inhibitor since no gold standard exists for diagnosing this condition. Such an empiric trial should not precede visualization of the vocal folds to exclude other causes of hoarseness. When used, the American Academy of Otolaryngology—Head and Neck Surgery recommends twice-daily therapy with full-strength proton pump inhibitor (eg, omeprazole 40 mg orally twice daily, or equivalent) for a minimum of 3 months. Patients may note improvement in symptoms after 3 months, but the changes in the larynx often take 6 months to resolve. If symptoms improve and cessation of therapy leads to symptoms again, then a proton pump inhibitor is resumed at the lowest dose effective for remission, usually daily but at times on a demand basis. Although H2-receptor antagonists are an alternative to proton pump inhibitors, they are generally both less clinically effective and less cost-effective. Nonresponders should undergo pH testing and manometry.

Twenty-four-hour pH monitoring of the pharynx should best document laryngopharyngeal reflux and is advocated by some as the initial management step but it is costly, more difficult, and less available than lower esophageal monitoring alone. Double pH probe (proximal and distal esophageal probes) testing is the best option for evaluation, since lower esophageal pH monitoring alone does not correlate well with laryngopharyngeal reflux symptoms. Oropharyngeal pH probe testing is available, but its ability to predict response to reflux treatment in patients with laryngopharyngeal reflux is not known.

Epiglottitis

Epiglottitis (or, more correctly, supraglottitis) should be suspected when a patient presents with a rapidly developing sore throat or when odynophagia (pain on swallowing) is out of proportion to apparently minimal oropharyngeal findings on examination. It is more common in diabetic patients and may be viral or bacterial in origin. Rarely in the era of H influenzae type b vaccine is this bacterium isolated in adults. Unlike in children, indirect laryngoscopy is generally safe and

may demonstrate a swollen, erythematous epiglottis. Lateral plain radiographs may demonstrate an enlarged epiglottis (the epiglottis “thumb sign”). Initial treatment is hospitalization for intravenous antibiotics— eg, ceftizoxime, 1–2 g intravenously every 8–12 hours; or cefuroxime, 750–1500 mg intravenously every 8 hours; and dexamethasone, usually 4–10 mg as initial bolus, then 4 mg intravenously every 6 hours—and observation of the airway. Corticosteroids may be tapered as symptoms and signs resolve. Similarly, substitution of oral antibiotics may be appropriate to complete a 10-day course. Less than 10% of adults require intubation. Indications for intubation are dyspnea, rapid pace of sore throat (where progression to airway compromise may occur before the effects of corticosteroids and antibiotics), and endolaryngeal abscess noted on CT imaging. If the patient is not intubated, prudence suggests monitoring oxygen saturation with continuous pulse oximetry and initial admission to a monitored unit.

VOCAL FOLD PARALYSIS

Vocal fold paralysis can result from a lesion or damage to either the vagus or recurrent laryngeal nerve and usually results in breathy dysphonia and effortful voicing. Common causes **of unilateral recurrent laryngeal nerve** involvement include thyroid surgery (and occasionally thyroid cancer), other neck surgery (anterior discectomy and carotid endarterectomy), and mediastinal or apical involvement by lung cancer. Skull base tumors often involve or abut upon lower cranial nerves and may affect the vagus nerve directly, or the vagus nerve may be damaged during surgical management of the lesion. While iatrogenic injury is the most common cause of unilateral vocal fold paralysis, the second most common cause is idiopathic. However, before deciding whether the paralysis is due to iatrogenic injury or is idiopathic, the clinician must exclude other causes, such as malignancy. In the absence of other cranial neuropathies, a CT scan with contrast from the skull base to the aorto-pulmonary window (the span of the recurrent laryngeal nerve) should be performed. If other cranial nerve deficits or high vagal weakness with palate paralysis is noted, an MRI scan of the brain and brainstem is warranted.

Unlike unilateral fold paralysis**, bilateral fold paralysis** usually causes inspiratory stridor with deep inspiration. If the onset of bilateral fold paralysis is insidious, it may be asymptomatic at rest, and the patient may have a normal voice. However, the acute onset of bilateral vocal fold paralysis with inspiratory stridor at rest should be managed by a specialist immediately in a critical care environment. Causes of bilateral fold paralysis include thyroid surgery, esophageal cancer, and ventricular shunt malfunction. Unilateral or bilateral fold immobility may also be seen in cricoarytenoid arthritis secondary to advanced rheumatoid arthritis, intubation injuries, glottic and subglottic stenosis, and, of course, laryngeal cancer. The goal of intervention is the creation of a safe airway with minimal reduction in voice quality and airway protection from aspiration. A number of fold lateralization procedures for bilateral paralysis have been advocated as a means of removing the tracheotomy tube.

Unilateral vocal fold paralysis is occasionally temporary and may take over a year to resolve spontaneously. Surgical management of persistent or irrecoverable symptomatic unilateral vocal fold paralysis has evolved over the last several decades. The primary goal is medialization of the paralyzed fold in order to create a stable platform for vocal fold vibration. Additional goals include improving pulmonary toilet by facilitating of cough and advancing diet. Success has been reported for years with injection laryngoplasty using Teflon, Gelfoam, fat, and collagen. Teflon is the only permanent injectable material, but its use is discouraged because of granuloma formation within the vocal folds of some patients. Temporary injectable materials, such as collagen or fat, provide excellent temporary restoration of voice and can be placed under local or general anesthesia. Once the paralysis is determined to be permanent, formal medialization thyroplasty may be performed by creating a small window in the thyroid cartilage and placing an implant between the thyroarytenoid muscle and inner table of the thyroid cartilage. This procedure moves the vocal fold medially and creates a stable platform for bilateral, symmetric mucosal vibration.

TRACHEOSTOMY & CRICOTHYROTOMY

There are two primary indications for tracheotomy: airway obstruction at or above the level of the larynx and respiratory failure requiring prolonged mechanical ventilation. In an acute emergency, cricothyrotomy secures an airway more rapidly than tracheotomy, with fewer potential immediate complications, such as pneumothorax and hemorrhage. Percutaneous dilatational tracheotomy as an elective bedside (or intensive care unit) procedure has undergone scrutiny in recent years as an alternative to tracheotomy. In experienced hands, the various methods of percutaneous tracheotomy have been documented to be safe in carefully selected patients. Simultaneous videobronchoscopy can reduce the incidence of major complications. The major cost reduction comes from avoiding the operating room. Bedside tracheotomy (in the intensive care unit) achieves similar cost reduction and is advocated by some experts as slightly less costly than the percutaneous procedures.

The most common indication for elective tracheotomy is the need for prolonged mechanical ventilation. There is no firm rule about how many days a patient must be intubated before conversion to tracheotomy should be advised. The incidence of serious complications, such as subglottic stenosis increases with extended endotracheal intubation. As soon as it is apparent that the patient will require protracted ventilatory support, tracheotomy should replace the endotracheal tube. Less frequent indications for tracheostomy are life-threatening aspiration pneumonia, the need to improve pulmonary toilet to correct problems related to insufficient clearing of tracheobronchial secretions, and sleep apnea.

Posttracheotomy care requires humidified air to prevent secretions from crusting and occluding the inner cannula of the tracheotomy tube. The tracheotomy tube should be cleaned several times daily. The most frequent early complication of tracheotomy is dislodgment of the tracheotomy tube. Surgical creation of an

inferiorly based tracheal flap sutured to the inferior neck skin may make reinsertion of a dislodged tube easier. It should be recalled that the act of swallowing requires elevation of the larynx, which is limited by tracheotomy. Therefore, frequent tracheal and bronchial suctioning is often required to clear the aspirated saliva as well as the increased tracheobronchial secretions. Care of the skin around the stoma is important to prevent maceration and secondary infection.

Control questions

1. Anatomical and physiological information about, nose, throat, throat, ear.
2. Basic methods of research in otorhinolaryngology: surveys, external examination, rhinoscopy, pharyngoscopy, laryngoscopy, tracheobronchoscopy, otoscopy, audiometry, vestibularometry.
3. Causes, mechanisms of development, clinical picture and pharmacotherapy of rhinitis.
4. Etipathogenesis, clinical manifestations and basic directions of pharmacotherapy of otitis media.
5. Acute respiratory diseases - etiology, clinical picture, pharmacotherapy.
6. Influenza - etiopathogenesis, clinical picture, complications, pharmacotherapy.
7. Paragripposis infection - etiopathogenesis, clinical picture, complications, pharmacotherapy.
8. Adenovirus infection - etiopathogenesis, clinical picture, complications, pharmacotherapy.
9. Respiratory syncytial viral infection - etiopathogenesis, clinical picture, complications, pharmacotherapy.
10. Rhinovirus infection - etiopathogenesis, clinical picture, complications, pharmacotherapy.
11. Rheumatoid infection - etiopathogenesis, clinical picture, complications, pharmacotherapy.
12. Etiology, pathogenesis, clinic and pharmacotherapy of pharyngitis and laryngitis.
13. The role of pharmacist in preventing the complications of drug therapy for ENT diseases.

List of practical works

A. Homework.

1. To study the etiology, pathogenesis of diseases of the upper respiratory tract.
2. To know the classification and the clinic of diseases of the upper respiratory tract.
3. To study the main directions of treatment of diseases of the upper respiratory tract.
4. Study the main principles of the treatment of influenza.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data of laboratory and instrumental studies, examination of consultants, records of the attending physician) and the letter of medical appointments.
3. At examination of the patient to allocate subjective, physical, laboratory-instrumental signs of diseases of the respiratory tract.
4. Write a clinical diagnosis:
5. a) the underlying disease; complications of the underlying disease;
6. b) concomitant diseases.
7. Determine a group of lesions necessary for correction of existing disorders.
8. On the basis of theoretical data and own observations, to make a choice of the specific drug of the examined patient.

Control the level of knowledge

1. Fill in the table "Methods of study of otorhinolaryngology".

Research methods	Definition concept	Clinical significance
1. Rhinoscopy		
2. Pharyngoscopy		
3. Laryngoscopy		
4. Otoscopy		
5. Audiometry		
6. Vestibulometry		

2. Fill in the table "Basic directions of pharmacotherapy of rhinitis".

Directions of pharmacotherapy	Pharmacological groups	Medications
1. Hyperthermia. 2. Desensitizing therapy. 3. Dilution of viscous secretions. 4. In chronic catarrhal rhinitis. 5. For chronic hypertrophic rhinitis.		

3. Fill in the table "Basic directions of pharmacotherapy of chronic purulent otitis media".

Directions of pharmacotherapy	Pharmacological groups	Medications
1. Influence on microflora		
2. Presence of signs of allergy		
3. The presence of a perforation hole.		
4. Reducing intoxication		
5. Local treatment.		

Solution of situational tasks

1. A patient, 19 years old, complains of dry cough, muscle aches, and fever to 39° C. During the week, they were disturbed by sore throat, subfebrile. Objectively: hard breathing. In the blood: L. - 7.0 • 10^9 /l, the leukocyte formula is normal. ESR - 26 mm / h. X-ray data of the chest organs: strengthening of the pulmonary picture, focal shadows of weak intensity in the lower parts of the right lung.

Formulate the diagnosis. Plan of treatment.

2. A child, 5 years old, is ill 2nd day. Premobidny background is not burdened. There is a slight general weakness, fever to 37.3° C, loss of appetite, frequent wet cough, significant discharge from the nose. Objectively: BD - 25 per minute. Percussion - pulmonary sound. Aussually, on both sides hears the middle-and large-bulging wheezing, after the cough the character of wheezing changes. Diagnosed acute respiratory infections, acute bronchitis.

Assign an optimal treatment, justify it.

3. In the patient V., 35 years old, against the background of high body temperature with acute rhinopharyngitis, there were bubbles with a transparent content on the upper lip. On the 2-3rd day the contents of the bubbles clouded, bubbles merged into a multisensing bubble. After the survey, it became clear that the patient was similar in the past.

What can be the previous diagnosis of a patient? Determine the main direction of pharmacotherapy in this case.

4. Pregnant is 26 years old, the term of pregnancy is 32 weeks. Submits complaints about nasal congestion and pain in the right ear, pain in swallowing. The condition got worse 3 days ago, when it felt weakened, nodding in the throat. The

following day, joined the above listed complaints. Appeared at the pharmacy for a bactrim, motivating this desire to begin the treatment of "colds."

What should be the tactic of the pharmacist? Answer substantiate. Type recipes.

Test tasks

1. To detect laryngitis, use:
1. Audiometry.
2. Laryngoscopy.
3. Pharyngoscopy.
4. Biopsy.
5. Vestibulometry.

2. For local treatment of acute rhinitis apply:
1. Lidocaine.
2. Nitrate of silver.
3. Galazolin.
4. Peroxide of hydrogen.
5. Sodium hydrogencarbonate.

3. The main areas of pharmacotherapy of pharyngitis are the following, except:
1. Reduce irritation of the throat mucus.
2. Influence on the infectious process.
3. Stimulation of regenerative processes.
4. Influence on pain syndrome.
5. Hyposensitization.

4. For local treatment of otitis using infusion of drops in the ear, use:
1. A solution of boric alcohol.
2. Glucose solution.
3. Novocaine solution.
4. Naphthysine.
5. Isotonic solution of sodium chloride.

5. The main pathogenetic link for laryngitis are:
1. Inflammatory process in the mucous membrane of the larynx.
2. Thickening of the mucous membrane of the palatine arches and the back of the throat.
3. Autoinfection by the microbes.
4. Allergic-hyperergic reaction
5. Reduced adaptive capacity of the body to the cold.

6. When hypertrophic laryngitis is used:

1. Anesthetic inhalation.
2. Isotonic solution of sodium chloride.
3. The solution of Lugol.
4. Silver Nitrate.
5. Hydrocortisone solution.

7. For local treatment of allergic rhinitis use:
1. Naphthysine.
2. Galazolin.
3. Bekonaze
4. Pharmazolyn.
5. Kalanchoe juice.

DISORDERS OF THE LOWER AIRWAYS

Tracheal obstruction may be intrathoracic (below the suprasternal notch) or extrathoracic. Fixed tracheal obstruction may be caused by acquired or congenital tracheal stenosis, primary or secondary tracheal neoplasms, extrinsic compression (tumors of the lung, thymus, or thyroid; lymphadenopathy; congenital vascular rings; aneurysms; etc), foreign body aspiration, tracheal granulomas and papillomas, and tracheal trauma. Tracheomalacia, foreign body aspiration, and retained secretions may cause variable tracheal obstruction.

Acquired **tracheal stenosis** is usually secondary to previous tracheotomy or endotracheal intubation. Dyspnea, cough, and inability to clear pulmonary secretions occur weeks to months after tracheal decannulation or extubation. Physical findings may be absent until tracheal diameter is reduced 50% or more, when wheezing, a palpable tracheal thrill, and harsh breath sounds may be detected. The diagnosis is usually confirmed by plain films or CT of the trachea. Complications include recurring pulmonary infection and life-threatening respiratory failure. Management is directed toward ensuring adequate ventilation and oxygenation and avoiding manipulative procedures that may increase edema of the tracheal mucosa. Surgical reconstruction, endotracheal stent placement, or laser photoresection may be required.

Bronchial obstruction may be caused by retained pulmonary secretions, aspiration, foreign bodies, bronchomalacia, bronchogenic carcinoma, compression by extrinsic masses, and tumors metastatic to the airway. Clinical and radiographic findings vary depending on the location of the obstruction and the degree of airway narrowing. Symptoms include dyspnea, cough, wheezing, and, if infection is present, fever and chills. A history of recurrent pneumonia in the same lobe or segment or slow resolution (more than 3 months) of pneumonia on successive radiographs suggests the possibility of bronchial obstruction and the need for bronchoscopy.

Roentgenographic findings include **atelectasis** (local parenchymal collapse), postobstructive infiltrates, and air trapping caused by unidirectional expiratory obstruction. CT scanning may demonstrate the nature and exact location of

obstruction of the central bronchi. MRI may be superior to CT for delineating the extent of underlying disease in the hilum, but it is usually reserved for cases in which CT findings are equivocal. Bronchoscopy is the definitive diagnostic study, particularly if tumor or foreign body aspiration is suspected. The finding of bronchial breath sounds on physical examination or an air bronchogram on chest radiograph in an area of atelectasis rules out complete airway obstruction. Bronchoscopy is unlikely to be of therapeutic benefit in this situation.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

ESSENTIALS OF DIAGNOSIS

- History of cigarette smoking.
- Chronic cough, dyspnea, and sputum production.
- Rhonchi, decreased intensity of breath sounds, and prolonged expiration on physical examination.
- Airflow limitation on pulmonary function testing that is not fully reversible and is most often progressive.

General Considerations

The American Thoracic Society defines COPD as a disease state characterized by the presence of airflow obstruction due to **chronic bronchitis** or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible. The NHLBI estimates that 15 million Americans have been diagnosed with COPD; an equal number are thought to be afflicted but remain undiagnosed. Grouped together, COPD and asthma now represent the fourth leading cause of death in the United States, with over 140,000 deaths reported annually. The death rate from COPD is increasing rapidly, especially among elderly men.

Most patients with COPD have features of both emphysema and chronic bronchitis. Chronic bronchitis is a clinical diagnosis defined by excessive secretion of bronchial mucus and is manifested by daily productive cough for 3 months or more in at least 2 consecutive years. **Emphysema** is a pathologic diagnosis that denotes abnormal permanent enlargement of air spaces distal to the terminal bronchiole, with destruction of their walls and without obvious fibrosis.

Cigarette smoking is clearly the most important cause of COPD in North America and Western Europe. Nearly all smokers suffer an accelerated decline in lung function that is dose- and duration-dependent. Fifteen percent develop progressively disabling symptoms in their 40s and 50s. Approximately 80% of patients seen for COPD have significant exposure to tobacco smoke. The remaining 20% frequently have a combination of exposures to environmental tobacco smoke, occupational dusts and chemicals, and indoor air pollution from biomass fuel used for cooking and heating in poorly ventilated buildings. Outdoor air pollution, airway infection, familial factors, and allergy have also been implicated in chronic bronchitis, and hereditary factors (deficiency of alpha-1-antiprotease [alpha-1-

antitrypsin]) have been implicated. Atopy and the tendency for bronchoconstriction to develop in response to nonspecific airway stimuli may be important risks.

Clinical Findings

A. Symptoms and Signs

Patients with COPD characteristically present in the fifth or sixth decade of life complaining of excessive cough, sputum production, and shortness of breath. Symptoms have often been present for 10 years or more. Dyspnea is noted initially only on heavy exertion, but as the condition progresses it occurs with mild activity. In severe disease, dyspnea occurs at rest. As the disease progresses, two symptom patterns tend to emerge, historically referred to as “pink puffers” and “blue bloaters”. Most COPD patients have pathologic evidence of both disorders, and their clinical course may involve other factors, such as central control of ventilation and concomitant sleep-disordered breathing.

Pneumonia, pulmonary hypertension, cor pulmonale, and chronic respiratory failure characterize the late stage of COPD. **A hallmark of COPD is the periodic exacerbation of symptoms beyond normal day-to-day variation, often including increased dyspnea, an increased frequency or severity of cough, and increased sputum volume or change in sputum character.** These exacerbations are commonly precipitated by infection (more often viral than bacterial) or environmental factors. Exacerbations of COPD vary widely in severity but typically require a change in regular therapy.

B. Laboratory Findings

Spirometry provides objective information about pulmonary function and assesses the response to therapy. Pulmonary function tests early in the course of COPD reveal only evidence of abnormal closing volume and reduced midexpiratory flow rate. Reductions in FEV1 and in the ratio of forced expiratory volume to vital capacity (FEV1 % or FEV1 /FVC ratio) occur later. In severe disease, the FVC is markedly reduced. Lung volume measurements reveal a marked increase in residual volume (RV), an increase in total lung capacity (TLC), and an elevation of the RV/TLC ratio, indicative of air trapping, particularly in emphysema.

Arterial blood gas measurements characteristically show no abnormalities early in COPD other than an increased A–a–Do2 . Indeed, measurement is unnecessary unless (1) hypoxemia or hypercapnia is suspected, (2) the FEV1 is less than 40% of predicted, or (3) there are clinical signs of right heart failure. Hypoxemia occurs in advanced disease, particularly when chronic bronchitis predominates. Compensated respiratory acidosis occurs in patients with chronic respiratory failure, particularly in chronic bronchitis, with worsening of acidemia during acute exacerbations.

Positive sputum cultures are poorly correlated with acute exacerbations, and research techniques demonstrate evidence of preceding viral infection in a majority of patients with exacerbations. The ECG may show sinus tachycardia and, in advanced disease, chronic pulmonary hypertension may produce

electrocardiographic abnormalities typical of cor pulmonale. Supraventricular arrhythmias (multifocal atrial tachycardia, atrial flutter, and atrial fibrillation) and ventricular irritability also occur.

C. Imaging

Radiographs of patients with chronic bronchitis typically show only nonspecific peribronchial and perivascular markings. Plain radiographs are insensitive for the diagnosis of emphysema; they show hyperinflation with flattening of the diaphragm or peripheral arterial deficiency in about half of cases. CT of the chest, particularly using highresolution CT, is more sensitive and specific than plain radiographs for its diagnosis. In advanced disease, pulmonary hypertension may be suggested by enlargement of central pulmonary arteries on radiographs, and Doppler echocardiography provides an estimate of pulmonary artery pressure.

Differential Diagnosis

Clinical, imaging, and laboratory findings should enable the clinician to distinguish COPD from other obstructive pulmonary disorders, such as asthma, bronchiectasis, cystic fibrosis, bronchopulmonary mycosis, and central airflow obstruction. Asthma is characterized by complete or nearcomplete reversibility of airflow obstruction. Bronchiectasis is distinguished from COPD by recurrent pneumonia and hemoptysis, digital clubbing, and characteristic imaging abnormalities. Patients with severe alpha-1-antitrypsin deficiency have a family history of the disorder and the finding of panacinar bibasilar emphysema early in life, usually in the third or fourth decade; hepatic cirrhosis and hepatocellular carcinoma may develop. Cystic fibrosis occurs in children, adolescents, and young adults. Mechanical obstruction of the central airways can be distinguished from COPD by flow-volume loops.

Complications

Acute bronchitis, pneumonia, pulmonary thromboembolism, atrial dysrhythmias (such as atrial fibrillation, atrial flutter, and multifocal atrial tachycardia), and concomitant left ventricular failure may worsen otherwise stable COPD. Pulmonary hypertension, cor pulmonale, and chronic respiratory failure are common in advanced COPD. Spontaneous pneumothorax occurs in a small fraction of patients with emphysema. Hemoptysis may result from chronic bronchitis or may signal bronchogenic carcinoma.

Prevention

COPD is largely preventable through elimination of longterm exposure to tobacco smoke or other inhaled toxins. Smokers with early evidence of airflow limitation can significantly alter their disease by smoking cessation. Smoking cessation slows the decline in FEV1 in middle-aged smokers with mild airways obstruction. Vaccination against seasonal and epidemic influenza A (H1N1) and pneumococcal infection may also be of benefit.

Treatment

The treatment of COPD is guided by the severity of symptoms or the presence of an exacerbation of stable symptoms. Standards for the management of patients with stable COPD and COPD exacerbations from the American Thoracic Society and the Global Initiative for Obstructive Lung Disease (GOLD), a joint expert committee of the NHLBI and the WHO, are incorporated in the recommendations below.

A. Ambulatory Patients

1. Smoking cessation—The single most important intervention in smokers with COPD is to encourage smoking cessation. Simply telling a patient to quit succeeds 5% of the time. Behavioral approaches, ranging from clinician advice to intensive group programs, may improve cessation rates. Pharmacologic therapy includes bupropion, nicotine replacement (transdermal patch, gum, lozenge, inhaler, or nasal spray), varenicline (a partial agonist of nicotinic acetylcholine receptors), and cytisine. Combined pharmacotherapies (two forms of nicotine replacement, or nicotine replacement and bupropion), with or without behavioral approaches, have been recommended. Varenicline is effective but use has been limited by concerns of neuropsychiatric side effects. Electronic cigarettes are being aggressively marketed as an aid for tobacco cigarette cessation. One RCT showed electronic cigarettes to be noninferior to nicotine transdermal patches. Most pulmonologists do not recommend electronic cigarettes as a tobacco cessation aid, based on safety concerns (they are not regulated and contain a variety of chemicals), and limited clinical trial data, although some clinicians will not discourage motivated smokers who refuse to consider standard approaches from trying electronic cigarettes.

2. Oxygen therapy—Supplemental oxygen for patients with resting hypoxemia is the only therapy with evidence of improvement in the natural history of COPD. Proved benefits of home oxygen therapy in hypoxemic patients include longer survival, reduced hospitalizations, and better quality of life. Survival in hypoxemic patients with COPD treated with supplemental oxygen therapy is directly proportionate to the number of hours per day oxygen is administered: in COPD hypoxemic patients treated with continuous oxygen for 24 hours daily, the survival after 36 months is about 65%—significantly better than the survival rate of about 45% in those treated with only nocturnal oxygen. Oxygen by nasal prongs must be given for at least 15 hours a day unless therapy is specifically intended only for exercise or sleep. In COPD patients with borderline low-normal resting oxygen levels (Pao2 between 56 mm Hg and 69 mm Hg), however, several studies of supplemental oxygen therapy showed no survival benefit. COPD patients with normal or low-normal resting oxygen levels who desaturate with exertion improve their exercise tolerance and shorten recovery from dyspnea when supplemental oxygen therapy is used during activity, but there is no evidence of a mortality benefit. Requirements for US Medicare coverage for a patient’s home use of

oxygen and oxygen equipment are listed in Table . Arterial blood gas analysis is preferred over oximetry to guide initial oxygen therapy. Hypoxemic patients with pulmonary hypertension, chronic cor pulmonale, erythrocytosis, impaired cognitive function, exercise intolerance, nocturnal restlessness, or morning headache are particularly likely to benefit from home oxygen therapy.

Home oxygen therapy: Requirements for Medicare coverage

Group I (any of the following):
1. Pao2 ≤ 55 mm Hg or Sao2 ≤ 88% taken while awake, at rest, breathing room air.
2. During sleep (prescription for nocturnal oxygen use only):
a. Pao2 ≤ 55 mm Hg or Sao2 ≤ 88% for a patient whose awake, resting, room air Pao2 is ≥ 56 mm Hg or Sao2 ≥ 89%,
or
b. Decrease in Pao2 > 10 mm Hg or decrease in Sao2 > 5% associated with symptoms or signs reasonably attributed to hypoxemia (eg, impaired cognitive processes, nocturnal restlessness, insomnia).
3. During exercise (prescription for oxygen use only during exercise):
a. Pao2 ≤ 55 mg Hg or Sao2 ≤ 88% taken during exercise for a patient whose awake, resting, room air Pao2 is ≥ 56 mm Hg or Sao2 ≥ 89%, and
b. There is evidence that the use of supplemental oxygen during exercise improves the hypoxemia that was demonstrated during exercise while breathing room air.

Group II2:
Pao2 = 56–59 mm Hg or Sao2 = 89% if there is evidence of any of the following:
1. Dependent edema suggesting heart failure.
2. P pulmonale on ECG (P wave > 3 mm in standard leads II, III, or aVF).
3. Hematocrit > 56%.

Home oxygen may be supplied by liquid oxygen systems, compressed gas cylinders, or oxygen concentrators. Most patients benefit from having both stationary and portable systems. For most patients, a flow rate of 1–3 L/min achieves a Pao2 greater than 55 mm Hg.. Medicare covers approximately 80% of home oxygen expenses. **Transtracheal oxygen** is an alternative method of delivery and may be useful for patients who require higher flows of oxygen than can be delivered via the nose or who are experiencing troublesome side effects from nasal delivery, such as nasal drying or epistaxis. Reservoir nasal cannulas or “pendants” and demand (pulse) oxygen delivery systems are also available to conserve oxygen.

3. Inhaled bronchodilators—Bronchodilators do not alter the inexorable decline in lung function that is a hallmark of COPD, but they improve symptoms, exercise tolerance, and overall health status. Aggressiveness of bronchodilator therapy should be matched to the severity of the patient’s disease. In patients who experience no symptomatic improvement, bronchodilators should be discontinued.

The most commonly prescribed short-acting bronchodilators are the anticholinergic ipratropium bromide and beta-2-agonists (eg, albuterol, metaproterenol), delivered by MDI or as an inhalation solution by nebulizer. **Ipratropium bromide is generally preferred to the short-acting beta-2-agonists as a first-line agent because of its longer duration of action and absence of sympathomimetic side effects**. Some studies have suggested that ipratropium achieves superior bronchodilation in COPD patients. Typical doses are two to four puffs (36–72 mcg) every 6 hours. Short-acting beta-2-agonists are less expensive and have a more rapid onset of action, commonly leading to greater patient satisfaction. At maximal doses, beta-2-agonists have bronchodilator action equivalent to that of ipratropium but may cause tachycardia, tremor, or hypokalemia. **There does not appear to be any advantage of scheduled use of short-acting beta- 2-agonists compared with as-needed administration**. Use of both short-acting beta-2-agonists and anticholinergics at submaximal doses leads to improved bronchodilation compared with either agent alone but does not improve dyspnea.

Long-acting beta-2-agonists (eg, formoterol, salmeterol, indacaterol, arformoterol, vilanterol) and anticholinergics (tiotropium, aclidinum, and umeclidinum) appear to achieve bronchodilation that is equivalent or superior to what is experienced with ipratropium, in addition to similar improvements in health status. Although more expensive than short-acting agents, long-acting bronchodilators may have superior clinical efficacy in persons with advanced disease. One RCT of long-term administration of tiotropium added to standard therapy reported fewer exacerbations or hospitalizations, and improved dyspnea scores, in the tiotropium group. Tiotropium had no effect on long-term decline in lung function, however. Another RCT comparing the effects of tiotropium with those of salmeterol-fluticasone over 2 years reported no difference in the risk of COPD exacerbation. The incidence of pneumonia was higher in the salmeterol-fluticasone group, yet dyspnea scores were lower and there was a mortality benefit compared with tiotropium.

The symptomatic benefits of long-acting bronchodilators are firmly established. Increased exacerbations and mortality in patients treated with salmeterol have not been observed in COPD patients, and several studies report a trend toward lower mortality in patients treated with salmeterol alone, compared with placebo. In addition, a 4-year tiotropium trial reported fewer cardiovascular events in the intervention group. Subsequent meta-analyses that include the 4-year tiotropium trial did not find an increase in cardiovascular events in treated patients. Most practitioners believe that the documented benefits of anticholinergic therapy outweigh any potential risks.

4. Corticosteroids—Multiple large clinical trials have reported a reduction in the frequency of COPD exacerbations and an increase in self-reported functional status in COPD patients treated with inhaled corticosteroids. These same trials demonstrate no effect of inhaled corticosteroids on mortality or the characteristic decline in lung function experienced by COPD patients. Thus, inhaled

corticosteroids alone should not be considered first-line therapy in stable COPD patients.

However, combination therapy with an inhaled corticosteroid and a long-acting beta-2-agonist reduces the frequency of exacerbations and improves self-reported functional status in COPD patients, compared with placebo or with sole use of inhaled corticosteroids, long-acting beta-2-agonists, or anticholinergics. In one RCT, addition of an inhaled corticosteroid/long-acting beta-2-agonist to tiotropium therapy in COPD patients did not reduce the frequency of exacerbations but did improve hospitalization rates and functional status.

Apart from acute exacerbations, COPD is not generally responsive to oral corticosteroid therapy. Compared with patients receiving placebo, only 10–20% of stable outpatients with COPD given oral corticosteroids will have a greater than 20% increase in FEV1 . **There may be a subset of steroid-responsive COPD patients more likely to benefit from long-term oral or inhaled corticosteroids**. Since there are no clinical predictors to identify such responders, empiric trials of oral corticosteroids are common. If an empiric trial of oral corticosteroid is conducted, a baseline FEV1 should be documented when the patient is stable (ie, not measured during an exacerbation), on maximal longterm bronchodilator therapy, and obtained immediately after a bronchodilator administration. After a 3- to 4-week trial of 0.25–0.5 mg/kg oral prednisone, the corticosteroid should only be continued if there is a 20% or greater increase in FEV1 over this baseline value. Responders to oral corticosteroids are usually switched to inhaled agents, but there are few data to guide this practice. Oral corticosteroids have well-recognized adverse effects, so it is prudent to minimize cumulative exposure. It is rare for a patient to be truly “corticosteroid-dependent” when all other available therapies are optimized.

5. Theophylline—Oral theophylline is a fourth-line agent for treating COPD patients who do not achieve adequate symptom control with inhaled anticholinergic, beta-2-agonist, and corticosteroid therapies. Sustained-release theophylline improves hemoglobin saturation during sleep in COPD patients and is a first-line agent for those with sleeprelated breathing disorders. Theophylline improves dyspnea ratings, exercise performance, and pulmonary function in many patients with stable COPD. Its benefits result from bronchodilation; anti-inflammatory properties; and extrapulmonary effects on diaphragm strength, myocardial contractility, and kidney function. Theophylline toxicity is a significant concern due to the medication’s narrow therapeutic window, and long-term administration requires careful monitoring of serum levels. Despite potential for adverse effects, theophylline continues to have a beneficial role in carefully selected patients.

6. Antibiotics—Antibiotics are commonly prescribed to outpatients with COPD for the following indications: (1) to treat an acute exacerbation, (2) to treat acute bronchitis, and (3) to prevent acute exacerbations of chronic bronchitis (prophylactic antibiotics). In patients with COPD, antibiotics appear to improve

outcomes slightly in all three situations. **Patients with a COPD exacerbation associated with increased sputum purulence accompanied by dyspnea or an increase in the quantity of sputum are thought to benefit the most from antibiotic therapy**. The choice of antibiotic depends on local bacterial resistance patterns and individual risk of Pseudomonas aeruginosa infection (history of Pseudomonas isolation, FEV1 less than 50% of predicted, recent hospitalization [2 or more days in the past 3 months], more than three courses of antibiotics within the past year, use of systemic corticosteroids). Oral antibiotic options include doxycycline (100 mg every 12 hours), trimethoprim-sulfamethoxazole (160/800 mg every 12 hours), a cephalosporin (eg, cefpodoxime 200 mg every 12 hours or cefprozil 500 mg every 12 hours), a macrolide (eg, azithromycin 500 mg followed by 250 mg daily for 5 days), a fluoroquinolone (eg, ciprofloxacin 500 mg every 12 hours), and amoxicillin-clavulanate (875/125 mg every 12 hours). Suggested duration of therapy is 3–7 days and depends on response to therapy; some studies suggest that 5 days is as effective as 7 days but with fewer adverse effects. There are few controlled trials of antibiotics in severe COPD exacerbations, but prompt administration is appropriate, particularly in persons with risk factors for poor outcomes (age older than 65 years, FEV1 less than 50% predicted, three or more exacerbations in the past year, antibiotic therapy within the past 3 months, comorbid conditions, such as cardiac disease). In COPD patients subject to frequent exacerbations despite optimal medical therapy, azithromycin (daily or three times weekly) and moxifloxacin (a 5-day course 1 week in 8 over 48 weeks) were modestly effective in clinical trials at reducing the frequency of exacerbations.

7. Pulmonary rehabilitation—Graded aerobic physical exercise programs (eg, walking 20 minutes three times weekly or bicycling) are helpful to prevent deterioration of physical condition and to improve patients' ability to carry out daily activities. Training of inspiratory muscles by inspiring against progressively larger resistive loads reduces dyspnea and improves exercise tolerance, health status, and respiratory muscle strength in some but not all patients. Pursed-lip breathing to slow the rate of breathing and abdominal breathing exercises to relieve fatigue of accessory muscles of respiration may reduce dyspnea in some patients. Many patients undergo these exercise and educational interventions in a structured rehabilitation program. In a number of studies, pulmonary rehabilitation has been shown to improve exercise capacity, decrease hospitalizations, and enhance quality of life. Referral to a comprehensive rehabilitation program is recommended in patients who have severe dyspnea, reduced quality of life, or frequent hospitalizations despite optimal medical therapy.

8. Other measures—In patients with chronic bronchitis, increased mobilization of secretions may be accomplished through the use of adequate systemic hydration, effective cough training methods, or the use of a hand-held flutter device and postural drainage, sometimes with chest percussion or vibration. Postural drainage and chest percussion should be used only in selected patients with excessive amounts of retained secretions that cannot be cleared by coughing and

other methods; these measures are of no benefit in pure emphysema. Expectorant-mucolytic therapy has generally been regarded as unhelpful in patients with chronic bronchitis. Cough suppressants and sedatives should be avoided.

Human alpha-1-antitrypsin is available for replacement therapy in emphysema due to congenital deficiency (PiZZ or null genotype) of alpha-1-antiprotease (alpha-1-antitrypsin). Patients over 18 years of age with airflow obstruction by spirometry and serum levels less than 11 mcmol/L (~50 mg/dL) are potential candidates for replacement therapy. Alpha-1-antitrypsin is administered intravenously in a dose of 60 mg/kg body weight once weekly. Severe dyspnea in spite of optimal medical management may warrant a clinical trial of an opioid (eg, morphine 5–10 mg orally every 3–4 hours, oxycodone 5–10 mg orally every 4–6 hours, sustained-release morphine 10 mg orally once daily). Sedative-hypnotic drugs (eg, diazepam, 5 mg three times daily) marginally improve intractable dyspnea but cause significant drowsiness; they may benefit very anxious patients. Transnasal positive-pressure ventilation at home to rest the respiratory muscles is an approach to improve respiratory muscle function and reduce dyspnea in patients with severe COPD.

B. Hospitalized Patients

Management of the hospitalized patient with an acute exacerbation of COPD includes (1) supplemental oxygen (titrated to maintain Sao2 between 90% and 94% or Pao2 between 60 mm Hg and 70 mm Hg), (2) inhaled ipratropium bromide (500 mcg by nebulizer, or 36 mcg by MDI with spacer, every 4 hours as needed) plus beta-2-agonists (eg, albuterol 2.5 mg diluted with saline to a total of 3 mL by nebulizer, or MDI, 90 mcg per puff, four to eight puffs via spacer, every 1–4 hours as needed), (3) corticosteroids (prednisone 30–40 mg orally per day for 7–10 days is usually sufficient, even 5 days may be adequate), (4) broadspectrum antibiotics, and (5) in selected cases, chest physiotherapy.

For patients without risk factors for Pseudomonas, management options include a fluoroquinolone (eg, levofloxacin 750 mg orally or intravenously per day, or moxifloxacin 400 mg orally or intravenously every 24 hours) or a third-generation cephalosporin (eg, ceftriaxone 1 g intravenously per day, or cefotaxime 1 g intravenously every 8 hours).

For patients with risk factors for Pseudomonas, therapeutic options include piperacillin-tazobactam (4.5 g intravenously every 6 hours), ceftazidime (1 g intravenously every 8 hours), cefepime (1 g intravenously every 12 hours), or levofloxacin (750 mg orally or intravenously per day for 3–7 days).

Theophylline should not be initiated in the acute setting, but patients taking theophylline prior to acute hospitalization should have their theophylline serum levels measured and maintained in the therapeutic range. **Oxygen therapy should not be withheld for fear of worsening respiratory acidemia; hypoxemia is more detrimental than hypercapnia**. Cor pulmonale usually responds to measures that reduce pulmonary artery pressure, such as supplemental oxygen and correction of acidemia; bed rest, salt restriction, and diuretics may add some benefit. Cardiac dysrhythmias, particularly multifocal atrial tachycardia, usually respond to

aggressive treatment of COPD itself. Atrial flutter may require DC cardioversion after initiation of the above therapy. If progressive respiratory failure ensues, tracheal intubation and mechanical ventilation are necessary. In clinical trials of COPD patients with hypercapnic acute respiratory failure, **noninvasive positive-pressure ventilation (NPPV)** delivered via face mask reduced the need for intubation and shortened lengths of stay in the intensive care unit (ICU). Other studies have suggested a lower risk of nosocomial infections and less use of antibiotics in COPD patients treated with NPPV. These benefits do not appear to extend to hypoxemic respiratory failure or to patients with acute lung injury or acute respiratory distress syndrome (ARDS).

C. Surgery for COPD

1. Lung transplantation—Requirements for lung transplantation are severe lung disease, limited activities of daily living, exhaustion of medical therapy, ambulatory status, potential for pulmonary rehabilitation, limited life expectancy without transplantation, adequate function of other organ systems, and a good social support system. Average total charges for lung transplantation through the end of the first postoperative year exceed $250,000. The 2-year survival rate after lung transplantation for COPD is 75%. Complications include acute rejection, opportunistic infection, and obliterative bronchiolitis. Substantial improvements in pulmonary function and exercise performance have been noted after transplantation.

2. Lung volume reduction surgery—Lung volume reduction surgery (LVRS), or reduction pneumoplasty, is a surgical approach to relieve dyspnea and improve exercise tolerance in patients with advanced diffuse emphysema and lung hyperinflation. Bilateral resection of 20–30% of lung volume in selected patients results in modest improvements in pulmonary function, exercise performance, and dyspnea. The duration of any improvement as well as any mortality benefit remains uncertain. Prolonged air leaks occur in up to 50% of patients postoperatively. Mortality rates in centers with the largest experience with LVRS range from 4% to 10%.

The National Emphysema Treatment Trial compared LVRS with medical treatment in a randomized, multicenter clinical trial of 1218 patients with severe emphysema. Overall, surgery improved exercise capacity but not mortality when compared with medical therapy. The persistence of this benefit remains to be defined. Subgroup analysis suggested that patients with upper lobe predominant emphysema and low exercise capacity might have improved survival, while other groups suffered excess mortality when randomized to surgery

3. Bullectomy—Bullectomy is an older surgical procedure for palliation of dyspnea in patients with severe bullous emphysema. Bullectomy is most commonly pursued when a single bulla occupies at least 30–50% of the hemithorax.

Prognosis

The outlook for patients with clinically significant COPD is poor. The degree of pulmonary dysfunction at the time the patient is first seen is an important predictor of survival: median survival of patients with FEV1 1 L or less is about 4 years. A multidimensional index (the BODE index), which includes body mass index (BMI), airway obstruction (FEV1), dyspnea (Medical Research Council dyspnea score), and exercise capacity is a tool that predicts death and hospitalization better than FEV1 alone.

Comprehensive care programs, cessation of smoking, and supplemental oxygen may reduce the rate of decline of pulmonary function, but therapy with bronchodilators and other approaches probably has little, if any, impact on the natural course of COPD.

Dyspnea at the end of life can be extremely uncomfortable and distressing to the patient and family. As patients near the end of life, meticulous attention to palliative care is essential to effectively manage dyspnea.

When to Refer

• COPD onset occurs before the age of 40.
• Frequent exacerbations (two or more a year) despite optimal treatment.
• Severe or rapidly progressive COPD.
• Symptoms disproportionate to the severity of airflow obstruction.
• Need for long-term oxygen therapy.
• Onset of comorbid illnesses (eg, bronchiectasis, heart failure, or lung cancer).

When to Admit

• Severe symptoms or acute worsening that fails to respond to outpatient management.
• Acute or worsening hypoxemia, hypercapnia, peripheral edema, or change in mental status.
• Inadequate home care, or inability to sleep or maintain nutrition/hydration due to symptoms.
• The presence of high-risk comorbid conditions.

BRONCHIECTASIS

ESSENTIALS OF DIAGNOSIS

- Chronic productive cough with dyspnea and wheezing.
- Radiographic findings of dilated, thickened airways and scattered, irregular opacities.

General Considerations

Bronchiectasis is a congenital or acquired disorder of the large bronchi characterized by permanent, abnormal dilation and destruction of bronchial walls. It may be caused by recurrent inflammation or infection of the airways and may be localized or diffuse. Cystic fibrosis causes about half of all cases of bronchiectasis. Other causes include lung infection (tuberculosis, fungal infections, lung abscess,

pneumonia), abnormal lung defense mechanisms (humoral immunodeficiency, alpha-1-antiprotease [alpha-1-antitrypsin] deficiency with cigarette smoking, mucociliary clearance disorders, rheumatic diseases), and localized airway obstruction (foreign body, tumor, mucoid impaction). Immunodeficiency states that may lead to bronchiectasis include congenital or acquired panhypogammaglobulinemia; common variable immunodeficiency; selective IgA, IgM, and IgG subclass deficiencies; and acquired immunodeficiency from cytotoxic therapy, AIDS, lymphoma, multiple myeloma, leukemia, and chronic kidney and liver diseases. Most patients with bronchiectasis have panhypergammaglobulinemia, however, presumably reflecting an immune system response to chronic airway infection. Acquired primary bronchiectasis is now uncommon in the United States because of improved control of bronchopulmonary infections.

Clinical Findings

A. Symptoms and Signs

Symptoms of bronchiectasis include chronic cough with production of copious amounts of purulent sputum, hemoptysis, and pleuritic chest pain. Dyspnea and wheezing occur in 75% of patients. Weight loss, anemia, and other systemic manifestations are common. Physical findings are nonspecific, but persistent crackles at the lung bases are common. Clubbing is infrequent in mild cases but is common in severe disease. Copious, foul-smelling, purulent sputum is characteristic. Obstructive pulmonary dysfunction with hypoxemia is seen in moderate or severe disease.

B. Imaging

Radiographic abnormalities include dilated and thickened bronchi that may appear as “tram tracks” or as ring-like markings. Scattered irregular opacities, atelectasis, and focal consolidation may be present. High-resolution CT is the diagnostic study of choice.

C. Microbiology

Haemophilus influenzae is the most common organism recovered from non–cystic fibrosis patients with bronchiectasis. P aeruginosa, S pneumoniae, and Staphylococcus aureus are commonly identified. Nontuberculous mycobacteria are seen less commonly. Patients with Pseudomonas infection experience an accelerated course, with more frequent exacerbations and more rapid decline in lung function.

Treatment

Treatment of acute exacerbations consists of antibiotics, daily chest physiotherapy with postural drainage and chest percussion, and inhaled bronchodilators. Hand-held flutter valve devices may be as effective as chest physiotherapy in clearing secretions. Antibiotic therapy should be guided by sputum smears and cultures. If a specific bacterial pathogen cannot be isolated, then

empiric oral antibiotic therapy for 10–14 days is appropriate. Common regimens include amoxicillin or amoxicillin-clavulanate (500 mg every 8 hours), ampicillin or tetracycline (250–500 mg four times daily), trimethoprim-sulfamethoxazole (160/800 mg every 12 hours), or ciprofloxacin (500–750 mg twice daily). It is important to screen patients for infection with nontuberculous mycobacteria because these organisms may underlie a lack of treatment response. Preventive or suppressive treatment is sometimes given to stable outpatients with bronchiectasis who have copious purulent sputum. Prolonged macrolide therapy (azithromycin 500 mg three times a week for 6 months or 250 mg daily for 12 months) has been found to decrease the frequency of exacerbations compared to placebo. High-dose amoxicillin (3 g/day) or alternating cycles of the antibiotics listed above given orally for 2–4 weeks are also used, although this practice is not supported by clinical trial data. In patients with underlying cystic fibrosis, inhaled aerosolized aminoglycosides reduce colonization by Pseudomonas species, improve FEV1 , and reduce hospitalizations. Complications of bronchiectasis include hemoptysis, cor pulmonale, amyloidosis, and secondary visceral abscesses at distant sites (eg, brain). Bronchoscopy is sometimes necessary to evaluate hemoptysis, remove retained secretions, and rule out obstructing airway lesions. Massive hemoptysis may require embolization of bronchial arteries or surgical resection. Surgical resection is otherwise reserved for the few patients with localized bronchiectasis and adequate pulmonary function in whom conservative management fails.

ALLERGIC BRONCHOPULMONARY MYCOSIS

Allergic bronchopulmonary mycosis is a pulmonary hypersensitivity disorder caused by allergy to fungal antigens that colonize the tracheobronchial tree. It usually occurs in atopic asthmatic individuals who are 20–40 years of age, in response to antigens of Aspergillus species. For this reason, the disorder is commonly referred to as allergic bronchopulmonary aspergillosis (ABPA). Primary criteria for the diagnosis of ABPA include (1) a clinical history of asthma, (2) peripheral eosinophilia, (3) immediate skin reactivity to Aspergillus antigen, (4) precipitating antibodies to Aspergillus antigen, (5) elevated serum IgE levels, (6) pulmonary infiltrates (transient or fixed), and (7) central bronchiectasis. If the first six of these seven primary criteria are present, the diagnosis is almost certain. Secondary diagnostic criteria include identification of Aspergillus in sputum, a history of brown-flecked sputum, and late skin reactivity to Aspergillus antigen. High-dose prednisone (0.5–1 mg/kg orally per day) for at least 2 months is the treatment of choice, and the response in early disease is usually excellent. Depending on the overall clinical situation, prednisone can then be cautiously tapered. Relapses are frequent, and protracted or repeated treatment with corticosteroids is not uncommon. Patients with corticosteroid-dependent disease may benefit from itraconazole (200 mg orally three times a day with food for 3 days, followed by twice daily for at least 16 weeks) without added toxicity. Bronchodilators are also helpful. Complications include hemoptysis, severe bronchiectasis, and pulmonary fibrosis.

BRONCHIOLITIS

ESSENTIALS OF DIAGNOSIS

- Insidious onset of cough and dyspnea.
- Irreversible airflow obstruction on pulmonary function testing.
- Minimal findings on chest radiograph.
- Relevant exposure or risk factors: toxic fumes, viral infections, organ transplantation, connective tissue disease.

General Considerations

Bronchiolitis is a generic term applied to varied inflammatory processes that affect the bronchioles, which are small conducting airways less than 2 mm in diameter. In infants and children, bronchiolitis is common and usually caused by respiratory syncytial virus or adenovirus infection. In adults, bronchiolitis is less common but is encountered in multiple clinical settings. Disorders associated with bronchiolitis include organ transplantation, connective tissue diseases, and hypersensitivity pneumonitis. Inhalational injuries as well as postinfectious and drug-induced causes are identified by association with a known exposure or illness prior to the onset of symptoms. Idiopathic cases are characterized by the insidious onset of dyspnea or cough and include cryptogenic organizing pneumonitis (COP).

Clinical Findings

Acute bronchiolitis is most commonly seen following viral infection in children.

Constrictive bronchiolitis (also referred to as obliterative bronchiolitis, or bronchiolitis obliterans) is relatively infrequent although it is the most common finding following inhalation injury. It may also be seen in rheumatoid arthritis; medication reactions; and chronic rejection following heart-lung, lung, or bone marrow transplant. Patients with constrictive bronchiolitis have airflow obstruction on spirometry; minimal radiographic abnormalities; and a progressive, deteriorating clinical course.

Proliferative bronchiolitis is associated with diverse pulmonary disorders, including infection, aspiration, ARDS, hypersensitivity pneumonitis, connective tissue diseases, and organ transplantation. Compared with constrictive bronchiolitis, proliferative bronchiolitis is more likely to have an abnormal chest radiograph.

Cryptogenic organizing pneumonitis (COP) formally referred to as **bronchiolitis obliterans with organizing pneumonia** (BOOP) affects men and women between the ages of 50 and 70 years, typically with a dry cough, dyspnea, and constitutional symptoms that may be present for weeks to months prior to seeking medical attention. A history of a preceding viral illness is present in half of cases. Pulmonary function testing typically reveals a restrictive ventilatory defect and impaired oxygenation. The chest radiograph frequently shows bilateral patchy, ground-glass or alveolar infiltrates, although other patterns have been described

Follicular bronchiolitis is most commonly associated with connective tissue disease, especially rheumatoid arthritis and Sjögren syndrome, and with immunodeficiency states.

Respiratory bronchiolitis usually occurs without symptoms or physiologic evidence of lung impairment.

Diffuse panbronchiolitis is most frequently diagnosed in Japan. Men are affected about twice as often as women, two-thirds are nonsmokers, and most patients have a history of chronic pansinusitis. Patients complain of dyspnea, cough, and sputum production, and chest examination shows crackles and rhonchi. Pulmonary function tests reveal obstructive abnormalities, and the chest radiograph shows a distinct pattern of diffuse, small, nodular shadows with hyperinflation.

Treatment

Constrictive bronchiolitis is relatively unresponsive to corticosteroids and is frequently progressive. Corticosteroids are effective in two-thirds of patients with proliferative bronchiolitis, and improvement can be prompt. Therapy is initiated with prednisone at 1 mg/kg/day orally for 1–3 months. The dose is then tapered slowly to 20–40 mg/day, depending on the response, and weaned over the subsequent 3–6 months as tolerated. Relapses are common if corticosteroids are stopped prematurely or tapered too quickly. Most patients with COP recover following corticosteroid treatment. Diffuse panbronchiolitis is effectively treated with azithromycin.

PULMONARY INFECTIONS
PNEUMONIA

This section sets forth the evaluation and management of pulmonary infiltrates in immunocompetent persons separately from the approach to immunocompromised persons—defined as those with HIV disease, absolute neutrophil counts less than 1000/mcL (1.0×10^9/L), current or recent exposure to myelosuppressive or immunosuppressive medications, or those currently taking prednisone in a dosage greater than 5 mg/day.

1. Community-Acquired Pneumonia

ESSENTIALS OF DIAGNOSIS

- Fever or hypothermia, tachypnea, cough with or without sputum, dyspnea, chest discomfort, sweats or rigors (or both).
- Bronchial breath sounds or inspiratory crackles on chest auscultation.
- Parenchymal opacity on chest radiograph.
- Occurs outside of the hospital or within 48 hours of hospital admission in a patient not residing in a long-term care facility.

General Considerations

Community-acquired pneumonia (CAP) is a common disorder, with approximately 4–5 million cases diagnosed each year in the United States, 25% of which require hospitalization. It is the most deadly infectious disease in the United

States and the eighth leading cause of death. Mortality in milder cases treated as outpatients is less than 1%. Among patients hospitalized for CAP, in-hospital mortality is approximately 10–12% and 1-year mortality (in those over age 65) is greater than 40%. Risk factors for the development of CAP include advanced age; alcoholism; tobacco use; comorbid medical conditions, especially asthma or COPD; and immunosuppression.

The patient's history, physical examination, and imaging studies are essential to establishing a diagnosis of CAP. None of these efforts identifies a specific microbiologic cause, however. Sputum examination may be helpful in selected patients but 40% of patients cannot produce an evaluable sputum sample and Gram stain and culture lack sensitivity for the most common causes of pneumonia. Since patient outcomes improve when the initial antibiotic choice is appropriate for the infecting organism, the American Thoracic Society and the Infectious Diseases Society of America recommend empiric treatment based on epidemiologic data. Such treatment improves initial antibiotic coverage, reduces unnecessary hospitalization, and appears to improve 30-day survival.

Decisions regarding hospitalization and ICU care should be based on prognostic criteria (see below).

Recommended empiric antibiotics for community-acquired pneumonia.

Outpatient management

1. *For previously healthy patients who have not taken antibiotics within the past 3 months:*

a. A macrolide (clarithromycin, 500 mg orally twice a day; or azithromycin, 500 mg orally as a first dose and then 250 mg orally daily for 4 days, or 500 mg orally daily for 3 days), or

b. Doxycycline, 100 mg orally twice a day.

2. *For patients with such comorbid medical conditions as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; asplenia; immunosuppressant conditions or use of immunosuppressive drugs; or use of antibiotics within the previous 3 months (in which case, an alternative from a different antibiotic class should be selected):*

a. A respiratory fluoroquinolone (moxifloxacin, 400 mg orally daily; gemifloxacin, 320 mg orally daily; levofloxacin, 750 mg orally daily) or

b. A macrolide (as above) plus a beta-lactam (amoxicillin, 1 g orally three times a day; amoxicillin-clavulanate, 2 g orally twice a day are preferred to cefpodoxime, 200 mg orally twice a day; cefuroxime, 500 mg orally twice a day).

3. *In regions with a high rate (>25%) of infection with high level (MIC≥16 mcg/mL) macrolide-resistant Streptococcus pneumoniae, consider use of alternative agents listed above in (2) for patients with comorbidities.*

Inpatient management not requiring intensive care

1. A respiratory fluoroquinolone

a. See above for oral therapy.
b. For intravenous therapy, moxifloxacin, 400 mg daily; levofloxacin, 750 mg daily; ciprofloxacin, 400 mg every 8–12 hours or

2. A macrolide plus a beta-lactam
a. See above for oral therapy.
b. For intravenous therapy, ampicillin, 1–2 g every 4–6 hours; cefotaxime, 1–2 g every 4–12 hours; ceftriaxone, 1–2 g every 12–24 hours.

Inpatient intravenous management requiring intensive care

1. *Azithromycin (500 mg orally as a first dose and then 250 mg orally daily for 4 days, or 500 mg orally daily for 3 days) or a respiratory fluoroquinolone plus an antipneumococcal beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam, 1.5–3 g every 6 hours).*

2. For patients allergic to beta-lactam antibiotics, a fluoroquinolone plus aztreonam (1–2 g every 6–12 hours).

3. *For patients at risk for Pseudomonas infection*

a. An antipneumococcal, antipseudomonal beta-lactam (piperacillin-tazobactam, 3.375–4.5 g every 6 hours; cefepime, 1–2 g twice a day; imipenem, 0.5–1 g every 6–8 hours; meropenem, 1 g every 8 hours) plus ciprofloxacin (400 mg every 8–12 hours) or levofloxacin, or

b. The above beta-lactam plus an aminoglycoside (gentamicin, tobramycin, amikacin, all weight-based dosing administered daily adjusted to appropriate trough levels) plus azithromycin or a respiratory fluoroquinolone.

4. For patients at risk for methicillin-resistant Staphylococcus aureus infection, add vancomycin (interval dosing based on renal function to achieve serum trough concentration 15–20 mcg/mL) or linezolid (600 mg twice a day).

(MIC, minimum inhibitory concentration)

Definition & Pathogenesis

CAP is diagnosed outside of the hospital in ambulatory patients who are not residents of nursing homes or other long-term care facilities. It may also be

diagnosed in a previously ambulatory patient within 48 hours after admission to the hospital.

Pulmonary defense mechanisms (cough reflex, mucociliary clearance system, immune responses) normally prevent the development of lower respiratory tract infections following aspiration of oropharyngeal secretions containing bacteria or inhalation of infected aerosols. CAP occurs when there is a defect in one or more of these normal defense mechanisms or when a large infectious inoculum or a virulent pathogen overwhelms the immune response.

Prospective studies fail to identify the cause of CAP in 40–60% of cases; two or more causes are identified in up to 5% of cases. Bacteria are more commonly identified than viruses. The most common bacterial pathogen identified in most studies of CAP is S pneumoniae, accounting for approximately two-thirds of bacterial isolates. Other common bacterial pathogens include H influenzae, M pneumoniae, C pneumoniae, S aureus, Neisseria meningitidis, M catarrhalis, Klebsiella pneumoniae, other gram-negative rods, and Legionella species. Common viral causes of CAP include influenza virus, respiratory syncytial virus, adenovirus, and parainfluenza virus. A detailed assessment of epidemiologic risk factors may aid in diagnosing pneumonias due to the following uncommon causes: Chlamydophila psittaci (psittacosis), Coxiella burnetii (Q fever), Francisella tularensis (tularemia), endemic fungi (Blastomyces, Coccidioides, Histoplasma), and sin nombre virus (hantavirus pulmonary syndrome).

Clinical Findings

A. Symptoms and Signs

Most patients with CAP experience an acute or subacute onset of fever, cough with or without sputum production, and dyspnea. Other common symptoms include sweats, chills, rigors, chest discomfort, pleurisy, hemoptysis, fatigue, myalgias, anorexia, headache, and abdominal pain.

Common physical findings include fever or hypothermia, tachypnea, tachycardia, and arterial oxygen desaturation. Many patients appear acutely ill. Chest examination often reveals inspiratory crackles and bronchial breath sounds. Dullness to percussion may be observed if lobar consolidation or a parapneumonic pleural effusion is present. The clinical evaluation is less than 50% sensitive compared to chest imaging for the diagnosis of CAP (see Imaging section below). In most patients, therefore, a chest radiograph is essential to the evaluation of suspected CAP.

B. Diagnostic Testing

Diagnostic testing for a specific infectious cause of CAP is not generally indicated in ambulatory patients treated as outpatients because empiric antibiotic therapy is almost always effective in this population. In ambulatory outpatients whose presentation (travel history, exposure) suggests an etiology not covered by standard therapy (eg, Coccidioides) or public health concerns (eg, Mycobacterium tuberculosis, influenza), diagnostic testing is appropriate. Diagnostic testing is recommended in hospitalized CAP patients for multiple reasons: the likelihood of

an infectious cause unresponsive to standard therapy is higher in more severe illness, the inpatient setting allows narrowing of antibiotic coverage as specific diagnostic information is available, and the yield of testing is improved in more acutely ill patients.

Diagnostic testing results are used to guide initial antibiotic therapy, permit adjustment of empirically chosen therapy to a specific infectious cause or resistance pattern, and facilitate epidemiologic analysis. There are three widely available, rapid point-of-care diagnostic tests that may guide initial therapy: the sputum Gram stain, urinary antigen tests for S pneumonia and Legionella species, and rapid antigen detection tests for influenza. Sputum Gram stain is neither sensitive nor specific for S pneumonia, the most common cause of CAP. The usefulness of a sputum Gram stain lies in broadening initial coverage in patients to be hospitalized for CAP, most commonly to cover S aureus (including community-acquired methicillin-resistant strains, CA-MRSA) or gram-negative rods. Urinary antigen assays for Legionella pneumophilia and S pneumoniae are at least as sensitive and specific as sputum Gram stain and culture. Results are available immediately and are not affected by early initiation of antibiotic therapy. Positive tests may allow narrowing of initial antibiotic coverage. Urinary antigen assay for S pneumoniae should be ordered for patients with leukopenia, asplenia, active alcohol use, chronic severe liver disease, pleural effusion, and those requiring ICU admission. Urinary antigen assay for L pneumophilia should be ordered for patients with active alcohol use, travel within 2 weeks, pleural effusion, and those requiring ICU admission. Rapid influenza testing has intermediate sensitivity but high specificity. Positive tests may reduce unnecessary antibacterial use and direct isolation of hospitalized patients.

Additional microbiologic testing including pre-antibiotic sputum and blood cultures (at least two sets with needle sticks at separate sites) has been standard practice for patients with CAP who require hospitalization. The yield of blood and sputum cultures is low. However, false-positive results are common, and the impact of culture results on patient outcomes is small. As a result, targeted testing based on specific indications is recommended. Culture results are not available prior to initiation of antibiotic therapy. Their role is to allow narrowing of initial empiric antibiotic coverage, adjustment of coverage based on specific antibiotic resistance patterns, to identify unsuspected pathogens not covered by initial therapy, and to provide information for epidemiologic analysis.

Apart from microbiologic testing, hospitalized patients should undergo complete blood count with differential and a chemistry panel (including serum glucose, electrolytes, urea nitrogen, creatinine, bilirubin, and liver enzymes). Hypoxemic patients should have arterial blood gases sampled. Test results help assess severity of illness and guide evaluation and management. HIV testing should be considered in all adult patients, and performed in those with risk factors.

C. Imaging

A pulmonary opacity on chest radiography or CT scan is required to establish a diagnosis of CAP. Radiographic findings range from patchy airspace opacities to

lobar consolidation with air bronchograms to diffuse alveolar or interstitial opacities. Additional findings can include pleural effusions and cavitation.

Chest imaging cannot identify a specific microbiologic cause of CAP, however. There is no pattern of radiographic abnormalities pathognomonic of any infectious cause. Chest imaging may help assess severity and response to therapy over time. Progression of pulmonary opacities during antibiotic therapy or lack of radiographic improvement over time are poor prognostic signs and also raise concerns about secondary or alternative pulmonary processes. Clearing of pulmonary opacities in patients with CAP can take 6 weeks or longer. Clearance is usually quickest in younger patients, nonsmokers, and those with only single-lobe involvement.

D. Special Examinations

Patients with CAP who have significant pleural fluid collections may require diagnostic thoracentesis (glucose, lactate dehydrogenase [LD], and total protein levels; leukocyte count with differential; pH determination) with pleural fluid Gram stain and culture. Positive pleural cultures indicate the need for tube thoracostomy drainage. Patients with cavitary opacities should have sputum fungal and mycobacterial cultures. Sputum induction and fiberoptic bronchoscopy to obtain samples of lower respiratory secretions are indicated in patients who cannot provide expectorated sputum samples or who may have Pneumocystis jirovecii or M tuberculosis pneumonia. Serologic assays, polymerase chain reaction tests, specialized culture tests, and other diagnostic tests for organisms such as viruses, Legionella, M pneumoniae, and C pneumoniae may be performed when these diagnoses are suspected.

Differential Diagnosis

The differential diagnosis of lower respiratory tract infection is extensive and includes upper respiratory tract infections, reactive airway diseases, heart failure, cryptogenic organizing pneumonitis, lung cancer, pulmonary vasculitis, pulmonary thromboembolic disease, and atelectasis.

Treatment

Two general principles guide antibiotic therapy once the diagnosis of CAP is established: **prompt** initiation of a medication to which the etiologic pathogen is **susceptible**.

In patients who require specific diagnostic evaluation, sputum and culture specimens should be obtained prior to initiation of antibiotics. Since early administration of antibiotics to acutely ill patients is associated with improved outcomes, **obtaining diagnostic specimens or test results should not delay the initial dose of antibiotics by more than 6 hours from presentation.**

Optimal antibiotic therapy would be pathogen directed, but a definitive microbiologic diagnosis is rarely available on or within 6 hours of presentation. A syndromic approach to therapy, based on clinical presentation and chest imaging, does not reliably predict the microbiology of CAP. Therefore, initial antibiotic

choices are typically empiric, based on acuity (treatment as an outpatient, inpatient, or in the ICU), patient risk factors for specific pathogens, and local antibiotic resistance patterns.

Since S pneumoniae remains a common cause of CAP in all patient groups, local prevalence of drug-resistant S pneumoniae significantly affects initial antibiotic choice. Prior treatment with one antibiotic in a pharmacologic class (eg, beta-lactam, macrolide, fluoroquinolone) predisposes the emergence of drug-resistant S pneumoniae, with resistance developing against that class of antibiotics to which the pathogen was previously exposed. Definitions of resistance have shifted based on observations of continued clinical efficacy at achievable serum levels. In CAP, for parenteral penicillin G or oral amoxicillin, susceptible strains have a minimum inhibitory concentration (MIC) 2 mcg/mL or less; intermediate resistance is defined as an MIC between 2 mcg/mL and 4 mcg/mL because treatment failures are uncommon with MIC 4 mcg/mL or less. Macrolide resistance has increased; approximately one-third of S pneumoniae isolates now show in vitro resistance to macrolides. Treatment failures have been reported but remain rare compared to the number of patients treated; current in vivo efficacy appears to justify maintaining macrolides as firstline therapy except in areas where there is a high prevalence of resistant strains. S pneumoniae resistant to fluoroquinolones is rare in the United States (1% to levofloxacin, 2% to ciprofloxacin) but is increasing.

Community-acquired methicillin-resistant S aureus (CA-MRSA) is genetically and phenotypically different from hospital-acquired MRSA strains. CA-MRSA is a rare cause of necrotizing pneumonia, empyema, respiratory failure, and shock; it appears to be associated with prior influenza infection. Linezolid may be preferred to vancomycin in treatment of CA-MRSA pulmonary infection. For expanded discussions of specific antibiotics.

A. Treatment of Outpatients

The most common etiologies of CAP in outpatients who do not require hospitalization are S pneumoniae; M pneumoniae; C pneumoniae; and respiratory viruses, including influenza. For previously healthy patients with no recent (90 days) use of antibiotics, the recommended treatment is a macrolide (clarithromycin or azithromycin) or doxycycline.

In patients at risk for drug resistance (antibiotic therapy within the past 90 days, age greater than 65 years, comorbid illness, immunosuppression, exposure to a child in daycare), the recommended treatment is a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) or a macrolide plus a beta-lactam (high-dose amoxicillin and amoxicillin-clavulanate are preferred to cefpodoxime and cefuroxime).

In regions where there is a high incidence of macrolideresistant S pneumoniae, initial therapy in patients with no comorbidities may include a respiratory fluoroquinolone or the combination of a beta-lactam added to a macrolide. There are limited data to guide recommendations for duration of treatment. The decision should be influenced by the severity of illness, etiologic pathogen, response to therapy, other medical problems, and complications. Most

experts recommend administering a minimum of 5 days of therapy and continuing antibiotics until the patient is afebrile for 48–72 hours.

C. Treatment of Hospitalized and ICU Patients

The most common etiologies of CAP in patients who require hospitalization but not intensive care are S pneumoniae, M pneumoniae, C pneumoniae, H influenza, Legionella species, and respiratory viruses. Some patients have aspiration as an immediate precipitant to the CAP without a specific bacterial etiology. First-line therapy in hospitalized patients is a respiratory fluoroquinolone (eg, moxifloxacin, gemifloxacin, or levofloxacin) or the combination of a macrolide (clarithromycin or azithromycin) plus a beta-lactam (cefotaxime, ceftriaxone, or ampicillin).

Almost all patients admitted to a hospital for treatment of CAP receive intravenous antibiotics. However, no studies in hospitalized patients demonstrated superior outcomes with intravenous antibiotics compared with oral antibiotics, as long as patients were able to tolerate the oral therapy and the medication was well absorbed. Duration of inpatient antibiotic treatment is the same as for outpatients.

The most common etiologies of CAP in patients who require admission to intensive care are S pneumoniae, Legionella species, H influenza, Enterobacteriaceae species, S aureus, and Pseudomonas species. First-line therapy in ICU patients with CAP is either azithromycin or a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) combined with an antipneumococcal beta-lactam (cefotaxime, ceftriaxone, or ampicillinsulbactam). In patients at risk for Pseudomonas infection, one of two following regimens can be used: an antipneumococcal, antipseudomonal beta-lactam (piperacillintazobactam, cefepime, imipenem, meropenem) plus ciprofloxacin or levofloxacin or the above antipneumococcal beta-lactam plus an aminoglycoside (gentamicin, tobramycin, amikacin) plus either azithromycin or a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).

Prevention

Polyvalent pneumococcal vaccine (containing capsular polysaccharide antigens of 23 common strains of S pneumoniae) has the potential to prevent or lessen the severity of the majority of pneumococcal infections in immunocompetent patients. Indications for pneumococcal vaccination include age 65 years or older or any chronic illness that increases the risk of CAP. Immunocompromised patients and those at highest risk for fatal pneumococcal infections should receive a single revaccination 6 years after the first vaccination. Immunocompetent persons 65 years of age or older should receive a second dose of vaccine if the patient first received the vaccine 6 or more years previously and was under 65 years old at the time of vaccination.

The seasonal influenza vaccine is effective in preventing severe disease due to influenza virus with a resulting positive impact on both primary influenza pneumonia and secondary bacterial pneumonias. The seasonal influenza vaccine is administered annually to persons at risk for complications of influenza infection

(age 65 years or older, residents of long-term care facilities, patients with pulmonary or cardiovascular disorders, patients recently hospitalized with chronic metabolic disorders) as well as health care workers and others who are able to transmit influenza to high-risk patients.

Hospitalized patients who would benefit from pneumococcal and influenza vaccines should be vaccinated during hospitalization. The vaccines can be given simultaneously, and may be administered as soon as the patient has stabilized.

When to Admit

Once a diagnosis of CAP is made, the first management decision is to determine the site of care: Is it safe to treat the patient at home or does he or she require hospital or intensive care admission? There are two widely used clinical prediction rules available to guide admission and triage decisions, the **Pneumonia Severity Index (PSI)** and the **CURB-65.**

A. Hospital Admission Decision

The PSI is a validated prediction model that uses 20 items from demographics, medical history, physical examination, laboratory results, and imaging to stratify patients into five risk groups. The PSI is weighted toward discrimination at low predicted mortality. In conjunction with clinical judgment, it facilitates safe decisions to treat CAP in the outpatient setting. An online PSI risk calculator is available at http://internalmedicine.osu.edu/pulmonary/cap/10849.cfm. The CURB-65 assesses five simple, independent predictors of increased mortality (confusion, uremia, respiratory rate, blood pressure, and age greater than 65) to calculate a 30-day predicted mortality (http: // www. mdcalc. com/curb- 65-severity-score-community-acquired-pneumonia/). Compared with the PSI, the simpler CURB-65 is less discriminating at low mortality but excellent at identifying patients with high mortality who may benefit from ICU-level care. A modified version (CRB-65) dispenses with serum blood urea nitrogen and eliminates the need for laboratory testing. Both have the advantage of simplicity: Patients with zero CRB-65 predictors have a low predicted mortality (less than 1%) and usually do not need hospitalization; hospitalization should be considered for those with one or two predictors, since they have an increased risk of death; and urgent hospitalization (with consideration of ICU admission) is required for those with three or four predictors.

B. Intensive Care Unit Admission Decision

Expert opinion has defined major and minor criteria to identify patients at high risk for death. Major criteria are septic shock with need for vasopressor support and respiratory failure with need for mechanical ventilation. Minor criteria are respiratory rate 30 breaths or more per minute, hypoxemia (defined as Pao2 /Fio2 250 or less), hypothermia (core temperature less than 36.0°C), hypotension requiring aggressive fluid resuscitation, confusion/disorientation, multilobar pulmonary opacities, leukopenia due to infection with WBC less than 4000/mcL (less than 4.0×10^9/L), thrombocytopenia with platelet count less than 100,000/mcL

(less than 100×10^9/L), uremia with blood urea nitrogen 20 mg/dL or more (7.1 mmol/L or more), metabolic acidosis, or elevated lactate level. Either one major criterion or three or more minor criteria of illness severity generally require ICU-level care.

In addition to pneumonia-specific issues, good clinical practice always makes an admission decision in light of the whole patient. Additional factors suggesting need for inpatient hospitalization include the following:

• Exacerbations of underlying disease (eg, heart failure) that would benefit from hospitalization.

• Other medical or psychosocial needs (such as cognitive dysfunction, psychiatric disease, homelessness, drug abuse, lack of outpatient resources, or poor overall functional status).

• Failure of outpatient therapy, including inability to maintain oral intake and medications.

2. Nosocomial Pneumonia (Hospital-Acquired, Ventilator-Associated, and Health Care– Associated)

ESSENTIALS OF DIAGNOSIS

- Hospital-acquired pneumonia (HAP) occurs more than 48 hours after admission to the hospital or other health care facility and excludes any infection present at the time of admission.
- Health care–associated pneumonia (HCAP) occurs in community members whose extensive contact with healthcare has changed their risk for virulent and drug-resistant organisms.
- Ventilator-associated pneumonia (VAP) develops following endotracheal intubation and mechanical ventilation.
- At least two of the following: fever, leukocytosis, purulent sputum.
- New or progressive parenchymal opacity on chest radiograph.
- Especially common in patients requiring intensive care or mechanical ventilation.

General Considerations

Hospitalized patients carry different flora with different resistance patterns than healthy patients in the community, and their health status may place them at higher risk for more severe infection. The diagnostic approach and antibiotic treatment of patients with hospital-acquired pneumonia (HAP) is, therefore, different from patients with CAP. Similarly, management of patients in whom pneumonia develops following endotracheal intubation and mechanical ventilation (ventilator-associated pneumonia or VAP) should address issues specific to this group of patients. Some community members have extensive contact with the healthcare system and carry flora that more closely resemble hospitalized patients than healthy community residents. When pneumonia develops in these persons, the infection is referred to as health care–associated pneumonia (HCAP). Initial

management and antibiotic therapy should be targeted to the common flora and specific risk factors for severe disease.

Considered together, these nosocomial pneumonias (HAP/VAP/HCAP) represent an important cause of morbidity and mortality despite widespread use of preventive measures, advances in diagnostic testing, and potent new antimicrobial agents. HAP is the second most common cause of infection among hospital inpatients and is the leading cause of death due to infection with mortality rates ranging from 20% to 50%. While a minority of cases occurs in ICU patients, the highest-risk patients are those in ICUs or who are being mechanically ventilated; these patients also experience higher morbidity and mortality from HAP. As management of more chronic illnesses shifts to the outpatient setting, more cases of HCAP are caused by unusual organisms, and there is a high frequency of drug resistance. Definitive identification of the infectious cause of a lower respiratory infection is rarely available on presentation, thus, rather than pathogen-directed antibiotic treatment, the choice of empiric therapy is informed by epidemiologic and patient data.

Definition & Pathogenesis

HAP develops more than 48 hours after admission to the hospital and VAP develops in a mechanically ventilated patient more than 48 hours after endotracheal intubation. HCAP is defined as pneumonia that occurs in a nonhospitalized patient with extensive healthcare contact.

Risk factors for health care–associated pneumonia:

- Antibiotic therapy in the preceding 90 days.
- Acute care hospitalization for at least 2 days in the preceding 90 days.
- Residence in a nursing home or extended care facility.
- Home infusion therapy, including chemotherapy, within the past 30 days.
- Long-term dialysis within the past 30 days.
- Home wound care.
- Family member with an infection involving a multiple drug-resistant pathogen.
- Immunosuppressive disease or immunosuppressive therapy.

Three factors distinguish nosocomial pneumonia from CAP: (1) different infectious causes; (2) different antibiotic susceptibility patterns, specifically, a higher incidence of drug resistance; and (3) poorer underlying health status of patients putting them at risk for more severe infections. Since access to the lower respiratory tract occurs primarily through microaspiration, nosocomial pneumonia starts with a change in upper respiratory tract flora. Colonization of the pharynx and possibly the stomach with bacteria is the most important step in the pathogenesis of nosocomial pneumonia. Pharyngeal colonization is promoted by exogenous factors (eg, instrumentation of the upper airway with nasogastric and endotracheal tubes; contamination by dirty hands, equipment, and contaminated aerosols; and treatment

with broad-spectrum antibiotics that promote the emergence of drug-resistant organisms) and patient factors (eg, malnutrition, advanced age, altered consciousness, swallowing disorders, and underlying pulmonary and systemic diseases). Within 48 hours of admission, 75% of seriously ill hospitalized patients have their upper airway colonized with organisms from the hospital environment.

Organisms prevalent in nosocomial pneumonias

(Nosocomial pneumonias include hospital-associated pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care– associated pneumonia (HCAP)):

- Streptococcus pneumonia, often drug-resistant, in HCAP
- Staphylococcus aureus, methicillin-sensitive (MSSA) S aureus, methicillin-resistant (MRSA)
- Gram-negative rods, non-ESBL (extended-spectrum beta-lactamase)
- ESBL-producing gram-negative rods, including Klebsiella pneumonia, Escherichia coli, and Enterobacter species
- Pseudomonas aeruginosa
- Acinetobacter species

Impaired cellular and mechanical defense mechanisms in the lungs of hospitalized patients raise the risk of infection after aspiration has occurred.

Gastric acid may play a role in protection against nosocomial pneumonias. Observational studies have suggested that elevation of gastric pH due to antacids, H2 -receptor antagonists, proton pump inhibitors (PPIs), or enteral feeding is associated with gastric microbial overgrowth, tracheobronchial colonization, and HAP/VAP. Sucralfate, a cytoprotective agent that does not alter gastric pH, is associated with a trend toward a lower incidence of VAP. The Infectious Diseases Society of America and other professional organizations recommend that acid-suppressive medications (H2-receptor antagonists and PPIs) only be given to patients at high risk for stress gastritis.

The microbiology of the nosocomial pneumonias differs from CAP but is substantially the same among HAP, VAP, and HCAP. The most common organisms responsible for HAP include S aureus (both methicillinsensitive S aureus and MRSA), P aeruginosa, gram-negative rods, including non-extended spectrum beta-lactamase (non-ESBL)–producing and ESBL-producing (Enterobacter species, K pneumoniae, and Escherichia coli) organisms. VAP patients may be infected with Acinetobacter species and Stenotrophomonas maltophilia. HCAP patients may have common organisms (S pneumoniae, H influenzae) that are more likely to be drug-resistant, or flora that resemble HAP. Anaerobic organisms (bacteroides, anaerobic streptococci, fusobacterium) may also cause pneumonia in the hospitalized patient; when isolated, they are commonly part of a polymicrobial flora. Mycobacteria, fungi, chlamydiae, viruses, rickettsiae, and protozoal organisms are uncommon causes of nosocomial pneumonias.

Clinical Findings

A. Symptoms and Signs

The symptoms and signs associated with nosocomial pneumonias are nonspecific; however, two or more clinical findings (fever, leukocytosis, purulent sputum) in the setting of a new or progressive pulmonary opacity on chest radiograph were approximately 70% sensitive and 75% specific for the diagnosis of VAP in one study. Other findings include those listed above for CAP. The differential diagnosis of new lower respiratory tract symptoms and signs in hospitalized patients includes heart failure, atelectasis, aspiration, ARDS, pulmonary thromboembolism, pulmonary hemorrhage, and medication reactions.

B. Laboratory Findings

Diagnostic evaluation for suspected nosocomial pneumonia includes blood cultures from two different sites. Blood cultures can identify the pathogen in up to 20% of all patients with nosocomial pneumonias; positivity is associated with increased risk of complications and other sites of infection. Blood counts and clinical chemistry tests do not establish a specific diagnosis of HCAP; however, they help define the severity of illness and identify complications. The assessment of oxygenation by an arterial blood gas or pulse oximetry determination helps define the severity of illness and determines the need for assisted ventilation. Thoracentesis for pleural fluid analysis should be considered in patients with pleural effusions.

Examination of sputum is attended by the same disadvantages as in CAP. Gram stains and cultures of sputum are neither sensitive nor specific in the diagnosis of nosocomial pneumonias. The identification of a bacterial organism by culture of sputum does not prove that the organism is a lower respiratory tract pathogen. However, it can be used to help identify bacterial antibiotic sensitivity patterns and as a guide to adjusting empiric therapy.

C. Imaging

Radiographic findings in HAP/VAP are nonspecific and often confounded by other processes that led initially to hospitalization or ICU admission.

D. Special Examinations

Endotracheal aspiration using a sterile suction catheter and fiberoptic bronchoscopy with bronchoalveolar lavage or a protected specimen brush can be used to obtain lower respiratory tract secretions for analysis, most commonly in patients with VAP. Endotracheal aspiration cultures have significant negative predictive value but limited positive predictive value in the diagnosis of specific infectious causes of HAP/VAP. An invasive diagnostic approach using quantitative culture of bronchoalveolar lavage samples or protected specimen brush samples in patients in whom VAP is suspected leads to significantly less antibiotic use, earlier attenuation of organ dysfunction, and fewer deaths at 14 days.

Treatment

Treatment of the nosocomial pneumonias, like treatment of CAP, is usually empiric. Because of the high mortality rate, therapy should be started as soon as pneumonia is suspected. There is no consensus on the best regimens because this patient population is heterogeneous and local flora and resistance patterns must be taken into account.

Recommended empiric antibiotics for nosocomial pneumonias.

When there is low risk for multiple drug–resistant pathogens, use one of the following:

- Ceftriaxone, 1–2 g intravenously every 12–24 hours
- Gemifloxacin, 320 mg orally daily
- Moxifloxacin, 400 mg orally or intravenously daily
- Levofloxacin, 750 mg orally or intravenously daily
- Ciprofloxacin, 400 mg intravenously every 8–12 hours
- Ampicillin-sulbactam, 1.5–3 g intravenously every 6 hours
- Piperacillin-tazobactam 3.375–4.5 g intravenously every 6 hours
- Ertapenem, 1 g intravenously daily.

When there is higher risk for multiple drug–resistant pathogens, use one agent from each of the following categories:

1. Antipseudomonal coverage

a. Cefepime, 1–2 g intravenously twice a day or ceftazidime, 1–2 g intravenously every 8 hours

b. Imipenem, 0.5–1 g intravenously every 6–8 hours or meropenem, 1 g intravenously every 8 hours

c. Piperacillin-tazobactam, 3.375–4.5 g intravenously every 6 hours

d. For penicillin-allergic patients, aztreonam, 1–2 g intravenously every 6–12 hours

2. A second antipseudomonal agent

a. Levofloxacin, 750 mg intravenously daily or ciprofloxacin, 400 mg intravenously every 8–12 hours Intravenous gentamicin, tobramycin, amikacin, all weight-based dosing administered daily adjusted to appropriate trough levels

b. Coverage for MRSA (methicillin-resistant Staphylococcus aureus) if appropriate with either 3. a. Intravenous vancomycin (interval dosing based on renal function to achieve serum trough concentration 15–20 mcg/mL) or

b. Linezolid, 600 mg intravenously twice a day.

After results of sputum, blood, and pleural fluid cultures are available, it may be possible to de-escalate initially broad therapy. Duration of antibiotic therapy should be individualized based on the pathogen, severity of illness, response to

therapy, and comorbid conditions. Data from one large trial assessing treatment outcomes in VAP suggested that 8 days of antibiotics is as effective as 15 days, except in cases caused by P aeruginosa.

PULMONARY TUBERCULOSIS

ESSENTIALS OF DIAGNOSIS

- Fatigue, weight loss, fever, night sweats, and productive cough.
- Risk factors for acquisition of infection: household exposure, incarceration, drug use, travel to an endemic area.
- Chest radiograph: pulmonary opacities, most often apical. Acid-fast bacilli on smear of sputum or sputum culture positive for M tuberculosis.

General Considerations

Tuberculosis is one of the world's most widespread and deadly illnesses. M tuberculosis, the organism that causes tuberculosis infection and disease, infects one-third of the world's population. In 2013, there were 9 million new cases of tuberculosis worldwide with 1.5 million people dying of the disease. In the United States, an estimated 11 million people are infected with M tuberculosis and in 2013 there were 9582 active cases. Tuberculosis occurs disproportionately among disadvantaged populations, such as the malnourished, homeless, and those living in overcrowded and substandard housing. There is an increased occurrence of tuberculosis among HIV-positive individuals.

Infection with M tuberculosis begins when a susceptible person inhales airborne droplet nuclei containing viable organisms. Tubercle bacilli that reach the alveoli are ingested by alveolar macrophages. Infection follows if the inoculum escapes alveolar macrophage microbicidal activity. Once infection is established, lymphatic and hematogenous dissemination of tuberculosis typically occurs before the development of an effective immune response. This stage of infection, **primary tuberculosis**, is usually clinically and radiographically silent. In most persons with intact cellmediated immunity, T-cells and macrophages surround the organisms in granulomas that limit their multiplication and spread. The infection is contained but not eradicated, since viable organisms may lie dormant within granulomas for years to decades.

Individuals with **latent tuberculosis infection** do not have active disease and cannot transmit the organism to others. However, reactivation of disease may occur if the host's immune defenses are impaired. **Active tuberculosis will develop in approximately 6% of individuals with latent tuberculosis infection who are not given preventive therapy**; half of these cases occur in the 2 years following primary infection. Diverse conditions such as gastrectomy, silicosis, diabetes mellitus, and an impaired immune response (eg, HIV infection; therapy with corticosteroids, tumor necrosis factor inhibitors or other immunosuppressive drugs) are associated with an increased risk of reactivation.

In approximately 5% of cases, the immune response is inadequate to contain the primary infection and **progressive primary tuberculosis** develops,

accompanied by both pulmonary and constitutional symptoms as described below. The clinical presentation does not definitively distinguish primary disease from reactivation of latent tuberculosis infection. Standard teaching has held that 90% of tuberculosis in adults represents activation of latent disease. However, DNA fingerprinting of the bacillus suggests that as many as one-third of new cases of tuberculosis in urban populations are primary infections resulting from person-to-person transmission.

The prevalence of drug-resistant strains is increasing worldwide; however, in the United States, the rate of drugresistant isolates has fallen to less than 1%. Risk factors for drug resistance include immigration from countries with a high prevalence of drug-resistant tuberculosis, close and prolonged contact with individuals with drug-resistant tuberculosis, unsuccessful previous therapy, and nonadherence to treatment. Drug resistance may be single or multiple. **Drug-resistant tuberculosis** is resistant to one first-line antituberculous drug, either isoniazid or rifampin. **Multidrug-resistant tuberculosis** is resistant to isoniazid and rifampin, and possibly additional agents. **Extensively drug-resistant tuberculosis** is resistant to isoniazid, rifampin, fluoroquinolones, and either aminoglycosides or capreomycin or both. Outcomes of drug-resistant tuberculosis treatment are worse than when the isolate is drugsensitive, but outcomes appear to vary with HIV status. In a review of extensively drug-resistant tuberculosis cases in the United States, mortality was 10% and 68% in HIVnegative and HIV-positive patients, respectively.

Clinical Findings

A. Symptoms and Signs

The patient with pulmonary tuberculosis typically presents with slowly progressive constitutional symptoms of malaise, anorexia, weight loss, fever, and night sweats. Chronic cough is the most common pulmonary symptom. It may be dry at first but typically becomes productive of purulent sputum as the disease progresses. Blood-streaked sputum is common, but significant hemoptysis is rarely a presenting symptom; life-threatening hemoptysis may occur in advanced disease. Dyspnea is unusual unless there is extensive disease. Rarely, the patient is asymptomatic. On physical examination, the patient appears chronically ill and malnourished. On chest examination, there are no physical findings specific for tuberculosis infection. The examination may be normal or may reveal classic findings such as posttussive apical rales.

B. Laboratory Findings

Definitive diagnosis depends on recovery of M tuberculosis from cultures or identification of the organism by DNA or RNA amplification techniques. Three consecutive morning sputum specimens are advised. Fluorochrome staining with rhodamine-auramine of concentrated, digested sputum specimens is performed initially as a screening method, with confirmation by the Kinyoun or ZiehlNeelsen stains. Demonstration of acid-fast bacilli on sputum smear does not establish a diagnosis of M tuberculosis, since nontuberculous mycobacteria may colonize the

airways and are increasingly recognized to cause clinical illness in patients with underlying structural lung disease.

In patients thought to have tuberculosis who cannot produce satisfactory specimens or when the smear of the spontaneously expectorated sputum is negative for acidfast bacilli, sputum induction with 3% hypertonic saline should be performed. Flexible bronchoscopy with bronchial washings has similar diagnostic yield to induced sputum; transbronchial lung biopsies do not significantly increase the diagnostic yield but may lead to earlier diagnosis by identifying tissue granulomas. Post-bronchoscopy expectorated sputum specimens should be collected. Early morning aspiration of gastric contents after an overnight fast is suitable only for culture and not for stained smear because nontuberculous mycobacteria may be present in the stomach in the absence of tuberculous infection. Positive blood cultures for M tuberculosis are uncommon in patients with normal CD4 cell counts, but the organism may be cultured from blood in up to 50% of HIV-seropositive patients with tuberculosis whose CD4 cell counts are less than 100/mcL (less than 0.1×10^9/L).

Traditional light-microscopic examination of stained sputum for acid-fast bacilli and culture of sputum specimens remain the mainstay of tuberculosis diagnosis. The slow rate of mycobacterial growth, the urgency to provide early, appropriate treatment to patients to improve their outcomes and limit community spread, and concerns about potential drug toxicities in patients treated empirically who do not have tuberculosis infection, have fostered interest in rapid diagnostic techniques. Molecular diagnostics offer multiple options and many advantages at significantly increased expense. Nucleic acid amplification testing not only detects M tuberculosis (NAAT-TB) but it also identifies resistance markers (NAAT-R). NAAT-TB can identify M tuberculosis within hours of sputum processing, allowing early isolation and treatment, but the negative predictive value is low in smear-negative patients. NAAT-R allows rapid identification of primary drug resistance and is indicated in the following patients: (1) those treated previously for tuberculosis, (2) those born (or who lived for more than 1 year) in a country with moderate tuberculosis incidence or a high incidence of multiple drug-resistant isolates, (3) contacts of patients with multidrug-resistant tuberculosis, or (4) those who are HIV seropositive. Clinical suspicion remains the critical factor in interpreting all these studies. Standard drug susceptibility testing of culture isolates is considered routine for the first isolate of M tuberculosis, when a treatment regimen is failing, and when sputum cultures remain positive after 2 months of therapy.

Needle biopsy of the pleura reveals granulomatous inflammation in approximately 60% of patients with pleural effusions caused by M tuberculosis. Pleural fluid cultures are positive for M tuberculosis in less than 23–58% of cases of pleural tuberculosis. Culture of three pleural biopsy specimens combined with microscopic examination of a pleural biopsy yields a diagnosis in up to 90% of patients with pleural tuberculosis. Tests for pleural fluid adenosine deaminase (approximately 90% sensitivity and specificity for pleural tuberculosis at levels greater than 70 units/L) and interferon-gamma (89% sensitivity, 97% specificity in

a recent meta-analysis) can be extremely helpful diagnostic aids, particularly in making decisions to pursue invasive testing in complex cases.

C. Imaging

Contrary to traditional teaching, molecular analysis demonstrates that radiographic abnormalities in pulmonary tuberculosis do not distinguish primary disease from reactivation of latent tuberculosis. The only independent predictor of an atypical pattern on chest radiograph—that is, not associated with upper lobe or cavitary disease—is an impaired host immune response. In elderly patients, lower lobe infiltrates with or without pleural effusion are frequently encountered. Lower lung tuberculosis may masquerade as pneumonia or lung cancer. A "miliary" pattern (diffuse small nodular densities) can be seen with hematologic or lymphatic dissemination of the organism. Immunocompromised patients—particularly those with late-stage HIV infection—often display lower lung zone, diffuse, or miliary infiltrates; pleural effusions; and involvement of hilar, and, in particular, mediastinal lymph nodes.

Resolution of active tuberculosis leaves characteristic radiographic findings. Dense nodules in the pulmonary hila, with or without obvious calcification, upper lobe fibronodular scarring, and bronchiectasis with volume loss are common findings. Ghon (calcified primary focus) and Ranke (calcified primary focus and calcified hilar lymph node) complexes are seen in a minority of patients.

D. Special Examinations

Testing for latent tuberculosis infection is used to evaluate an asymptomatic person in whom M tuberculosis infection is suspected (eg, following contact exposure) or to establish the prevalence of tuberculosis infection in a population. Testing may be used in a person with symptoms of active tuberculosis, but a positive test does not distinguish between active and latent infection. Routine testing of individuals at low risk for tuberculosis is not recommended.

The traditional approach to testing for latent tuberculosis infection is the **tuberculin skin test**. The Mantoux test is the preferred method: 0.1 mL of purified protein derivative (PPD) containing 5 tuberculin units is injected intradermally on the volar surface of the forearm using a 27-gauge needle on a tuberculin syringe. The **transverse width in millimeters of induration** at the skin test site is measured after 48–72 hours. To optimize test performance, criteria for determining a positive reaction vary depending on the likelihood of infection. Sensitivity and specificity of the tuberculin skin test are high: 77% and 97%, respectively. Specificity falls to 59% in populations previously vaccinated with bacillus Calmette-Guérin (BCG, an attenuated form of Mycobacterium bovis). False-negative tuberculin skin test reactions may result from improper testing technique; concurrent infections, including fulminant tuberculosis; malnutrition; advanced age; immunologic disorders; malignancy; corticosteroid therapy; chronic kidney disease; and HIV infection. Some individuals with latent tuberculosis infection may have a negative tuberculin skin test when tested many years after exposure. **Anergy testing is not recommended for routine use to distinguish a true-negative result from**

anergy. Poor anergy test standardization and lack of outcome data limit the evaluation of its effectiveness. Interpretation of the tuberculin skin test in persons who have previously received BCG vaccination is the same as in those who have not had BCG.

Interferon gamma release assays (including the QuantiFERON and T-SPOT tests) are in vitro assays of CD4+ T-cell–mediated interferon gamma release in response to stimulation by specific M tuberculosis antigens. The antigens are absent from all BCG strains and most nontuberculous mycobacteria; therefore, in whole blood, the specificity of interferon gamma release assays is superior to the tuberculin skin test in BGC-vaccinated individuals. Sensitivity is comparable to the tuberculin skin test: 60–90% depending on the specific assay and study population. Sensitivity is reduced by HIV infection, particularly in patients with low CD4 counts. Specificity is high, greater than 95%. Potential advantages of interferon gamma release assay testing include fewer falsepositive results from prior BCG vaccination, better discrimination of positive responses due to nontuberculous mycobacteria, and the requirement for only one patient contact (ie, no need for the patient to return to have the tuberculin skin test read 48–72 hours later). Disadvantages include the need for specialized laboratory equipment and personnel, and the substantially increased cost compared to the tuberculin skin test.

In endemic areas, interferon gamma release assays are no more sensitive than the tuberculin skin test in active tuberculosis (20–40% false-negative rate) and cannot distinguish active from latent disease. Interferon gamma release assays should not be used to exclude active tuberculosis.

Guidelines established by the CDC allow interferon gamma release assays to be used interchangeably with the tuberculin skin testing in the diagnosis of latent tuberculosis infection. Interferon gamma release assays are preferred in patients with prior BCG vaccination; the tuberculin skin test is preferred in children under 5 years old. Routine use of both tests is not recommended. In individuals with a positive tuberculin skin test but a low prior probability of latent tuberculosis infection and low risk for progression to active disease, the interferon gamma release assay may be helpful as a confirmatory test to exclude a false-positive tuberculin skin test.

Treatment

General Measures

The goals of therapy are to eliminate all tubercle bacilli from an infected individual while avoiding the emergence of clinically significant drug resistance. The basic principles of antituberculous treatment are (1) to administer multiple medications to which the organisms are susceptible; (2) to add at least two new antituberculous agents to a regimen when treatment failure is suspected; (3) to provide the safest, most effective therapy in the shortest period of time; and (4) to ensure adherence to therapy.

All suspected and confirmed cases of tuberculosis should be reported promptly to local and state public health authorities. Public health departments will perform case investigations on sources and patient contacts to determine if

other individuals with untreated, infectious tuberculosis are present in the community. They can identify infected contacts eligible for treatment of latent tuberculous infection and ensure that a plan for monitoring adherence to therapy is established for each patient with tuberculosis. Patients with tuberculosis should be treated by clinicians who are skilled in the management of this infection. Clinical expertise is especially important in cases of drug-resistant tuberculosis.

Nonadherence to antituberculous treatment is a major cause of treatment failure, continued transmission of tuberculosis, and the development of medication resistance. Adherence to treatment can be improved by providing detailed patient education about tuberculosis and its treatment in addition to a case manager who oversees all aspects of an individual patient's care. **Directly observed therapy (DOT)**, which requires that a health care worker physically observe the patient ingest antituberculous medications in the home, clinic, hospital, or elsewhere, also improves adherence to treatment. The importance of direct observation of therapy cannot be overemphasized. The CDC recommends DOT for all patients with drug-resistant tuberculosis and for those receiving intermittent (twice- or thriceweekly) therapy.

Hospitalization for initial therapy of tuberculosis is not necessary for most patients. It should be considered if a patient is incapable of self-care or is likely to expose new, susceptible individuals to tuberculosis. Hospitalized patients with active disease require a private room with negative-pressure ventilation until tubercle bacilli are no longer found in their sputum ("smear-negative") on three consecutive smears taken on separate days.

Treatment of Tuberculosis in HIV-Negative Persons

Most patients with previously untreated pulmonary tuberculosis can be effectively treated with either a 6-month or a 9-month regimen, though the 6-month regimen is preferred. The initial phase of a 6-month regimen consists of 2 months of daily isoniazid, rifampin, pyrazinamide, and ethambutol. Once the isolate is determined to be isoniazidsensitive, ethambutol may be discontinued. If the M tuberculosis isolate is susceptible to isoniazid and rifampin, the second phase of therapy consists of isoniazid and rifampin for a minimum of 4 additional months, with treatment to extend at least 3 months beyond documentation of conversion of sputum cultures to negative for M tuberculosis. If DOT is used, medications may be given intermittently using one of three regimens: (1) Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin two or three times each week for 4 months if susceptibility to isoniazid and rifampin is demonstrated. (2) Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 weeks, then administration of the same agents twice a week for 6 weeks followed by administration of isoniazid and rifampin twice each week for 4 months if susceptibility to isoniazid and rifampin is demonstrated. (3) Isoniazid, rifampin, pyrazinamide, and ethambutol three times a week for 6 months.

Patients who cannot or should not (eg, pregnant women) take pyrazinamide should receive daily isoniazid and rifampin along with ethambutol for 4–8 weeks. If susceptibility to isoniazid and rifampin is demonstrated or drug resistance is

unlikely, ethambutol can be discontinued and isoniazid and rifampin may be given twice a week for a total of 9 months of therapy. If drug resistance is a concern, patients should receive isoniazid, rifampin, and ethambutol for 9 months. Patients with smear- and culture-negative disease (eg, pulmonary tuberculosis diagnosed on clinical grounds) and patients for whom drug susceptibility testing is not available can be treated with 6 months of isoniazid and rifampin combined with pyrazinamide for the first 2 months. This regimen assumes low prevalence of drug resistance. Previous guidelines have used streptomycin interchangeably with ethambutol. Increasing worldwide streptomycin resistance has made this medication less useful as empiric therapy.

When a twice-weekly or thrice-weekly regimen is used instead of a daily regimen, the dosages of isoniazid, pyrazinamide, and ethambutol or streptomycin must be increased. Fixed-dose combinations of isoniazid and rifampin (Rifamate) and of isoniazid, rifampin, and pyrazinamide (Rifater) are available to simplify treatment. Single tablets improve compliance but are more expensive than the individual medications purchased separately.

Treatment of Tuberculosis in HIV-Positive

Persons Management of tuberculosis is complex in patients with concomitant HIV disease. Experts in the management of both tuberculosis and HIV disease should be involved in the care of such patients.

The basic approach to HIV-positive patients with tuberculosis is similar to that detailed above for patients without HIV disease. Additional considerations in HIVpositive patients include: (1) longer duration of therapy and (2) drug interactions between rifamycin derivatives such as rifampin and rifabutin used to treat tuberculosis and some of the protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs), used to treat HIV (see http://www.cdc.gov/tb/). DOT should be used for all HIV-positive tuberculosis patients. Pyridoxine (vitamin B6), 25–50 mg orally each day, should be administered to all HIV-positive patients being treated with isoniazid to reduce central and peripheral nervous system side effects.

Treatment of Drug-Resistant Tuberculosis

Patients with drug-resistant M tuberculosis infection require careful supervision and management. Clinicians who are unfamiliar with the treatment of drug-resistant tuberculosis should seek expert advice. Tuberculosis resistant only to isoniazid can be successfully treated with a 6-month regimen of rifampin, pyrazinamide, and ethambutol or streptomycin or a 12-month regimen of rifampin and ethambutol. When isoniazid resistance is documented during a 9-month regimen without pyrazinamide, isoniazid should be discontinued. If ethambutol was part of the initial regimen, rifampin and ethambutol should be continued for a minimum of 12 months. If ethambutol was not part of the initial regimen, susceptibility tests should be repeated and two other medications to which the organism is susceptible should be added. Treatment of M tuberculosis isolates

resistant to agents other than isoniazid and treatment of drug resistance in HIV-infected patients require expert consultation.

Multidrug-resistant tuberculosis and extensively drugresistant tuberculosis call for an individualized daily DOT plan under the supervision of an experienced clinician. Treatment regimens are based on the patient's overall status and the results of susceptibility studies. Most drug-resistant isolates are resistant to at least isoniazid and rifampin and require a minimum of three drugs to which the organism is susceptible. These regimens are continued until culture conversion is documented, and then a two-drug regimen is continued for at least another 12 months. Some experts recommend at least 18–24 months of a three-drug regimen.

Treatment of Extrapulmonary Tuberculosis

In most cases, regimens that are effective for treating pulmonary tuberculosis are also effective for treating extrapulmonary disease. However, many experts recommend 9 months of therapy when miliary, meningeal, or bone and joint disease is present. Treatment of skeletal tuberculosis is enhanced by early surgical drainage and debridement of necrotic bone. Corticosteroid therapy has been shown to help prevent constrictive pericarditis from tuberculous pericarditis and to reduce neurologic complications from tuberculous meningitis.

Treatment of Pregnant or Lactating Women

Tuberculosis in pregnancy is usually treated with isoniazid, rifampin, and ethambutol for 2 months, followed by isoniazid and rifampin for an additional 7 months. Ethambutol can be stopped after the first month if isoniazid and rifampinsusceptibility is confirmed. Since the risk of teratogenicity with pyrazinamide has not been clearly defined, pyrazinamide should be used only if resistance to other drugs is documented and susceptibility to pyrazinamide is likely. Streptomycin is contraindicated in pregnancy because it may cause congenital deafness. Pregnant women taking isoniazid should receive pyridoxine (vitamin B6), 10–25 mg orally once a day, to prevent peripheral neuropathy.

Small concentrations of antituberculous drugs are present in breast milk. First-line therapy is not known to be harmful to nursing newborns at these concentrations. Therefore, breastfeeding is not contraindicated while receiving first-line antituberculous therapy. Lactating women receiving other agents should consult a tuberculosis expert.

Treatment Monitoring

Adults should have measurements of a complete blood count (including platelets) and serum bilirubin, hepatic enzymes, urea nitrogen, and creatinine before starting therapy for tuberculosis. Visual acuity and red-green color vision tests are recommended before initiation of ethambutol and serum uric acid before starting pyrazinamide. Audiometry should be performed if streptomycin therapy is initiated.

Routine monitoring of laboratory tests for evidence of medication toxicity during therapy is not recommended, unless baseline results are abnormal or liver disease is suspected. Monthly questioning for symptoms of medication toxicity is

advised. Patients should be educated about common side effects of antituberculous medications and instructed to seek medical attention should these symptoms occur. Monthly follow-up of outpatients is recommended, including sputum smear and culture for M tuberculosis, until cultures convert to negative. Patients with negative sputum cultures after 2 months of treatment should have at least one additional sputum smear and culture performed at the end of therapy. Patients with drug-resistant isolates should have sputum cultures performed monthly during the entire course of treatment. A chest radiograph at the end of therapy provides a useful baseline for any future films.

Patients whose cultures do not become negative or whose symptoms do not resolve despite 3 months of therapy should be evaluated for nonadherence to the regimen and for drug-resistant organisms. DOT is required for the remainder of the treatment regimen, and the addition of at least two drugs not previously given should be considered pending repeat drug susceptibility testing. The clinician should seek expert assistance if drug resistance is newly found, if the patient remains symptomatic, or if smears or cultures remain positive.

Patients with only a clinical diagnosis of pulmonary tuberculosis (smears and cultures negative for M tuberculosis) whose symptoms and radiographic abnormalities are unchanged after 3 months of treatment usually either have another process or have had tuberculosis in the past.

Treatment of Latent Tuberculosis

Treatment of latent tuberculous infection is essential to controlling and eliminating tuberculosis. Treatment of latent tuberculous infection substantially reduces the risk that infection will progress to active disease. Targeted testing with the tuberculin skin test or interferon gamma release assays is used to identify persons who are at high risk for tuberculosis and who stand to benefit from treatment of latent infection. Table 9–13 gives the tuberculin skin test criteria for treatment of latent tuberculous infection. In general, patients with a positive tuberculin skin test or interferon gamma release assay who are at increased risk for exposure or disease are treated. It is essential that each person who meets the criteria for treatment of latent tuberculous infection undergo a careful assessment to exclude active disease. A history of past treatment for tuberculosis and contraindications to treatment should be sought. All patients at risk for HIV infection should be tested for HIV. Patients suspected of having tuberculosis should receive one of the recommended multidrug regimens for active disease until the diagnosis is confirmed or excluded.

Some close contacts of persons with active tuberculosis should be evaluated for treatment of latent tuberculous infection despite a negative tuberculin skin test reaction (less than 5 mm induration). These include immunosuppressed persons and those who may develop disease quickly after tuberculous infection. Close contacts who have a negative tuberculin skin test reaction on initial testing should be retested 10–12 weeks later.

Several treatment regimens for both HIV-negative and HIV-positive persons are available for the treatment of latent tuberculous infection: (1) **Isoniazid**: A 9-

month oral regimen (minimum of 270 doses administered within 12 months) is considered optimal. Dosing options include a daily dose of 300 mg or twice-weekly doses of 15 mg/kg. Persons at risk for developing isoniazid-associated peripheral neuropathy (diabetes mellitus, uremia, malnutrition, alcoholism, HIV infection, pregnancy, seizure disorder) may be given supplemental pyridoxine (vitamin B6), 10–50 mg/day. (2) **Rifampin and pyrazinamide**: A 2-month oral regimen (60 doses administered within 3 months) of daily rifampin (10 mg/kg up to a maximum dose of 600 mg) and pyrazinamide (15–20 mg/kg up to a maximum dose of 2 g) is recommended. This regimen has been associated with significant hepatotoxicity, so careful laboratory monitoring is required. (3) **Rifampin**: Patients who cannot tolerate isoniazid or pyrazinamide can be considered for a 4-month regimen (minimum of 120 doses administered within 6 months) of rifampin. HIVpositive patients receiving protease inhibitors or NNRTIs who are given rifampin require management by experts in both tuberculosis and HIV disease.

Contacts of persons with isoniazid-resistant, rifampinsensitive tuberculosis should receive a 2-month regimen of rifampin and pyrazinamide or a 4-month regimen of daily rifampin alone. Contacts of persons with drug-resistant tuberculosis should receive two drugs to which the infecting organism has demonstrated susceptibility. Contacts in whom the tuberculin skin test or interferon gamma release assay is negative and contacts who are HIV seronegative may be observed without treatment or treated for 6 months. HIV-positive contacts should be treated for 12 months. All contacts of persons with multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis should have 2 years of follow-up regardless of treatment.

Persons with a positive tuberculin skin test (5 mm or more of induration) and fibrotic lesions suggestive of old tuberculosis on chest radiographs who have no evidence of active disease and no history of treatment for tuberculosis should receive 9 months of isoniazid, or 2 months of rifampin and pyrazinamide, or 4 months of rifampin (with or without isoniazid). Pregnant or breastfeeding women with latent tuberculosis should receive either daily or twice-weekly isoniazid with pyridoxine (vitamin B6).

Baseline laboratory testing is indicated for patients at risk for liver disease, patients with HIV infection, women who are pregnant or within 3 months of delivery, and persons who use alcohol regularly. Patients receiving treatment for latent tuberculous infection should be evaluated once a month to assess for symptoms and signs of active tuberculosis and hepatitis and for adherence to their treatment regimen. Routine laboratory testing during treatment is indicated for those with abnormal baseline laboratory tests and for those at risk for developing liver disease.

Vaccine BCG is an antimycobacterial vaccine developed from an attenuated strain of M bovis. Millions of individuals worldwide have been vaccinated with BCG. However, it is not generally recommended in the United States because of the low prevalence of tuberculous infection, the vaccine’s interference with the ability to determine latent tuberculous infection using tuberculin skin test reactivity, and its variable effectiveness in prophylaxis of pulmonary tuberculosis. BCG vaccination

in the United States should only be undertaken after consultation with local health officials and tuberculosis experts. Vaccination of health care workers should be considered on an individual basis in settings in which a high percentage of tuberculosis patients are infected with strains resistant to both isoniazid and rifampin, in which transmission of such drug-resistant M tuberculosis and subsequent infection are likely, and in which comprehensive tuberculous infection-control precautions have been implemented but have not been successful. The BCG vaccine is contraindicated in persons with impaired immune responses due to disease or medications.

Prognosis

Almost all properly treated immunocompetent patients with tuberculosis can be cured. Relapse rates are less than 5% with current regimens. The main cause of treatment failure is nonadherence to therapy.

PLEURAL DISEASES

PLEURITIS

Pain due to acute pleural inflammation is caused by irritation of the parietal pleura. Such pain is localized, sharp, and fleeting; it is made worse by coughing, sneezing, deep breathing, or movement. When the central portion of the diaphragmatic parietal pleura is irritated, pain may be referred to the ipsilateral shoulder. There are numerous causes of pleuritis. The setting in which pleuritic pain develops helps narrow the differential diagnosis. In young, otherwise healthy individuals, pleuritis is usually caused by viral respiratory infections or pneumonia. The presence of pleural effusion, pleural thickening, or air in the pleural space requires further diagnostic and therapeutic measures. Simple rib fracture may cause severe pleurisy.

Treatment of pleuritis consists of treating the underlying disease. Analgesics and anti-inflammatory medications (eg, indomethacin, 25 mg orally two or three times daily) are often helpful for pain relief. Codeine (30–60 mg orally every 8 hours) or other opioids may be used to control cough associated with pleuritic chest pain if retention of airway secretions is not a likely complication. Intercostal nerve blocks are sometimes helpful but the benefit is usually transient.

PLEURAL EFFUSION

ESSENTIALS OF DIAGNOSIS

- May be asymptomatic; chest pain frequently seen in the setting of pleuritis, trauma, or infection; dyspnea is common with large effusions.
- Dullness to percussion and decreased breath sounds over the effusion.
- Radiographic evidence of pleural effusion.
- Diagnostic findings on thoracentesis.

General Considerations

There is constant movement of fluid from parietal pleural capillaries into the pleural space at a rate of 0.01 mL/kg body weight/h. Absorption of pleural fluid occurs through parietal pleural lymphatics. The resultant homeostasis leaves 5–15 mL of fluid in the normal pleural space. A pleural effusion is an abnormal accumulation of fluid in the pleural space. Pleural effusions may be classified by differential diagnosis or by underlying pathophysiology. Five pathophysiologic processes account for most pleural effusions: increased production of fluid in the setting of normal capillaries due to increased hydrostatic or decreased oncotic pressures (**transudates**); increased production of fluid due to abnormal capillary permeability (**exudates**); decreased lymphatic clearance of fluid from the pleural space (exudates); infection in the pleural space (**empyema**); and bleeding into the pleural space (**hemothorax**). **Parapneumonic pleural effusions** are exudates that accompany bacterial pneumonias.

Diagnostic thoracentes is should be performed whenever there is a new pleural effusion and no clinically apparent cause. Observation is appropriate in some situations (eg, symmetric bilateral pleural effusions in the setting of heart failure), but an atypical presentation or failure of an effusion to resolve as expected warrants thoracentesis. Sampling allows visualization of the fluid in addition to chemical and microbiologic analyses to identify the underlying pathophysiologic process.

Causes of pleural fluid transudates and exudates

Transudates:

- Heart failure (> 90% of cases)
- Cirrhosis with ascites
- Nephrotic syndrome
- Peritoneal dialysis
- Myxedema
- Atelectasis (acute)
- Constrictive pericarditis
- Superior vena cava obstruction
- Pulmonary embolism

Exudates:

- Pneumonia (parapneumonic effusion)
- Cancer
- Pulmonary embolism
- Bacterial infection
- Tuberculosis
- Connective tissue disease
- Viral infection
- Fungal infection
- Rickettsial infection

- Parasitic infection
- Asbestos
- Meigs syndrome
- Pancreatic disease
- Uremia
- Chronic atelectasis
- Trapped lung
- Chylothorax
- Sarcoidosis
- Drug reaction
- Post-myocardial injury syndrome

Clinical Findings

Symptoms and Signs Patients with pleural effusions most often report dyspnea, cough, or respirophasic chest pain. Symptoms are more common in patients with existing cardiopulmonary disease. Small pleural effusions are less likely to be symptomatic than larger effusions. Physical findings are usually absent in small effusions. Larger effusions may present with dullness to percussion and diminished or absent breath sounds over the effusion. Compressive atelectasis may cause bronchial breath sounds and egophony just above the effusion. A massive effusion with increased intrapleural pressure may cause contralateral shift of the trachea and bulging of the intercostal spaces. A pleural friction rub indicates infarction or pleuritis.

Laboratory Findings

The gross appearance of pleural fluid helps identify several types of pleural effusion. Grossly purulent fluid signifies empyema. Milky white pleural fluid should be centrifuged. A clear supernatant above a pellet of white cells indicates empyema, whereas a persistently turbid supernatant suggests a **chylous effusion**; analysis of this supernatant reveals chylomicrons and a high triglyceride level (greater than 100 mg/dL [1 mmol/L]), often from disruption of the thoracic duct. **Hemorrhagic pleural effusion** is a mixture of blood and pleural fluid. Ten thousand red cells per milliliter create blood-tinged pleural fluid; 100,000 red cells/mL create grossly bloody pleural fluid. **Hemothorax** is the presence of gross blood in the pleural space, usually following chest trauma or instrumentation. It is defined as a ratio of pleural fluid hematocrit to peripheral blood hematocrit greater than 0.5.

Pleural fluid samples should be sent for measurement of protein, glucose, and LD in addition to total and differential white blood cell counts. Chemistry determinations are used to classify effusions as transudates or exudates. This classification is important because the differential diagnosis and subsequent evaluation for each entity is vastly different. **A pleural exudate** is an effusion that has one or more of the following laboratory features: (1) ratio of pleural fluid protein to serum protein greater than 0.5; (2) ratio of pleural fluid LD to serum LD

greater than 0.6; (3) pleural fluid LD greater than twothirds the upper limit of normal serum LD. **Pleural transudates** occur in the setting of normal capillary integrity and demonstrate none of the laboratory features of exudates. A transudate suggests the absence of local pleural disease; characteristic laboratory findings include a glucose equal to serum glucose, pH between 7.40 and 7.55, and fewer than 1.0×10^3 white blood cells/mcL (1.0×10^9 /L) with a predominance of mononuclear cells.

Heart failure accounts for 90% of transudates. Bacterial pneumonia and cancer are the most common causes of exudative effusion.

Pleural fluid pH is useful in the assessment of parapneumonic effusions. A pH below 7.30 suggests the need for drainage of the pleural space. An elevated amylase level in pleural fluid suggests pancreatitis, pancreatic pseudocyst, adenocarcinoma of the lung or pancreas, or esophageal rupture.

Suspected tuberculous pleural effusion should be evaluated by thoracentesis with culture along with pleural biopsy, since pleural fluid culture positivity for M tuberculosis is low (less than 23–58% of cases). Closed pleural biopsy reveals granulomatous inflammation in approximately 60% of patients, and culture of three pleural biopsy specimens combined with histologic examination of a pleural biopsy for granulomas yields a diagnosis in up to 90% of patients. Tests for pleural fluid adenosine deaminase (approximately 90% sensitivity and specificity for pleural tuberculosis at levels greater than 70 units/L) and interferon-gamma (89% sensitivity, 97% specificity in a meta-analysis) can be extremely helpful diagnostic aids, particularly in making decisions to pursue invasive testing in complex patients.

Between 40% and 80% of exudative pleural effusions are malignant, while over 90% of malignant pleural effusions are exudative. Almost any form of cancer may cause effusions, but the most common causes are lung cancer (one-third of cases) and breast cancer. In 5–10% of malignant pleural effusions, no primary tumor is identified. The term "**paramalignant**" pleural effusion refers to an effusion in a patient with cancer when repeated attempts to identify tumor cells in the pleura or pleural fluid are nondiagnostic but when there is a presumptive relation to the underlying malignancy. For example, superior vena cava syndrome with elevated systemic venous pressures causing a transudative effusion would be "paramalignant."

Pleural fluid specimens should be sent for cytologic examination in all cases of exudative effusions in patientssuspected of harboring an underlying malignancy. The diagnostic yield depends on the nature and extent of the underlying malignancy. Sensitivity is between 50% and 65%. A negative cytologic examination in a patient with a high prior probability of malignancy should be followed by one repeat thoracentesis. If that examination is negative, thoracoscopy is preferred to closed pleural biopsy. The sensitivity of thoracoscopy is 92–96%.

Imaging

The lung is less dense than water and floats on pleural fluid that accumulates in dependent regions. Subpulmonary fluid may appear as lateral displacement of the

apex of the diaphragm with an abrupt slope to the costophrenic sulcus or a greater than 2 cm separation between the gastric air bubble and the lung. On a standard upright chest radiograph, approximately 75–100 mL of pleural fluid must accumulate in the posterior costophrenic sulcus to be visible on the lateral view, and 175–200 mL must be present in the lateral costophrenic sulcus to be visible on the frontal view. Chest CT scans may identify as little as 10 mL of fluid. At least 1 cm of fluid on the decubitus view is necessary to permit blind thoracentesis. Ultrasonography is useful to guide thoracentesis in the setting of smaller effusions.

Pleural fluid may become trapped (loculated) by pleural adhesions, thereby forming unusual collections along the lateral chest wall or within lung fissures. Round or oval fluid collections in fissures that resemble intraparenchymal masses are called pseudotumors. Massive pleural effusion causing opacification of an entire hemithorax is most commonly caused by cancer but may be seen in tuberculosis and other diseases.

Treatment

Transudative Pleural Effusion Transudative pleural effusions characteristically occur in the absence of pleural disease. Therefore, treatment is directed at the underlying condition. Therapeutic thoracentesis for severe dyspnea typically offers only transient benefit. Pleurodesis and tube thoracostomy are rarely indicated.

Malignant Pleural Effusion

Chemotherapy or radiation therapy or both offer temporary control in some malignant effusions but are generally ineffective in lung cancer in the pleural space except for small-cell lung cancer. Asymptomatic malignant effusions usually do not require specific treatment. Symptomatic patients should have a therapeutic thoracentesis. If symptoms are relieved but the effusion returns, the options are serial thoracenteses, attempted pleurodesis, or placement of an indwelling drainage catheter that the patient can access at home. Choice among these options depends on the rate of reaccumulation in addition to the functional status, tolerance for discomfort, and life expectancy of the patient. Consultation with a thoracic specialist is advised.

Parapneumonic Pleural Effusion

Parapneumonic pleural effusions are divided into three categories: simple or uncomplicated, complicated, and empyema. **Uncomplicated parapneumonic effusions** are free-flowing sterile exudates of modest size that resolve quickly with antibiotic treatment of pneumonia. They do not need drainage. **Empyema** is gross infection of the pleural space indicated by positive Gram stain or culture. Empyema should always be drained by tube thoracostomy to facilitate clearance of infection and to reduce the probability of fibrous encasement of the lung, causing permanent pulmonary impairment.

Complicated parapneumonic effusions present the most difficult management decisions. They tend to be larger than simple parapneumonic effusions

and to show more evidence of inflammatory stimuli, such as low glucose level, low pH, or evidence of loculation. Inflammation probably reflects ongoing bacterial invasion of the pleural space despite rare positive bacterial cultures. The morbidity associated with complicated effusions is due to their tendency to form a fibropurulent pleural "peel," trapping otherwise functional lung and leading to permanent impairment. Tube thoracostomy is indicated when pleural fluid glucose is less than 60 mg/dL (less than 3.3 mmol/L) or the pH is less than 7.2. These thresholds have not been prospectively validated and should not be interpreted strictly. The clinician should consider drainage of a complicated effusion if the pleural fluid pH is between 7.2 and 7.3 or the LD is greater than 1000 units/L (greater than 20 mckat/L). Pleural fluid cell count and protein have little diagnostic value in this setting.

Tube thoracostomy drainage of empyema or complicated parapneumonic effusions is frequently complicated by loculation that prevents adequate drainage. Intrapleural instillation of fibrinolytic agents has not been shown in controlled trials to improve drainage. The combination of intrapleural tissue plasminogen activator and deoxyribonuclease (DNase), an enzyme that catalyses extracellular DNA and degrades biofilm formation within the pleural cavity, has been found to improve clinical outcome (increased drainage, decreased length of stay and surgical referral) compared with placebo or either agent alone.

Hemothorax

A small-volume hemothorax that is stable or improving on chest radiographs may be managed by close observation. In all other cases, hemothorax is treated by immediate insertion of a large-bore thoracostomy tube to: (1) drain existing blood and clot, (2) quantify the amount of bleeding, (3) reduce the risk of fibrothorax, and (4) permit apposition of the pleural surfaces in an attempt to reduce hemorrhage. Thoracotomy may be indicated to control hemorrhage, remove clot, and treat complications such as bronchopleural fistula formation.

Control questions

1. Anatomical and physiological features of the bronchial tree, lungs, pleura.
2. Clinical examination of a patient with respiratory disease (history, examination, palpation, percussion, auscultation).
3. Diagnostic manipulations (sputum research, puncture of the pleural cavity, biopsy of the lungs, bronchoscopy).
4. Radiation diagnostics. (X-ray and X-ray, tomography, bronchography, pneumoscintiography).
5. The main pathogens of respiratory tract infections.
6. Microbiological research methods
7. The main subjective symptoms of respiratory diseases.
8. The main objective symptoms of respiratory diseases.

9. Etiology, pathogenesis, clinic, diagnostics and basic directions of pharmacotherapy of pneumonia.
10. Etiology, pathogenesis, clinic, diagnostics and basic directions of pharmacotherapy of acute bronchitis.
11. Etiology, pathogenesis, clinic, diagnostics and main directions of pharmacotherapy of chronic obstructive bronchitis.
12. Etiology, pathogenesis, clinic, diagnostics and basic directions of pharmacotherapy of bronchiectasis.
13. Etiology, pathogenesis, clinic, diagnostics and basic directions of pharmacotherapy of pleurisies (dry, exudative, purulent).
14. Etiology, pathogenesis, clinic, diagnostics and basic directions of pharmacotherapy of tuberculosis.
15. Recipes: Clarithromycin, Amoxiclav, Zinat, Zeftriaxon, Ambroxol, Acetylcysteine, Isoniazid, Rifampicin, Ciprofloxacin.

List of practical works

A. Homework.

1. To study the etiology, pathogenesis of diseases of the lower respiratory tract.
2. To know the classification and clinic of diseases of the lower respiratory tract.
3. To study the main directions of treatment of diseases of the lower respiratory tract.
4. To study the basic principles of treatment of tuberculosis.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data of laboratory and instrumental studies, examination of consultants, records of the attending physician) and the letter of medical appointments.
3. At examination of the patient to allocate subjective, physical, laboratory-instrumental signs of diseases of the respiratory tract.
4. Write a clinical diagnosis:
5. a) the underlying disease; complications of the underlying disease;
6. b) concomitant diseases.
7. Determine a group of lesions necessary for correction of existing disorders.
8. On the basis of theoretical data and own observations, to make a choice of the specific drug of the examined patient.

Control the level of knowledge

1. Fill in the table "Diagnostic capabilities of physical methods for the study of patients with respiratory diseases".

Parameters	Definition	Diagnostic value for diseases of the respiratory system
1. Overview: - respiration rate - difficult breathing -terminal -body chest -coracal deformity of the chest		
2.Percussion: -clear pulmonary percussion sound -break down percussion sound -perfect shade of percussion sound		
3. Auscultation		
4. Dry rust		
5.Volohy rattles		
6.Crepitation		
7. Vesicular breathing		
8. Hard breathing		
9. Bronchial breathing		

2. Fill in the table "Diagnostic value, essence of instrumental methods of investigation of respiratory organs"

Research methods	Definition, the essence of the method	Diagnostic capabilities of the method
Radial -radiography -radioscopy -tomography -bronchography		

Spirometric parameters: -life lung capacity (-formed cell - volume of forced exhalation for 1 sec. -peak expiration rate		

3. To make a scheme of treatment of pneumonia indicating the directions of pharmacotherapy and the names of drugs.

№	Kind pharmacotherapy	Pharmacotherapeutic groups	Medicine
1.	Etiotropic therapy		
2.	Pathogenetic		
3.	Symptomatic		

4. To make the scheme of pharmacotherapy of acute bronchitis:

№	Kind pharmacotherapy	Pharmacotherapeutic groups	Medicine	Direction and purpose of pharmacotherapy
1.	Etiotropic therapy			
2.	Pathogenetic			
3.	Symptomatic			

5. To draw up a treatment plan for tuberculosis:

№	Kind pharmacotherapy	Pharmacotherapeutic groups	Medicine
1.	Etiotropic therapy		
2.	Pathogenetic		
3.	Symptomatic		

6. Fill in the table "Pathological breathing noises".

Type of respiratory noise	The mechanism of noise formation	Clinical examples
a. Dry wheezing b. Moist raucous c. Crepitation d Noise of pleurisy friction		

7. Fill in the table "Pharmacotherapy for pulmonary tuberculosis".

Etiopathogenesis	Direction of pharmacotherapy	Pharmacotherapeutic groups	Medicine
1. Mycobacterium tuberculosis 2. Specific ignition 3.Sorption of scar tissue 4. Reducing the level of total protein in the blood.			

8. Fill in the table "Normal forms of the chest".

Forms of the chest	Clinical description
a. Normostenichnaya b. Hypertensive c. Asthenic	

9. To draw up a scheme of pharmacotherapy for chronic bronchitis:

№	Kind pharmacotherapy	Pharmacotherapeutic groups	Medicine	Direction and purpose of pharmacotherapy
1.	Etiotropic therapy			
2.	Pathogenetic			
3.	Symptomatic			

Solution of situational tasks

1. In the department delivered a sick 42 years with complaints of an increase in body temperature to 39.8oS, a cough with a small amount of sputum, sweating. In the objective study: in the lungs right below the shoulder blade zone of percussion sound, hard breath, wet wheezing. Another physician prescribed sick penicillin for 250 thousand. 4 times a day. Give evaluation of pharmacotherapy. Your diagnosis? Assign the therapy, name the drug 1 line.

2. In a patient 23 years old, with right-sided pneumonia receiving treatment with benzylpenicillin at a dose of 6 million USD. day, on the third day the low-grade temperature is maintained, the dullness of the percussion sound correspondingly to the lower lobe of the lungs, the damp rustle of wheezing.

Tactics of patient management?

3. In a 3-year-old child who had pneumonia, jaundice appeared (tetracycline was not given to the child). With further clarification of the medical history it was found out that the child received ascorutin, rondomicin, calcium chloride, aspirin, analgin.

Explain the cause of the jaundice. Your conclusions, conclusions?

4. Another physician is called to a patient 27 years old who was in the department for pneumonia. Complaint with weakness, dizziness. Objectively - covered with cold sweat, cyanotic lips, pulse - 93 beats per minute, rhythmic, weak filling, BP-90/55 mm Hg. Art. The voice is slightly hoarse. The nurse reported that 40 minutes. Back to the patient a regular penicillin injection was performed. Your diagnosis? Specify the option and degree of severity of the patient's condition. Plan of treatment. Prevention.

5. A man, 27 years old, complains about coughing with rusting sputum, chest pain during breathing, and an increase in body temperature up to 39° C. Ill sickly after overcooling. Objectively: BD-30 for 1 min, heart rate-92 for 1 min, AT-130/80 mm Hg. Art. In the lungs to the right of the IV rib to the bottom - increased vocal tremor, blunt percussion sound, bronchial breathing. Formulate the diagnosis. Plan of treatment.

6. A man, 46 years old, found pneumonia with multiple decay cavities in both lungs. Treatment with penicillin was ineffective. In the study of lavage content of the bronchi, there was a golden staphylococcus, which has a resistance to methylpencillin. Patient's treatment plan. Appointment of the most optimal antibacterial drug.

7. Patient A., 35 years old, complains about an increase in body temperature to 38^0C, dry cough, pain in the left half of the chest, shortness of breath. Ill sickly after overcooling. At examination: mild cyanosis of the lips and cheeks, the frequency of breathing - 26 for 1 minute. With percussion: shorten the percussion sound to the left below the shoulder blade. Auscultation: In the same place, wet rattles are listening. Total blood count: leukocytes-15,0x10^9 /l, SOE-25 mm / h.

Your previous diagnosis. What additional research methods should be used in this situation? Your recommendations about the possible treatment tactics. Prescribe recipes.

8. A child 6 years old with a diagnosis - pneumonia. Receives intramuscular penicillin for 3 days. The body temperature remains at 39^0C, disturbs the cough

with sputum removal, respiratory rate - 30 for 1 minute, heart rate - 120 beats. for 1 minute, there is no cyanosis.

Your recommendations for further therapy tactics. Type recipes.

9. Patient K., 30 years old, became ill acutely: there was a cough, a general weakness, the temperature of the body increased to 38.6^0C. Was called a district therapist who diagnosed a community-acquired pneumonia in the lower lobe of the right lung. Due to the mild course of the disease, the patient should not be sent to a hospital. As an antibacterial drug was prescribed norsulfazol 0.5 g 3 times a day.

Make a correction of appointments. What other medicines should the patient recommend? Type recipes.

10. Patient N., 45 years. Submits complaints of dry cough, fever to 38.5^0 C, malaise, headache. He suffered acutely as a result of overcooling. Ill 2 days. Objectively: percussion above the lungs - clear lung sound, auscultatory - hard breathing, dry whistling wheezing.

The presence of any disease can be assumed in this case? Which drugs can be recommended for the treatment of the patient?

Test tasks

1. The patient of the elderly has been diagnosed with hospital pneumonia. Treated with gentamicin. Which side effect most often occurs when using antibiotics in this group?

A. Hematotoxic action.
B. Ototoxic action.
C. Defeat of the liver.
D. Thrombophlebitis.
E. Pseudomembranous colitis.

2. Basic therapy of chronic obstructive bronchitis in the initial stages includes:

1. antibacterial therapy
2. mucolytic therapy
3. bronchodilator therapy
4. Physiotherapy
5. anti-inflammatory therapy

3. The main method of assessing the severity of the course of chronic obstructive bronchitis is:

1. X-ray examination of the lungs
2. bronchoscopic examination
3. spirometry

4. auscultation
5. percussion

4. The basis of the treatment of pneumonia is:

1. oxygen therapy
2. physiotherapy
3. bronchodilator therapy
4. immunomodulatory therapy
5. antibacterial therapy

5. The main method of diagnosis of pneumonia is:

1. auscultation.
2. percussion
3. spirometry
4. X-ray examination
5. sputum research.

6. The main causes of acute bronchitis include:

1. smoking tobacco
2. viral infection
3. pollution of the air pool
4. the use of medicines
5. alcohol abuse.

7. What is the pathway for theophylline to be the least effective in respiratory diseases?

1. oral
2. intramuscular
3. intravenous
4. by electrophoresis
5. rectal

8. What is the pathway for theophylline to be the least effective in respiratory diseases?

1. oral
2. intramuscular
3. intravenous
4. by electrophoresis
5. rectal

9. The most common cause of pneumonia is:

1. Pseudomanadas
2. E. coli
3. Protea
4. Pneumococcus
5. Staphylococcus aureus

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TOPIC 8. Bronchial asthma: etiology, pathogenesis, classification, clinic, principles of treatment

Actuality of topic.

Bronchial asthma (BA) is currently one of the most common human diseases and there is a steady increase in this disease. Data from epidemiological studies in recent years have shown that the incidence of asthma has reached the level of more than 7% among adults and more than 10% among children, posing a serious social, epidemiological and medical problem.

The main purpose of asthma treatment is to improve the quality of life of the patient by preventing aggravation, providing normal lung function, maintaining normal levels of physical activity, excluding side effects from the use of drugs.

Purpose of the lesson: The student must learn the etiopathogenetic factors, modern clinical classification, pathogenesis, clinical symptoms, methods of laboratory and functional diagnostics. Bronchial asthma, chronic obstructive pulmonary disease. Know the principles of treatment, the requirements for the drugs used for their treatment. Have a concept about asthmatic status, principles of providing urgent care.

ASTHMA

ESSENTIALS OF DIAGNOSIS

- Episodic or chronic symptoms of airflow obstruction.
- Reversibility of airflow obstruction, either spontaneously or following bronchodilator therapy.
- Symptoms frequently worse at night or in the early morning.
- Prolonged expiration and diffuse wheezes on physical examination.
- Limitation of airflow on pulmonary function testing or positive bronchoprovocation challenge.

General Considerations

Asthma is a common disease, affecting approximately 8–10% of the population. It is slightly more common in male children (younger than 14 years) and in female adults. There is a genetic predisposition to asthma. Prevalence, hospitalizations, and fatal asthma have all increased in the United States over the past 20 years. Each year, approximately 1.75 million emergency department visits, 480,000 hospital admissions, and more than 3000 deaths in the United States are attributed to asthma. Hospitalization rates have been highest among blacks and children, and death rates are consistently highest among blacks aged 15–24 years.

Definition & Pathogenesis

Asthma is a chronic inflammatory disorder of the airways. No single histopathologic feature is pathognomonic but common findings include inflammatory cell infiltration with eosinophils, neutrophils, and lymphocytes (especially T lymphocytes); goblet cell hyperplasia, sometimes with plugging of small airways with thick mucus; collagen deposition beneath the basement membrane; hypertrophy of bronchial smooth muscle; airway edema; mast cell activation; and denudation of airway epithelium. This airway inflammation underlies disease chronicity and contributes to airway hyper-responsiveness and airflow limitation.

The strongest identifiable predisposing factor for the development of asthma is atopy, but obesity is increasingly recognized as a risk factor. Exposure of sensitive patients to inhaled allergens increases airway inflammation, airway hyper-responsiveness, and symptoms. Symptoms may develop immediately (immediate asthmatic response) or 4–6 hours after allergen exposure (late asthmatic response). Common allergens include house dust mites (often found in pillows, mattresses, upholstered furniture, carpets, and drapes), cockroaches, cat dander, and seasonal pollens. Substantially reducing exposure reduces pathologic findings and clinical symptoms.

Nonspecific precipitants of asthma include exercise, upper respiratory tract infections, rhinosinusitis, postnasal drip, aspiration, gastroesophageal reflux, changes in the weather, and stress. Exposure to **products of combustion** (eg, from tobacco, crack cocaine, methamphetamines, and other agents) increases asthma symptoms and the need for medications and reduces lung function. **Air pollution**

(increased air levels of respirable particles, ozone, SO2 , and NO2) precipitate asthma symptoms and increase emergency department visits and hospitalizations. Selected individuals may experience asthma symptoms after exposure to aspirin, nonsteroidal anti-inflammatory drugs, or tartrazine dyes. Other **medications** may precipitate asthma symptoms. **Occupational asthma** is triggered by various agents in the workplace and may occur weeks to years after initial exposure and sensitization. Women may experience **catamenial asthma** at predictable times during the menstrual cycle. **Exercise-induced bronchoconstriction** begins during exercise or within 3 minutes after its end, peaks within 10–15 minutes, and then resolves by 60 minutes. This phenomenon is thought to be a consequence of the airways' attempt to warm and humidify an increased volume of expired air during exercise. "**Cardiac asthma"** is wheezing precipitated by decompensated heart failure.

Clinical Findings

Symptoms and signs vary widely among patients as well as individually over time. Asthma is characterized by episodic wheezing, difficulty in breathing, chest tightness, and cough. Excess sputum production is common. The frequency of asthma symptoms is highly variable. Some patients have infrequent, brief attacks of asthma while others may suffer nearly continuous symptoms. Asthma symptoms may occur spontaneously or be precipitated or exacerbated by many different triggers as discussed above. Asthma symptoms are frequently worse at night; circadian variations in bronchomotor tone and bronchial reactivity reach their nadir between 3 am and 4 am, increasing symptoms of bronchoconstriction.

Some physical examination findings increase the probability of asthma. Nasal mucosal swelling, secretion increases, and polyps are often seen in patients with allergic asthma. Eczema, atopic dermatitis, or other allergic skin disorders may also be present. Wheezing or a prolonged expiratory phase during normal breathing correlates well with the presence of airflow obstruction. (Wheezing during forced expiration does not.) Chest examination may be normal between exacerbations in patients with mild asthma. During severe asthma exacerbations, airflow may be too limited to produce wheezing, and the only diagnostic clue on auscultation may be globally reduced breath sounds with prolonged expiration. Hunched shoulders and use of accessory muscles of respiration suggest an increased work of breathing.

Classification of Asthma Severity

(≥ 12 years of age)

Impairment, Symptoms ≤ 2 days/week, Nighttime awakenings ≤ 2x/month, Short-acting β2-agonist use for symptom control (not prevention of EIB) ≤ 2 days/week

Persistent*:*

- *Mild* , Symptoms > 2 days/week but not daily, Nighttime awakenings 3−4x/month, Short-acting β2-agonist use for symptom control (not prevention of EIB) > 2 days/week but not daily, and not more than 1x on any day

- *Moderate,* Symptoms daily, Nighttime awakenings > 1x/week but not nightly, Short-acting β2-agonist use for symptom control (not prevention of EIB) - daily
- *Severe,* Symptoms throughout the day, Nighttime awakenings often 7x/week, Short-acting β2-agonist use for symptom control (not prevention of EIB) - several times per day.

Laboratory Findings

Arterial blood gas measurements may be normal during a mild asthma exacerbation, but respiratory alkalosis and an increase in the alveolar-arterial oxygen difference (A–a–Do2) are common. During severe exacerbations, hypoxemia develops and the Paco2 returns to normal. The combination of an increased Paco2 and respiratory acidosis may indicate impending respiratory failure and the need for mechanical ventilation.

Pulmonary Function Testing

Clinicians are able to identify airflow obstruction on examination, but they have limited ability to assess its severity or to predict whether it is reversible. The evaluation for asthma should therefore include **spirometry** (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], FEV1/FVC) before and after the administration of a short-acting bronchodilator. These measurements help determine the presence and extent of airflow obstruction and whether it is immediately reversible. Airflow obstruction is indicated by a reduced FEV1/FVC ratio. Significant reversibility of airflow obstruction is defined by an increase of 12% or more and 200 mL in FEV1 or FVC after inhaling a short-acting bronchodilator. **A positive bronchodilator response strongly confirms the diagnosis of asthma but a lack of responsiveness in the pulmonary function laboratory does not preclude success in a clinical trial of bronchodilator therapy**. Severe airflow obstruction results in significant air trapping, with an increase in residual volume and consequent reduction in FVC, resulting in a pattern that may mimic a restrictive ventilatory defect.

Bronchial provocation testing with inhaled histamine or methacholine may be useful when asthma is suspected but spirometry is nondiagnostic. Bronchial provocation is not recommended if the FEV1 is less than 65% of predicted. A positive methacholine test is defined as a fall in the FEV1 of 20% or more at exposure to a concentration of 16 mg/mL or less. A negative test has a negative predictive value for asthma of 95%. Exercise challenge testing may be useful in patients with symptoms of exercise-induced bronchospasm.

Peak expiratory flow (PEF) meters are handheld devices designed as personal monitoring tools. PEF monitoring can establish peak flow variability, quantify asthma severity, and provide both patient and clinician with objective measurements on which to base treatment decisions. There are conflicting data about whether measuring PEF improves asthma outcomes, but doing so is recommended to help confirm the diagnosis of asthma, to improve asthma control

in patients with poor perception of airflow obstruction, and to identify environmental and occupational causes of symptoms. Predicted values for PEF vary with age, height, and gender but are poorly standardized. **Comparison with reference values is less helpful than comparison with the patient's own baseline**. PEF shows diurnal variation. It is generally lowest on first awakening and highest several hours before the midpoint of the waking day. PEF should be measured in the morning before the administration of a bronchodilator and in the afternoon after taking a bronchodilator. A 20% change in PEF values from morning to afternoon or from day to day suggests inadequately controlled asthma. PEF values less than 200 L/min indicate severe airflow obstruction.

Additional Testing

Routine chest radiographs in patients with asthma are usually normal or show only hyperinflation. Other findings may include bronchial wall thickening and diminished peripheral lung vascular shadows. Chest imaging is indicated when pneumonia, another disorder mimicking asthma, or a complication of asthma such as pneumothorax is suspected.

Skin testing or in vitro testing to assess sensitivity to environmental allergens can identify atopy in patients with persistent asthma who may benefit from therapies directed at their allergic diathesis. Evaluations for paranasal sinus disease or gastroesophageal reflux should be considered in patients with pertinent, severe, or refractory asthma symptoms.

Complications

Complications of asthma include exhaustion, dehydration, airway infection, and tussive syncope. Pneumothorax occurs but is rare. Acute hypercapnic and hypoxemic respiratory failure occurs in severe disease.

Differential Diagnosis

Patients who have atypical symptoms or poor response to therapy may have a condition that mimics asthma. These disorders typically fall into one of four categories: **upper airway disorders**, lower airway disorders, systemic vasculitides, and psychiatric disorders. Upper airway disorders that mimic asthma include vocal fold paralysis, vocal fold dysfunction syndrome, foreign body aspiration, laryngotracheal masses, tracheal narrowing, tracheobronchomalacia, and airway edema (eg, angioedema or inhalation injury). **Lower airway disorders** include nonasthmatic chronic obstructive pulmonary disease (COPD) (chronic bronchitis or emphysema), bronchiectasis, allergic bronchopulmonary mycosis, cystic fibrosis, eosinophilic pneumonia, and bronchiolitis obliterans. **Systemic vasculitides** with pulmonary involvement may have an asthmatic component, such as eosinophilic granulomatosis with polyangiitis. **Psychiatric causes** include conversion disorders ("functional" asthma), emotional laryngeal wheezing, vocal fold dysfunction, or episodic laryngeal dyskinesis. Rarely, Münchausen syndrome or malingering may explain a patient's complaints.

NAEPP 3 Diagnosis & Management Guidelines

The third Expert Panel Report of the National Asthma Education and Prevention Program (NAEPP), in conjunction with the Global Initiative for Asthma (GINA), a collaboration between the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO), provides guidelines for diagnosis and management of asthma (NAEPP 3). This report identifies four components of chronic asthma diagnosis and management: (1) assessing and monitoring asthma severity and asthma control, (2) patient education designed to foster a partnership for care, (3) control of environmental factors and comorbid conditions that affect asthma, and (4) pharmacologic agents for asthma.

1. Assessing and monitoring asthma severity and asthma control—Severity is the intrinsic intensity of the disease process. **Control** is the degree to which symptoms and limitations on activity are minimized by therapy. Responsiveness is the ease with which control is achieved with therapy. NAEPP 3 guidelines emphasize control over classifications of severity, since the latter is variable over time and in response to therapy. A measure of severity on initial presentation is helpful, however, in guiding the initiation of therapy. Control of asthma is assessed in terms of impairment (frequency and intensity of symptoms and functional limitations) and risk (the likelihood of acute exacerbations or chronic decline in lung function). A key insight is that these two domains of control may respond differently to treatment: some patients may have minimal impairment yet remain at risk for severe exacerbations, for example, in the setting of an upper respiratory tract infection.

2. Patient education designed to foster a partnership for care—Active self-management reduces urgent care visits and hospitalizations and improves perceived control of asthma. Therefore, an outpatient preventive approach that includes self-management education is an integral part of effective asthma care.

All patients, but particularly those with poorly controlled symptoms or history of severe exacerbations, should have a written **asthma action plan** that includes instructions for daily management and measures to take in response to specific changes in status. Patients should be taught to recognize symptoms—especially patterns indicating inadequate asthma control or predicting the need for additional therapy.

3. Control of environmental factors and comorbid conditions that affect asthma—Significant reduction in exposure to nonspecific airway irritants or to inhaled allergens in atopic patients may reduce symptoms and medication needs. Comorbid conditions that impair asthma management, such as rhinosinusitis, gastroesophageal reflux, obesity, and obstructive sleep apnea, should be identified and treated. This search for complicating conditions is particularly crucial in the initial evaluation of new asthma, and in patients who have difficult-to-control symptoms or frequent exacerbations.

4. Pharmacologic agents for asthma—Asthma medications can be divided into two categories: quick-relief (**reliever**) medications that act principally by direct relaxation of bronchial smooth muscle, thereby promoting prompt reversal of acute

airflow obstruction to relieve accompanying symptoms, and long-term control (**controller**) medications that act primarily to attenuate airway inflammation and that are taken daily independent of symptoms to achieve and maintain control of persistent asthma.

Most asthma medications are administered orally or by inhalation. Inhalation of an appropriate agent results in a more rapid onset of pulmonary effects as well as fewer systemic effects compared with oral administration of the same dose. Proper inhaler technique and the use of an inhalation chamber (a "spacer") with metered-dose inhalers (MDIs) decrease oropharyngeal deposition and improve drug delivery to the lung. Nebulizer therapy is reserved for acutely ill patients and those who cannot use inhalers because of difficulties with coordination, understanding, or cooperation.

Treatment

The goals of asthma therapy are to minimize chronic symptoms that interfere with normal activity (including exercise), to prevent recurrent exacerbations, to reduce or eliminate the need for emergency department visits or hospitalizations, and to maintain normal or near-normal pulmonary function. These goals should be met while providing pharmacotherapy with the fewest adverse effects and while satisfying patients' and families' expectations of asthma care. **NAEPP 3 recommendations emphasize daily anti-inflammatory therapy with inhaled corticosteroids as the cornerstone of treatment of persistent asthma.**

Long-Term Control Medications

Anti-inflammatory agents, long-acting bronchodilators, and leukotriene modifiers comprise the important longterm control medications. Other classes of agents are mentioned briefly below as well.

1. Anti-inflammatory agents—Corticosteroids are the most potent and consistently effective anti-inflammatory agents currently available. They reduce both acute and chronic inflammation, resulting in improved airflow, decreased airway hyper-responsiveness, and fewer asthma exacerbations. These agents may also potentiate the action of beta-adrenergic agonists.

Inhaled corticosteroids (*Beclomethasone* HFA 40 or 80 mcg/puff, *Budesonide* DPI 90, 180, or 200 mcg/inhalation, *Flunisolide* 250 mcg/puff, *Flunisolide* HFA 80 mcg/puff, *Fluticasone* HFA/MDI: 44, 110, or 220 mcg/puff, DPI: 50, 100, or 250 mcg/inhalation, *Mometasone* DPI 200 mcg/puff, *Triamcinolone acetonide* 75 mcg/puff) are preferred, first-line agents for all patients with persistent asthma. Patients with persistent symptoms or asthma exacerbations who are not taking an inhaled corticosteroid should be started on one. The most important determinants of agent selection and appropriate dosing are the patient's status and response to treatment. Dosages for inhaled corticosteroids vary depending on the specific agent and delivery device. For most patients, twice-daily dosing provides adequate control of asthma. Once-daily dosing may be sufficient in selected patients. Maximum responses from inhaled corticosteroids may not be observed for months. The use of an inhalation chamber coupled with mouth

washing after inhaled corticosteroid use decreases local side effects (cough, dysphonia, oropharyngeal candidiasis) and systemic absorption. Dry powder inhalers (DPIs) are not used with an inhalation chamber. Systemic effects (adrenal suppression, osteoporosis, skin thinning, easy bruising, and cataracts) may occur with high-dose inhaled corticosteroid therapy.

Systemic corticosteroids (Methylprednisolone, Prednisolone, Prednisone) oral or parenteral are most effective in achieving prompt control of asthma during exacerbations or when initiating long-term asthma therapy in patients with severe symptoms. In patients with refractory, poorly controlled asthma, systemic corticosteroids may be required for the long-term suppression of symptoms. Repeated efforts should be made to reduce the dose to the minimum needed to control symptoms. Alternateday treatment is preferred to daily treatment. Concurrent treatment with calcium supplements and vitamin D should be initiated to prevent corticosteroid-induced bone mineral loss in long-term administration. Bone mineral density testing after 3 or more months of systemic corticosteroid lifetime use can guide the use of bisphosphonates for treatment of steroid-induced osteoporosis. Rapid discontinuation of systemic corticosteroids after long-term use may precipitate adrenal insufficiency.

2. Long-acting bronchodilators

A. Mediator inhibitors—*Cromolyn sodium* and *nedocrom*il are long-term control medications that prevent asthma symptoms and improve airway function in patients with mild persistent or exercise-induced asthma. These agents modulate mast cell mediator release and eosinophil recruitment and inhibit both early and late asthmatic responses to allergen challenge and exercise-induced bronchospasm. They can be effective when taken before an exposure or exercise but do not relieve asthmatic symptoms once present. The clinical response to these agents is less predictable than to inhaled corticosteroids. Nedocromil may help reduce the dose requirements for inhaled corticosteroids. Both agents have excellent safety profiles.

B. Beta-adrenergic agonists—Long-acting beta-2- agonists (*Salmeterol, Formoterol*) provide bronchodilation for up to 12 hours after a single dose. Salmeterol and formoterol are the two long-acting beta-2-agonists available for asthma in the United States. They are administered via dry powder delivery devices. They are indicated for long-term prevention of asthma symptoms, nocturnal symptoms, and for prevention of exercise-induced bronchospasm. When added to low and medium daily doses of inhaled corticosteroids, long-acting beta-2-agonists provide control equivalent to what is achieved by doubling the inhaled corticosteroid dose. Side effects are minimal at standard doses. **Longacting beta-2-agonists should not be used as monotherapy** since they have no anti-inflammatory effect and since monotherapy with long-acting beta-2-agonists has been associated in two large studies with a small but statistically significant increased risk of severe or fatal asthma attacks. This increased risk has not been fully explained but may relate to genetic variation in the beta-adrenergic receptor and remains an area of controversy. The efficacy of combined inhaled corticosteroid and long-acting beta-2-agonist therapy has led to the marketing of

combination medications that deliver both agents simultaneously. Combination inhalers containing formoterol and budesonide have shown efficacy in both maintenance and rescue, given formoterol's short time to onset.

C. Anticholinergics—The long-acting anticholinergic *tiotropium* has been studied as add-on therapy for patients who have either a bronchodilator response or a positive methacholine challenge that is not adequately controlled with a low-dose inhaled corticosteroid. After 14 weeks of treatment, the addition of tiotropium resulted in improvements in PEF, FEV1 , and symptom control; the improvements were greater than those achieved by doubling the dose of the inhaled corticosteroid for the same period of time. The addition of tiotropium was not inferior to the addition of salmeterol. In patients with asthma receiving inhaled corticosteroids and long-acting beta-2-agonists who suffered at least one exacerbation in the preceding year, the addition of tiotropium resulted in a small improvement in peak FEV1 as well as a modest increase in time to next exacerbation.

D. Phosphodiesterase inhibitors—*Theophylline* provides mild bronchodilation in asthmatic patients. Theophylline also has anti-inflammatory and immunomodulatory properties, enhances mucociliary clearance, and strengthens diaphragmatic contractility. Sustained-release theophylline preparations are effective in controlling nocturnal symptoms and as added therapy in patients with moderate or severe persistent asthma whose symptoms are inadequately controlled by inhaled corticosteroids. When added to inhaled corticosteroids, theophylline may allow equivalent control at lower corticosteroid doses.

Theophylline serum concentrations need to be monitored closely owing to the medication's narrow toxictherapeutic range, individual differences in metabolism, and the effects of many factors on drug absorption and metabolism. At therapeutic doses, potential adverse effects include insomnia, aggravation of dyspepsia and gastroesophageal reflux, and urination difficulties in men with prostatic hyperplasia. Dose-related toxicities include nausea, vomiting, tachyarrhythmias, headache, seizures, hyperglycemia, and hypokalemia.

3. Leukotriene modifiers—Leukotrienes are potent biochemical mediators that contribute to airway obstruction and asthma symptoms by contracting airway smooth muscle, increasing vascular permeability and mucus secretion, and attracting and activating airway inflammatory cells. Zileuton is a 5-lipoxygenase inhibitor that decreases leukotriene production, and zafirlukast and montelukast are cysteinyl leukotriene receptor antagonists. In randomized controlled trials (RCTs), these agents caused modest improvements in lung function and reductions in asthma symptoms and lessened the need for beta-2-agonist rescue therapy. These agents are alternatives to low-dose inhaled corticosteroids in patients with mild persistent asthma, although, as monotherapy, their effect is generally less than inhaled corticosteroids. In real-life community trials, leukotriene receptor antagonists were equivalent in efficacy to an inhaled corticosteroid as first-line long-term controller medication or to a long-acting beta-2-agonist as add-on therapy. Zileuton can cause reversible elevations in plasma aminotransferase levels. Eosinophilic granulomatosis with polyangiitis has been diagnosed in a small

number of patients who have taken montelukast or zafirlukast, perhaps due to corticosteroid withdrawal rather than a direct drug effect.

4. Desensitization—Immunotherapy for specific allergens may be considered in selected asthma patients who have exacerbations when exposed to allergens to which they are sensitive and when unresponsive to environmental control measures or other therapies. Studies show a reduction in asthma symptoms in patients treated with single-allergen immunotherapy. Because of the risk of immunotherapyinduced bronchoconstriction, it should be administered only in a setting where such complications can be immediately treated.

5. Omalizumab—*Omalizumab* is a recombinant antibody that binds IgE without activating mast cells. In clinical trials in patients with moderate to severe asthma and elevated IgE levels, omalizumab reduced the need for corticosteroids.

6. Vaccination—Patients with asthma should receive pneumococcal vaccination (Pneumovax) and annual influenza (both seasonal and epidemic influenza A [H1N1]) vaccinations. Inactive vaccines (Pneumovax) are associated with few side effects, but the use of the live attenuated influenza vaccine intranasally may be associated with asthma exacerbations in young children.

7. Oral sustained-release beta-2-agonists—These agents are reserved for patients with bothersome nocturnal asthma symptoms or moderate to severe persistent asthma who do not respond to other therapies.

Quick-Relief Medications

Short-acting bronchodilators and systemic corticosteroids are the important quick-relief medications.

1. Beta-adrenergic agonists—Short-acting inhaled beta-2-agonists, including *albuterol, levalbuterol, bitolterol, pirbuterol, and terbutaline*, are the most effective bronchodilators during exacerbations. All patients with acute symptoms should have immediate access to one of these agents. There is no convincing evidence to support the use of one agent over another. Beta-2-agonists relax airway smooth muscle and cause a prompt increase in airflow and decrease in symptoms. Administration before exercise effectively prevents exercise-induced bronchoconstriction. Beta-2-selective agents may produce less cardiac stimulation than those with mixed beta-1 and beta-2 activities, although clinical trials have not consistently demonstrated this finding.

Inhaled beta-adrenergic therapy is as effective as oral or parenteral therapy in relaxing airway smooth muscle and improving acute asthma and offers the advantages of rapid onset of action (less than 5 minutes) with fewer systemic side effects. Repetitive administration produces incremental bronchodilation. One or two inhalations of a shortacting inhaled beta-2-agonist from an MDI are usually sufficient for mild to moderate symptoms. Severe exacerbations frequently require

higher doses: **6–12 puffs every 30–60 minutes of albuterol by MDI with an inhalation chamber or 2.5 mg by nebulizer provide equivalent bronchodilation**. Administration by nebulization does not offer more effective delivery than MDIs used correctly but does provide higher doses. With most beta-2-agonists, the recommended dose by nebulizer for acute asthma (albuterol, 2.5 mg) is 25–30 times that delivered by a single activation of the MDI (albuterol, 0.09 mg). This difference suggests **that standard dosing of inhalations from an MDI will often be insufficient in the setting of an acute exacerbation.** Independent of dose, nebulizer therapy may be more effective in patients who are unable to coordinate inhalation of medication from an MDI because of age, agitation, or severity of the exacerbation. Scheduled daily use of short-acting beta-2-agonists is not recommended. Increased use (more than one canister a month) or lack of expected effect indicates diminished asthma control and the need for additional long-term control therapy.

2. Anticholinergics—Anticholinergic agents reverse vagally mediated bronchospasm but not allergen- or exerciseinduced bronchospasm. They may decrease mucus gland hypersecretion. Ipratropium bromide, a quaternary derivative of atropine free of atropine's side effects, is less effective than beta-2-agonists for relief of acute bronchospasm, but it is the inhaled drug of choice for patients with intolerance to beta-2-agonists or with bronchospasm due to betablocker medications. Ipratropium bromide reduces the rate of hospital admissions when added to inhaled short-acting beta-2-agonists in patients with moderate to severe asthma exacerbations.

3. Corticosteroids—Systemic corticosteroids are effective primary treatment for patients with moderate to severe asthma exacerbations and for patients with exacerbations who do not respond promptly and completely to inhaled beta-2-agonist therapy. These medications speed the resolution of airflow obstruction and reduce the rate of relapse. Delays in administering corticosteroids may result in delayed benefits from these important agents. **Therefore, oral corticosteroids should generally be prescribed for early administration at home** in patients with moderate to severe asthma. The minimal effective dose of systemic corticosteroids for asthma patients has not been identified. Outpatient prednisone "burst" therapy is 0.5–1 mg/kg/day (typically 40–60 mg) in 1–2 doses for 3–10 days. Severe exacerbations requiring hospitalization typically require 1 mg/kg of prednisone or methylprednisolone every 6–12 hours for 48 hours or until the FEV1 (or PEF rate) returns to 50% of predicted (or 50% of baseline). The dose is then decreased to 60–80 mg/day until the PEF reaches 70% of predicted or personal best. No clear advantage has been found for higher doses of corticosteroids. It may be prudent to administer corticosteroids intravenously to critically ill patients to avoid concerns about altered gastrointestinal absorption.

4. Antimicrobials—Multiple studies suggest that infections with viruses (rhinovirus) and bacteria (Mycoplasma pneumoniae, Chlamydophila pneumoniae) predispose to acute exacerbations of asthma and may underlie chronic, severe

asthma. **The use of empiric antibiotics is, however, not recommended in routine asthma exacerbations because there is no consistent evidence to support improved clinical outcomes**. Antibiotics should be considered when there is a high likelihood of acute bacterial respiratory tract infection, such as for patients with fever or purulent sputum and evidence of pneumonia or bacterial sinusitis.

Treatment of Asthma Exacerbations

NAEPP 3 asthma treatment algorithms begin with an assessment of the severity of a patient's baseline asthma. Adjustments to that algorithm follow a stepwise approach based on a careful assessment of asthma control. Most instances of uncontrolled asthma are mild and can be managed successfully by patients at home with the telephone assistance of a clinician. More severe exacerbations require evaluation and management in an urgent care or emergency department setting.

A. Mild Exacerbations

Mild asthma exacerbations are characterized by only minor changes in airway function (PEF more than 80%) and minimal symptoms and signs of airway dysfunction. Many such patients respond quickly and fully to an inhaled short-acting beta-2-agonist alone. However, an inhaled short-acting beta-2-agonist may need to be continued at increased doses, eg, every 3–4 hours for 24–48 hours. In patients not taking an inhaled corticosteroid, initiating one should be considered during the mild exacerbation. In patients already taking an inhaled corticosteroid, a 7-day course of oral corticosteroids (0.5–1.0 mg/kg/day) may be necessary. Doubling the dose of inhaled corticosteroid is not effective and is not recommended in the NAEPP 3 guidelines.

B. Moderate Exacerbations

The principal goals of treatment of moderate asthma exacerbations are correction of hypoxemia, reversal of airflow obstruction, and reduction of the likelihood of recurrence of obstruction. Early intervention may lessen the severity and shorten the duration of an exacerbation. Of paramount importance is the correction of hypoxemia through the use of supplemental oxygen. Airflow obstruction is treated with continuous administration of an inhaled short-acting beta-2-agonist and the early administration of systemic corticosteroids. Serial measurements of lung function to quantify the severity of airflow obstruction and its response to treatment are useful. The improvement in FEV1 after 30 minutes of treatment correlates significantly with the severity of the asthma exacerbation. Serial measurement of airflow in the emergency department may reduce the rate of hospital admissions for asthma exacerbations. The post-exacerbation care plan is important. Regardless of the severity, all patients should be provided with necessary medications and education in how to use them, instruction in self-assessment, a follow-up appointment, and an action plan for managing recurrence.

C.

D. Severe Exacerbations

Severe exacerbations of asthma can be life-threatening, so treatment should be started immediately. All patients with a severe exacerbation should immediately receive oxygen, high doses of an inhaled short-acting beta-2-agonist, and systemic corticosteroids. A brief history pertinent to the exacerbation can be completed while such treatment is being initiated. More detailed assessments, including laboratory studies, usually add little early on and so should be postponed until after therapy is instituted.

Oxygen therapy is very important because asphyxia is a common cause of asthma deaths. Supplemental oxygen should be given to maintain an Sao2 greater than 90% or a Pao2 greater than 60 mm Hg. Oxygen-induced hypoventilation is extremely rare, and concern for hypercapnia should never delay correction of hypoxemia.

Frequent high-dose delivery of **an inhaled short-acting beta-2-agonist** is indicated and usually well tolerated in severe airway obstruction. Some studies suggest that continuous therapy is more effective than intermittent administration of these agents, but there is no clear consensus as long as similar doses are administered. At least three MDI or nebulizer treatments should be given in the first hour of therapy. Thereafter, the frequency of administration varies according to the improvement in airflow and symptoms and the occurrence of side effects. Ipratropium bromide reduces the rate of hospital admissions when added to inhaled short-acting beta-2-agonists in patients with moderate to severe asthma exacerbations.

Systemic corticosteroids are administered as detailed above. **Intravenous magnesium sulfate** (2 g intravenously over 20 minutes) produces a detectable improvement in airflow and may reduce hospitalization rates in acute severe asthma (FEV1 less than 25% of predicted on presentation or failure to respond to initial treatment).

Mucolytic agents (eg, acetylcysteine, potassium iodide) may worsen cough or airflow obstruction. Anxiolytic and hypnotic drugs are generally contraindicated in severe asthma exacerbations because of their potential respiratory depressant effects.

In the **emergency department setting**, **repeat assessment** of patients with severe exacerbations should be done after the initial dose of inhaled bronchodilator and again after three doses of inhaled bronchodilators (60–90 minutes after initiating treatment). The response to initial treatment is a better predictor of the need for hospitalization than is the severity of an exacerbation on presentation. The decision to hospitalize a patient should be based on the duration and severity of symptoms, severity of airflow obstruction, arterial blood gas results (if available), course and severity of prior exacerbations, medication use at the time of the exacerbation, access to medical care and medications, adequacy of social support and home conditions, and presence of psychiatric illness. In general, discharge to home is appropriate if the PEF or FEV1 has returned to 60% or more of predicted or personal best and symptoms are minimal or absent. Patients with a rapid

response to treatment should be observed for 30 minutes after the most recent dose of bronchodilator to ensure stability of response before discharge.

In the **intensive care setting**, a small subset of patients will not respond to treatment and will progress to impending respiratory failure due to a combination of worsening airflow obstruction and respiratory muscle fatigue. Since such patients can deteriorate rapidly, they must be monitored in a critical care setting. Intubation of an acutely ill asthma patient is technically difficult and is best done semi-electively, before the crisis of a respiratory arrest. At the time of intubation, the patient's intravascular volume should be closely monitored because hypotension commonly follows the administration of sedative medications and the initiation of positive-pressure ventilation; these patients are often dehydrated due to poor recent oral intake and high insensible losses.

The main goals of mechanical ventilation are to ensure adequate oxygenation and to avoid barotrauma. Controlled hypoventilation with permissive hypercapnia is often required to limit airway pressures. Frequent high-dose delivery of inhaled short-acting beta-2-agonists should be continued along with anti-inflammatory agents as discussed above. Many questions remain regarding the optimal delivery of inhaled beta-2-agonists to intubated, mechanically ventilated patients.

When to Refer

• Atypical presentation or uncertain diagnosis of asthma, particularly if additional diagnostic testing is required (bronchoprovocation challenge, allergy skin testing, rhinoscopy, consideration of occupational exposure).

• Complicating comorbid problems, such as rhinosinusitis, tobacco use, multiple environmental allergies, suspected allergic bronchopulmonary mycosis.

• Suboptimal response to therapy.

• Patient not meeting goals of asthma therapy after 3–6 months of treatment.

• Requires high-dose inhaled corticosteroids for control.

• More than two courses of oral prednisone therapy in the past 12 months.

• Any life-threatening asthma exacerbation or exacerbation requiring hospitalization in the past 12 months.

• Presence of social or psychological issues interfering with asthma management.

Control questions

1. Subjective and objective methods of studying patients with asthma.
2. Laboratory and instrumental methods for the study of patients with asthma.
3. Classification of asthma according to severity:
4. Intermittent BA, clinical picture, diagnostics;
5. Light persistent asthma, clinical picture, diagnostics;
6. Medium degree persistent asthma, clinical picture, diagnosis;

7. Heavy persistent asthma, clinical picture, diagnosis.

8. Complications of asthma - pneumosclerosis, emphysema of the lungs.

9. Principles of treatment of asthma. Etiotropic, pathogenetic and symptomatic therapy.

10. Complications of pharmacotherapy of asthma.

11. Treatment of exacerbation of asthma depending on severity:

12. Etiology, pathogenesis, clinic, diagnostics and main directions of pharmacotherapy of COPD.

13. Etiology, pathogenesis, clinic, diagnostics and basic directions of pharmacotherapy of bronchiectasis disease.

14. The role of pharmacist in improving the effectiveness of therapy for patients with asthma and COPD.

15. Recipes: Ipratropium bromide, Combivent, Berodual, Serevent, Flikosotid, Beklomet, Budesonid, Prednisolone, Isoniazid, Taylod.

List of practical works

A. Homework.

1. To study the etiology, pathogenesis of asthma and COPD.
2. To know the classification and the clinic of asthma and COPD.
3. To study the basic directions of treatment of asthma and COPD.
4. Study the basic principles of emergency assistance in the event of an asthma attack.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data of laboratory and instrumental studies, examination of consultants, records of the attending physician) and the letter of medical appointments.
3. At examination of the patient to allocate subjective, physical, laboratory-instrumental signs of diseases of the respiratory tract.
4. Write a clinical diagnosis:
5. a) the underlying disease; complications of the underlying disease;
6. b) concomitant diseases.
7. Determine a group of lesions necessary for correction of existing disorders.
8. On the basis of theoretical data and own observations, to make a choice of the specific drug of the examined patient.

Control the level of knowledge

1. To make the scheme of treatment of bronchial asthma:

№	Directions pharmacotherapy	Pharmacological groups	Drugs	Single dose, multiplicity and

				route of administration
1.	Regulation of tone of smooth muscle of bronchi.			
2.	Treatment of an attack is poisonous			
3.	Influence on the inflammatory process.			
4.	Anxiety attack warning			
5.	Improve sputum release			

2. To make a scheme of treatment of COPD:

№	**Directions pharmacotherapy**	**Pharmacological groups**	**Drugs**	**Single dose, multiplicity and route of administration**
1.	Regulation of tone of smooth muscle of bronchi.			
2.	Treatment of the onset of difficult breathing			
3.	Prevention of allergic complications			
4.	Improve sputum release			

3. Fill in the table "Pharmacotherapy for bronchial asthma."

Etiopathogenesis	**Directions pharmacotherapy**	**Pharmacological groups**	**Drugs**
1.Spam of the bronchi 2. Inflammation of the bronchi 3. Hust, bundle of sputum 4.Sensibilization			

4. Fill in the table "Pharmacotherapy for acute obstructive bronchitis".

Вид фармакотерапії	Pharmacological groups	Drugs
1. Etiotropic therapy 2. Pathogenetic 3. Symptomatic		

Solution of situational tasks

1. A patient, 23 years old, enrolled in a department with a diagnosis - right-sided lower limb pneumonia. From anamnesis it is known that a patient from 8 years suffers from infectious-allergic bronchial asthma. Attacks are provoked by book and house dust. To remove attacks, use theophylline, which takes 10 tabl. per day On the background of the clinic of the main illness of the patient there are signs of a pronounced syndrome of bronchial obstruction and overdose of theophylline.

Propose a treatment plan for major and concomitant diseases, indicating specific drugs, their doses, routes of administration.

2. A patient, 53 years old, suffers from bronchial asthma of infectious-allergic origin, chronic bronchitis for 10 years. It marks the annual exacerbations in the autumn-winter period. In the department entered the state of asthmatic status. Objectively: breathing is frequent (40 for 1 min.), Noisy, whistling. Above the lungs a lot of dry whistling wheezing is heard. Percussion - box sound. Cardiac activity is rhythmic, heart rate and ST - 110 for 1 min., Blood pressure - 140/80 mm Hg, heart tones muffled. Mucous cyanotic, burning legs.

Suggest a specific treatment plan for this patient, indicating the drugs, their doses, paths and administration regimen.

3. In a patient 30 years after the bite of a bee in the area of the spinal appendage of the 7th cervical vertebra, there was a swelling of the face, severe breathing difficulty, excitement, and then unconscious condition. Heart rate - 120 per 1 minute, blood pressure - 80/40 mm Hg. Art. Above the lungs hears the dry whistling wheezing against the background of expiratory dyspnea.

Formulate the diagnosis. Imagine a plan for providing urgent medical care.

4. The patient, 55 years old, suffers from hypertonic disease of stage II, coronary heart disease, atherosclerotic cardiosclerosis with circulatory insufficiency I st., Chronic obstructive bronchitis. He engaged in self-medication: he took tracicor 80, adelfan, eufillin. Delivered to the department for loss of consciousness that arose on the background of growing bronchospasm. At examination - neurological symptomatology is absent. At ECG - acute focal changes in the myocardium were not detected, AKD - 140/80 mm Hg, heart rate - 82 in 1 min. What is the probable cause of the occurrence of bronchospasm and fainting, in the absence of clinical signs of exacerbation of chronic obstructive bronchitis and signs of acute coronary pathology.

Give specific recommendations for further pharmacotherapy of the patient.

5. A patient has 48 years of bronchial asthma. In connection with attacks, suffocation uses inhalations of iadrin. The drug caused a heartbeat in the patient.

Note which stimulation of the receptors caused tachycardia and palpitations in the patient, list the undesirable effects, what tactic is the further management of the patient?

6. A 62 year old patient suffering from nonatopic bronchial asthma, accompanied by a strong bronchodilitis. After appointment with a therapeutic purpose atropine in the patient initially noted improvement of the condition - bronchodilitis decreased sharply. However, after 10 days the condition deteriorated again: there was a fever (up to 38^{o}C), shortness of breath, cough with sputum hardly detachable, heart rate - 90 beats in 1 min.

What causes of such changes will I become ill? List all the unwanted effects of the drug that caused the condition? Prevention of complications, first aid.

7. The patient has a stable recurrent syndrome of bronchial obstruction with reduced sensitivity to cholinergic and adrenergic drugs for 45 years. Bronchial asthma suffers from over 10 years.

What can be used to reduce the frequency and severity of the asthma attacks?

8. To improve the drainage function of the bronchi, sputum discharge, a 52-year-old patient suffering from bronchial asthma, a medicinal product is prescribed. Twenty-four hours after the start of the drug, the patient appeared in the throat, runny nose, tearing.

What drug is the patient receiving?

9. A patient 56 years old, is on a stationary treatment in a therapeutic department with an exacerbation of the course of bronchial asthma. Combined therapy includes intravenous injection of 10 ml of 2.4% of eufillin at 10 o'clock in the morning.

What are the safety criteria for Eufylline?

10. Patient R., 40 years old, suffers from severe persistent bronchial asthma. Complaints for daily attacks of breathlessness. Frequent (up to 30 times a day) the use of salbutamol in attacks of breathlessness. When viewed, the chest is emphysematous, inflamed, percussion sound over the lung box. Breath of a rigid, mass of dry whistling wheezing on both sides.

Your previous diagnosis. Suggest a pharmacotherapy plan.

Test tasks

1. In what clinical situations prescribe antibiotics for bronchial asthma?

1. in the presence of a multitude of dry wheezing on both sides
2. in the presence of signs of bacterial infection in the broncho-pulmonary system

3. with severe exacerbation of asthma
4. when exacerbation of asthma caused by respiratory viral infection
5. when exacerbated by asthma in the elderly.

2. In bronchial asthma, intal is prescribed:
1. to treat an attack of strangulation
2. as a bronchodilator
3. as a mucolytic
4. as an antiviral agent
5. to prevent attacks of breathlessness

3. Preparations for the choice to treat an asthma attack in asthma are:
1. theophylline
2. atrovent (ipratropium bromide).
3. becamethasone dipropionate
4. beta-2 agonists
5. crowns

4. For long-term treatment of asthma preference:
1. an oral route of administration
2. parenteral route of administration of drugs
3. an inhalation method of administration of a drug
4. introduction of drugs by electrophoresis
5. there are no clear guidelines on how to enter

5. The basis of therapy for persistent asthma is:
1. bronchodilator therapy
2. infusion therapy
3. receiving antibiotic drugs
4. anti-inflammatory therapy
5. intensive mucolytic therapy

6. Violation of such receptors leads to bronchodilation:
1. Alpha-adrenergic receptors
2. H1-receptor histaminergic
3. M1-cholinergic receptors
4. N-cholinergic receptors
5. Beta2-adrenoreceptors

7. M-cholinolytics are widely used at
1. asthma
2. chronic obstructive pulmonary disease
3. pneumonia
4. acute bronchitis
5. tuberculosis of the lungs

8. Specific immunotherapy is effective at:
1. acute bronchitis
2. pneumonia
3. chronic bronchitis
4. asthma
5. tuberculosis

9. Aspirin can cause exacerbation of the following disease:
1. acute bronchitis
2. asthma
3. emphysema of the lungs
4. chronic obstructive bronchitis
5. nosocomial pneumonia

10. Inhaled glucocorticoids include:
1.budesonid
2. salmeterol
3. phenoterol
4. ambroxol
5. salbutamol

11. Which of the following drugs are used in the onset of bronchial asthma?
A. Beta-2 agonists.
B. Beta-2-adrenoblockers.
C. Anticholinergics.
D. Mukoliki.
E. Inhaled glucocorticosteroids.

12. A short-acting beta-2 agonist is:
A. Ipratropium bromide.
B. Salmeterol.
C. Salbutamol.
D. Formoterol.
E. Budesonid.

13. The long-acting beta-2 agonists group includes:
A. Salbutamol
B. Phenoterol.
C. Terbutaline.
D. Salmeterol.
E. Isoprenaline.

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TOPIC 9, 10 Principles of pharmacotherapy of diseases of the esophagus, stomach and intestine.

Actuality of topic.

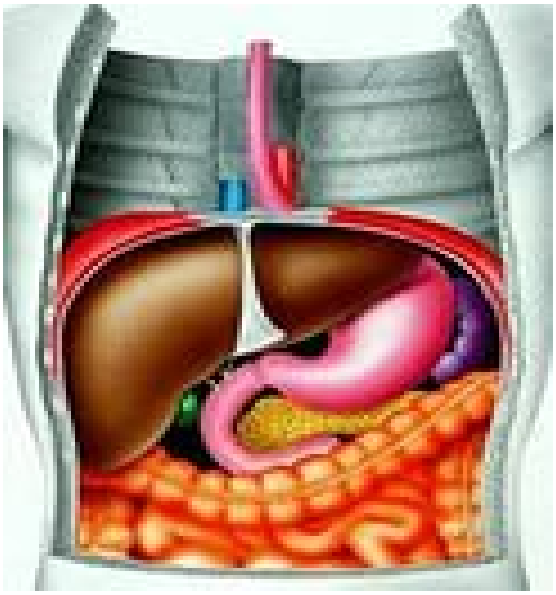
The prevalence of various diseases in people of all age categories, the violation of the diet and the quality of products, the prevalence of risk factors contribute to the presence of gastrointestinal disorders, both in the practice of the doctor, and directly at the reception in the pharmacist. The most common diseases of the esophagus and stomach are gastroesophageal reflux disease (GERD), gastritis, peptic ulcer, and cancer. GERD is one of the pathologies of the digestive system, which has a tendency to develop numerous complications. The high degree of distribution, severe clinic, significantly impairs the quality of life of patients, the tendency to develop life-threatening complications and often an unusual clinical course make GERD one of the most pressing problems of modern gastroenterology. The constant increase in morbidity requires careful study of the mechanisms of its development, improvement of methods of early diagnosis and development of effective measures of pathogenetic treatment. Pulmonary disease affects up to 5% of the adult population, men are ill 3-4 times more often than women.

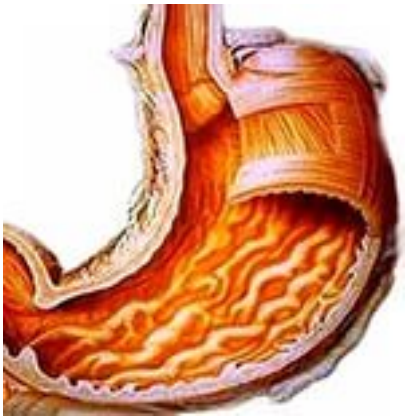
The pathology of the intestine, which is based on stressful situations, infectious

processes, undesirable effects in the appointment of drugs (antibiotics, anti-inflammatory, etc.), the impact of chemical and toxic substances, immunological disorders, is one of the leading places in the structure of the morbidity of the population. Knowledge of the basic etiopathogenetic mechanisms of these changes allows the doctor of any specialty to be guided in the diversity of pathology and to choose the correct, necessary for a specific patient of the drug to correct the pathological changes detected.

Purpose of the lesson: The student should know gastroesophageal reflux disease (etiology, pathogenesis, risk factors, clinic, diagnostic methods, principles of treatment). Etiology, pathogenesis, clinical manifestations, methods of diagnosis of acute and chronic gastritis (type A, type B), directions of pharmacotherapy. Peptic ulcer of the stomach and 12-digestive system: etiology (role of Nelicobacter pylori), pathogenesis, diagnostic methods, directions of pharmacotherapy. Acquire the requirements for the medicines used to treat these diseases.

The student must learn the anatomical and physiological features of the functioning of the small and large intestines. Basic intestinal diseases: etiology, pathogenesis, clinical manifestations, diagnostic methods, principles of pharmacotherapy. Concept about dysbiosis, clinical and diagnostic principles of choice of pharmacotherapy. Ethiopathogenetic factors of intestinal diseases and requirements for medicinal products used for the treatment of intestinal pathology.





DISEASES OF THE ESOPHAGUS

Symptoms: heartburn, dysphagia, and odynophagia almost always indicate a primary esophageal disorder.

A. Heartburn

Heartburn (pyrosis) is the feeling of substernal burning, often radiating to the neck. Caused by the reflux of acidic (or, rarely, alkaline) material into the esophagus, it is highly specific for GERD.

B. Dysphagia

Difficulties in swallowing may arise from problems in transferring the food bolus from the oropharynx to the upper esophagus (oropharyngeal dysphagia) or from impaired transport of the bolus through the body of the esophagus (esophageal dysphagia). The history usually leads to the correct diagnosis.

1. Oropharyngeal dysphagia—The oropharyngeal phase of swallowing is a complex process requiring elevation of the tongue, closure of the nasopharynx, relaxation of the upper esophageal sphincter, closure of the airway, and pharyngeal peristalsis. A variety of mechanical and neuromuscular conditions can disrupt this process. Problems with the oral phase of swallowing cause drooling or spillage of food from the mouth, inability to chew or initiate swallowing, or dry mouth. Pharyngeal dysphagia is characterized by an immediate sense of the bolus catching in the neck, the need to swallow repeatedly to clear food from the pharynx, or coughing or choking during meals. There may be associated dysphonia, dysarthria, or other neurologic symptoms.

2. Esophageal dysphagia—Esophageal dysphagia may be caused by mechanical obstructions of the esophagus or by motility disorders. Patients with mechanical obstruction experience dysphagia, primarily for solids. This is recurrent, predictable, and, if the lesion progresses, will worsen as the lumen narrows. Patients with motility disorders have dysphagia for both solids and liquids. It is episodic, unpredictable, and can be progressive.

C. Odynophagia

Odynophagia is sharp substernal pain on swallowing that may limit oral intake. It usually reflects severe erosive disease. It is most commonly associated with infectious esophagitis due to Candida, herpesviruses, or CMV, especially in immunocompromised patients. It may also be caused by corrosive injury due to caustic ingestions and by pill-induced ulcers.

Diagnostic Studies

A. Upper Endoscopy

Endoscopy is the study of choice for evaluating persistent heartburn, dysphagia, odynophagia, and structural abnormalities detected on barium esophagography. In addition to direct visualization, it allows biopsy of mucosal abnormalities and of normal mucosa (to evaluate for eosinophilic esophagitis) as well as dilation of strictures.

B. Videoesophagography

Oropharyngeal dysphagia is best evaluated with rapidsequence videoesophagography.

C. Barium Esophagography

Patients with esophageal dysphagia often are evaluated first with a radiographic barium study to differentiate between mechanical lesions and motility disorders, providing important information about the latter in particular. In patients with esophageal dysphagia and a suspected motility disorder, barium esophagoscopy should be obtained first. In patients in whom there is a high suspicion of a mechanical lesion, many clinicians will proceed first to endoscopic evaluation because it better identifies mucosa lesions (eg, erosions) and permits mucosal biopsy and dilation. However, barium study is more sensitive for detecting subtle esophageal narrowing due to rings, achalasia, and proximal esophageal lesions.

D. Esophageal Manometry

Esophageal motility may be assessed using manometric techniques. They are indicated: (1) to determine the location of the LES to allow precise placement of a conventional electrode pH probe; (2) to establish the etiology of dysphagia in patients in whom a mechanical obstruction cannot be found, especially if a diagnosis of achalasia is suspected by endoscopy or barium study; (3) for the preoperative assessment of patients being considered for antireflux surgery to exclude an alternative diagnosis (eg, achalasia) or possibly to assess peristaltic function in the esophageal body. High-resolution manometry may be superior to conventional manometry for distinguishing motility disorders.

E. Esophageal pH Recording and Impedance Testing

The pH within the esophageal lumen may be monitored continuously for 24–48 hours. There are two kinds of systems in use: catheter-based and wireless. Traditional systems use a long transnasal catheter that is connected directly to the recording device. Wireless systems are increasingly used; in these systems, a capsule is attached directly to the esophageal mucosa under endoscopic visualization and data are transmitted by radiotelemetry to the recording device. The recording provides information about the amount of esophageal acid reflux and the temporal correlations between symptoms and reflux.

Esophageal pH monitoring devices provide information about the amount of esophageal acid reflux but not nonacid reflux. Techniques using combined pH and multichannel intraluminal impedance allow assessment of acid and nonacid liquid reflux. They may be useful in evaluation of patients with atypical reflux symptoms or persistent symptoms despite therapy with proton pump inhibitors to diagnose hypersensitivity, functional symptoms, and symptoms caused by nonacid reflux.

GASTROESOPHAGEAL REFLUX DISEASE

ESSENTIALS OF DIAGNOSIS

- Heartburn; may be exacerbated by meals, bending, or recumbency.
- Typical uncomplicated cases do not require diagnostic studies.
- Endoscopy demonstrates abnormalities in onethird of patients.

General Considerations

GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms or complications. GERD affects 20% of adults, who

report at least weekly episodes of heartburn, and up to 10% complain of daily symptoms. Although most patients have mild disease, esophageal mucosal damage (reflux esophagitis) develops in up to one-third and more serious complications develop in a few others. Several factors may contribute to GERD.

A. Dysfunction of the Gastroesophageal Junction

The antireflux barrier at the gastroesophageal junction depends on LES pressure, the intra-abdominal location of the sphincter (resulting in a "flap valve" caused by angulation of the esophageal-gastric junction), and the extrinsic compression of the sphincter by the crural diaphragm. In most patients with GERD, baseline LES pressures are normal (10–35 mm Hg). Most reflux episodes occur during transient relaxations of the LES that are triggered by gastric distention by a vagovagal reflex. A subset of patients with GERD have an incompetent (less than 10 mm Hg) LES that results in increased acid reflux, especially when supine or when intra-abdominal pressures are increased by lifting or bending. A hypotensive sphincter is present in up to 50% of patients with severe erosive GERD.

Hiatal hernias are found in one-fourth of patients with nonerosive GERD, three-fourths of patients with severe erosive esophagitis, and over 90% of patients with Barrett esophagus. They are caused by movement of the LES above the diaphragm, resulting in dysfunction of the gastroesophageal junction reflux barrier. Hiatal hernias are common and may cause no symptoms; however, in patients with gastroesophageal reflux, they are associated with higher amounts of acid reflux and delayed esophageal acid clearance, leading to more severe esophagitis and Barrett esophagus. Increased reflux episodes occur during normal swallowing-induced relaxation, transient LES relaxations, and straining due to reflux of acid from the hiatal hernia sac into the esophagus.

Truncal obesity may contribute to GERD, presumably due to an increased intra-abdominal pressure, which contributes to dysfunction of the gastroesophageal junction and increased likelihood of hiatal hernia.

B. Irritant Effects of Refluxate

Esophageal mucosal damage is related to the potency of the refluxate and the amount of time it is in contact with the mucosa. Acidic gastric fluid (pH less than 4.0) is extremely caustic to the esophageal mucosa and is the major injurious agent in the majority of cases. In some patients, reflux of bile or alkaline pancreatic secretions may be contributory. Most acid reflux episodes occur after meals, despite the buffering effect of food that raises intragastric pH. In fact, meal-stimulated acid secretion from the proximal stomach mixes poorly with gastric contents, forming an unbuffered "acid pocket" that floats on top of the meal contents. In patients with GERD, this acid pocket is located near the gastroesophageal junction and may extend into the LES or hiatal hernia.

C. Abnormal Esophageal Clearance Acid refluxate normally is cleared and neutralized by esophageal peristalsis and salivary bicarbonate. One-half of patients with severe GERD have diminished clearance due to hypotensive peristaltic contractions (less than 30 mm Hg) or intermittent failed peristalsis after swallowing. Certain medical conditions such as scleroderma are associated with diminished peristalsis. Sjögren syndrome, anticholinergic medications, and oral

radiation therapy may exacerbate GERD due to impaired salivation.

D. Delayed Gastric Emptying Impaired gastric emptying due to gastroparesis or partial gastric outlet obstruction potentiates GERD.

Clinical Findings

A. Symptoms and Signs

The typical symptom is heartburn. This most often occurs 30–60 minutes after meals and upon reclining. Patients often report relief from taking antacids or baking soda. When this symptom is dominant, the diagnosis is established with a high degree of reliability. Many patients, however, have less specific dyspeptic symptoms with or without heartburn. Overall, a clinical diagnosis of gastroesophageal reflux has a sensitivity and specificity of only 65%. Severity is not correlated with the degree of tissue damage. In fact, some patients with severe esophagitis are only mildly symptomatic. Patients may complain of regurgitation—the spontaneous reflux of sour or bitter gastric contents into the mouth. Dysphagia occurs in one-third of patients and may be due to erosive esophagitis, abnormal esophageal peristalsis, or the development of an esophageal stricture.

"Atypical" or "extraesophageal" manifestations of gastroesophageal disease may occur, including asthma, chronic cough, chronic laryngitis, sore throat, noncardiac chest pain, and sleep disturbances. Gastroesophageal reflux, especially unrecognized nocturnal reflux, may be either a causative or an exacerbating factor in a subset of these patients. In the absence of heartburn or regurgitation, atypical symptoms are unlikely to be related to gastroesophageal reflux.

Physical examination and laboratory data are normal in uncomplicated disease.

B. Special Examinations

Initial diagnostic studies are not warranted for patients with typical GERD symptoms suggesting uncomplicated reflux disease. Patients with typical symptoms of heartburn and regurgitation should be treated empirically with a once daily proton pump inhibitor for 4–8 weeks. Symptomatic response to empiric treatment (while clinically desirable) only has a 78% sensitivity and 54% specificity for GERD. Therefore, further investigation is required in patients with symptoms that persist despite empiric proton pump inhibitor therapy to identify complications of reflux disease and to diagnose other conditions, particularly in patients with "alarm features" (troublesome dysphagia, odynophagia, weight loss, iron deficiency anemia).

1. Upper endoscopy—Upper endoscopy is excellent for documenting the type and extent of tissue damage in gastroesophageal reflux; for detecting other gastroesophageal lesions that may mimic GERD; and for detecting GERD complications, including esophageal stricture, Barrett metaplasia, and esophageal adenocarcinoma. In the absence of prior antisecretory therapy, up to one-third of patients with GERD have visible mucosal damage (known as reflux esophagitis), characterized by single or multiple erosions or ulcers in the distal esophagus at the squamocolumnar junction. In patients treated with a proton pump inhibitor prior to

endoscopy, preexisting reflux esophagitis may be partially or completely healed. The Los Angeles (LA) classification grades reflux esophagitis on a scale of A (one or more isolated mucosal breaks 5 mm or less that do not extend between the tops of two mucosal folds) to D (one or more mucosal breaks that involve at least 75% of the esophageal circumference).

2. Barium esophagography—This study should not be performed to diagnose GERD. In patients with severe dysphagia, it is sometimes obtained prior to endoscopy to identify a stricture.

3. Esophageal pH or combined esophageal pH-impedance testing—Esophageal pH monitoring is unnecessary in most patients but may be indicated to document abnormal esophageal acid exposure in patients who have atypical or extraesophageal symptoms or who are being considered for antireflux surgery. Combined impedance-pH monitoring is indicated in patients with persistent symptoms despite proton pump inhibitor therapy to determine whether symptoms are caused by acid or nonacid reflux (40%) or are unrelated to reflux and indicative of a functional disorder.

Differential Diagnosis

Symptoms of GERD may be similar to those of other diseases such as esophageal motility disorders, peptic ulcer, angina pectoris, or functional disorders. Reflux erosive esophagitis may be confused with pill-induced damage, eosinophilic esophagitis, or infections (CMV, herpes, Candida).

Complications

A. Barrett Esophagus

This is a condition in which the squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium containing goblet and columnar cells (specialized intestinal metaplasia). Present in up to 10% of patients with chronic reflux, Barrett esophagus is believed to arise from chronic reflux-induced injury to the esophageal squamous epithelium; however, it is also increased in patients with truncal obesity independent of GERD. Barrett esophagus is suspected at endoscopy from the presence of orange, gastric type epithelium that extends upward from the stomach into the distal tubular esophagus in a tongue-like or circumferential fashion. Biopsies obtained at endoscopy confirm the diagnosis. Three types of columnar epithelium may be identified: gastric cardiac, gastric fundic, and specialized intestinal metaplasia. There is agreement that the latter carries an increased risk of dysplasia; however, some authorities believe that gastric cardiac mucosa also raises risk.

Barrett esophagus does not provoke specific symptoms but gastroesophageal reflux does. Most patients have a long history of reflux symptoms, such as heartburn and regurgitation. Barrett esophagus should be treated with long-term proton pump inhibitors once or twice daily to control reflux symptoms. Although these medications do not appear to cause regression of Barrett esophagus, they may reduce the risk of cancer. Paradoxically, one-third of patients report minimal or no symptoms of GERD, suggesting decreased acid sensitivity of Barrett epithelium.

Indeed, over 90% of individuals with Barrett esophagus in the general population do not seek medical attention.

The most serious complication of Barrett esophagus is esophageal adenocarcinoma. It is believed that most adenocarcinomas of the esophagus and many such tumors of the gastric cardia arise from dysplastic epithelium in Barrett esophagus. In recent studies, the incidence of adenocarcinoma in patients with Barrett esophagus has been estimated at 0.12–0.33%/year. Although this still is an 11-fold increased risk compared with patients without Barrett esophagus, adenocarcinoma of the esophagus remains a relatively uncommon malignancy in the United States (7000 cases/year). Given the large number of adults with chronic GERD relative to the small number in whom adenocarcinoma develops, 2011 clinical guidelines recommend against endoscopic screening for Barrett esophagus in adults with GERD except in those with multiple risk factors for adenocarcinoma (chronic GERD, hiatal hernia, obesity, white race, male gender, and age 50 years of older).

In patients known to have Barrett esophagus, surveillance endoscopy every 3–5 years is recommended to look for low- or high-grade dysplasia or adenocarcinoma. The risk of progression to adenocarcinoma is a 0.8% risk per year for patients with low-grade dysplasia and a 6% risk per year for high-grade dysplasia. Patients with low-grade dysplasia require repeat endoscopic surveillance in 6 months to exclude coexisting high-grade dysplasia or cancer and, if low-grade dysplasia persists, endoscopic surveillance should be repeated yearly.

Approximately 13% of patient with high-grade dysplasia may harbor an unrecognized invasive esophageal cancer. Therefore, patients with high-grade dysplasia should undergo repeat staging endoscopy with resection of visible mucosal nodules and random mucosal biopsies in order to exclude invasive cancer. The subsequent management of patients with intramucosal cancer or high-grade dysplasia has rapidly evolved. Until recently, esophagectomy was recommended for patients deemed to have a low operative risk; however, this procedure is associated with high morbidity and mortality rates (40% and 1–5%, respectively). Therefore, it is now recommended that endoscopic therapy be performed for most patients with high-grade dysplasia or intramucosal adenocarcinoma. Endoscopic therapies can remove or ablate dysplastic Barrett epithelium, using mucosal snare resection and radiofrequency wave ablation electrocautery. Snare resection is performed of visible neoplastic mucosal nodules to exclude submucosal invasion (which favors surgical resection). Of the patients who have cancer confined to the mucosa, less than 2% have recurrence of cancer or high-grade dysplasia after snare resection. Radiofrequency wave ablation electrocautery is used to ablate Barrett epithelium with flat (non-nodular) dysplasia and to ablate Barrett epithelium that remains after snare resection of dysplastic mucosal nodules. The efficacy of endoscopic ablation therapies in patients with Barrett dysplasia is supported by several studies. When high-dose proton pump inhibitors are administered to normalize intraesophageal pH, radiofrequency wave ablation electrocautery eradication of Barrett columnar epithelium is followed by complete healing with normal squamous epithelium in greater than 90% of patients. In a 2011 randomized, sham-controlled trial in 127

patients with Barrett dysplasia with 3-year follow up, eradication of high-grade dysplasia occurred in 98% after radiofrequency ablation (HALO) and progression to cancer was only 0.55%/year. After initial ablation, Barrett esophagus recurs (with or without dysplasia) in up to 33% within 2 years, justifying periodic surveillance endoscopy.

Endoscopic ablation techniques have a risk of complications (bleeding, perforation, strictures). Therefore, endoscopic eradication therapy currently is not recommended for patients with nondysplastic Barrett esophagus for whom the risk of developing esophageal cancer is low and treatment does not appear to be cost-effective.

B. Peptic Stricture

Stricture formation occurs in about 5% of patients with esophagitis. It is manifested by the gradual development of solid food dysphagia progressive over months to years. Often there is a reduction in heartburn because the stricture acts as a barrier to reflux. Most strictures are located at the gastroesophageal junction. Endoscopy with biopsy is mandatory in all cases to differentiate peptic stricture from stricture by esophageal carcinoma. Active erosive esophagitis is often present. Up to 90% of symptomatic patients are effectively treated with dilation with graduated polyvinyl catheters passed over a wire placed at the time of endoscopy or fluoroscopically, or balloons passed fluoroscopically or through an endoscope. Dilation is continued over one to several sessions. A luminal diameter of 13–17 mm is usually sufficient to relieve dysphagia. Longterm therapy with a proton pump inhibitor is required to decrease the likelihood of stricture recurrence. Some patients require intermittent dilation to maintain luminal patency, but operative management for strictures that do not respond to dilation is seldom required. Refractory strictures may benefit from endoscopic injection of triamcinolone into the stricture.

Treatment

A. Medical Treatment

The goal of treatment is to provide symptomatic relief, to heal esophagitis (if present), and to prevent complications. In the majority of patients with uncomplicated disease, empiric treatment is initiated based on a compatible history without the need for further confirmatory studies. Patients not responding and those with suspected complications undergo further evaluation with upper endoscopy or esophageal manometry and pH recording (see above).

1. Mild, intermittent symptoms—Patients with mild or intermittent symptoms that do not impact adversely on quality of life may benefit from lifestyle modifications with medical interventions taken as needed. Patients may find that eating smaller meals and elimination of acidic foods (citrus, tomatoes, coffee, spicy foods), foods that precipitate reflux (fatty foods, chocolate, peppermint, alcohol), and cigarettes may reduce symptoms. Weight loss should be recommended for patients who are overweight or have had recent weight gain. All patients should be advised to avoid lying down within 3 hours after meals (the period of greatest reflux). Patients with nocturnal symptoms should also elevate the head of the bed on 6-inch blocks or a foam wedge to reduce reflux and enhance esophageal

clearance.

Patients with infrequent heartburn (less than once weekly) may be treated on demand with antacids or oral H2 -receptor antagonists. Antacids provide rapid relief of heartburn; however, their duration of action is less than 2 hours. Many are available over the counter. Those containing magnesium should not be used for patients with kidney disease, and patients with acute or chronic kidney disease should be cautioned appropriately.

All oral H2 -receptor antagonists are available in overthe-counter formulations: cimetidine 200 mg, ranitidine and nizatidine 75 mg, famotidine 10 mg—all of which are half of the typical prescription strength. When taken for active heartburn, these agents have a delay in onset of at least 30 minutes. However, once these agents take effect, they provide heartburn relief for up to 8 hours. When taken before meals known to provoke heartburn, these agents reduce the symptom.

2. Troublesome symptoms

A. Initial therapy—Patients with troublesome reflux symptoms and patients with known complications of GERD should be treated with a once-daily oral proton pump inhibitor (omeprazole or rabeprazole, 20 mg; omeprazole, 40 mg with sodium bicarbonate; lansoprazole, 30 mg; dexlansoprazole, 60 mg; esomeprazole or pantoprazole, 40 mg) taken 30 minutes before breakfast for 4–8 weeks. Because there appears to be little difference between these agents in efficacy or side effect profiles, the choice of agent is determined by cost. Oral omeprazole, 20 mg, and lansoprazole, 15 mg, are available as over-the-counter formulations. Once-daily proton pump inhibitors achieve adequate control of heartburn in 80–90% of patients, complete heartburn resolution in over 50%, and healing of erosive esophagitis (when present) in over 80%. Because of their superior efficacy and ease of use, proton pump inhibitors are preferred to H2 -receptor antagonists for the treatment of acute and chronic GERD. Approximately 10–20% of patients do not achieve symptom relief with a once-daily dose within 2–4 weeks and require a twice-daily proton pump inhibitor (taken 30 minutes before breakfast and dinner). Patients with inadequate symptom relief with empiric twice-daily proton pump inhibitor therapy should undergo evaluation with upper endoscopy. Many providers prefer to prescribe initial twice-daily proton pump inhibitor therapy for patients who have documented severe erosive esophagitis (Los Angeles Grade C or D), Barrett esophagus, or peptic stricture.

B. Long-term therapy—In those who achieve good symptomatic relief with a course of empiric once-daily proton pump inhibitor, therapy may be discontinued after 8–12 weeks. Most patients (over 80%) will experience relapse of GERD symptoms, usually within 3 months. Patients whose symptoms relapse may be treated with either continuous proton pump inhibitor therapy, intermittent 2–4 week courses, or “on demand” therapy (ie, drug taken until symptoms abate) depending on symptom frequency and patient preference. Alternatively, twice daily H2 -receptor antagonists may be used to control symptoms in patients without erosive esophagitis. Patients who require twice-daily proton pump inhibitor therapy for initial symptom control and patients with complications of GERD, including severe erosive esophagitis, Barrett esophagus, or peptic stricture, should be maintained on

longterm therapy with a once- or twice-daily proton pump inhibitor titrated to the lowest effective dose to achieve satisfactory symptom control.

Side effects of proton pump inhibitors are uncommon. Headache, diarrhea, and abdominal pain may occur with any of the agents but generally resolve when another formulation is tried. Potential risks of long-term use of proton pump inhibitors include an increased risk of infectious gastroenteritis (including C difficile), iron and vitamin B12 deficiency, hypomagnesemia, pneumonia, hip fractures (possibly due to impaired calcium absorption), and fundic gland polyps (which appear to be of no clinical significance).

3. Extraesophageal reflux manifestations—Establishing a causal relationship between gastroesophageal reflux and extraesophageal symptoms (eg, asthma, hoarseness, cough, sleep disturbances) is difficult. Gastroesophageal reflux seldom is the sole cause of extraesophageal disorders but may be a contributory factor. Although ambulatory esophageal pH testing can document the presence of increased acid esophageal reflux, it does not prove a causative connection. Current guidelines recommend that a trial of a twice-daily proton pump inhibitor be administered for 2–3 months in patients with suspected extraesophageal GERD syndromes who Improvement of extraesophageal symptoms suggests but does not prove that acid reflux is the causative factor. Esophageal impedance-pH testing may be performed in patients whose extraesophageal symptoms persist after 3 months of twice-daily proton pump inhibitor therapy and may be considered before proton pump inhibitor therapy in patients without typical GERD symptoms in whom other causes of extraesophageal symptoms have been excluded.also have typical GERD symptoms.

4. Unresponsive disease—Approximately 5% do not respond to twice-daily proton pump inhibitors or a change to a different proton pump inhibitor. These patients should undergo endoscopy for detection of severe, inadequately treated reflux esophagitis and for other gastroesophageal lesions (including eosinophilic esophagitis) that may mimic GERD. The presence of active erosive esophagitis usually is indicative of inadequate acid suppression and can almost always be treated successfully with higher proton pump inhibitor doses (eg, esomeprazole, 40 mg twice daily). Alginate is a naturally occurring polymer that forms a viscous raft that floats on the gastric acid pocket and significantly reduces postprandial reflux episodes in patients with GERD and large hiatal hernias. A proprietary antacid-alginate formulation (Gaviscon Double Action Liquid) is available in Europe but not the United States. Truly refractory esophagitis may be caused by gastrinoma with gastric acid hypersecretion (Zollinger-Ellison syndrome), pill-induced esophagitis, resistance to proton pump inhibitors, and medical noncompliance. Patients without endoscopically visible esophagitis should undergo ambulatory impedance-pH monitoring while taking a twice-daily proton pump inhibitor to determine whether the symptoms are correlated with acid or nonacid reflux episodes. The pH study is performed on therapy if the suspicion for GERD is high (to determine whether therapy has adequately suppressed acid esophageal reflux) and off therapy if the suspicion for GERD is low (to determine whether the patient has reflux disease). Combined esophageal pH monitoring with impedance

monitoring is preferred over pH testing alone because of its ability to detect both acid and nonacid reflux events. Approximately 60% of patients with unresponsive symptoms do not have increased reflux and may be presumed to have a functional disorder. Treatment with a low-dose tricyclic antidepressant (eg, imipramine or nortriptyline 25 mg at bedtime) may be beneficial.

B. Surgical Treatment

Surgical fundoplication affords good to excellent relief of symptoms and healing of esophagitis in over 85% of properly selected patients and can be performed laparoscopically with low complication rates in most instances. Although patient satisfaction is high, typical reflux symptoms recur in 10–30% of patients. Furthermore, new symptoms of dysphagia, bloating, increased flatulence, dyspepsia, or diarrhea develop in over 30% of patients. In 2011, results from a randomized trial comparing laparoscopic fundoplication with prolonged medical therapy (esomeprazole 40 mg/day) for chronic GERD were reported. After 5 years, adequate GERD symptom control (symptom remission) was similar, occurring in 85–92% of patients; however, patients who had undergone fundoplication had increased dysphagia, bloating, and flatulence. In 2012, the FDA approved a novel, minimally invasive magnetic artificial sphincter for the treatment of GERD. The device is made up of a flexible, elastic string of titanium beads (wrapped around a magnetic core) that is placed laparoscopically below the diaphragm at the gastroesophageal junction. A 2013 prospective study of 100 patients reported that 64% of patients had significant reductions in esophageal acid reflux. Further experience with this device is needed before widespread adoption can be recommended.

Surgical treatment is not recommended for patients who are well controlled with medical therapies but should be considered for: (1) otherwise healthy, carefully selected patients with extraesophageal manifestations of reflux, as these symptoms often require high doses of proton pump inhibitors and may be more effectively controlled with antireflux surgery; (2) those with severe reflux disease who are unwilling to accept lifelong medical therapy due to its expense, inconvenience, or theoretical risks; and (3) patients with large hiatal hernias and persistent regurgitation despite proton pump inhibitor therapy. Gastric bypass (rather than fundoplication) should be considered for obese patients with GERD.

When to Refer

- Patients with typical GERD whose symptoms do not resolve with empiric management with a twice-daily proton pump inhibitor.
- Patients with suspected extraesophageal GERD symptoms that do not resolve with 3 months of twice-daily proton pump inhibitor therapy.
- Patients with significant dysphagia or other alarm symptoms for upper endoscopy.
- Patients with Barrett esophagus for endoscopic surveillance.
- Patients who have Barrett esophagus with dysplasia or early mucosal cancer.

• Surgical fundoplication is considered.

INFECTIOUS ESOPHAGITIS

ESSENTIALS OF DIAGNOSIS

- Immunosuppressed patient.
- Odynophagia, dysphagia, and chest pain.
- Endoscopy with biopsy establishes diagnosis.

General Considerations

Infectious esophagitis occurs most commonly in immunosuppressed patients. Patients with AIDS, solid organ transplants, leukemia, lymphoma, and those receiving immunosuppressive drugs are at particular risk for opportunistic infections. Candida albicans, herpes simplex, and CMV are the most common pathogens. Candida infection may occur also in patients who have uncontrolled diabetes and those being treated with systemic corticosteroids, radiation therapy, or systemic antibiotic therapy. Herpes simplex can affect normal hosts, in which case the infection is generally self-limited.

Clinical Findings

A. Symptoms and Signs

The most common symptoms are odynophagia and dysphagia. Substernal chest pain occurs in some patients. Patients with candidal esophagitis are sometimes asymptomatic. Oral thrush is present in only 75% of patients with candidal esophagitis and 25–50% of patients with viral esophagitis and is therefore an unreliable indicator of the cause of esophageal infection. Patients with esophageal CMV infection may have infection at other sites such as the colon and retina. Oral ulcers (herpes labialis) are often associated with herpes simplex esophagitis.

B. Special Examinations

Treatment may be empiric. For diagnostic certainty, endoscopy with biopsy and brushings (for microbiologic and histopathologic analysis) is preferred because of its high diagnostic accuracy. The endoscopic signs of candidal esophagitis are diffuse, linear, yellow-white plaques adherent to the mucosa. CMV esophagitis is characterized by one to several large, shallow, superficial ulcerations. Herpes esophagitis results in multiple small, deep ulcerations.

Treatment

A. Candidal Esophagitis

Systemic therapy is required for esophageal candidiasis. An empiric trial of antifungal therapy is often administered without performing diagnostic endoscopy. Initial therapy is generally with fluconazole, 400 mg on day 1, then 200– 400 mg/day orally for 14–21 days. Patients not responding to empiric therapy within 3–5 days should undergo endoscopy with brushings, biopsy, and culture to distinguish

resistant fungal infection from other infections (eg, CMV, herpes). Esophageal candidiasis not responding to fluconazole therapy may be treated with itraconazole suspension (not capsules), 200 mg/day orally, or voriconazole, 200 mg orally twice daily. Refractory infection may be treated intravenously with caspofungin, 50 mg daily.

B. Cytomegalovirus Esophagitis

In patients with HIV infection, immune restoration with highly active antiretroviral therapy (HAART) is the most effective means of controlling CMV disease. Initial therapy is with ganciclovir, 5 mg/kg intravenously every 12 hours for 3–6 weeks. Neutropenia is a frequent dose-limiting side effect. Once resolution of symptoms occurs, it may be possible to complete the course of therapy with oral valganciclovir, 900 mg once daily. Patients who either do not respond to or cannot tolerate ganciclovir are treated acutely with foscarnet, 90 mg/kg intravenously every 12 hours for 3–6 weeks. The principal toxicity is acute renal injury, hypocalcemia, and hypomagnesemia.

C. Herpetic Esophagitis

Immunocompetent patients may be treated symptomatically and generally do not require specific antiviral therapy. Immunosuppressed patients may be treated with oral acyclovir, 400 mg orally five times daily, or 250 mg/m2 intravenously every 8–12 hours, usually for 14–21 days. Oral famciclovir, 500 mg orally three times daily, or valacyclovir, 1 g twice daily, are also effective but more expensive than generic acyclovir. Nonresponders require therapy with foscarnet, 40 mg/kg intravenously every 8 hours for 21 days.

Prognosis

Most patients with infectious esophagitis can be effectively treated with complete symptom resolution. Depending on the patient's underlying immunodeficiency, relapse of symptoms off therapy can raise difficulties. Long-term suppressive therapy is sometimes required.

PILL-INDUCED ESOPHAGITIS

A number of different medications may injure the esophagus, presumably through direct, prolonged mucosal contact or mechanisms that disrupt mucosal integrity. The most commonly implicated are the NSAIDs, potassium chloride pills, quinidine, zalcitabine, zidovudine, alendronate and risedronate, emepronium bromide, iron, vitamin C, and antibiotics (doxycycline, tetracycline, clindamycin, trimethoprimsulfamethoxazole). Because injury is most likely to occur if pills are swallowed without water or while supine, hospitalized or bed-bound patients are at greater risk. Symptoms include severe retrosternal chest pain, odynophagia, and dysphagia, often beginning several hours after taking a pill. These may occur suddenly and persist for days. Some patients (especially the elderly) have relatively little pain, presenting with dysphagia. Endoscopy may reveal one to several discrete

ulcers that may be shallow or deep. Chronic injury may result in severe esophagitis with stricture, hemorrhage, or perforation. Healing occurs rapidly when the offending agent is eliminated. To prevent pill-induced damage, patients should take pills with 4 oz of water and remain upright for 30 minutes after ingestion. Known offending agents should not be given to patients with esophageal dysmotility, dysphagia, or strictures.

Mallory-Weiss Syndrome
(Mucosal Laceration of Gastroesophageal Junction)

ESSENTIALS OF DIAGNOSIS

- Hematemesis; usually self-limited.
- Prior history of vomiting, retching in 50%.
- Endoscopy establishes diagnosis.

General Considerations

Mallory-Weiss syndrome is characterized by a nonpenetrating mucosal tear at the gastroesophageal junction that is hypothesized to arise from events that suddenly raise transabdominal pressure, such as lifting, retching, or vomiting. Alcoholism is a strong predisposing factor. MalloryWeiss tears are responsible for approximately 5% of cases of upper gastrointestinal bleeding.

Clinical Findings

A. Symptoms and Signs

Patients usually present with hematemesis with or without melena. A history of retching, vomiting, or straining is obtained in about 50% of cases.

B. Special Examinations

As with other causes of upper gastrointestinal hemorrhage, upper endoscopy should be performed after the patient has been appropriately resuscitated. The diagnosis is established by identification of a 0.5- to 4-cm linear mucosal tear usually located either at the gastroesophageal junction or, more commonly, just below the junction in the gastric mucosa.

Differential Diagnosis

At endoscopy, other potential causes of upper gastrointestinal hemorrhage are found in over 35% of patients with Mallory-Weiss tears, including peptic ulcer disease, erosive gastritis, arteriovenous malformations, and esophageal varices. Patients with underlying portal hypertension are at higher risk for continued or recurrent bleeding.

Treatment

Patients are initially treated as needed with fluid resuscitation and blood transfusions. Most patients stop bleeding spontaneously and require no therapy. Endoscopic hemostatic therapy is employed in patients who have continuing active

bleeding. Injection with epinephrine (1:10,000), cautery with a bipolar or heater probe coagulation device, or mechanical compression of the artery by application of an endoclip or band is effective in 90–95% of cases. Angiographic arterial embolization or operative intervention is required in patients who fail endoscopic therapy.

CHEST PAIN OF UNDETERMINED ORIGIN

One-third of patients with chest pain undergo negative cardiac evaluation. Patients with recurrent noncardiac chest pain thus pose a difficult clinical problem. Because coronary artery disease is common and can present atypically, it must be excluded prior to evaluation for other causes. Causes of noncardiac chest pain may include the following.

A. Chest Wall and Thoracic Spine Disease

These are easily diagnosed by history and physical examination.

B. Gastroesophageal Reflux

Up to 50% of patients have increased amounts of gastroesophageal acid reflux or a correlation between acid reflux episodes and chest pain demonstrated on esophageal pH testing. An empiric 4-week trial of acid-suppressive therapy with a high-dose proton pump inhibitor is recommended (eg, omeprazole or rabeprazole, 40 mg orally twice daily; lansoprazole, 30–60 mg orally twice daily; or esomeprazole or pantoprazole, 40 mg orally twice daily), especially in patients with reflux symptoms. In patients with persistent symptoms, ambulatory esophageal pH or impedance and pH study may be useful to exclude definitively a relationship between acid and nonacid reflux episodes and chest pain events.

C. Esophageal Dysmotility

Esophageal motility abnormalities such as diffuse esophageal spasm or hypertensive peristalsis (nutcracker esophagus) are uncommon causes of noncardiac chest pain. In patients with chest pain and dysphagia, a barium swallow radiograph should be obtained to look for evidence of achalasia or diffuse esophageal spasm. Esophageal manometry with balloon distention is not routinely performed because of low specificity and the unlikelihood of finding a clinically significant disorder, but it may be recommended in patients with frequent symptoms.

D. Heightened Visceral Sensitivity

Some patients with noncardiac chest pain report pain in response to a variety of minor noxious stimuli such as physiologically normal amounts of acid reflux, inflation of balloons within the esophageal lumen, injection of intravenous edrophonium (a cholinergic stimulus), or intracardiac catheter manipulation. Low doses of oral antidepressants such as trazodone 50 mg or imipramine 10–50 mg reduce chest pain symptoms and are thought to reduce visceral afferent awareness. In a 2010 controlled crossover trial, over 50% of patients treated with venlafaxine, 75 mg once daily at bedtime, achieved symptomatic improvement compared with only 4% treated with placebo.

E. Psychological Disorders

A significant number of patients have underlying depression, anxiety, and panic disorder. Patients reporting dyspnea, sweating, tachycardia, suffocation, or fear of dying should be evaluated for panic disorder.

DISEASES OF THE STOMACH & DUODENUM
GASTRITIS & GASTROPATHY

The term “gastropathy” should be used to denote conditions in which there is epithelial or endothelial damage without inflammation, and “gastritis” should be used to denote conditions in which there is histologic evidence of inflammation. In clinical practice, the term “gastritis” is commonly applied to three categories: (1) erosive and hemorrhagic “gastritis” (gastropathy); (2) nonerosive, nonspecific (histologic) gastritis; and (3) specific types of gastritis, characterized by distinctive histologic and endoscopic features diagnostic of specific disorders.

Classification of Gastritis

I. Acute gastritis

A. Acute H. pylori infection
B. Other acute Infectious gastritides:
1. Bacterial (other than H. pylori)
2. H. heilmannii
3. Phlegmonous
4. Mycobacterial
5. Syphilitic
6. Viral
7. Parasitic
8. Fungal

II. Chronic atrophic gastritis

A. Type A: Autoimmune, body-predominant
B. Type B: H. pylori–related, antral-predominant
C. Indeterminate

III. Uncommon forms of gastritis

A. Lymphocytic
B. Eosinophilic
C. Crohn’s disease
D. Sarcoidosis
E. Isolated granulomatous gastritis
F. Russell body gastritis

1. Erosive & Hemorrhagic "Gastritis" (Gastropathy)

ESSENTIALS OF DIAGNOSIS

- Most commonly seen in alcoholic or critically ill patients, or patients taking NSAIDs.
- Often asymptomatic; may cause epigastric pain, nausea, and vomiting.
- May cause hematemesis; usually in significant bleeding.

General Considerations

The most common causes of erosive gastropathy are medications (especially NSAIDs), alcohol, stress due to severe medical or surgical illness, and portal hypertension ("portal gastropathy"). Major risk factors for stress gastritis include mechanical ventilation, coagulopathy, trauma, burns, shock, sepsis, central nervous system injury, liver failure, kidney disease, and multiorgan failure. The use of enteral nutrition reduces the risk of stress-related bleeding. Uncommon causes of erosive gastropathy include ischemia, caustic ingestion, and radiation. Erosive and hemorrhagic gastropathy typically are diagnosed at endoscopy, often being performed because of dyspepsia or upper gastrointestinal bleeding. Endoscopic findings include subepithelial hemorrhages, petechiae, and erosions. These lesions are superficial, vary in size and number, and may be focal or diffuse. There usually is no significant inflammation on histologic examination.

Clinical Findings

A. Symptoms and Signs

Erosive gastropathy is usually asymptomatic. Symptoms, when they occur, include anorexia, epigastric pain, nausea, and vomiting. There is poor correlation between symptoms and the number or severity of endoscopic abnormalities. The most common clinical manifestation of erosive gastritis is upper gastrointestinal bleeding, which presents as hematemesis, "coffee grounds" emesis, or bloody aspirate in a patient receiving nasogastric suction, or as melena. Because erosive gastritis is superficial, hemodynamically significant bleeding is rare.

B. Laboratory Findings

The laboratory findings are nonspecific. The hematocrit is low if significant bleeding has occurred; iron deficiency may be found.

C. Special Examinations

Upper endoscopy is the most sensitive method of diagnosis. Although bleeding from gastritis is usually insignificant, it cannot be distinguished on clinical grounds from more serious lesions such as peptic ulcers or esophageal varices. Hence, endoscopy is generally performed within 24 hours in patients with upper gastrointestinal bleeding to identify the source. An upper gastrointestinal series is sometimes obtained in lieu of endoscopy in patients with hemodynamically insignificant upper gastrointestinal bleeds to exclude serious lesions but is insensitive for the detection of gastritis.

Differential Diagnosis

Epigastric pain may be due to peptic ulcer, gastroesophageal reflux, gastric cancer, biliary tract disease, food poisoning, viral gastroenteritis, and functional dyspepsia. With severe pain, one should consider a perforated or penetrating ulcer, pancreatic disease, esophageal rupture, ruptured aortic aneurysm, gastric volvulus, gastrointestinal ischemia, and myocardial colic. Causes of upper gastrointestinal bleeding include peptic ulcer disease, esophageal varices, Mallory-Weiss tear, and angiodysplasias.

Specific Causes & Treatment

A. Stress Gastritis

1. Prophylaxis—Stress-related mucosal erosions and subepithelial hemorrhages may develop within 72 hours in critically ill patients. Clinically overt bleeding occurs in 6% of ICU patients, but clinically important bleeding in less than 1.5%. Bleeding is associated with a higher mortality rate but is seldom the cause of death. Two of the most important risk factors for bleeding are coagulopathy (platelets less than 50,000/mcL or INR greater than 1.5) and respiratory failure with the need for mechanical ventilation for over 48 hours. When these two risk factors are absent, the risk of significant bleeding is only 0.1%. Other risk factors include traumatic brain injury, severe burns, sepsis, vasopressor therapy, corticosteroid therapy, and prior history of peptic ulcer disease and gastrointestinal bleeding. Early enteral tube feeding may decrease the risk of significant bleeding.

Prophylaxis should be routinely administered to critically ill patients with risk factors for significant bleeding upon admission. Prophylactic suppression of gastric acid with intravenous H2 -receptor antagonists or proton pump inhibitors (oral or intravenous) has been shown to reduce the incidence of clinically overt and significant bleeding but may increase the risk of nosocomial pneumonia. A 2012 meta-analysis of 13 randomized trials found that oral and intravenous proton pump inhibitors significantly decreased the incidence of clinically significant bleeding compared with intravenous H2 -receptor antagonists (1.3% vs 6.6%, OR 0.30).

The optimal, cost-effective prophylactic regimen remains uncertain, hence clinical practices vary. For patients with nasoenteric tubes, immediate-release omeprazole (40 mg at 1 and 6 hours on day 1; then 40 mg once daily beginning on day 2) may be preferred because of lower cost and ease of administration. For patients requiring intravenous administration, continuous intravenous infusions of H2 -receptor antagonists provide adequate control of intragastric pH in most patients in the following doses over 24 hours: cimetidine (900–1200 mg), ranitidine (150 mg), or famotidine (20 mg). Alternatively, intravenous proton pump inhibitors, although more expensive, may be preferred due to superior efficacy. The optimal dosing of intravenous proton pump inhibitors is uncertain; however, in clinical trials pantoprazole doses ranging from 40 mg to 80 mg and administered every 8–24 hours appear equally effective.

2. Treatment—Once bleeding occurs, patients should receive continuous infusions of a proton pump inhibitor (esomeprazole or pantoprazole, 80 mg

intravenous bolus, followed by 8 mg/h continuous infusion) as well as sucralfate suspension, 1 g orally every 4 to 6 hours. Endoscopy should be performed in patients with clinically significant bleeding to look for treatable causes, especially stressrelated peptic ulcers with active bleeding or visible vessels. When bleeding arises from diffuse gastritis, endoscopic hemostasis techniques are not helpful.

B. NSAID Gastritis

Of patients receiving NSAIDs in clinical trials, 25–50% have gastritis and 10–20% have ulcers at endoscopy; however, symptoms of significant dyspepsia develop in about 5%. NSAIDs that are more selective for the cyclooxygenase (COX)-2 enzyme ("coxibs"), such as celecoxib, etodolac, and meloxicam, decrease the incidence of endoscopically visible ulcers by approximately 75% and significant ulcer complications by up to 50% compared with nonselective NSAIDs (nsNSAIDs) (see below). However, a twofold increase in the incidence in cardiovascular complications (myocardial infarction, cerebrovascular infarction, and death) in patients taking coxibs compared with placebo led to the withdrawal of two highly selective coxibs (rofecoxib and valdecoxib) from the market by the manufacturers.

Celecoxib and all currently available nsNSAIDs (with notable exception of aspirin and possibly naproxen) are associated with increased risk of cardiovascular complications and therefore should be used with caution in patients with cardiovascular risk factors.

In population surveys, the rate of dyspepsia is increased 1.5- to 2-fold with nsNSAID and coxib use. However, dyspeptic symptoms correlate poorly with significant mucosal abnormalities or the development of adverse clinical events (ulcer bleeding or perforation). Given the frequency of dyspeptic symptoms in patients taking NSAIDs, it is neither feasible nor desirable to investigate all such cases. Patients with alarm symptoms or signs, such as severe pain, weight loss, vomiting, gastrointestinal bleeding, or anemia, should undergo diagnostic upper endoscopy. For other patients, symptoms may improve with discontinuation of the agent, reduction to the lowest effective dose, or administration with meals. Proton pump inhibitors have demonstrated efficacy in controlled trials for the treatment of NSAID-related dyspepsia and superiority to H2 -receptor antagonists for healing of NSAID-related ulcers even in the setting of continued NSAID use. Therefore, an empiric 2–4 week trial of an oral proton pump inhibitor (omeprazole, rabeprazole, or esomeprazole 20–40 mg/day; lansoprazole or dexlansoprazole, 30 mg/day; pantoprazole, 40 mg/day) is recommended for patients with NSAIDrelated dyspepsia, especially those in whom continued NSAID treatment is required. If symptoms do not improve, diagnostic upper endoscopy should be conducted.

C. Alcoholic Gastritis

Excessive alcohol consumption may lead to dyspepsia, nausea, emesis, and minor hematemesis—a condition sometimes labeled "alcoholic gastritis." However, it is not proven that alcohol alone actually causes significant erosive gastritis. Therapy with H2 -receptor antagonists, proton pump inhibitors, or sucralfate for 2–

4 weeks often is empirically prescribed.

D. Portal Hypertensive Gastropathy

Portal hypertension commonly results in gastric mucosal and submucosal congestion of capillaries and venules, which is correlated with the severity of the portal hypertension and underlying liver disease. Usually asymptomatic, it may cause chronic gastrointestinal bleeding in 10% of patients and, less commonly, clinically significant bleeding with hematemesis. Treatment with propranolol or nadolol reduces the incidence of recurrent acute bleeding by lowering portal pressures. Patients who fail propranolol therapy may be successfully treated with portal decompressive procedures (see section above on treatment of esophageal varices).

2. Nonerosive, Nonspecific Gastritis

The diagnosis of nonerosive gastritis is based on histologic assessment of mucosal biopsies. Endoscopic findings are normal in many cases and do not reliably predict the presence of histologic inflammation. The main types of nonerosive gastritis are those due to H pylori infection, those associated with pernicious anemia, and eosinophilic gastritis.

Helicobacter pylori Gastritis

H pylori is a spiral gram-negative rod that resides beneath the gastric mucous layer adjacent to gastric epithelial cells. Although not invasive, it causes gastric mucosal inflammation with PMNs and lymphocytes. The mechanisms of injury and inflammation may in part be related to the products of two genes, vacA and cagA.

In developed countries the prevalence of H pylori is rapidly declining. In the United States, the prevalence rises from less than 10% in non-immigrants under age 30 years to over 50% in those over age 60 years. The prevalence is higher in non-whites and immigrants from developing countries and is correlated inversely with socioeconomic status. Transmission is from person to person, mainly during infancy and childhood; however, the mode of transmission is unknown.

Acute infection with H pylori may cause a transient clinical illness characterized by nausea and abdominal pain that may last for several days and is associated with acute histologic gastritis with PMNs. After these symptoms resolve, the majority progress to chronic infection with chronic, diffuse mucosal inflammation (gastritis) characterized by PMNs and lymphocytes. Although chronic H pylori infection with gastritis is present in 30–50% of the population, most persons are asymptomatic and suffer no sequelae. Three gastritis phenotypes occur which determine clinical outcomes. Most infected people have a mild, diffuse gastritis that does not disrupt acid secretion and seldom causes clinically important outcomes. About 15% of infected people have inflammation that predominates in the gastric antrum but spares the gastric body (where acid is secreted). People with this phenotype tend to have increased gastrin; increased acid production; and increased risk of developing peptic ulcers, especially duodenal ulcers. An even smaller subset of infected adults have inflammation that predominates in the gastric

body. Over time, this may lead to destruction of acid-secreting glands with resultant mucosal atrophy, decreased acid secretion, and intestinal metaplasia. This phenotype is associated with an increased risk of gastric ulcers and gastric cancer. Long-term treatment with proton pump inhibitors can potentiate the development of H pylori–associated atrophic gastritis. Chronic H pylori gastritis leads to the development of duodenal or gastric ulcers in up to 10%, gastric cancer in 0.1–3%, and low-grade B cell gastric lymphoma (mucosa-associated lymphoid tissue lymphoma; MALToma) in less than 0.01%.

Eradication of H pylori may be achieved with antibiotics in over 85% of patients and leads to resolution of the chronic gastritis (see section on Peptic Ulcer Disease). Testing for H pylori is indicated for patients with either active or a past history of documented peptic ulcer disease or gastric MALToma and for patients with a family history of gastric carcinoma. Testing and empiric treatment is costeffective in young patients (less than 55 years of age) with uncomplicated dyspepsia prior to further medical evaluation. The role of testing and treating H pylori in patients with functional dyspepsia remains controversial but is generally recommended. H pylori eradication decreases the risk of gastric cancer in patients with peptic ulcer disease. Some groups recommend population-based screening of all asymptomatic persons in regions in which there is a high prevalence of H pylori and gastric cancer (such as Japan, Korea, and China) to reduce the incidence of gastric cancer. Population-based screening of asymptomatic individuals is not recommended in western countries, in which the incidence of gastric cancer is low, but should be considered in immigrants from highprevalence regions.

1. Noninvasive testing for H pylori—Although serologic tests are easily obtained and widely available, most clinical guidelines no longer endorse their use for testing for H pylori infection because they are less accurate than other noninvasive tests that measure active infection. Laboratory-based quantitative serologic ELISA tests have an overall accuracy of only 80%. In comparison, the fecal antigen immunoassay and urea breath test have excellent sensitivity and specificity (greater than 95%). Although more expensive and cumbersome to perform, these tests of active infection are more costeffective in most clinical settings because they reduce unnecessary treatment for patients without active infection.

Recent proton pump inhibitors or antibiotics significantly reduce the sensitivity of urea breath tests and fecal antigen assays (but not serologic tests). Prior to testing, proton pump inhibitors should be discontinued for 7–14 days and antibiotics for at least 28 days

2. Endoscopic testing for H pylori—Endoscopy is not indicated to diagnose H pylori infection in most circumstances. However, when it is performed for another reason, gastric biopsy specimens can be obtained for detection of H pylori and tested for active infection by urease production. This simple, inexpensive test has excellent sensitivity (90%) and specificity (95%). In patients with active upper gastrointestinal bleeding or patients recently taking proton pump inhibitors or antibiotics, histologic assessment for H pylori is preferred. Histologic assessment of biopsies from the gastric antrum and body is more definitive but more expensive

than a rapid urease test. Histologic assessment is also indicated in patients with suspected MALTomas and, possibly, in patients with suspected infection whose rapid urease test is negative. However, serologic testing is the most costeffective means of confirming H pylori infection in patients with a negative rapid urease test.

Pernicious Anemia Gastritis

Pernicious anemia gastritis is an autoimmune disorder involving the fundic glands with resultant achlorhydria, decreased intrinsic factor secretion, and vitamin B12 malabsorption. Of patients with B12 deficiency, less than half have pernicious anemia. Most patients have malabsorption secondary to aging or chronic H pylori infection that results in atrophic gastritis, hypochlorhydria, and impaired release of B12 from food. Fundic histology in pernicious anemia is characterized by severe gland atrophy and intestinal metaplasia caused by autoimmune destruction of the gastric fundic mucosa. Anti-intrinsic factor antibodies are present in 70% of patients. Achlorhydria leads to pronounced hypergastrinemia (greater than 1000 pg/mL) due to loss of acid inhibition of gastrin G cells. Hypergastrinemia may induce hyperplasia of gastric enterochromaffinlike cells that may lead to the development of small, multicentric carcinoid tumors in 5% of patients. Metastatic spread is uncommon in lesions smaller than 2 cm. The risk of gastric adenocarcinoma is increased threefold, with a prevalence of 1–3%. Endoscopy with biopsy is indicated in patients with pernicious anemia at the time of diagnosis. Patients with dysplasia or small carcinoids require periodic endoscopic surveillance.

3. Specific Types of Gastritis

A number of disorders are associated with specific mucosal histologic features.

Infections

Acute bacterial infection of the gastric submucosa and muscularis with a variety of aerobic or anaerobic organisms produces a rare, rapidly progressive, life-threatening condition known as phlegmonous or necrotizing gastritis, which requires broad-spectrum antibiotic therapy and, in many cases, emergency gastric resection. Viral infection with CMV is seen in patients with AIDS and after bone marrow or solid organ transplantation. Endoscopic findings include thickened gastric folds and ulcerations. Fungal infection with mucormycosis and Candida may occur in immunocompromised and diabetic patients. Larvae of Anisakis marina ingested in raw fish or sushi may become embedded in the gastric mucosa, producing severe abdominal pain. Pain persists for several days until the larvae die. Endoscopic removal of the larvae provides rapid symptomatic relief.

PEPTIC ULCER DISEASE

ESSENTIALS OF DIAGNOSIS

- History of dyspepsia present in 80–90% of patients with variable

relationship to meals.

- Ulcer symptoms characterized by rhythmicity and periodicity.
- Ulcer complications present without antecedent symptoms in 10–20% of patients.
- Most NSAID-induced ulcers are asymptomatic. » Upper endoscopy with gastric biopsy for H pylori is the diagnostic procedure of choice in most patients.
- Gastric ulcer biopsy or documentation of complete healing necessary to exclude gastric malignancy.

General Considerations

Peptic ulcer is a break in the gastric or duodenal mucosa that arises when the normal mucosal defensive factors are impaired or are overwhelmed by aggressive luminal factors such as acid and pepsin. By definition, ulcers extend through the muscularis mucosae and are usually over 5 mm in diameter. In the United States, there are about 500,000 new cases per year of peptic ulcer and 4 million ulcer recurrences; the lifetime prevalence of ulcers in the adult population is approximately 10%. Ulcers occur five times more commonly in the duodenum, where over 95% are in the bulb or pyloric channel. In the stomach, benign ulcers are located most commonly in the antrum (60%) and at the junction of the antrum and body on the lesser curvature (25%).

Ulcers occur slightly more commonly in men than in women (1.3:1). Although ulcers can occur in any age group, duodenal ulcers most commonly occur in patients between the ages of 30 and 55 years, whereas gastric ulcers are more common in patients between the ages of 55 and 70 years. Ulcers are more common in smokers and in patients taking NSAIDs on a long-term basis (see below). Alcohol, dietary factors, and stress do not appear to cause ulcer disease. The incidence of duodenal ulcer disease has been declining dramatically for the past 30 years, but the incidence of gastric ulcers appears to be increasing as a result of the widespread use of NSAIDs and low-dose aspirin.

Etiology

There are two major causes of peptic ulcer disease: NSAIDs and chronic H pylori infection. Evidence of H pylori infection or NSAID ingestion should be sought in all patients with peptic ulcer. Less than 5–10% of ulcers are caused by other conditions, including acid hypersecretory states (such as Zollinger-Ellison syndrome or systemic mastocytosis), CMV (especially in transplant recipients), Crohn disease, lymphoma, medications (eg, alendronate), chronic medical illness (cirrhosis or chronic kidney disease), or are idiopathic. NSAID and H pylori-associated ulcers will be presented in this section; Zollinger-Ellison syndrome will be discussed subsequently.

A. H pylori–Associated Ulcers

H pylori infection with associated gastritis and, in some cases, duodenitis appears to be a necessary cofactor for the majority of duodenal and gastric ulcers

not associated with NSAIDs. Ulcer disease will develop in an estimated 10% of infected patients. The prevalence of H pylori infection in duodenal ulcer patients is 75–90%. The association with gastric ulcers is lower, but H pylori is found in most patients in whom NSAIDs cannot be implicated.

The natural history of H pylori–associated peptic ulcer disease is well defined. In the absence of specific antibiotic treatment to eradicate the organism, 85% of patients will have an endoscopically visible recurrence within 1 year. Half of these will be symptomatic. After successful eradication of H pylori with antibiotics, ulcer recurrence rates are reduced dramatically to 5–20% at 1 year. Most of these ulcer recurrences are due to NSAID use or, rarely, reinfection with H pylori.

B. NSAID-Induced Ulcers

There is a 10–20% prevalence of gastric ulcers and a 2–5% prevalence of duodenal ulcers in long-term NSAID users. Approximately 2–5%/year of long-term NSAID users will have an ulcer that causes clinically significant dyspepsia or a serious complication. The incidence of serious gastrointestinal complications (hospitalization, bleeding, perforation) is 0.2–1.9%/year. Meta-analyses of clinical trials detected an increased risk of upper gastrointestinal bleeding in patients taking low-dose aspirin (1 of 1000), coxibs (2 of 1000), and nsNSAIDs (4–6 of 1000). The risk of NSAID complications is greater within the first 3 months of therapy and in patients who are older than 60 years; who have a prior history of ulcer disease; or who take NSAIDs in combination with aspirin, corticosteroids, or anticoagulants.

Traditional nsNSAIDs inhibit prostaglandins through reversible inhibition of both COX-1 and COX-2 enzymes. Aspirin causes irreversible inhibition of COX-1 and COX-2 as well as of platelet aggregation. Coxibs (or selective NSAIDs) preferentially inhibit COX-2—the principal enzyme involved in prostaglandin production at sites of inflammation—while providing relative sparing of COX-1, the principal enzyme involved with mucosal cytoprotection in the stomach and duodenum. Celecoxib is the only coxib currently available in the United States, although other older NSAIDs (etodolac, meloxicam) may have similar COX-2/COX-1 selectivity.

Coxibs decrease the incidence of endoscopically visible ulcers by approximately 75% compared with nsNSAIDs. Of greater clinical importance, the risk of significant clinical events (obstruction, perforation, bleeding) is reduced by up to 50% in patients taking coxibs versus nsNSAIDs. However, a twofold increase in the incidence in cardiovascular complications (myocardial infarction, cerebrovascular infarction, and death) has been detected in patients taking coxibs compared with placebo, prompting the voluntary withdrawal of two coxibs (rofecoxib and valdecoxib) from the market by the manufacturers. In two large, prospective, randomized controlled trials testing the efficacy of coxibs on polyp prevention, celecoxib was associated with a 1.3- to 3.4-fold increased risk of cardiovascular complications versus placebo; the risk was greatest in patients taking higher doses of celecoxib. A review by an FDA panel suggested that all NSAIDs (other than aspirin and, possibly, naproxen) may be associated with an increased

risk of cardiovascular complications, but concluded that celecoxib, which has less COX-2 selectivity than rofecoxib and valdecoxib, does not have higher risk than other nsNSAIDs when used in currently recommended doses (200 mg/day).

Use of even low-dose aspirin (81–325 mg/day) leads to a twofold increased risk of gastrointestinal bleeding complications. In randomized controlled trials, the absolute annual increase of gastrointestinal bleeding attributable to low-dose aspirin is only 0.12% higher than with placebo therapy. However, in population studies, gastrointestinal bleeding occurs in 1.2% of patients each year. Patients with a prior history of peptic ulcers or gastrointestinal bleeding have a markedly increased risk of complications on lowdose aspirin. It should be noted that low-dose aspirin in combination with NSAIDs or coxibs increases the risk of ulcer complications by up to tenfold compared with NSAIDs or low-dose aspirin alone.

H pylori infection increases the risk of ulcer disease and complications over threefold in patients taking NSAIDs or low-dose aspirin. It is hypothesized that NSAID initiation may potentiate or aggravate ulcer disease in susceptible infected individuals.

Clinical Findings

A. Symptoms and Signs

Epigastric pain (dyspepsia), the hallmark of peptic ulcer disease, is present in 80–90% of patients. However, this complaint is not sensitive or specific enough to serve as a reliable diagnostic criterion for peptic ulcer disease. The clinical history cannot accurately distinguish duodenal from gastric ulcers. Less than 25% of patients with dyspepsia have ulcer disease at endoscopy. Twenty percent of patients with ulcer complications such as bleeding have no antecedent symptoms (“silent ulcers”). Nearly 60% of patients with NSAID-related ulcer complications do not have prior symptoms.

Pain is typically well localized to the epigastrium and not severe. It is described as gnawing, dull, aching, or “hunger-like.” Approximately 50% of patients report relief of pain with food or antacids (especially duodenal ulcers) and a recurrence of pain 2–4 hours later. However, many patients deny any relationship to meals or report worsening of pain. Two-thirds of duodenal ulcers and one-third of gastric ulcers cause nocturnal pain that awakens the patient. A change from a patient’s typical rhythmic discomfort to constant or radiating pain may reflect ulcer penetration or perforation. Most patients have symptomatic periods lasting up to several weeks with intervals of months to years in which they are pain free (periodicity). Nausea and anorexia may occur with gastric ulcers. Significant vomiting and weight loss are unusual with uncomplicated ulcer disease and suggest gastric outlet obstruction or gastric malignancy. The physical examination is often normal in uncomplicated peptic ulcer disease. Mild, localized epigastric tenderness to deep palpation may be present. FOBT or FIT is positive in one-third of patients.

B. Laboratory Findings

Laboratory tests are normal in uncomplicated peptic ulcer disease but are ordered to exclude ulcer complications or confounding disease entities. Anemia

may occur with acute blood loss from a bleeding ulcer or less commonly from chronic blood loss. Leukocytosis suggests ulcer penetration or perforation. An elevated serum amylase in a patient with severe epigastric pain suggests ulcer penetration into the pancreas. A fasting serum gastrin level to screen for Zollinger-Ellison syndrome is obtained in some patients (see below).

C. Endoscopy

Upper endoscopy is the procedure of choice for the diagnosis of duodenal and gastric ulcers. Duodenal ulcers are virtually never malignant and do not require biopsy. Three to 5 percent of benign-appearing gastric ulcers prove to be malignant. Hence, biopsies of the ulcer margin are almost always performed. Provided that the gastric ulcer appears benign to the endoscopist and adequate biopsy specimens reveal no evidence of cancer, dysplasia, or atypia, the patient may be monitored without further endoscopy. If these conditions are not fulfilled, follow-up endoscopy should be performed 12 weeks after the start of therapy to document complete healing; nonhealing ulcers are suspicious for malignancy

D. Imaging

Because barium upper gastrointestinal series is less sensitive for detection of ulcers and less accurate for distinguishing benign from malignant ulcers, it has been supplanted by upper endoscopy in most settings. Abdominal CT imaging is obtained in patients with suspected complications of peptic ulcer disease (perforation, penetration, or obstruction).

E. Testing for H pylori

In patients in whom an ulcer is diagnosed by endoscopy, gastric mucosal biopsies should be obtained both for a rapid urease test and for histologic examination. The specimens for histology are discarded if the urease test is positive. In patients with a history of peptic ulcer or when an ulcer is diagnosed by upper gastrointestinal series, noninvasive assessment for H pylori with fecal antigen assay or urea breath testing should be done, which both have a sensitivity and specificity of 95%. Proton pump inhibitors may cause false-negative urea breath tests and fecal antigen tests and should be withheld for at least 14 days before testing. Because of its lower sensitivity (85%) and specificity (79%), serologic testing should not be performed unless fecal antigen testing or urea breath testing is unavailable.

Differential Diagnosis

Peptic ulcer disease must be distinguished from other causes of epigastric distress (dyspepsia). Over 50% of patients with dyspepsia have no obvious organic explanation for their symptoms and are classified as having functional dyspepsia (see sections above on Dyspepsia and Functional Dyspepsia). Atypical gastroesophageal reflux may be manifested by epigastric symptoms. Biliary tract disease is characterized by discrete, intermittent episodes of pain that should not be confused with other causes of dyspepsia. Severe epigastric pain is atypical for

peptic ulcer disease unless complicated by a perforation or penetration. Other causes include acute pancreatitis, acute cholecystitis or choledocholithiasis, esophageal rupture, gastric volvulus, gastric or intestinal ischemia, and ruptured aortic aneurysm.

Pharmacologic Agents

The pharmacology and use of several agents that enhance the healing of peptic ulcers is briefly discussed here. They may be divided into three categories: (1) acid-antisecretory agents, (2) mucosal protective agents, and (3) agents that promote healing through eradication of H pylori.

A. Acid-Antisecretory Agents

1. Proton pump inhibitors—Proton pump inhibitors covalently bind the acid-secreting enzyme H+-K+-ATPase, or "proton pump," permanently inactivating it. Restoration of acid secretion requires synthesis of new pumps, which have a half-life of 18 hours. Thus, although these agents have a serum half-life of less than 60 minutes, their duration of action exceeds 24 hours.

There are six oral proton pump inhibitors currently available: omeprazole, rabeprazole, esomeprazole, lansoprazole, dexlansoprazole, and pantoprazole. The available oral agents inhibit over 90% of 24-hour acid secretion, compared with under 65% for H2-receptor antagonists in standard dosages. Despite minor differences in their pharmacology, they are equally efficacious in the treatment of peptic ulcer disease. Treatment with oral proton pump inhibitors results in over 90% healing of duodenal ulcers after 4 weeks and 90% of gastric ulcers after 8 weeks when given once daily (30 minutes before breakfast) at the following recommended doses: omeprazole, 20–40 mg; esomeprazole, 40 mg; rabeprazole, 20 mg; lansoprazole, 30 mg; dexlansoprazole, 30–60 mg; pantoprazole, 40 mg. Compared with H2 -receptor antagonists, proton pump inhibitors provide faster pain relief and more rapid ulcer healing.

The proton pump inhibitors are remarkably safe for short-term therapy. Long-term use may lead to mild decreases in vitamin B12, iron, and calcium absorption. Observational studies suggest an increased risk of enteric infections, including C difficile and bacterial gastroenteritis, a modest (1.4-fold) increased risk of hip fracture, and pneumonia. Serum gastrin levels rise significantly in 3% of patients receiving long-term therapy but return to normal limits within 2 weeks after discontinuation.

2. H2-receptor antagonists—Although H2 -receptor antagonists are effective in the treatment of peptic ulcer disease, proton pump inhibitors are now the preferred agents because of their ease of use and superior efficacy. Four H2 -receptor antagonists are available: cimetidine, ranitidine, famotidine, and nizatidine. For uncomplicated peptic ulcers, H2 -receptor antagonists may be administered once daily at bedtime as follows: ranitidine and nizatidine 300 mg, famotidine 40 mg, and cimetidine 800 mg. Duodenal and gastric ulcer healing rates of 85–90% are obtained within 6 weeks and 8 weeks, respectively.

B. Agents Enhancing Mucosal Defenses

Bismuth sucralfate, misoprostol, and antacids all have been shown to promote ulcer healing through the enhancement of mucosal defensive mechanisms. Given the greater efficacy and safety of antisecretory agents and better compliance of patients, these agents are no longer used as first-line therapy for active ulcers in most clinical settings.

C. H pylori Eradication Therapy

Eradication of H pylori has proved difficult. Combination regimens that use two or three antibiotics with a proton pump inhibitor or bismuth are required to achieve adequate rates of eradication and to reduce the number of failures due to antibiotic resistance. In the United States, up to 50% of strains are resistant to metronidazole and 13% are resistant to clarithromycin. At present, experts disagree on the optimal regimen; however, updated Maastricht consensus guidelines were published in 2012. Ideally, the optimal regimen would be determined by antibiotic susceptibility testing. However, this requires endoscopic biopsy, and few laboratories are equipped for H pylori cultures. Thus, in most clinical settings, therapy is chosen empirically. In areas of low clarithromycin resistance, including the United States, a 14-day course of "triple therapy," with an oral proton pump inhibitor, clarithromycin 500 mg, and amoxicillin 1 g (or, if penicillin allergic, metronidazole 500 mg), all given twice daily for 14 days, is still recommended for first-line therapy. Unfortunately, this regimen achieves rates of eradication only 75% or more. "Quadruple therapy," with a proton pump inhibitor, bismuth, tetracycline, and metronidazole or tinidazole for 14 days is a more complicated but also more effective regimen. In a 2011 randomized, controlled trial, the per protocol eradication rates were 93% with quadruple therapy and 70% with triple therapy. A 2013 large multicenter European controlled trial conducted in regions of high clarithromycin resistance reported 92% eradication with a 14-day quadruple therapy consisting of a proton pump inhibitor, amoxicillin, clarithromycin, and nitroimidazole (the latter drug not available in the United States). Bismuth-based quadruple therapy is recommended as first-line therapy for patients in areas with high clarithromycin resistance (greater than 20%), in patients who have previously been treated with a macrolide antibiotic, or as second-line therapy for patients whose infection persists after an initial course of triple therapy. Several studies reported eradication rates of more than 90% using a 10-day sequential regimen consisting of four drugs: a proton pump inhibitor and amoxicillin for 5 days, followed by a proton pump inhibitor, clarithromycin, and tinidazole for 5 days. A 2013 meta-analysis did not detect superiority compared with 14-day triple therapy or bismuth-based therapy, except in patients with organisms exhibiting clarithromycin resistance.

Medical Treatment

Patients should be encouraged to eat balanced meals at regular intervals. There is no justification for bland or restrictive diets. Moderate alcohol intake is not harmful. Smoking retards the rate of ulcer healing and increases the frequency of

recurrences and should be prohibited.

A. Treatment of H pylori–Associated Ulcers

1. Treatment of active ulcer—The goals of treatment of active H pylori–associated ulcers are to relieve dyspeptic symptoms, to promote ulcer healing, and to eradicate H pylori infection. Uncomplicated H pylori–associated ulcers should be treated for 10–14 days with one of the proton pump inhibitor-based H pylori eradication regimens listed in Table 15–10. At that point, no further antisecretory therapy is needed, provided the ulcer was small (less than 1 cm) and dyspeptic symptoms have resolved. For patients with large or complicated ulcers, an antisecretory agent should be continued for an additional 2–4 weeks (duodenal ulcer) or 4–6 weeks (gastric ulcer) after completion of the antibiotic regimen to ensure complete ulcer healing. A once-daily oral proton pump inhibitor is recommended. Confirmation of H pylori eradication is recommended for all patients more than 4 weeks after completion of antibiotic therapy and more than 2 weeks after discontinuation of the proton pump inhibitor either with noninvasive tests (urea breath test, fecal antigen test) or endoscopy with biopsy for histology.

2. Therapy to prevent recurrence—Successful eradication reduces ulcer recurrences to less than 20% after 1–2 years. The most common cause of recurrence after antibiotic therapy is failure to achieve successful eradication. Once cure has been achieved, reinfection rates are less than 0.5% per year. Although H pylori eradication has reduced the need for long-term maintenance antisecretory therapy to prevent ulcer recurrences, there remains a subset of patients who require long-term therapy with a proton pump inhibitor once daily. This subset includes patients with H pylori–positive ulcers who have not responded to repeated attempts at eradication therapy, patients with a history of H pylori–positive ulcers who have recurrent ulcers despite successful eradication, and patients with idiopathic ulcers (ie, H pylori–negative and not taking NSAIDs). In all patients with recurrent ulcers, NSAID usage (unintentional or surreptitious) and hypersecretory states (including gastrinoma) should be excluded.

B. Treatment of NSAID-Associated Ulcers

1. Treatment of active ulcers—In patients with NSAIDinduced ulcers, the offending agent should be discontinued whenever possible. Both gastric and duodenal ulcers respond rapidly to therapy with H2 -receptor antagonists or proton pump inhibitors once NSAIDs are eliminated. In some patients with severe inflammatory diseases, it may not be feasible to discontinue NSAIDs. These patients should be treated with concomitant proton pump inhibitors once daily, which results in ulcer healing rates of approximately 80% at 8 weeks in patients continuing to take NSAIDs. All patients with NSAID-associated ulcers should undergo testing for H pylori infection. Antibiotic eradication therapy should be given if H pylori tests are positive.

2. Prevention of NSAID-induced ulcers—Clinicians should carefully weigh the benefits of NSAID therapy with the risks of cardiovascular and gastrointestinal complications. Both coxibs and nsNSAIDs with the possible exception of naproxen

increase the risk of cardiovascular complications. Ulcer complications occur in up to 2% of all nsNSAID-treated patients per year but in up to 10–20% per year of patients with multiple risk factors. These include age over 60 years, history of ulcer disease or complications, concurrent use of antiplatelet therapy (low-dose aspirin or clopidogrel, or both), concurrent therapy with anticoagulants or corticosteroids, and serious underlying medical illness. After considering the patient's risk of cardiovascular and gastrointestinal complications due to NSAID use, the clinician can decide what type of NSAID (nsNSAID vs coxib) is appropriate and what strategies should be used to reduce the risk of such complications. To minimize cardiovascular and gastrointestinal risks, all NSAIDs should be used at the lowest effective dose and for the shortest time necessary.

A. Test for and treat H pylori infection—All patients with a known history of peptic ulcer disease who are treated with NSAIDs or antiplatelet agents (aspirin, clopidogrel) should be tested for H pylori infection and treated, if positive. Although H pylori eradication may decrease the risk of NSAID-related complications, cotherapy with a proton pump inhibitor is still required in high-risk patients.

B. Proton pump inhibitor—Treatment with an oral proton pump inhibitor given once daily (rabeprazole 20 mg, omeprazole 20–40 mg, lansoprazole 30 mg, dexlansoprazole 30–60 mg, or pantoprazole or esomeprazole 40 mg) is effective in the prevention of NSAID-induced gastric and duodenal ulcers and is approved by the FDA for this indication. Among high-risk patients taking nsNSAIDs or coxibs, the incidence of endoscopically visible gastric and duodenal ulcers after 6 months of therapy in patients treated with esomeprazole 20–40 mg/day was 5%, compared with 17% who were given placebo. Nonetheless, proton pump inhibitors are not fully protective in high-risk patients in preventing NSAID-related complications. In prospective, controlled trials of patients with a prior history of NSAID-related ulcer complications, the incidence of recurrent bleeding was almost 5% after 6 months in patients taking nsNSAIDs and a proton pump inhibitor. In prospective, controlled trials of patients with a prior history of ulcer complications related to low-dose aspirin, the incidence of recurrent ulcer bleeding in patients taking low-dose aspirin alone was approximately 15% per year compared with 0–2% per year in patients taking low-dose aspirin and proton pump inhibitor and 9–14% per year in patients taking clopidogrel. Thus, proton pump inhibitors are highly effective in preventing complications related to low-dose aspirin, even in high-risk patients. Enteric coating of aspirin may reduce direct topical damage to the stomach but does not reduce complications.

C. Recommendations to reduce risk of ulcer complications from nsNSAIDs and coxibs—For patients with a low-risk of cardiovascular disease who have no risk factors for gastrointestinal complications, an nsNSAID alone may be given. For patients with one or two gastrointestinal risk factors, a coxib alone or an nsNSAID with a proton pump inhibitor once daily should be given to reduce the risk of gastrointestinal complications. NSAIDs should be avoided if possible in patients with multiple risk factors; if required, however, combination therapy with a

coxib or a partially COX-2 selective nsNSAIDs (etodolac, meloxicam) and a proton pump inhibitor once daily is recommended. For patients with an increased risk of cardiovascular complications, it is preferable to avoid NSAIDs, if possible. If an NSAID is required, naproxen is preferred because it appears to have reduced risk of cardiovascular complications compared with other nsNSAIDs. Coxibs should not be prescribed in patients with increased cardiovascular risk. Almost all patients with increased cardiovascular risk also will be taking antiplatelet therapy with low-dose aspirin or clopidogrel, or both. Because combination therapy with an nsNSAID and antiplatelet therapy increases the risks of gastrointestinal complications, these patients should all receive cotherapy with a proton pump inhibitor once daily or misoprostol.

D. Recommendations to reduce risk of ulcer complications with use of antiplatelet agents—The risk of significant gastrointestinal complications in persons taking low-dose aspirin (81–325 mg/day) or clopidogrel, or both, for cardiovascular prophylaxis is 0.5%/year. Aspirin, 81 mg/day, is recommended in most patients because it has a lower risk of gastrointestinal complications but equivalent cardiovascular protection compared with higher aspirin doses. Complications are increased with combinations of aspirin and clopidogrel or aspirin and anticoagulants. Patients with dyspepsia or prior ulcer disease should be tested for H pylori infection and treated, if positive. Patients younger than age 60–70 who have no other risk factors for gastrointestinal complications may be treated with lowdose aspirin alone without a proton pump inhibitor or misoprostol. Virtually all other patients who require lowdose aspirin or aspirin and anticoagulant therapy should receive a proton pump inhibitor once daily. At the present time, the optimal management of patients who require dual antiplatelet therapy with clopidogrel and aspirin is uncertain. Clopidogrel is a prodrug that is activated by the cytochrome P450 CYP2C19 enzyme. All proton pump inhibitors inhibit CYP2C19 to varying degrees, with omeprazole having the highest and pantoprazole the least level of inhibition. In vitro and in vivo platelet aggregation studies demonstrate that proton pump inhibitors (especially omeprazole) may attenuate the antiplatelet effects of clopidogrel, although the clinical importance of this interaction is uncertain. In 2009 the FDA issued a warning that patients should avoid using clopidogrel with omeprazole, stating further that the safety of other proton pump inhibitors also was uncertain. Faced with this warning, the optimal strategy to reduce the risk of gastrointestinal bleeding in patients taking clopidogrel (with or without aspirin) is uncertain. A 2010 expert consensus panel concluded that once daily treatment with an oral proton pump inhibitor (pantoprazole 40 mg; rabeprazole 20 mg; lansoprazole or dexlansoprazole 30 mg) may still be recommended for patients who have an increased risk of gastrointestinal bleeding (prior history of peptic ulcer disease or gastrointestinal bleeding; concomitant NSAIDs). In keeping with the FDA warning and product labeling, omeprazole and esomeprazole should not be used. For patients with a lower risk of gastrointestinal bleeding, the risks and benefits of proton pump inhibitors must be weighed. Pending further recommendations, an acceptable alternative is to treat with an oral H2 -receptor

antagonist (famotidine 20 mg, ranitidine 150 mg, nizatidine 150 mg) twice daily. Cimetidine is a CYP2C19 inhibitor and should not be used. An alternate strategy is ticagrelor, an antiplatelet agent approved for use with low-dose aspirin in the treatment of acute coronary syndrome. Like clopidogrel, ticagrelor blocks the platelet ADP p2y12 receptor; however, it does not require hepatic activation, it does not interact with the CYP2C19 enzyme, and its efficacy is not diminished by proton pump inhibitors.

C. Refractory Ulcers

Ulcers that are truly refractory to medical therapy are now uncommon. Less than 5% of ulcers are unhealed after 8 weeks of once daily therapy with proton pump inhibitors, and almost all benign ulcers heal with twice daily therapy. Thus, noncompliance is the most common cause of ulcer nonhealing. NSAID and aspirin use, sometimes surreptitious, are commonly implicated in refractory ulcers and must be stopped. H pylori infection should be sought and the infection treated, if present, in all refractory ulcer patients. Single or multiple linear gastric ulcers may occur in large hiatal hernias where the stomach slides back and forth through the diaphragmatic hiatus ("Cameron lesions"), which may be a cause of iron deficiency anemia. Other causes of nonhealing ulcers include acid hypersecretion (Zollinger-Ellison syndrome), unrecognized malignancy (adenocarcinoma or lymphoma), medications causing gastrointestinal ulceration (eg, iron or bisphosphonates), Crohn disease, and unusual infections (H heilmanii, CMV, mucormycosis). Fasting serum gastrin levels should be obtained to exclude gastrinoma with acid hypersecretion (Zollinger-Ellison syndrome). Repeat ulcer biopsies are mandatory after 2–3 months of therapy in all nonhealed ulcers to look for malignancy or infection. Patients with persistent nonhealing ulcers are referred for surgical therapy after exclusion of NSAID use and persistent H pylori infection.

COMPLICATIONS OF PEPTIC ULCER DISEASE

1. Gastrointestinal Hemorrhage

ESSENTIALS OF DIAGNOSIS

- "Coffee grounds" emesis, hematemesis, melena, or hematochezia.
- Emergent upper endoscopy is diagnostic and therapeutic.

General Considerations

Approximately 50% of all episodes of upper gastrointestinal bleeding are due to peptic ulcer. Clinically significant bleeding occurs in 10% of ulcer patients. About 80% of patients stop bleeding spontaneously and generally have an uneventful recovery; the remaining 20% have more severe bleeding. The overall mortality rate for ulcer bleeding is 7%, but it is higher in the elderly, in patients with comorbid medical problems, and in patients with hospital-associated bleeding. Mortality is also higher in patients who present with persistent hypotension or shock, bright red blood in the vomitus or nasogastric lavage fluid, or severe coagulopathy.

Clinical Findings

A. Symptoms and Signs

Up to 20% of patients have no antecedent symptoms of pain; this is particularly true of patients receiving NSAIDs. Common presenting signs include melena and hematemesis. Massive upper gastrointestinal bleeding or rapid gastrointestinal transit may result in hematochezia rather than melena; this may be misinterpreted as signifying a lower tract bleeding source. Nasogastric lavage that demonstrates “coffee grounds” or bright red blood confirms an upper tract source. Recovered nasogastric lavage fluid that is negative for blood does not exclude active bleeding from a duodenal ulcer.

B. Laboratory Findings

The hematocrit may fall as a result of bleeding or expansion of the intravascular volume with intravenous fluids. The BUN may rise as a result of absorption of blood nitrogen from the small intestine and prerenal azotemia.

Treatment

The assessment and initial management of upper gastrointestinal tract bleeding are discussed above. Specific issues pertaining to peptic ulcer bleeding are described below.

A. Medical Therapy

1. Antisecretory agents—Intravenous proton pump inhibitors should be administered for 3 days in patients with ulcers whose endoscopic appearance suggests a high risk of rebleeding after endoscopic therapy. Intravenous proton pump inhibitors have been associated with a reduction in rebleeding, transfusions, the need for further endoscopic therapy, and surgery in the subset of patients with high-risk ulcers, ie, an ulcer with active bleeding, visible vessel, or adherent clot. After initial successful endoscopic treatment of ulcer hemorrhage, intravenous esomeprazole, pantoprazole, or omeprazole (80 mg bolus injection, followed by 8 mg/h continuous infusion for 72 hours) reduces the rebleeding rate from approximately 20% to less than 10%; however, intravenous omeprazole is not available in the United States. High-dose oral proton pump inhibitors (omeprazole 40 mg twice daily) also appear to be effective in reducing rebleeding but have not been compared with the intravenous regimen. Intravenous H2 -receptor antagonists have not been demonstrated to be of any benefit in the treatment of acute ulcer bleeding.

2. Long-term prevention of rebleeding—Recurrent ulcer bleeding develops within 3 years in one-third of patients if no specific therapy is given. In patients with bleeding ulcers who are H pylori-positive, successful eradication effectively prevents recurrent ulcer bleeding in almost all cases. It is therefore recommended that all patients with bleeding ulcers be tested for H pylori infection and treated if positive. Four to 8 weeks after completion of antibiotic therapy, a urea breath or fecal antigen test for H pylori should be administered or endoscopy performed with

biopsy for histologic confirmation of successful eradication. In patients in whom H pylori persists or the small subset of patients whose ulcers are not associated with NSAIDs or H pylori, long-term acid suppression with a once-daily proton pump inhibitor should be prescribed to reduce the likelihood of recurrence of bleeding.

B. Endoscopy

Endoscopy is the preferred diagnostic procedure in almost all cases of upper gastrointestinal bleeding because of its high diagnostic accuracy, its ability to predict the likelihood of recurrent bleeding, and its availability for therapeutic intervention in high-risk lesions. Endoscopy should be performed within 24 hours in most cases. In cases of severe active bleeding, endoscopy is performed as soon as patients have been appropriately resuscitated and are hemodynamically stable.

On the basis of clinical and endoscopic criteria, it is possible to predict which patients are at a higher risk of rebleeding and therefore to make more rational use of hospital resources. Nonbleeding ulcers under 2 cm in size with a base that is clean have a less than 5% chance of rebleeding. Most young (under age 60 years), otherwise healthy patients with clean-based ulcers may be safely discharged from the emergency department or hospital after endoscopy. Ulcers that have a flat red or black spot have a less than 10% chance of significant rebleeding. Patients who are hemodynamically stable with these findings should be admitted to a hospital ward for 24–72 hours and may begin immediate oral feedings and antiulcer (or anti-H pylori) medication.

By contrast, the risk of rebleeding or continued bleeding in ulcers with a nonbleeding visible vessel is 50%, and with active bleeding it is 80–90%. Endoscopic therapy with thermocoagulation (bipolar or heater probes) or application of endoscopic clips (akin to a staple) is the standard of care for such lesions because it reduces the risk of rebleeding, the number of transfusions, and the need for subsequent surgery. The optimal treatment of ulcers with a dense clot that adheres despite vigorous washing is controversial; removal of the clot followed by endoscopic treatment of an underlying vessel may be considered in selected high-risk patients. For actively bleeding ulcers, a combination of epinephrine injection followed by thermocoagulation or clip application commonly is used. These techniques achieve successful hemostasis of actively bleeding lesions in 90% of patients. After endoscopic therapy followed by an intravenous proton pump inhibitor, significant rebleeding occurs in less than 10%, of which over 70% can be managed successfully with repeat endoscopic treatment. After endoscopic treatment, patients should remain hospitalized for at least 72 hours, when the risk of rebleeding falls to below 3%.

C. Surgical Treatment

Patients with recurrent bleeding or bleeding that cannot be controlled by endoscopic techniques should be evaluated by a surgeon. However, less than 5% of patients treated with hemostatic therapy require surgery for continued or recurrent bleeding. Overall surgical mortality for emergency ulcer bleeding is less than 6%. The prognosis is poorer for patients over age 60 years, those with serious

underlying medical illnesses or chronic kidney disease, and those who require more than 10 units of blood transfusion. Percutaneous arterial embolization is an alternative to surgery for patients in whom endoscopic therapy has failed.

2. Ulcer Perforation

Perforations develop in less than 5% of ulcer patients, usually from ulcers on the anterior wall of the stomach or duodenum. Perforation results in a chemical peritonitis that causes sudden, severe generalized abdominal pain that prompts most patients to seek immediate attention. Elderly or debilitated patients and those receiving long-term corticosteroid therapy may experience minimal initial symptoms, presenting late with bacterial peritonitis, sepsis, and shock. On physical examination, patients appear ill, with a rigid, quiet abdomen and rebound tenderness. Hypotension develops later after bacterial peritonitis has developed. If hypotension is present early with the onset of pain, other abdominal emergencies should be considered such as a ruptured aortic aneurysm, mesenteric infarction, or acute pancreatitis. Leukocytosis is almost always present. A mildly elevated serum amylase (less than twice normal) is sometimes seen. Abdominal CT usually establishes the diagnosis without need for further studies. The absence of free air may lead to a misdiagnosis of pancreatitis, cholecystitis, or appendicitis. Laparoscopic perforation closure can be performed in many centers, significantly reducing operative morbidity compared with open laparotomy.

3. Gastric Outlet Obstruction

Gastric outlet obstruction occurs in less than 2% of patients with ulcer disease and is due to edema or cicatricial narrowing of the pylorus or duodenal bulb. With the advent of potent antisecretory therapy with proton pump inhibitors and the eradication of H pylori, obstruction now is less commonly caused by peptic ulcers than by gastric neoplasms or extrinsic duodenal obstruction by intra-abdominal neoplasms. The most common symptoms are early satiety, vomiting, and weight loss. Later, vomiting may develop that typically occurs one to several hours after eating and consists of partially digested food contents. Patients may develop dehydration, metabolic alkalosis, and hypokalemia. On physical examination, a succussion splash may be heard in the epigastrium. In most cases, nasogastric aspiration will result in evacuation of a large amount (greater than 200 mL) of foulsmelling fluid, which establishes the diagnosis. Patients are treated initially with intravenous isotonic saline and KCl to correct fluid and electrolyte disorders, an intravenous proton pump inhibitor, and nasogastric decompression of the stomach. Upper endoscopy is performed after 24–72 hours to define the nature of the obstruction and to exclude gastric neoplasm.

ZOLLINGER-ELLISON SYNDROME (Gastrinoma)

ESSENTIALS OF DIAGNOSIS

- Peptic ulcer disease; may be severe and atypical.
- Gastric acid hypersecretion.

- Diarrhea common, relieved by nasogastric suction.
- Most cases are sporadic; 25% with multiple endocrine neoplasia type 1 (MEN 1).

General Considerations

Zollinger-Ellison syndrome is caused by gastrin-secreting gut neuroendocrine tumors (gastrinomas), which result in hypergastrinemia and acid hypersecretion. Less than 1% of peptic ulcer disease is caused by gastrinomas. Primary gastrinomas may arise in the pancreas (25%), duodenal wall (45%), or lymph nodes (5–15%), and in other locations or of unknown primary (20%). Approximately 80% arise within the "gastrinoma triangle" bounded by the porta hepatis, the neck of the pancreas, and the third portion of the duodenum. Most gastrinomas are solitary or multifocal nodules that are potentially resectable. Approximately 25% of patients have small multicentric gastrinomas associated with MEN 1 that are more difficult to resect. Over two-thirds of gastrinomas are malignant, and one-third have already metastasized to the liver at initial presentation.

Clinical Findings

A. Symptoms and Signs

Over 90% of patients with Zollinger-Ellison syndrome develop peptic ulcers. In most cases, the symptoms are indistinguishable from other causes of peptic ulcer disease and therefore the syndrome may go undetected for years. Ulcers usually are solitary and located in the duodenal bulb, but they may be multiple or occur more distally in the duodenum. Isolated gastric ulcers do not occur. Gastroesophageal reflux symptoms occur often. Diarrhea occurs in one-third of patients, in some cases in the absence of peptic symptoms. Gastric acid hypersecretion can cause direct intestinal mucosal injury and pancreatic enzyme inactivation, resulting in diarrhea, steatorrhea, and weight loss; nasogastric aspiration of stomach acid stops the diarrhea. Screening for Zollinger-Ellison syndrome with fasting gastrin levels should be obtained in patients with ulcers that are refractory to standard therapies, giant ulcers (larger than 2 cm), ulcers located distal to the duodenal bulb, multiple duodenal ulcers, frequent ulcer recurrences, ulcers associated with diarrhea, ulcers occurring after ulcer surgery, and patients with ulcer complications. Ulcer patients with hypercalcemia or family histories of ulcers (suggesting MEN 1) should also be screened. Finally, patients with peptic ulcers who are H pylori negative and who are not taking NSAIDs should be screened.

B. Laboratory Findings

The most sensitive and specific method for identifying Zollinger-Ellison syndrome is demonstration of an increased fasting serum gastrin concentration (greater than 150 pg/mL [150 ng/L]). Levels should be obtained with patients not taking H2 -receptor antagonists for 24 hours or proton pump inhibitors for 6 days. Withdrawal of the proton pump inhibitor may be accompanied by massive gastric hypersecretion with serious consequences and should be closely monitored. The median gastrin level is 500–700 pg/mL (500–700 ng/L), and 60% of patients have

levels less than 1000 pg/mL (1000 ng/L). Hypochlorhydria with increased gastric pH is a much more common cause of hypergastrinemia than is gastrinoma. Therefore, a measurement of gastric pH (and, where available, gastric secretory studies) is performed in patients with fasting hypergastrinemia. Most patients have a basal acid output of over 15 mEq/h. A gastric pH of greater than 3.0 implies hypochlorhydria and excludes gastrinoma. In a patient with a serum gastrin level of greater than 1000 pg/mL (1000 ng/L) and acid hypersecretion, the diagnosis of Zollinger-Ellison syndrome is established. With lower gastrin levels (150–1000 pg/mL [150–1000 ng/L]) and acid secretion, a secretin stimulation test may be performed to distinguish Zollinger-Ellison syndrome from other causes of hypergastrinemia. Intravenous secretin (2 units/kg) produces a rise in serum gastrin of over 200 pg/mL (200 ng/L) within 2–30 minutes in 85% of patients with gastrinoma. An elevated serum calcium suggests hyperparathyroidism and MEN 1 syndrome. In all patients with Zollinger-Ellison syndrome, a serum parathyroid hormone (PTH), prolactin, luteinizing hormone-follicle-stimulating hormone (LH-FSH), and growth hormone (GH) level should be obtained to exclude MEN 1.

C. Imaging

Imaging studies are obtained in an attempt to determine whether there is metastatic disease and, if not, to identify the site of the primary tumor. CT and MRI scans are commonly obtained first to look for large hepatic metastases and primary lesions, but they have low sensitivity for small lesions. Gastrinomas express somatostatin receptors that bind radiolabeled octreotide. Somatostatin receptor scintigraphy (SRS) with single photon emission computed tomography (SPECT) allows total body imaging for detection of primary gastrinomas in the pancreas and lymph nodes, primary gastrinomas in unusual locations, and metastatic gastrinomas (liver and bone). The 80% sensitivity for tumor detection of SRS exceeds all other imaging studies combined. If SRS is positive for tumor localization, further imaging studies are not necessary. In patients with negative SRS, endoscopic ultrasonography (EUS) may be useful to detect small gastrinomas in the duodenal wall, pancreas, or peripancreatic lymph nodes. With a combination of SRS and EUS, more than 90% of primary gastrinomas can be localized preoperatively.

Differential Diagnosis

Gastrinomas are one of several gut neuroendocrine tumors that have similar histopathologic features and arise either from the gut or pancreas. These include carcinoid, insulinoma, VIPoma, glucagonoma, and somatostatinoma. These tumors usually are differentiated by the gut peptides that they secrete; however, poorly differentiated neuroendocrine tumors may not secrete any hormones. Patients may present with symptoms caused by tumor metastases (jaundice, hepatomegaly) rather than functional symptoms. Once a diagnosis of a neuroendocrine tumor is established from the liver biopsy, the specific type of tumor can subsequently be determined. Both carcinoid and gastrinoma tumors may be detected incidentally during endoscopy after biopsy of a submucosal nodule and must be distinguished by subsequent studies. Hypergastrinemia due to gastrinoma must be distinguished

from other causes of hypergastrinemia. Atrophic gastritis with decreased acid secretion is detected by gastric secretory analysis. Other conditions associated with hypergastrinemia (eg, gastric outlet obstruction, vagotomy, chronic kidney disease) are associated with a negative secretin stimulation test.

Treatment

A. Metastatic Disease

The most important predictor of survival is the presence of hepatic metastases. In patients with multiple hepatic metastases, initial therapy should be directed at controlling hypersecretion. Oral proton pump inhibitors (omeprazole, esomeprazole, rabeprazole, pantoprazole, or lansoprazole) are given at a dose of 40–120 mg/day, titrated to achieve a basal acid output of less than 10 mEq/h. At this level, there is complete symptomatic relief and ulcer healing. Owing to the slow growth of these tumors, 30% of patients with hepatic metastases have a survival of 10 years.

B. Localized Disease

Cure can be achieved only if the gastrinoma can be resected before hepatic metastatic spread has occurred. Lymph node metastases do not adversely affect prognosis. Laparotomy should be considered in all patients in whom preoperative studies fail to demonstrate hepatic or other distant metastases. A combination of preoperative studies, duodenotomy with careful duodenal inspection, and intraoperative palpation and sonography allows successful localization and resection in the majority of cases. The 15-year survival of patients who do not have liver metastases at initial presentation is over 95%. Surgery usually is not recommended in patients with MEN 1 due to the presence of multifocal tumors and long-term survival in the absence of surgery in most patients.

Control questions

1. Anatomical and physiological features of the esophagus and stomach
2. Disorders of evacuation and motor functions of the stomach
3. Methods of study of the esophagus (physical, laboratory and instrumental).
4. Methods of study of the stomach (physical, laboratory and instrumental).
5. Review, palpation, percussion, auscultation of the stomach.
6. Gastroesophageal reflux disease (GERD): classification, principles of treatment.
7. Acute catarrhal gastritis - etiology, pathogenesis, clinical picture, principles of treatment.
8. Acute fibrinous gastritis - etiology, pathogenesis, clinical picture, complications, principles of treatment.
9. Acute phlegmonous gastritis - etiology, pathogenesis, clinical picture, complications, principles of treatment.
10. Chronic gastritis of type A - etiology, pathogenesis, pharmacotherapy.

11. Chronic gastritis type B - etiology, pathogenesis, clinical picture, pharmacotherapy.

12. Stomach ulcer - etiology, pathogenesis, clinical picture, complications, principles of treatment.

13. Diseases of the duodenal ulcer - etiology, pathogenesis, clinical picture, complications, principles of treatment.

14. Complications of peptic ulcer - penetration, malignancy, breakthrough (perforation), bleeding, stenosis.

15. Major groups of drugs used to treat peptic ulcer disease.

16. The role of pharmacist in the prevention of complications of pharmacotherapy of diseases of the digestive system.

17. To write in the recipes, write the indications for use for the following drugs: almagel, maalox, gastrocepin, de-nal, omeprazole, ranitidine, famotidine, metronidazole, clarithromycin, amoxicillin.

List of practical works

A. Homework.

1. To study the anatomical and physiological features of the gastrointestinal tract.

2. To know the classification and clinic of diseases of the esophagus and stomach.

3. To study the main directions of treatment of gastroesophageal reflux disease (GERD).

4. To be able to provide first aid to a patient with complications of peptic ulcer disease.

B. Independent practical work at the lesson.

1. Kurakia thematic patient in the ward.

2. To study the history of the disease (data of laboratory and instrumental studies, examination of consultants, records of the attending physician) and the letter of medical appointments.

3. At examination of the patient to allocate subjective, physical, laboratory-instrumental signs of diseases of the esophagus and stomach.

4. Write a clinical diagnosis:

5. a) the underlying disease; complications of the underlying disease;

6. b) concomitant diseases.

7. Determine a group of lesions necessary for correction of existing disorders.

8. On the basis of theoretical data and own observations, to make a choice of the specific drug of the examined patient.

9. To substantiate the duration of basic and supportive therapy.

10. To draw up an urgent medical plan for acute pain syndrome and for exacerbation of peptic ulcer disease.

Control the level of knowledge

1. Fill in the table "Types of Endoscopic Fiber Fiber Research".

Types of endoscopy	Characteristic of the method, object of research	Diagnostic value
1. Esophagoscopy 2. Gastroscopy 3. Duodenoscopy 4. Colonoscopy		

2. Fill out the table "Pharmacotherapy for chronic gastritis type A".

Direction of pharmacotherapy	Groups of medicines	Drugs, dose, route of administration
1. Effects on the modified mucous membrane 2. Correction of violations of gastric secretion 3. Vitamin therapy 4. Mineral waters		

3. Fill in the table "Medicines for the treatment of chronic gastritis type B."

Groups of medicines	Medicines	Dose, route of administration
1. Medicines for the eradication of Helicobacter pylori 2. Antacids 3.Prokinetics 4. Antisecretory drugs		

4. "Directions of pharmacotherapy of chronic gastritis":

Direction of pharmacotherapy	Groups of medicines
Influence on the mucous membrane of the stomach: Correction of gastric secretion disorders. Correction of violations of the motor function of the stomach. Eradication of Helicobacter pylori.	

5. "Pharmacotherapy of stomach ulcer and 12-gullet":

Groups of medicines	Medicines
A. BASIC MEDICINE I. Antisecretory drugs: 1. Anticholinergics Blockers of H2-histamine receptors Proton "pump" locks Antacids II Gastro-cytoprotectors: Stimulants of mucus formation Creating a protective film Enveloping and binding agents III Anti-chicken antibodies: Antibiotics Antiprotozoal drugs **B. ADDITIONAL MEDICINAL PRODUCTS** IV. Tools that stimulate reparative processes - repatriates V. Means that affect the motor function of the stomach and duodenum: 1. Gastrokinetes 2. Spasmolytics	

Solution of situational tasks

1. A patient 26 years old, entered the therapeutic department with a diagnosis of exacerbation of peptic ulcer disease of 12 gastroesophagitis with severe pain and dyspeptic syndrome. In the complex therapy to the patient prescribed atropine 0,1% solution of 0.5 ml subcutaneously 2 times a day. A week later, pain and heartburn significantly decreased, with dry mouth, nose, and somewhat worse eyesight.

Give an assessment of the pharmacodynamics of atropine. What is the further tactics of using this drug?

2. The patient, 32 years old, was admitted to treatment with a diagnosis: a peptic ulcer with localization of an ulcer in the 12th-small intestine bulb. In the functional study of gastric contents, increased stomach secretion (basal and stimulated), high levels of acidity. When endoscopy - the presence of chronic ulcers with a bleeding vessel.

Determine effective drugs for the treatment of this disease, their dose, time and multiplicity of administration, duration of treatment.

3. A patient 43 years old, is being treated at the gastroenterological department for the exacerbation of ulcerous disease of the 12 gastrointestinal tract. In the study, a moderate increase in the acidity of the gastric contents, the presence of H. pylori.

Conduct the choice of the preparation or drugs that cause scarring of the ulcer of the 12th gastrointestinal tract, indicate their effective dose, time and multiplicity of treatments, duration of treatment.

4. A patient 48 years old, an engineer, on the nature of work is often on business trips, turned to a clinic for an exacerbation of chronic gastritis. Worried about pain in the epigastric area after taking food, reducing appetite, biting with the smell of eaten food. In the study of gastric juice decreased the secretory function of the stomach, with fibrogastroskopy - signs of moderate atrophic process in the mucous membrane of the stomach. The physician of the patient is assigned a dissolved hydrochloric acid with pepsin in combination with pancreatin. After 2 weeks, the patient's condition improved significantly; from the complaints there was a sense of severity in the epigastric region after eating. In the future, the patient is recommended to continue to receive only dissolved hydrochloric acid during meals while observing the diet.

Explain the purpose of the appointment of these drugs at the first stage of treatment of the patient. Explain further tactics of the treating physician in relation to this patient.

5. A child, 10 years old, delivered ambulance to the hospital for acute poisoning with an acetic essence. The doctor subcutaneously injected 0.1 ml of a 1% solution of apomorphine hydrochloride, rinse the stomach with 0.5% tannin solution and injected into the stomach through the probe 10 g of activated charcoal. However, the condition of the patient soon deteriorated sharply, there were symptoms of peritonitis and progressive acidosis.

Describe the doctor's tactics and make adjustments to her.

6. The surgical department is delivered to the patient 42 years with gastrointestinal bleeding. During an endoscopic examination, an acute stomach ulcer was detected. In the history of: rheumatoid arthritis. Pharmacotherapy for arthritis was carried out.

Which drug caused the development of stomach ulcers and bleeding.

7. A man who suffers from a stomach ulcer of 12 gastrointestinal tract, the doctor prescribed an antacid drug. On the background of taking the drug appeared nausea and abdominal pain. The examination revealed violations of the acid-base balance in the direction of alkalosis.

What drug could cause this violation?

8. The patient is 21 years old, has acted with complaints of heartburn, pain in the epigastric region of the onset heart. At EGDFS an ulcer was detected along the anterior wall of the bulb of the duodenum. PH meter of gastric juice: acid-forming function of medium intensity with low alkaline reserves, cholinergic type of recipe.

Assign the most effective medication.

9. To you in the pharmacy the patient turned to the first signs of exacerbation of ulcer duodenum ("hungry" pain in the epigastrium, heartburn).

Your recommendations in this case. Write recipes for the proposed medicines.

10. A patient with ulcers of the duodenum with recipes for vicinal and almagel turned to you at the pharmacy. From anamnesis, you discovered that he had a Helicobacter pylori with fibrogastroduodenoscopy.

Your opinion about treatment tactics. Your recommendations. Prescribe recipes for missing drugs.

11. Sick Z., 27 years old, complains of a strong pressing pain in the epigastrium, closer to the median line, which occurs regularly between 24 and 3 hours, decreases after taking soda. A slight pain occurs there, after 1.5 - 2 hours after eating. The pain is accompanied by heartburn. These symptoms disturb the patient for about 15 days. Objectively: pronounced pain in the epigastrium with palpation.

Your previous diagnosis. Recommendations on therapy tactics. Type recipes.

12. A patient who entered the pharmacy complains of severe abdominal pain that arose suddenly after physical exertion, nausea, vomiting with a "vein of coffee", dizziness, general weakness. The patient is pale, covered with cold sticky sweat.

What could be the cause of this state? What is the precautionary tactic?

13. From the three treatment regimens below, choose the most appropriate treatment for chronic gastritis type A (I), chronic gastritis type A in combination with chronic pancreatitis (II), and for the treatment of patients with chronic gastritis type B (III):

- Omeprazole 20 mg 2 times a day, metronidazole 250 mg 4 times a day, clarithromycin 1000 mg 2 times daily;
- Acidine-pepsin 1 tab. 3 times a day, plantaglycid 1.0 g 3 times a day, pancreatin 1 tab. 3 times a day;

- De-nol 1 tab. 4 times a day, pepsidil 1 tablespoon 3 times a day, but-shpa 1 tab. 3 times a day.

Answer substantiate.

Test tasks

1. The use of motilium in chronic gastritis is an example:
1.Medicinal therapy.
2.Ethiological therapy.
3.Pathogenetic therapy.
4.Symptomatic therapy.
5. Antifermental therapy.

2. What is the main principle of therapy for chronic gastritis type A:
1. Complete substitution therapy (vitamins, hydrochloric acid, enzymes)
2. Antibacterial therapy directed against Helicobacter pylori and inflammation treatment
3. Application of means reducing the acidity, inhibitors of enzymes
4. Antioxidant therapy
5. Antianginal therapy.

3. What is the main principle of therapy for chronic gastritis type B:
1. Complete substitution therapy (vitamins, hydrochloric acid, enzymes)
2. Antibacterial therapy directed against Helicobacter pylori and inflammation treatment
3. Application of means reducing the acidity, inhibitors of enzymes
4. Antioxidant therapy
5. Antianginal therapy.

4. From the aforementioned anti-ulcer drugs, select medications for the eradication of Helicobacter pylori:
1.Malox.
2. Cimetidine.
3. Gastrotrazine.
4. Metronidazole.
5. Almagel.

5. From the following, select the H2-histamine receptor blocker.
1.Ranitidine.
2.De-nol
3. Suprastin.
4. No-sha
5. Omeprazole.

6. From the antibacterial agents listed below, select the means for the eradication of Helicobacter pylori:
1. Sulfadimezin
2. Penicillin.
3. Norfloxacin.
4. Clarithromycin.
5. Biseptol.

7. In order to accelerate the regeneration of the mucous membrane of the stomach appoint:
1.Almagel
2. Ranitidine.
3. Cerukal.
4. Venter.
5. Gastrotrazine.

8. From the three following treatment regimens, choose the most appropriate type A for chronic gastritis:
1 - de-nol 2 tables. 2 times a day, metronidazole 0.25 g 4 times a day, amoxicillin 500 mg 2 times daily intravenously
2 - natural gastric juice for 15 drops after meals, plantaglycid 1.0 3 times a day, motilium 1 tab. 2 times a day
3 - de-nol 1 tabl. 4 times a day, pepsidil 1 tbsp. l 3 times a day, gastrocepin 0.05 g 2 times a day

9. In a patient with chronic gastritis type A, chronic pancreatitis. Choose the most rational treatment scheme:
1 - De-nol 2 tables. 2 times a day, metronidazole 0.25 g 4 times a day, venter 1 tabl. 2 times a day
2.- Acidine-pepsin 1 tab. 3 p / d, cream 1 capsule while eating, plantaglycid 1.0 g 3 g/d
3 - De-nol 1 tabl. 4 times a day, pepsidil 1 tablespoon 3 times a day, gastrocepin 0.05 g 2 times a day

10. From the following diagrams, choose the most appropriate treatment for chronic gastritis type B:
1 - omeprazole 1 tablet. 2 g / d, metronidazole 0.25 g 4 times daily, clarithromycin 0.25 g 4 g/day
2 - acidine-pepsin 1 tab. 3 p / d, plantaglucid 1.0 g 3 times a day, festal 1 tab. 3 times a day
3 - de-nol 1 tabl. 4 times a day, pepsidil 1 tablespoon 3 times a day, gastrocepin 0.05 g 2 times a day

11. In the treatment of peptic ulcer drugs that reduce the acidity of gastric juice, it is advisable to appoint:

1. After food.
2. Immediately after eating.
3. Regardless of meal every three hours.
4. For 15-30 minutes before eating.
5. After 1 hour after eating.

12. In patients with ulcerous stomach and 12-digestive system receiving non-systemic antacids:
1. Shown only during the period of exacerbation.
2. Shows continued.
3. Indicated continuously before eating.
4. Indicated prophylactically in the autumn-spring period.
5.Shown continuously after meals.

DISEASES OF THE SMALL INTESTINE
MALABSORPTION

The term “malabsorption” denotes disorders in which there is a disruption of digestion and nutrient absorption.

Celiac Disease

ESSENTIALS OF DIAGNOSIS

- Typical symptoms: weight loss, chronic diarrhea, abdominal distention, growth retardation.
- Atypical symptoms: dermatitis herpetiformis, iron deficiency anemia, osteoporosis.
- Abnormal serologic test results.
- Abnormal small bowel biopsy.
- Clinical improvement on gluten-free diet.

General Considerations

Celiac disease (also called sprue, celiac sprue, and gluten enteropathy) is a permanent dietary disorder caused by an immunologic response to gluten, a storage protein found in certain grains, that results in diffuse damage to the proximal small intestinal mucosa with malabsorption of nutrients. Although symptoms may manifest between 6 months and 24 months of age after the introduction of weaning foods, the majority of cases present in childhood or adulthood. Population screening with serologic tests suggests that the disease is present in 1:100 whites of Northern European ancestry, in whom a clinical diagnosis of celiac disease is made in only 10%, suggesting that most cases are undiagnosed or asymptomatic. Celiac disease only develops in people with the HLA-DQ2 (95%) or -DQ8 (5%) class II molecules, which are present in 40% of the population. Although the precise pathogenesis is unclear, celiac disease arises in a small subset of genetically susceptible (-DQ2 or -DQ8) individuals when dietary gluten stimulates an inappropriate immunologic response.

Clinical Findings

The most important step in diagnosing celiac disease is to consider the diagnosis. Symptoms are present for more than 10 years in most adults before the correct diagnosis is established. Because of its protean manifestations, celiac disease is grossly underdiagnosed in the adult population.

A. Symptoms and Signs

The gastrointestinal symptoms and signs of celiac disease depend on the length of small intestine involved and the patient's age when the disease presents. "Classic" symptoms of malabsorption, including diarrhea, steatorrhea, weight loss, abdominal distention, weakness, muscle wasting, or growth retardation, more commonly present in infants (younger than 2 years). Older children and adults are less likely to manifest signs of serious malabsorption. They may report chronic diarrhea, dyspepsia, or flatulence due to colonic bacterial digestion of malabsorbed nutrients, but the severity of weight loss is variable. Many adults have minimal or no gastrointestinal symptoms but present with extraintestinal "atypical" manifestations, including fatigue, depression, iron deficiency anemia, osteoporosis, short stature, delayed puberty, amenorrhea, or reduced fertility. Approximately 40% of patients with positive serologic tests consistent with sprue have no symptoms of disease; the natural history of these patients with "silent" sprue is unclear.

Physical examination may be normal in mild cases or may reveal signs of malabsorption such as loss of muscle mass or subcutaneous fat, pallor due to anemia, easy bruising due to vitamin K deficiency, hyperkeratosis due to vitamin A deficiency, bone pain due to osteomalacia, or neurologic signs (peripheral neuropathy, ataxia) due to vitamin B12 or vitamin E deficiency. Abdominal examination may reveal distention with hyperactive bowel sounds.

Dermatitis herpetiformis is regarded as a cutaneous variant of celiac disease. It is a characteristic skin rash consisting of pruritic papulovesicles over the extensor surfaces of the extremities and over the trunk, scalp, and neck. Dermatitis herpetiformis occurs in less than 10% of patients with celiac disease; however, almost all patients who present with dermatitis herpetiformis have evidence of celiac disease on intestinal mucosal biopsy, though it may not be clinically evident.

B. Laboratory Findings

1. Routine laboratory tests—Depending on the severity of illness and the extent of intestinal involvement, nonspecific laboratory abnormalities may be present that may raise the suspicion of malabsorption and celiac disease. Limited proximal involvement may result only in microcytic anemia due to iron deficiency. Up to 5% of adults with iron deficiency not due to gastrointestinal blood loss have undiagnosed celiac disease. More extensive involvement results in a megaloblastic anemia due to folate or vitamin B12 deficiency. Low serum calcium or elevated alkaline phosphatase may reflect impaired calcium or vitamin D absorption with osteomalacia or osteoporosis. Dual-energy x-ray densitometry scanning is recommended for all patients with sprue to screen for osteoporosis. Elevations of prothrombin time, or decreased vitamin A or D levels reflect impaired fat-soluble

vitamin absorption. A low serum albumin may reflect small intestine protein loss or poor nutrition. Severe diarrhea may result in a nonanion gap acidosis and hypokalemia. Mild elevations of aminotransferases are found in up to 40%.

2. Serologic tests—Serologic tests should be performed in all patients in whom there is a suspicion of celiac disease. The recommended test is the IgA tissue transglutaminase (IgA tTG) antibody, which has a 95% sensitivity and 95% specificity for the diagnosis of celiac disease. Antigliadin antibodies are not recommended because of their lower sensitivity and specificity. IgA antiendomysial antibodies are no longer recommended due to the lack of standardization among laboratories. An IgA level should be obtained in patients with a negative IgA tTG antibody when celiac disease is strongly suspected because up to 3% of patients with celiac disease have IgA deficiency. A test that measures IgG antibodies to deamidated gliadin has excellent sensitivity and specificity and is useful in patients with IgA deficiency and young children. Levels of all antibodies become undetectable after 3–12 months of dietary gluten withdrawal and may be used to monitor dietary compliance, especially in patients whose symptoms fail to resolve after institution of a gluten-free diet.

C. Mucosal Biopsy

Endoscopic mucosal biopsy of the proximal duodenum (bulb) and distal duodenum is the standard method for confirmation of the diagnosis in patients with a positive serologic test for celiac disease. Mucosal biopsy should also be pursued in patients with negative serologies when symptoms and laboratory studies are strongly suggestive of celiac disease. At endoscopy, atrophy or scalloping of the duodenal folds may be observed. Histology reveals abnormalities ranging from intraepithelial lymphocytosis alone to extensive infiltration of the lamina propria with lymphocytes and plasma cells with hypertrophy of the intestinal crypts and blunting or complete loss of intestinal villi. An adequate normal biopsy excludes the diagnosis. Partial or complete reversion of these abnormalities occurs within 3–24 months after a patient is placed on a gluten-free diet, but symptom resolution remains incomplete in 50% of patients. If a patient with a compatible biopsy demonstrates prompt clinical improvement on a gluten-free diet and a decrease in antigliadin antibodies, a repeat biopsy is unnecessary.

Differential Diagnosis

Many patients with chronic diarrhea or flatulence are erroneously diagnosed as having irritable bowel syndrome. Celiac sprue must be distinguished from other causes of malabsorption, as outlined above. Severe panmalabsorption of multiple nutrients is almost always caused by mucosal disease. The histologic appearance of celiac sprue may resemble other mucosal diseases such as tropical sprue, bacterial overgrowth, cow’s milk intolerance, viral gastroenteritis, eosinophilic gastroenteritis, and mucosal damage caused by acid hypersecretion associated with gastrinoma. Documentation of clinical response to gluten withdrawal therefore is essential to the diagnosis.

Some patients complain of symptoms after gluten ingestion but do not have

serologic or histologic evidence of celiac disease. The frequency and cause of this entity is debated. A large 2013 study found that symptoms improved in gluten-sensitive patients when placed on a FODMAPrestricted diet and worsened to similar degrees when challenged in a double-blind crossover trial with gluten or whey proteins. These data suggest that nonceliac gluten sensitivity may not be a true entity and that the symptom improvement reported by patients with gluten restriction may be due to broader FODMAP elimination.

Treatment

Removal of all gluten from the diet is essential to therapy— all wheat, rye, and barley must be eliminated. Although oats appear to be safe for many patients, commercial products may be contaminated with wheat or barley during processing. Because of the pervasive use of gluten products in manufactured foods and additives, in medications, and by restaurants, it is imperative that patients and their families confer with a knowledgeable dietitian to comply satisfactorily with this lifelong diet. Several excellent dietary guides and patient support groups are available. Most patients with celiac disease also have lactose intolerance either temporarily or permanently and should avoid dairy products until the intestinal symptoms have improved on the glutenfree diet. Dietary supplements (folate, iron, calcium, and vitamins A, B12, D, and E) should be provided in the initial stages of therapy but usually are not required long-term with a gluten-free diet. Patients with confirmed osteoporosis may require long-term calcium, vitamin D, and bisphosphonate therapy.

Improvement in symptoms should be evident within a few weeks on the gluten-free diet. The most common reason for treatment failure is incomplete removal of gluten. Intentional or unintentional rechallenge with gluten may trigger acute severe diarrhea with dehydration, electrolyte imbalance, and may require TPN and intravenous or oral corticosteroids (prednisone 40 mg or budesonide 9 mg) for 2 or more weeks as a gluten-free diet is re-initiated

Prognosis & Complications

If appropriately diagnosed and treated, patients with celiac disease have an excellent prognosis. Celiac disease may be associated with other autoimmune disorders, including Addison disease, Graves disease, type 1 diabetes mellitus, myasthenia gravis, scleroderma, Sjögren syndrome, atrophic gastritis, and pancreatic insufficiency. In some patients, celiac disease may evolve and become refractory to the gluten-free diet. The most common cause is intentional or unintentional dietary noncompliance, which may be suggested by positive serologic tests. Celiac disease that is truly refractory to gluten withdrawal occurs in less than 5% and generally carries a poor prognosis. There are two types of refractory disease, which are distinguished by their intraepithelial lymphocyte phenotype. This diagnosis should be considered in patients previously responsive to the gluten-free diet in whom new weight loss, abdominal pain, and malabsorption develop.

Whipple Disease

ESSENTIALS OF DIAGNOSIS

- Multisystem disease.
- Fever, lymphadenopathy, arthralgias. » Weight loss, malabsorption, chronic diarrhea.
- Duodenal biopsy with periodic acid-Schiff (PAS)- positive macrophages with characteristic bacillus.

General Considerations

Whipple disease is a rare multisystem illness caused by infection with the bacillus Tropheryma whippelii. It may occur at any age but most commonly affects white men in the fourth to sixth decades. The source of infection is unknown, but no cases of human-to-human spread have been documented.

Clinical Findings

Symptoms and Signs

The clinical manifestations are protean; however, the most common are arthralgias, diarrhea, abdominal pain, and weight loss. Arthralgias or a migratory, nondeforming arthritis occurs in 80% and is typically the first symptom experienced. Gastrointestinal symptoms occur in approximately 75% of cases. They include abdominal pain, diarrhea, and some degree of malabsorption with distention, flatulence, and steatorrhea. Weight loss is the most common presenting symptom—seen in almost all patients. Loss of protein due to intestinal or lymphatic involvement may result in protein-losing enteropathy with hypoalbuminemia and edema. In the absence of gastrointestinal symptoms, the diagnosis often is delayed for several years. Intermittent low-grade fever occurs in over 50% of cases.

Physical examination may reveal hypotension (a late finding), low-grade fever, and evidence of malabsorption. Lymphadenopathy is present in 50%. Heart murmurs due to valvular involvement may be evident. Peripheral joints may be enlarged or warm, and peripheral edema may be present. Neurologic findings are cited above. Hyperpigmentation on sun-exposed areas is evident in up to 40%.

Histologic Evaluation

In most cases, the diagnosis of Whipple disease is established by endoscopic biopsy of the duodenum with histologic evaluation, which demonstrates infiltration of the lamina propria with PAS-positive macrophages that contain grampositive bacilli (which are not acid-fast) and dilation of the lacteals. Because the PAS stain is less sensitive and specific for extraintestinal Whipple disease, polymerase chain reaction (PCR) is used to confirm the diagnosis. Because asymptomatic central nervous system infection occurs in 40% of patients, examination of the cerebrospinal fluid by PCR for T whippelii should be performed routinely. The sensitivity of PCR is 97% and the specificity 100%.

Differential Diagnosis

Whipple disease should be considered in patients who present with signs of

malabsorption, fever of unknown origin, lymphadenopathy, seronegative arthritis, culturenegative endocarditis, or multisystem disease. Small bowel biopsy readily distinguishes Whipple disease from other mucosal malabsorptive disorders, such as celiac sprue.

Treatment

Antibiotic therapy results in a dramatic clinical improvement within several weeks, even in some patients with neurologic involvement. The optimal regimen is unknown. Complete clinical response usually is evident within 1–3 months; however, relapse may occur in up to one-third of patients after discontinuation of treatment. Therefore, prolonged treatment for at least 1 year is required. Drugs that cross the blood-brain barrier are preferred. A randomized controlled trial in 40 patients with 3–10 years follow-up demonstrated 100% remission with either ceftriaxone 1 g intravenously twice daily or meropenem 1 g intravenously three times daily for 2 weeks, followed by trimethoprim-sulfamethoxazole 160/800 mg twice daily for 12 months. After treatment, repeat duodenal biopsies for histologic analysis and cerebrospinal fluid PCR should be obtained every 6 months for at least 1 year. The absence of PAS-positive material predicts a low likelihood of clinical relapse.

Prognosis

If untreated, the disease is fatal. Because some neurologic signs may be permanent, the goal of treatment is to prevent this progression. Patients must be followed closely after treatment for signs of symptom recurrence.

Short Bowel Syndrome

Short bowel syndrome is the malabsorptive condition that arises secondary to removal of significant segments of the small intestine. The most common causes in adults are Crohn disease, mesenteric infarction, radiation enteritis, volvulus, tumor resection, and trauma. The type and degree of malabsorption depend on the length and site of the resection and the degree of adaptation of the remaining bowel.

Terminal Ileal Resection

Resection of the terminal ileum results in malabsorption of bile salts and vitamin B12, which are normally absorbed in this region. Patients with low serum vitamin B12 levels or resection of over 50 cm of ileum require monthly subcutaneous or intramuscular vitamin B12 injections. In patients with less than 100 cm of ileal resection, bile salt malabsorption stimulates fluid secretion from the colon, resulting in watery diarrhea. This may be treated with bile salt-binding resins (colestipol or cholestyramine, 2–4 g orally three times daily with meals or colesevelam, 625 mg, 1–3 tablets twice daily). Resection of over 100 cm of ileum leads to a reduction in the bile salt pool that results in steatorrhea and malabsorption of fat-soluble vitamins. Treatment is with a low-fat diet and vitamins supplemented with medium-chain triglycerides, which do not require micellar solubilization. Unabsorbed fatty acids bind with calcium, reducing its absorption and enhancing

the absorption of oxalate. Oxalate kidney stones may develop. Calcium supplements should be administered to bind oxalate and increase serum calcium. Cholesterol gallstones due to decreased bile salts are common also. In patients with resection of the ileocolonic valve, bacterial overgrowth may occur in the small intestine, further complicating malabsorption (as outlined above).

Extensive Small Bowel Resection

Resection of up to 40–50% of the total length of small intestine usually is well tolerated. A more massive resection may result in "short-bowel syndrome," characterized by weight loss and diarrhea due to nutrient, water, and electrolyte malabsorption. If the colon is preserved, 100 cm of proximal jejunum may be sufficient to maintain adequate oral nutrition with a low-fat, high complex-carbohydrate diet, though fluid and electrolyte losses may still be significant. In patients in whom the colon has been removed, at least 200 cm of proximal jejunum is typically required to maintain oral nutrition. Antidiarrheal agents (loperamide, 2–4 mg orally three times daily) slow transit and reduce diarrheal volume. Octreotide reduces intestinal transit time and fluid and electrolyte secretion. Gastric hypersecretion initially complicates intestinal resection and should be treated with proton pump inhibitors. Patients with less than 100–200 cm of proximal jejunum remaining almost always require parenteral nutrition. Teduglutide is a glucagon-like peptide-2 analogue that stimulates small bowel growth and absorption and is FDA approved for the treatment of short-bowel syndrome. In clinical trials, it resulted in a reduced need for parenteral nutrition. Small intestine transplantation is now being performed with reported 5-year graft survival rates of 40%. Currently, it is performed chiefly in patients in whom serious problems develop due to parenteral nutrition.

INTESTINAL TUBERCULOSIS

Intestinal tuberculosis is common in underdeveloped countries. Previously rare in the United States, its incidence has been rising in immigrant groups and patients with AIDS. It is caused by both Mycobacterium tuberculosis and M bovis. Active pulmonary disease is present in less than 50% of patients. The most frequent site of involvement is the ileocecal region; however, any region of the gastrointestinal tract may be involved. Intestinal tuberculosis may cause mucosal ulcerations or scarring and fibrosis with narrowing of the lumen. Patients may be without symptoms or complain of chronic abdominal pain, obstructive symptoms, weight loss, and diarrhea. An abdominal mass may be palpable. Complications include intestinal obstruction, hemorrhage, and fistula formation. The purified protein derivative (PPD) skin test may be negative, especially in patients with weight loss or AIDS. Barium radiography may demonstrate mucosal ulcerations, thickening, or stricture formation. Abdominal CT may show thickening of the cecum and ileocecal valve and massive lymphadenopathy. Colonoscopy may demonstrate an ulcerated mass, multiple ulcers with steep edges and adjacent small sessile polyps, small ulcers or erosions, or small diverticula, most commonly in the ileocecal region. The differential diagnosis includes Crohn disease, carcinoma, and

intestinal amebiasis. The diagnosis is established by either endoscopic or surgical biopsy revealing acid-fast bacilli, caseating granuloma, or positive cultures from the organism. Detection of tubercle bacilli in biopsy specimens by PCR is now the most sensitive means of diagnosis. Treatment with standard antituberculous regimens is effective.

DISEASES OF THE COLON & RECTUM

IRRITABLE BOWEL SYNDROME

ESSENTIALS OF DIAGNOSIS

- Chronic functional disorder characterized by abdominal pain or discomfort with alterations in bowel habits.
- Symptoms usually begin in late teens to early twenties.
- Limited evaluation to exclude organic causes of symptoms.

General Considerations

The functional gastrointestinal disorders are characterized by a variable combination of chronic or recurrent gastrointestinal symptoms not explicable by the presence of structural or biochemical abnormalities. Several clinical entities are included under this broad rubric, including chest pain of unclear origin (noncardiac chest pain), functional dyspepsia, and biliary dyskinesia (sphincter of Oddi dysfunction). There is a large overlap among these entities. For example, over 50% of patients with noncardiac chest pain and over one-third with functional dyspepsia also have symptoms compatible with irritable bowel syndrome. In none of these disorders is there a definitive diagnostic study. Rather, the diagnosis is a subjective one based on the presence of a compatible profile and the exclusion of similar disorders. Irritable bowel syndrome can be defined, therefore, as an idiopathic clinical entity characterized by chronic (more than 6 months) abdominal pain or discomfort that occurs in association with altered bowel habits. These symptoms may be continuous or intermittent. Consensus definition of irritable bowel syndrome is abdominal discomfort or pain that has two of the following three features: (1) relieved with defecation, (2) onset associated with a change in frequency of stool, or (3) onset associated with a change in form (appearance) of stool. Other symptoms supporting the diagnosis include abnormal stool frequency; abnormal stool form (lumpy or hard; loose or watery); abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); passage of mucus; and bloating or a feeling of abdominal distention. Patients may have other somatic or psychological complaints such as dyspepsia, heartburn, chest pain, headaches, fatigue, myalgias, urologic dysfunction, gynecologic symptoms, anxiety, or depression. The disorder is a common problem presenting to both gastroenterologists and primary care physicians. Up to 10% of the adult population have symptoms compatible with the diagnosis, but most never seek medical attention. Approximately two-thirds of patients with irritable bowel syndrome are women.

Pathogenesis

A number of pathophysiologic mechanisms have been identified and may

have varying importance in different individuals.

A. Abnormal Motility

A variety of abnormal myoelectrical and motor abnormalities have been identified in the colon and small intestine. In some cases, these are temporally correlated with episodes of abdominal pain or emotional stress. Whether they represent a primary motility disorder or are secondary to psychosocial stress is debated. Differences between patients with constipation-predominant and diarrhea-predominant syndromes are reported.

B. Visceral Hypersensitivity

Patients often have a lower visceral pain threshold, reporting abdominal pain at lower volumes of colonic gas insufflation or colonic balloon inflation than controls. Many patients complain of bloating and distention, which may be due to a number of different factors including increased visceral sensitivity, increased gas production (due to small bowel bacterial overgrowth or carbohydrate malabsorption), impaired gas transit through the intestine, or impaired rectal expulsion. Many patients report rectal urgency despite small rectal volumes of stool.

C. Enteric Infection

Symptoms compatible with irritable bowel syndrome develop within 1 year in up to 10% of patients after an episode of bacterial gastroenteritis compared with less than 2% of controls. Women and patients with increased life stressors at the onset of gastroenteritis appear to be at increased risk for developing “postinfectious” irritable bowel syndrome. Increased inflammatory cells have been found in the mucosa, submucosa, and muscularis of some patients with irritable bowel syndrome, but their importance is unclear. Chronic inflammation is postulated by some investigators to contribute to alterations in motility or visceral hypersensitivity.

Some investigators suggest that alterations in the numbers and distribution of bacterial species (estimated 30,000 different species) may affect bowel transit time, gas production, and sensitivity. An increase in breath hydrogen or methane excretion after lactulose ingestion in 65% of patients with irritable bowel syndrome has been reported, believed by some investigators to indicate small intestinal bacterial overgrowth. However, many investigators dispute these findings because overgrowth was confirmed in only 4% of patients using jejunal aspiration and bacterial culture. Small bowel bacterial overgrowth may be more likely in patients with bloating, postprandial discomfort, and loose stools. It is hypothesized that bacterial overgrowth may lead to alterations in immune alterations that affect motility or visceral sensitivity or to degradation of carbohydrates in the small intestine that may cause increased postprandial gas, bloating, and distention.

D. Psychosocial Abnormalities

More than 50% of patients with irritable bowel who seek medical attention

have underlying depression, anxiety, or somatization. By contrast, those who do not seek medical attention are similar psychologically to normal individuals. Psychological abnormalities may influence how the patient perceives or reacts to illness and minor visceral sensations. Chronic stress may alter intestinal motility or modulate pathways that affect central and spinal processing of visceral afferent sensation.

Clinical Findings

A. Symptoms and Signs

Irritable bowel is a chronic condition. Symptoms usually begin in the late teens to twenties. Symptoms should be present for at least 3 months before the diagnosis can be considered. The diagnosis is established in the presence of compatible symptoms and the judicious use of tests to exclude organic disease.

Abdominal pain usually is intermittent, crampy, and in the lower abdominal region. As previously stated, the onset of pain typically is associated with a change in stool frequency or form and commonly is relieved by defecation. It does not usually occur at night or interfere with sleep. Patients with irritable bowel syndrome may be classified into one of three categories based on the predominant bowel habit: irritable bowel syndrome with diarrhea; irritable bowel syndrome with constipation; or irritable bowel syndrome with mixed constipation and diarrhea. It is important to clarify what the patient means by these complaints. Patients with irritable bowel and constipation report infrequent bowel movements (less than three per week), hard or lumpy stools, or straining. Patients with irritable bowel syndrome with diarrhea refer to loose or watery stools, frequent stools (more than three per day), urgency, or fecal incontinence. Many patients report that they have a firm stool in the morning followed by progressively looser movements. Complaints of visible distention and bloating are common, though these are not always clinically evident.

The patient should be asked about “alarm symptoms” that suggest a diagnosis other than irritable bowel syndrome and warrant further investigation. The acute onset of symptoms raises the likelihood of organic disease, especially in patients older than 40–50 years. Nocturnal diarrhea, severe constipation or diarrhea, hematochezia, weight loss, and fever are incompatible with a diagnosis of irritable bowel syndrome and warrant investigation for underlying disease. Patients who have a family history of cancer, inflammatory bowel disease, or celiac disease should undergo additional evaluation.

A physical examination should be performed to look for evidence of organic disease and to allay the patient’s anxieties. The physical examination usually is normal. Abdominal tenderness, especially in the lower abdomen, is common but not pronounced. A new onset of symptoms in a patient over age 40 years warrants further examination.

B. Laboratory Findings and Special Examinations

In patients whose symptoms fulfill the diagnostic criteria for irritable bowel syndrome and who have no other alarm symptoms, evidence-based consensus

guidelines do not support further diagnostic testing, as the likelihood of serious organic diseases does not appear to be increased.

Although the vague nature of symptoms and patient anxiety may prompt clinicians to consider a variety of diagnostic studies, overtesting should be avoided. A 2013 study of primary care patients aged 30–50 years with suspected irritable bowel found that patients randomized to a strategy of extensive testing prior to diagnosis had higher health care costs but similar symptoms and satisfaction at 1 year as patients randomized to a strategy of minimal testing but a positive clinical diagnosis. The use of routine blood tests (complete blood count, chemistry panel, serum albumin, thyroid function tests, erythrocyte sedimentation rate) is unnecessary in most patients. Stool specimen examinations for ova and parasites should be obtained only in patients with increased likelihood of infection (eg, day care workers, campers, foreign travelers). Routine sigmoidoscopy or colonoscopy is not recommended in young patients with symptoms of irritable bowel syndrome without alarm symptoms but should be considered in patients who do not improve with conservative management. In all patients age 50 years or older who have not had a previous evaluation, colonoscopy should be obtained to exclude malignancy. When colonoscopy is performed, random mucosal biopsies should be obtained to look for evidence of microscopic colitis (which may have similar symptoms). In patients with irritable bowel syndrome with diarrhea, serologic tests for celiac disease should be performed. Routine testing for bacterial overgrowth with hydrogen breath tests are not recommended.

Differential Diagnosis

A number of disorders may present with similar symptoms. Examples include colonic neoplasia, inflammatory bowel disease (ulcerative colitis, Crohn disease, microscopic colitis), hyperthyroidism or hypothyroidism, parasites, malabsorption (especially celiac disease, bacterial overgrowth, lactase deficiency), causes of chronic secretory diarrhea (carcinoid), and endometriosis. Psychiatric disorders such as depression, panic disorder, and anxiety must be considered as well. Women with refractory symptoms have an increased incidence of prior sexual and physical abuse. These diagnoses should be excluded in patients with presumed irritable bowel syndrome who do not improve within 2–4 weeks of empiric treatment or in whom subsequent alarm symptoms develop.

Treatment

A. General Measures

As with other functional disorders, the most important interventions the clinician can offer are reassurance, education, and support. This includes identifying and responding to the patient's concerns, careful explanation of the pathophysiology and natural history of the disorder, setting realistic treatment goals, and involving the patient in the treatment process. Because irritable bowel symptoms are chronic, the patient's reasons for seeking consultation at this time should be determined. These may include major life events or recent psychosocial stressors, dietary or medication changes, concerns about serious underlying disease,

or reduced quality of life and impairment of daily activities. In discussing with the patient the importance of the mind-gut interaction, it may be helpful to explain that alterations in visceral motility and sensitivity may be exacerbated by environmental, social, or psychological factors such as foods, medications, hormones, and stress. Symptoms such as pain, bloating, and altered bowel habits may lead to anxiety and distress, which in turn may further exacerbate bowel disturbances due to disordered communication between the gut and the central nervous system. Fears that the symptoms will progress, require surgery, or degenerate into serious illness should be allayed. The patient should understand that irritable bowel syndrome is a chronic disorder characterized by periods of exacerbation and quiescence. The emphasis should be shifted from finding the cause of the symptoms to finding a way to cope with them. Moderate exercise is beneficial. Clinicians must resist the temptation to chase chronic complaints with new or repeated diagnostic studies.

B. Dietary Therapy

Patients commonly report dietary intolerances. Proposed mechanisms for dietary intolerance include food allergy, hypersensitivity, effects of gut hormones, changes in bacterial flora, increased bacterial gas production (arising in the small or large intestine), and direct chemical irritation. Fatty foods and caffeine are poorly tolerated by many patients with irritable bowel syndrome. In patients with diarrhea, bloating, and flatulence, lactose intolerance should be excluded with a hydrogen breath test or a trial of a lactose-free diet. A host of poorly absorbed, fermentable, monosaccharides and short-chain carbohydrates (“FODMAPS”) may exacerbate bloating, flatulence, and diarrhea in some patients. These include fructose (corn syrups, apples, pears, honey, watermelon, raisins), lactose, fructans (garlic, onions, leeks, asparagus, artichokes), wheat-based products (breads, pasta, cereals, cakes), sorbitol (stone fruits), and raffinose (legumes, lentils, brussel sprouts, soybeans, cabbage). Dietary restriction of these fermentable carbohydrates may improve symptoms. A 2014 crossover trial showed that patients experienced a marked reduction in overall symptoms, including bloating, pain, and flatus, while on the low FODMAP diet. A high-fiber diet and fiber supplements appears to be of little value in patients with irritable bowel syndrome. Many patients report little change in bowel frequency but increased gas and distention.

C. Pharmacologic Measures

More than two-thirds of patients with irritable bowel syndrome have mild symptoms that respond readily to education, reassurance, and dietary interventions. Drug therapy should be reserved for patients with moderate to severe symptoms that do not respond to conservative measures. These agents should be viewed as being adjunctive rather than curative. Given the wide spectrum of symptoms, no single agent is expected to provide relief in all or even most patients. Nevertheless, therapy targeted at the specific dominant symptom (pain, constipation, or diarrhea) may be beneficial.

1. Antispasmodic agents—Anticholinergic agents are used by some

practitioners for treatment of acute episodes of pain or bloating despite a lack of well-designed trials demonstrating efficacy. Available agents include hyoscyamine, 0.125 mg orally (or sublingually as needed) or sustained-release, 0.037 mg or 0.75 mg orally twice daily; dicyclomine, 10–20 mg orally; or methscopolamine 2.5–5 mg orally before meals and at bedtime. Anticholinergic side effects are common, including urinary retention, constipation, tachycardia, and dry mouth. Hence, these agents should be used with caution in the elderly and in patients with constipation. Peppermint oil formulations (which relax smooth muscle) may be helpful.

2. Antidiarrheal agents—Loperamide (2 mg orally three or four times daily) is effective for the treatment of patients with diarrhea, reducing stool frequency, liquidity, and urgency. It may best be used "prophylactically" in situations in which diarrhea is anticipated (such as stressful situations) or would be inconvenient (social engagements). Increased intracolonic bile acids due to alterations in enterohepatic circulation may contribute to diarrhea in a subset of patients with diarrhea. An empiric trial of bile salt-binding agents (cholestyramine 2–4 g with meals; colesevelam, 625 mg, 1–3 tablets twice daily) may be considered.

3. Anticonstipation agents—Treatment with oral osmotic laxatives polyethylene glycol 3350 (Miralax, 17–34 g/day) may increase stool frequency, improve stool consistency, and reduce straining. Lactulose or sorbitol produces increased flatus and distention, which are poorly tolerated in patients with irritable bowel syndrome and should be avoided. Lubiprostone (8 mcg orally twice daily) and linaclotide (290 mcg orally once daily) are newer agents approved for treatment of irritable bowel syndrome with constipation. Through different mechanisms, both stimulate increased intestinal chloride and fluid secretion, resulting in accelerated colonic transit. In clinical trials, lubiprostone led to global symptom improvement in 18% of patients compared with 10% of patients who received placebo. Trials of linaclotide included similar patient populations but measured different primary end points. Higher combined response rates (defined as greater than 30% reduction in abdominal pain and more than three spontaneous bowel movements per week, including an increase of one or more from baseline) were found in 12.5% of linaclotide-treated patients compared with 4% of placebotreated patients. Patients with intractable constipation should undergo further assessment for slow colonic transit and pelvic floor dysfunction.

4. Psychotropic agents—Patients with predominant symptoms of pain or bloating may benefit from low doses of tricyclic antidepressants, which are believed to have effects on motility, visceral sensitivity, and central pain perception that are independent of their psychotropic effects. Because of their anticholinergic effects, these agents may be more useful in patients with diarrhea-predominant than constipation-predominant symptoms. Oral nortriptyline, desipramine, or imipramine, may be started at a low dosage of 10 mg at bedtime and increased gradually to 50–150 mg as tolerated. Response rates do not correlate with dosage, and many patients respond to doses of 50 mg or less daily. Side effects are common, and lack of efficacy with one agent does not preclude benefit from another. Improvement should be evident within 4 weeks. The oral serotonin reuptake inhibitors (sertraline, 25–100 mg daily; citalopram 10–20 mg; paroxetine

20–50 mg daily; or fluoxetine, 10–40 mg daily) may lead to improvement in overall sense of well-being but have little impact on abdominal pain or bowel symptoms. Anxiolytics should not be used chronically in irritable bowel syndrome because of their habituation potential. Patients with major depression or anxiety disorders should be identified and treated with therapeutic doses of appropriate agents.

5. Serotonin receptor agonists and antagonists— Serotonin is an important mediator of gastrointestinal motility and sensation. In patients with irritable bowel syndrome with diarrhea, 5-HT3 antagonists may reduce diarrhea and improve overall symptoms through central and peripheral mechanisms. Alosetron is a 5-HT3 antagonist that is FDAapproved for the treatment of women with severe irritable bowel syndrome with predominant diarrhea. Unfortunately, due to cases of severe constipation and a small (1:1000) but significant risk of ischemic colitis, alosetron is restricted to women with severe irritable bowel syndrome with diarrhea who have not responded to conventional therapies and who have been educated about the relative risks and benefits of the agent. It should not be used in patients with constipation. A randomized crossover trial of another 5-HT3 antagonist, ondansetron 4–8 mg three times daily, showed overall superior symptom improvement, including stool frequency, consistency, and urgency. At this time, 5-HT3 antagonists may be considered after careful discussion of the risks and benefits in carefuly selected patients with severe diarrhea-predominant irritable bowel syndrome.

6. Nonabsorbable antibiotics—Rifaximin is not approved for the treatment of irritable bowel syndrome but may be considered in patients with refractory symptoms, especially bloating. A 2012 meta-analysis identified a 9.9% greater improvement in bloating compared with placebo, a modest gain that is similar to other less expensive therapies. Symptom improvement may be attributable to suppression of bacteria in either the small intestine or colon, resulting in decreased bacterial carbohydrate fermentation, diarrhea, and bloating.

7. Probiotics—Meta-analyses of small controlled clinical trials report improved symptoms in some patients treated with one probiotic, Bifidobacterium infantis, but not with another probiotic, Lactobacillus salivarius, or placebo. It is hypothesized that alterations in gut flora may reduce symptoms through suppression of inflammation or reduction of bacterial gas production, resulting in reduced distention, flatus, and visceral sensitivity. Such therapy is attractive because it is safe, well tolerated, and inexpensive. Although promising, further study is needed to define the efficacy and optimal formulations of probiotic therapy. The probiotics VSL#3 (1 packet twice daily) or Bifidobacterium infantis (1 tablet twice daily) have shown modest benefit in small studies.

D. Psychological Therapies

Cognitive-behavioral therapies, relaxation techniques, and hypnotherapy appear to be beneficial in some patients. Patients with underlying psychological abnormalities may benefit from evaluation by a psychiatrist or psychologist. Patients with severe disability should be referred to a pain treatment center.

Prognosis

The majority of patients with irritable bowel syndrome learn to cope with their symptoms and lead productive lives.

ANTIBIOTIC-ASSOCIATED COLITIS

ESSENTIALS OF DIAGNOSIS

- Most cases of antibiotic-associated diarrhea are not attributable to *C difficile* and are usually mild and self-limited.
- Symptoms of antibiotic-associated colitis vary from mild to fulminant; almost all colitis is attributable to *C difficile*.
- Diagnosis in most cases established by stool assay.

General Considerations

Antibiotic-associated diarrhea is a common clinical occurrence. Characteristically, the diarrhea occurs during the period of antibiotic exposure, is dose related, and resolves spontaneously after discontinuation of the antibiotic. In most cases, this diarrhea is mild, self-limited, and does not require any specific laboratory evaluation or treatment. Stool examination usually reveals no fecal leukocytes, and stool cultures reveal no pathogens. Although C difficile is identified in the stool of 15–25% of cases of antibioticassociated diarrhea, it is also identified in 5–10% of patients treated with antibiotics who do not have diarrhea. Most cases of antibiotic-associated diarrhea are due to changes in colonic bacterial fermentation of carbohydrates and are not due to C difficile.

Antibiotic-associated colitis is a significant clinical problem almost always caused by C difficile infection. Hospitalized patients are most susceptible. C difficile colitis is the major cause of diarrhea in patients hospitalized for more than 3 days, affecting 22 patients of every 1000. This anaerobic bacterium colonizes the colon of 3% of healthy adults. It is acquired by fecal-oral transmission. Found throughout hospitals in patient rooms and bathrooms, it is readily transmitted from patient to patient by hospital personnel. Fastidious hand washing and use of disposable gloves are helpful in minimizing transmission. C difficile is acquired in approximately 20% of hospitalized patients, most of whom have received antibiotics that disrupt the normal bowel flora and thus allow the bacterium to flourish. Although almost all antibiotics have been implicated, colitis most commonly develops after use of ampicillin, clindamycin, third-generation cephalosporins, and fluoroquinolones. C difficile colitis will develop in approximately one-third of infected patients. In clinical trials, prophylactic administration of the probiotics “DanActiv” and “Bio-K+,” containing Lactobacillus casei, Lactobacillus bulgaricus, and Streptococcus thermophilus, to hospitalized patients who are receiving antibiotics reduced the incidence of C difficile– associated diarrhea. Symptoms usually begin during or shortly after antibiotic therapy but may be delayed for up to 8 weeks. All patients with acute diarrhea should be asked about recent antibiotic exposure. Patients who are elderly; debilitated; immunocompromised; receiving multiple antibiotics or prolonged (more than 10 days) antibiotic therapy; receiving enteral tube feedings, proton

pump inhibitors, or chemotherapy; or who have inflammatory bowel disease have a higher risk of acquiring C difficile and developing C difficile–associated diarrhea.

The incidence and severity of C difficile colitis in hospitalized patients appear to be increasing, which is attributable to the emergence of a more virulent strain of C difficile (NAP1) that contains an 18-base pair deletion of the tcdC inhibitory gene, resulting in higher toxin A and B production. This hypervirulent strain has been associated with several hospital outbreaks of severe disease with up to 7% mortality.

Clinical Findings

A. Symptoms and Signs

Most patients report mild to moderate greenish, foulsmelling watery diarrhea 5–15 times per day with lower abdominal cramps. Physical examination is normal or reveals mild left lower quadrant tenderness. The stools may have mucus but seldom gross blood. In most patients, colitis is most severe in the distal colon and rectum. Over half of hospitalized patients diagnosed with C difficile colitis have a white blood count greater than 15,000/mcL, and C difficile should be considered in all hospitalized patients with unexplained leukocytosis.

Severe or fulminant disease occurs in 10–15% of patients. It is characterized by fever; hemodynamic instability; and abdominal distention, pain, and tenderness. Most patients have profuse diarrhea (up to 30 stools/day); however, diarrhea may be absent or appear to be improving in patients with fulminant disease or ileus. Laboratory data suggestive of severe disease include a white blood count greater than 30,000/mcL, albumin less than 2.5 g/dL (due to protein-losing enteropathy), elevated serum lactate, or rising creatinine.

B. Special Examinations

1. Stool studies—Pathogenic strains of C difficile produce two toxins: toxin A is an enterotoxin and toxin B is a cytotoxin. Rapid enzyme immunoassays (EIAs) for toxins A and B have a 75–90% sensitivity with a single stool specimen; sensitivity increases to 90–95% with two specimens. Until recently, EIA was the preferred diagnostic test in most clinical settings because it is inexpensive, easy to use, and results are available within 24 hours. However, nucleic acid amplification tests (eg, PCR assays) that amplify the toxin B gene have a 97% sensitivity and thus are superior to the EIA tests; these PCR assays are now preferred. Alternatively, some laboratories first perform an assay for glutamate dehydrogenase (a common C difficile antigen), which has a high sensitivity and negative predictive value (greater than 95%). A negative glutamate dehydrogenase assay effectively excludes infection, while a positive assay requires confirmation with PCR or EIA to determine whether the strain that is present is toxin producing.

2. Flexible sigmoidoscopy—Flexible sigmoidoscopy is not needed in patients who have typical symptoms and a positive stool toxin assay. Previously, it was useful in patients with severe symptoms when a rapid diagnosis was desired; however, the ready availability of the currently recommended assays obviates this

benefit. It also may clarify the diagnosis in patients with positive C difficile toxin assays who have atypical symptoms or who have persistent diarrhea despite appropriate therapy. In patients with mild to moderate symptoms, there may be no abnormalities or only patchy or diffuse, nonspecific colitis indistinguishable from other causes. In patients with severe illness, true **pseudomembranous** colitis is seen.

3. Imaging studies—Abdominal radiographs or noncontrast abdominal CT scans are obtained in patients with severe or fulminant symptoms to look for evidence of colonic dilation and wall thickening. Abdominal CT also is useful in the evaluation of hospitalized patients with abdominal pain or ileus without significant diarrhea, in whom the presence of colonic wall thickening suggests unsuspected C difficile colitis. CT scanning is also useful in the detection of possible perforation.

Differential Diagnosis

In the hospitalized patient in whom acute diarrhea develops after admission, the differential diagnosis includes simple antibiotic-associated diarrhea (not related to C difficile), enteral feedings, medications, and ischemic colitis. Other infectious causes are unusual in hospitalized patients in whom diarrhea develops more than 72 hours after admission, and it is not cost-effective to obtain stool cultures unless tests for C difficile are negative. Rarely, other organisms (staphylococci, Clostridium perfringens) have been associated with pseudomembranous colitis. Klebsiella oxytoca may cause a distinct form of antibioticassociated hemorrhagic colitis that is segmental (usually in the right or transverse colon); spares the rectum; and is more common in younger, healthier outpatients.

Complications

Severe colitis may progress quickly to fulminant disease, resulting in hemodynamic instability, respiratory failure, metabolic acidosis, megacolon (more than 7 cm diameter), perforation, and death. Chronic untreated colitis may result in weight loss and protein-losing enteropathy.

Treatment

A. Immediate Treatment

If possible, antibiotic therapy should be discontinued and therapy with metronidazole, vancomycin, or fidaxomicin (a poorly absorbable macrolide antibiotic) should be initiated. For patients with mild disease, oral metronidazole (500 mg orally three times daily), vancomycin (125 mg orally four times daily), or fidaxomicin, (200 mg orally two times daily) are equally effective for initial treatment. Vancomycin and fidaxomicin are significantly more expensive than metronidazole. Therefore, metronidazole remains the preferred first-line therapy in patients with mild disease, except in patients who are intolerant of metronidazole, pregnant women, and children. The duration of initial therapy is usually 10–14 days. Symptomatic improvement occurs in most patients within 72 hours.

For patients with severe disease, characterized by a white blood cell count greater than 15,000/mcL, serum albumin less than 3 g/dL, or a rise in serum creatinine to more than 1.5 times baseline, vancomycin, 125 mg orally four times daily, is the preferred agent because it achieves significantly higher response rates (97%) than metronidazole (76%). In patients with severe, complicated disease, characterized by fever higher than 38.5oC, hypotension, mental status changes, ileus, megacolon, or WBC greater than 30,000/mcL, intravenous metronidazole, 500 mg every 6 hours, should be given—supplemented by vancomycin (500 mg four times daily administered by nasoenteric tube) and, in some cases, vancomycin enemas (500 mg in 100 mL every 6 hours). Intravenous vancomycin does not penetrate the bowel and should not be used. The efficacy of fidaxomicin for severe or fulminant disease requires further investigation. Early surgical consultation is recommended for all patients with severe or fulminant disease. Total abdominal colectomy or loop ileostomy with colonic lavage may be required in patients with toxic megacolon, perforation, sepsis, or hemorrhage.

B. Treatment of Relapse

Up to 25% of patients have a relapse of diarrhea from C difficile within 1 or 2 weeks after stopping initial therapy. This may be due to reinfection or failure to eradicate the organism. In a 2011 multicenter, randomized controlled trial, patients treated with fidaxomicin had significantly lower recurrence rates (7.8%) of non-NAP1 C difficile strains than patients treated with vancomycin (23.6%). The recurrence rates were not different among patients with the NAP1 strain. Fidaxomicin may be appropriate for patients with C difficile infection or as initial therapy in patients believed to be at higher risk for recurrent disease. Controlled trials show that oral administration of a live yeast, Saccharomyces boulardii, 500 mg twice daily, reduces the incidence of relapse by 50%. The optimal treatment regimen for recurrent relapses is evolving. Most relapses respond promptly to a second course of the same regimen used for the initial episode. Some patients, however, have recurrent relapses that can be difficult to treat. For patients with two relapses, a 7-week tapering regimen of vancomycin is recommended: 125 mg orally four times daily for 14 days; twice daily for 7 days; once daily for 7 days; every other day for 7 days; and every third day for 2–8 weeks. Probiotic therapy is recommended as adjunctive therapy in patients with relapsing disease. For patients with three or more relapses, updated 2013 guidelines recommend consideration of an installation of a suspension of fecal bacteria from a healthy donor (“fecal microbiota transplant”). In uncontrolled case reports and case series involving several hundred patients, such “fecal transplantation” into the terminal ileum or proximal colon (by colonoscopy) or into the duodenum and jejunum (by nasoenteric tube) results in disease remission after a single treatment in over 90% of patients with recurrent C difficile infection. In a 2013 randomized study, duodenal infusion of donor feces led to resolution of C difficile diarrhea in 94%, which was dramatically higher than vancomycin treatment (31%), prompting early study termination. Despite uncertainties, fecal transplantation should be considered in patients with refractory infection. A 2014 open label study demonstrated resolution

of diarrhea in 18/20 (90%) patients with recurrent C difficile infection after oral treatment with capsules containing frozen feces from healthy volunteers.

INFLAMMATORY BOWEL DISEASE

The term "*inflammatory bowel disease*" includes *ulcerative colitis* and *Crohn disease*. Ulcerative colitis is a chronic, recurrent disease characterized by diffuse mucosal inflammation involving only the colon. Ulcerative colitis invariably involves the rectum and may extend proximally in a continuous fashion to involve part or all of the colon. Crohn disease is a chronic, recurrent disease characterized by patchy transmural inflammation involving any segment of the gastrointestinal tract from the mouth to the anus. Crohn disease and ulcerative colitis may be associated in 50% of patients with a number of extraintestinal manifestations, including oral ulcers, oligoarticular or polyarticular nondeforming peripheral arthritis, spondylitis or sacroiliitis, episcleritis or uveitis, erythema nodosum, pyoderma gangrenosum, hepatitis and sclerosing cholangitis, and thromboembolic events.

Pharmacologic Therapy

Although ulcerative colitis and Crohn disease appear to be distinct entities, the same pharmacologic agents are used to treat both. Despite extensive research, there are still no specific therapies for these diseases. The mainstays of therapy are 5-aminosalicylic acid derivatives, corticosteroids, immunomodulating agents (such as mercaptopurine or azathioprine and methotrexate), and biologic agents.

A. 5-Aminosalicylic Acid (5-ASA)

5-ASA is a topically active agent that has a variety of antiinflammatory effects. It is used in the active treatment of ulcerative colitis and Crohn disease and during disease inactivity to maintain remission. It is readily absorbed from the small intestine but demonstrates minimal colonic absorption. A number of oral and topical compounds have been designed to target delivery of 5-ASA to the colon or small intestine while minimizing absorption. Commonly used formulations of 5-ASA are sulfasalazine, mesalamine, and azo compounds. Side effects of these compounds are uncommon but include nausea, rash, diarrhea, pancreatitis, and acute interstitial nephritis.

1. Oral mesalamine agents—These 5-ASA agents are coated in various pH-sensitive resins (Asacol, Apriso, and Lialda) or packaged in timed-release capsules (Pentasa). Pentasa releases 5-ASA slowly throughout the small intestine and colon. Asacol, Apriso, and Lialda tablets dissolve at pH 6.0–7.0, releasing 5-ASA in the terminal small bowel and proximal colon. Lialda has a multi-matrix system that gradually releases 5-ASA throughout the colon.

2. Azo compounds—Sulfasalazine, balsalazide and olsalazine contain 5-ASA linked by an azo bond that requires cleavage by colonic bacterial azoreductases to release 5-ASA. Absorption of these drugs from the small intestine is negligible. After release within the colon, the 5-ASA works topically and is

largely unabsorbed.

Sulfasalazine contains 5-ASA linked to a sulfapyridine moiety. It is unclear whether the sulfapyridine group has any anti-inflammatory effects. One gram of sulfasalazine contains 400 mg of 5-ASA. The sulfapyridine group, however, is absorbed and may cause side effects in 15–30% of patients—much higher than with other 5-ASA compounds. Dose-related side effects include nausea, headaches, leukopenia, oligospermia, and impaired folate metabolism. Allergic and idiosyncratic side effects are fever, rash, hemolytic anemia, neutropenia, worsened colitis, hepatitis, pancreatitis, and pneumonitis. Because of its side effects, sulfasalazine is less frequently used than other 5-ASA agents. It should always be administered in conjunction with folate. Eighty percent of patients intolerant of sulfasalazine can tolerate mesalamine.

3. Topical mesalamine—5-ASA is provided in the form of suppositories (Canasa; 1000 mg) and enemas (Rowasa; 4 g/60 mL). These formulations can deliver much higher concentrations of 5-ASA to the distal colon than oral compounds. Side effects are uncommon.

B. Corticosteroids

A variety of intravenous, oral, and topical corticosteroid formulations have been used in inflammatory bowel disease. They have utility in the short-term treatment of moderate to severe disease. However, long-term use is associated with serious, potentially irreversible side effects and is to be avoided. The agents, route of administration, duration of use, and tapering regimens used are based more on personal bias and experience than on data from rigorous clinical trials. The most commonly used intravenous formulations have been hydrocortisone or methylprednisolone, which are given by continuous infusion or every 6 hours. Oral formulations are prednisone or methylprednisolone. Adverse events commonly occur during short-term systemic corticosteroid therapy, including mood changes, insomnia, dyspepsia, weight gain, edema, elevated serum glucose levels, acne, and moon facies. Side effects of long-term use include osteoporosis, osteonecrosis of the femoral head, myopathy, cataracts, and susceptibility to infections. Calcium and vitamin D supplementation should be administered to all patients receiving long-term corticosteroid therapy. Bone densitometry should be considered in patients with inflammatory bowel disease with other risk factors for osteoporosis and in all patients with a lifetime use of corticosteroids for 3 months or more. Topical preparations are provided as hydrocortisone suppositories (100 mg), foam (90 mg), and enemas (100 mg). Budesonide is an oral corticosteroid with high topical anti-inflammatory activity but low systemic activity due to high first-pass hepatic metabolism. A controlled-release formulation is available (Entocort) that targets delivery to the terminal ileum and proximal colon. An enteric coated, delayed-release formulation is available (Uceris) that is released at a pH greater than 7, targeting delivery to the colon. Budesonide produces less suppression of the hypothalamic-pituitary-adrenal axis and fewer steroid-related side effects than hydrocortisone or prednisone.

C. Immunomodulating Drugs:
Mercaptopurine, Azathioprine, or Methotrexate

Mercaptopurine and azathioprine are thiopurine drugs that are used in many patients with moderate to severe Crohn disease and ulcerative colitis either in combination with anti-TNF agents or in patients who are corticosteroiddependent in an attempt to reduce or withdraw the corticosteroids and to maintain patients in remission. Azathioprine is converted in vivo to mercaptopurine. It is believed that the active metabolite of mercaptopurine is 6-thioguanine. Monitoring of 6-thioguanine levels is performed in some clinical settings but is of unproven value in the management of most patients. Side effects of mercaptopurine and azathioprine, including allergic reactions (fever, rash, or arthralgias) and nonallergic reactions (nausea, vomiting, pancreatitis, hepatotoxicity, bone marrow suppression, infections), occur in 15% of patients. Thiopurines are associated with up to a fivefold increased risk of nonHodgkin lymphomas (1/1000 patient-years), increasing with age and length of drug exposure; with an increased risk of human papillomavirus (HPV)–related cervical dysplasia; and with an increased risk of non-melanoma skin cancer. Younger patients also are at risk for severe primary Epstein Barr virus (EBV) infection, if not previously exposed.

Three competing enzymes are involved in the metabolism of mercaptopurine to its active (6-thioguanine) and inactive metabolites. About 1 person in 300 has a homozygous mutation of one of the enzymes that metabolizes thiopurine methyltransferase (TPMT), placing them at risk for profound immunosuppression; 1 person in 9 is heterozygous for TPMT, resulting in intermediate enzyme activity. Measurement of TPMT functional activity is recommended prior to initiation of therapy. Treatment should be withheld in patients with absent TPMT activity. The most effective dose of mercaptopurine is 1–1.5 mg/kg. For azathioprine, it is 2–3 mg/kg daily. For patients with normal TPMT activity, both drugs may be initiated at the weight-calculated dose. A complete blood count should be obtained weekly for 4 weeks, biweekly for 4 weeks, and then every 1–3 months for the duration of therapy. Liver biochemical tests should be measured periodically. Some clinicians prefer gradual dose-escalation, especially for patients with intermediate TPMT activity or in whom TPMT measurement is not available; both drugs may be started at 25 mg/day and increased by 25 mg every 1–2 weeks while monitoring for myelosuppression until the target dose is reached. If the white blood count falls below 3000– 4000/mcL or the platelet count falls below 100,000/mcL, the medication should be held for at least 1 week before reducing the daily dose by 25–50 mg.

Methotrexate is used in the treatment of patients with inflammatory bowel disease, especially patients with Crohn disease who are intolerant of mercaptopurine. Methotrexate is an analog of dihydrofolic acid. Although at high doses it interferes with cell proliferation through inhibition of nucleic acid metabolism, at low doses it has antiinflammatory properties, including inhibition of expression of tumor necrosis factor (TNF) in monocytes and macrophages. Methotrexate may be given intramuscularly, subcutaneously, or orally. Side effects of methotrexate include nausea, vomiting, stomatitis, infections, bone marrow

suppression, hepatic fibrosis, and life-threatening pneumonitis. A complete blood count and liver function tests should be monitored every 1–3 months. Folate supplementation (1 mg/day) should be administered.

D. Biologic Therapies

Although the etiology of inflammatory bowel disorders is uncertain, it appears that an abnormal response of the mucosal innate immune system to luminal bacteria may trigger inflammation, which is perpetuated by dysregulation of cellular immunity. A number of biologic therapies are available or in clinical testing that more narrowly target various components of the immune system. Biologic agents are highly effective for patients with corticosteroid-dependent or refractory disease and potentially may improve the natural history of disease. The potential benefits of these agents, however, must be carefully weighed with their high cost and risk of serious and potentially life-threatening side effects.

1. Anti-TNF therapies—TNF is one of the key proinflammatory cytokines in the TH1 response. TNF exists in two biologically active forms: a soluble form (sTNF), which is enzymatically cleaved from its cell surface, and a membranebound precursor (tmTNF). When either form binds to the TNF-receptors on effector cells, they initiate a variety of signaling pathways that lead to inflammatory gene activation. Four monoclonal antibodies to TNF currently are available for the treatment of inflammatory bowel disease: infliximab, adalimumab, golimumab, and certolizumab. All four agents bind and neutralize soluble as well as membranebound TNF on macrophages and activated T lymphocytes, thereby preventing TNF stimulation of effector cells.

Infliximab is a chimeric (75% human/25% mouse) IgG1 antibody that is administered by intravenous infusion. A three-dose regimen of 5 mg/kg administered at 0, 2, and 6 weeks is recommended for acute induction, followed by infusions every 8 weeks for maintenance therapy. Acute infusion reactions occur in 5–10% of infusions but occur less commonly in patients receiving regularly scheduled infusions or concomitant immunomodulators (ie, azathioprine or methotrexate). Most reactions are mild or moderate (nausea; headache; dizziness; urticaria; diaphoresis; or mild cardiopulmonary symptoms that include chest tightness, dyspnea, or palpitations) and can be treated by slowing the infusion rate and administering acetaminophen and diphenhydramine. Severe reactions (hypotension, severe shortness of breath, rigors, severe chest discomfort) occur in less than 1% and may require oxygen, diphenhydramine, hydrocortisone, and epinephrine. Delayed serum sickness-like reactions occur in 1%. With repeated, intermittent intravenous injections, antibodies to infliximab develop in up to 40% of patients, which are associated with a shortened duration or loss of response and increased risk of acute or delayed infusion reactions. Giving infliximab in a regularly scheduled maintenance therapy (eg, every 8 weeks), concomitant use of infliximab with other immunomodulating agents (azathioprine, mercaptopurine, or methotrexate), or preinfusion treatment with corticosteroids (intravenous hydrocortisone 200 mg) significantly reduces the development of antibodies to

approximately 10%.

Adalimumab and golimumab are fully human IgG1 antibodies that are administered by subcutaneous injection. For adalimumab, a dose of 160 mg at week 0 and 80 mg at week 2 is recommended for acute induction, followed by maintenance therapy with 40 mg subcutaneously every other week. For golimumab, a dose of 200 mg at week 0 and 100 mg at week 2 is recommended for acute induction, followed by maintenance therapy with 100 mg subcutaneously every 4 weeks.

Certolizumab is a fusion compound in which the Fab1 portion of a chimeric (95% human/5% mouse) TNFantibody is bound to polyethylene glycol in order to prolong the drug half-life. A dose of 400 mg at weeks 0, 2, and 4 is recommended for acute induction, followed by maintenance therapy with 400 mg subcutaneously every 4 weeks. Injection site reactions (burning, pain, redness, itching) are relatively common but are usually minor and self-limited.

Acute and delayed hypersensitivity reactions are rare with subcutaneous anti-TNF therapies. Antibodies to adalimumab or golimumab develop in 5% of patients and to certolizumab in 10%, which may lead to shortened duration or loss of response to the drug.

Serious infections with anti-TNF therapies may occur in 2–5% of patients, including sepsis, pneumonia, abscess, and cellulitis; however, controlled studies suggest the increased risk may be attributable to increased severity of disease and concomitant use of corticosteroids. Patients treated with anti-TNF therapies are at increased risk for the development of opportunistic infections with intracellular bacterial pathogens including tuberculosis, mycoses (candidiasis, histoplasmosis, coccidioidomycosis, nocardiosis), and listeriosis, and with reactivation of viral infections, including hepatitis B, herpes simplex, varicella zoster, and EBV. Prior to use of these agents, patients should be screened for latent tuberculosis with PPD testing and a chest radiograph. Antinuclear and anti-DNA antibodies occur in a large percentage of patients; however, the development of drug-induced lupus is rare. All agents may cause severe hepatic reactions leading to acute hepatic failure; liver biochemical tests should be monitored routinely during therapy. Anti-TNF therapies increase the risk of non-melanoma skin cancer and, possibly, non-Hodgkin lymphoma. Most lymphomas, however, are associated with a combination of an anti-TNF agent and a thiopurine, and it appears that the risk of antiTNF monotherapy is very low. Rare cases of optic neuritis and demyelinating diseases, including multiple sclerosis have been reported. Anti-TNF therapies may worsen heart failure in patients with cardiac disease.

2. Anti-integrins—Two monoclonal antibodies are available that target integrins, decreasing the trafficking of circulating leukocytes through the vasculature and reducing chronic inflammation. Natalizumab is a humanized monoclonal antibody targeted against alpha-4-integrins that blocks leukocytes trafficking to the gut and brain. Although natalizumab is efficacious for the induction and maintenance of response and remission in patients with Crohn disease, there is an increased incidence of progressive multifocal

leukoencephalopathy (PML) caused by reactivation of the JC virus, in approximately 1:250 patients with a positive JC virus antibody test result receiving therapy for longer than 18 months. Vedolizumab is a new anti-integrin that blocks the alpha4 beta7 heterodimer, selectively blocking gut, but not brain, lymphocyte trafficking. The greater selectivity may prevent JC virus reactivation.

Crohn Disease

ESSENTIALS OF DIAGNOSIS

- Insidious onset.
- Intermittent bouts of low-grade fever, diarrhea, and right lower quadrant pain.
- Right lower quadrant mass and tenderness.
- Perianal disease with abscess, fistulas.
- Radiographic or endoscopic evidence of ulceration, stricturing, or fistulas of the small intestine or colon.

General Considerations

One-third of cases of Crohn disease involve the small bowel only, most commonly the terminal ileum (ileitis). Half of all cases involve the small bowel and colon, most often the terminal ileum and adjacent proximal ascending colon (ileocolitis). In 20% of cases, the colon alone is affected. One-third of patients have associated perianal disease (fistulas, fissures, abscesses). Less than 5% patients have symptomatic involvement of the upper intestinal tract. Unlike ulcerative colitis, Crohn disease is a transmural process that can result in mucosal inflammation and ulceration, stricturing, fistula development, and abscess formation. Cigarette smoking is strongly associated with the development of Crohn disease, resistance to medical therapy, and early disease relapse.

Clinical Findings

A. Symptoms and Signs

Because of the variable location of involvement and severity of inflammation, Crohn disease may present with a variety of symptoms and signs. In eliciting the history, the clinician should take particular note of fevers, the patient's general sense of well-being, weight loss, the presence of abdominal pain, the number of liquid bowel movements per day, and prior surgical resections. Physical examination should focus on the patient's temperature, weight, and nutritional status, the presence of abdominal tenderness or an abdominal mass, rectal examination, and extraintestinal manifestations (described below). Most commonly, there is one or a combination of the following clinical constellations.

1. Chronic inflammatory disease—This is the most common presentation and is often seen in patients with ileitis or ileocolitis. Patients report malaise, weight loss, and loss of energy. In patients with ileitis or ileocolitis, there may be diarrhea, which is usually nonbloody and often intermittent. In patients with colitis involving

the rectum or left colon, there may be bloody diarrhea and fecal urgency, which may mimic the symptoms of ulcerative colitis. Cramping or steady right lower quadrant or periumbilical pain is common. Physical examination reveals focal tenderness, usually in the right lower quadrant. A palpable, tender mass that represents thickened or matted loops of inflamed intestine may be present in the lower abdomen.

2. Intestinal obstruction—Narrowing of the small bowel may occur as a result of inflammation, spasm, or fibrotic stenosis. Patients report postprandial bloating, cramping pains, and loud borborygmi. This may occur in patients with active inflammatory symptoms (as above) or later in the disease from chronic fibrosis without other systemic symptoms or signs of inflammation.

3. Penetrating disease and fistulae—Sinus tracts that penetrate through the bowel, where they may be contained or form fistulas to adjacent structures, develop in a subset of patients. Penetration through the bowel can result in an intra-abdominal or retroperitoneal phlegmon or abscess manifested by fevers, chills, a tender abdominal mass, and leukocytosis. Fistulas between the small intestine and colon commonly are asymptomatic but can result in diarrhea, weight loss, bacterial overgrowth, and malnutrition. Fistulas to the bladder produce recurrent infections. Fistulas to the vagina result in malodorous drainage and problems with personal hygiene. Fistulas to the skin usually occur at the site of surgical scars.

4. Perianal disease—One-third of patients with either large or small bowel involvement develop perianal disease manifested by large painful skin tags, anal fissures, perianal abscesses, and fistulas.

5. Extraintestinal manifestations—Extraintestinal manifestations may be seen with both Crohn disease and ulcerative colitis. These include arthralgias, arthritis, iritis or uveitis, pyoderma gangrenosum, or erythema nodosum. Oral aphthous lesions are common. There is an increased prevalence of gallstones due to malabsorption of bile salts from the terminal ileum. Nephrolithiasis with urate or calcium oxalate stones may occur.

B. Laboratory Findings

There is a poor correlation between laboratory studies and the patient's clinical picture. Laboratory values may reflect inflammatory activity or nutritional complications of disease. A complete blood count and serum albumin should be obtained in all patients. Anemia may reflect chronic inflammation, mucosal blood loss, iron deficiency, or vitamin B12 malabsorption secondary to terminal ileal inflammation or resection. Leukocytosis may reflect inflammation or abscess formation or may be secondary to corticosteroid therapy. Hypoalbuminemia may be due to intestinal protein loss (protein-losing enteropathy), malabsorption, bacterial overgrowth, or chronic inflammation. The sedimentation rate or C-reactive protein level is elevated in many patients during active inflammation. Fecal calprotectin levels also are increased in patients with intestinal inflammation. Stool specimens are sent for examination for routine pathogens, ova and parasites, leukocytes, fat, and C difficile toxin.

C. Special Diagnostic

Studies In most patients, the initial diagnosis of Crohn disease is based on a compatible clinical picture with supporting endoscopic, pathologic, and radiographic findings. Colonoscopy usually is performed first to evaluate the colon and terminal ileum and to obtain mucosal biopsies. Typical endoscopic findings include aphthoid, linear or stellate ulcers, strictures, and segmental involvement with areas of normal-appearing mucosa adjacent to inflamed mucosa. In 10% of cases, it may be difficult to distinguish ulcerative colitis from Crohn disease. Granulomas on biopsy are present in less than 25% of patients but are highly suggestive of Crohn disease. CT or MR enterography or a barium upper gastrointestinal series with small bowel follow-through often is obtained in patients with suspected small bowel involvement. Suggestive findings include ulcerations, strictures, and fistulas; in addition, CT or MR enterography may identify bowel wall thickening and vascularity, mucosal enhancement, and fat stranding. Capsule imaging may help establish a diagnosis when clinical suspicion for small bowel involvement is high but radiographs are normal or nondiagnostic.

Complications

A. Abscess

The presence of a tender abdominal mass with fever and leukocytosis suggests an abscess. Emergent CT of the abdomen is necessary to confirm the diagnosis. Patients should be given broad-spectrum antibiotics. Percutaneous drainage or surgery is usually required.

B. Obstruction

Small bowel obstruction may develop secondary to active inflammation or chronic fibrotic stricturing and is often acutely precipitated by dietary indiscretion. Patients should be given intravenous fluids with nasogastric suction. Systemic corticosteroids are indicated in patients with symptoms or signs of active inflammation but are unhelpful in patients with inactive, fixed disease. Patients unimproved on medical management require surgical resection of the stenotic area or stricturoplasty.

C. Abdominal and Rectovaginal Fistulas

Many fistulas are asymptomatic and require no specific therapy. Most symptomatic fistulas eventually require surgical therapy; however, medical therapy is effective in a subset of patients and is usually tried first in outpatients who otherwise are stable. Large abscesses associated with fistulas require percutaneous or surgical drainage. After percutaneous drainage, long-term antibiotics are administered in order to reduce recurrent infections until the fistula is closed or surgically resected. Fistulas may close temporarily in response to TPN or oral elemental diets but recur when oral feedings are resumed. Anti-TNF agents may promote closure in up to 60% within 10 weeks; however, relapse occurs in over one-half of patients within 1 year despite continued therapy. Surgical therapy is required for symptomatic fistulas that do not respond to medical therapy. Fistulas that arise above (proximal to) areas of intestinal stricturing commonly require surgical treatment.

D. Perianal Disease

Patients with fissures, fistulas, and skin tags commonly have perianal discomfort. Successful treatment of active intestinal disease also may improve perianal disease. Specific treatment of perianal disease can be difficult and is best approached jointly with a surgeon with an expertise in colorectal disorders. Pelvic MRI is the best noninvasive study for evaluating perianal fistulas. Patients should be instructed on proper perianal skin care, including gentle wiping with a premoistened pad (baby wipes) followed by drying with a cool hair dryer, daily cleansing with sitz baths or a water wash, and use of perianal cotton balls or pads to absorb drainage. Oral antibiotics (metronidazole, 250 mg three times daily, or ciprofloxacin, 500 mg twice daily) may promote symptom improvement or healing in patients with fissures or uncomplicated fistulas; however, recurrent symptoms are common. Refractory fissures may benefit from mesalamine suppositories or topical 0.1% tacrolimus ointment. Immunomodulators or anti-TNF agents or both promote short-term symptomatic improvement from anal fistulas in two-thirds of patients and complete closure in up to one-half of patients; however, less than one-third maintain symptomatic remission during long-term maintenance treatment. Anorectal abscesses should be suspected in patients with severe, constant perianal pain, or perianal pain in association with fever. Superficial abscesses are evident on perianal examination, but deep perirectal abscesses may be detected by digital examination or pelvic CT scan. Depending on the abscess location, surgical drainage may be achieved by incision, or catheter or seton placement. Surgery should be considered for patients with severe, refractory symptoms but is best approached after medical therapy of the Crohn disease has been optimized.

E. Carcinoma

Patients with colonic Crohn disease are at increased risk for developing colon carcinoma; hence, annual screening colonoscopy to detect dysplasia or cancer is recommended for patients with a history of 8 or more years of Crohn colitis. Patients with Crohn disease have an increased risk of lymphoma and of small bowel adenocarcinoma; however, both are rare.

F. Hemorrhage

Unlike ulcerative colitis, severe hemorrhage is unusual in Crohn disease.

G. Malabsorption

Malabsorption may arise after extensive surgical resections of the small intestine and from bacterial overgrowth in patients with enterocolonic fistulas, strictures, and stasis resulting in bacterial overgrowth.

Differential Diagnosis

Chronic cramping abdominal pain and diarrhea are typical of both irritable bowel syndrome and Crohn disease, but radiographic examinations are normal in the former. Celiac disease may cause diarrhea with malabsorption. Acute fever and right lower quadrant pain may resemble appendicitis or Yersinia enterocolitica enteritis. Intestinal lymphoma causes fever, pain, weight loss, and abnormal small bowel radiographs that may mimic Crohn disease. Patients with undiagnosed AIDS may present with fever and diarrhea. Segmental colitis may be caused by

tuberculosis, E histolytica, Chlamydia, or ischemic colitis. C difficile or CMV infection may develop in patients with inflammatory bowel disease, mimicking disease recurrence. Diverticulitis with abscess formation may be difficult to distinguish acutely from Crohn disease. NSAIDs may exacerbate inflammatory bowel disease and may also cause NSAID-induced colitis characterized by small bowel or colonic ulcers, erosion, or strictures that tend to be most severe in the terminal ileum and right colon.

Treatment of Active Disease

Crohn disease is a chronic lifelong illness characterized by exacerbations and periods of remission. As no specific therapy exists, current treatment is directed toward symptomatic improvement and control of the disease process, in order to improve quality of life and reduce disease progression and complications. Although sustained clinical remission should be the therapeutic goal, this is achieved in less than one-third of patients. Choice of therapies depends on the disease location and severity, patient age and comorbidities, and patient preference. Early introduction of biologic therapy should be considered strongly in patients with risk factors for aggressive disease, including young age, perianal disease, structuring disease, or need for corticosteroids. All patients with Crohn disease should be counseled to discontinue cigarettes.

A. Nutrition

1. Diet—Patients should eat a well-balanced diet with as few restrictions as possible. Eating smaller but more frequent meals may be helpful. Patients with diarrhea should be encouraged to drink fluids to avoid dehydration. Many patients report that certain foods worsen symptoms, especially fried or greasy foods. Because lactose intolerance is common, a trial off dairy products is warranted if flatulence or diarrhea is a prominent complaint. Patients with obstructive symptoms should be placed on a low-roughage diet, ie, no raw fruits or vegetables, popcorn, nuts, etc. Resection of more than 100 cm of terminal ileum results in fat malabsorption for which a low-fat diet is recommended. Parenteral vitamin B12 (100 mcg intramuscularly per month) commonly is needed for patients with previous ileal resection or extensive terminal ileal disease.

2. Enteral therapy—Supplemental enteral therapy via nasogastric tube may be required for children and adolescents with poor intake and growth retardation.

3. Total parenteral nutrition—TPN is used short term in patients with active disease and progressive weight loss or those awaiting surgery who have malnutrition but cannot tolerate enteral feedings because of high-grade obstruction, high-output fistulas, severe diarrhea, or abdominal pain. It is required long term in a small subset of patients with extensive intestinal resections resulting in short bowel syndrome with malnutrition.

B. Symptomatic Medications

There are several potential mechanisms by which diarrhea may occur in Crohn disease in addition to active Crohn disease. A rational empiric treatment

approach often yields therapeutic improvement that may obviate the need for corticosteroids or immunosuppressive agents. Involvement of the terminal ileum with Crohn disease or prior ileal resection may lead to reduced absorption of bile acids that may induce secretory diarrhea from the colon. This diarrhea commonly responds to cholestyramine 2–4 g, colestipol 5 g, or colesevelam 625 mg one to two times daily before meals to bind the malabsorbed bile salts. Patients with extensive ileal disease (requiring more than 100 cm of ileal resection) have such severe bile salt malabsorption that steatorrhea may arise. Such patients may benefit from a low-fat diet; bile salt-binding agents will exacerbate the diarrhea and should not be given. Patients with Crohn disease are at risk for the development of small intestinal bacterial overgrowth due to enteral fistulas, ileal resection, and impaired motility and may benefit from a course of broad-spectrum antibiotics (see Bacterial Overgrowth, above). Other causes of diarrhea include lactase deficiency and short bowel syndrome (described in other sections). Use of oral antidiarrheal agents may provide benefit in some patients. Loperamide (2–4 mg), diphenoxylate with atropine (one tablet), or tincture of opium (5–15 drops) may be given as needed up to four times daily. Because of the risk of toxic megacolon, these drugs should not be used in patients with active severe colitis.

C. Specific Drug Therapy

1. 5-Aminosalicylic acid agents—Mesalamine has long been used as initial therapy for the treatment of mild to moderately active colonic and ileocolonic Crohn disease. However, meta-analyses of published and unpublished trial data suggest that mesalamine is of no value in either the treatment of active Crohn disease or the maintenance of remission. Current treatment guidelines recommend against its use for Crohn disease.

2. Antibiotics—Antibiotics also are widely used by clinicians for the treatment of active luminal Crohn disease, although meta-analyses of controlled trials suggest that they have little or no efficacy. It is hypothesized that antibiotics may reduce inflammation through alteration of gut flora, reduction of bacterial overgrowth, or treatment of microperforations. Oral metronidazole (10 mg/kg/day) or ciprofloxacin (500 mg twice daily), or rifaximin (800 mg twice daily) are commonly administered for 6–12 weeks.

3. Corticosteroids—Approximately one-half of patients with Crohn disease require corticosteroids at some time in their illness. Corticosteroids dramatically suppress the acute clinical symptoms or signs in most patients with both small and large bowel disease; however, they do not alter the underlying disease. An ileal-release budesonide preparation (Entocort), 9 mg once daily for 8–16 weeks, induces remission in 50–70% of patients with mild to moderate Crohn disease involving the terminal ileum or ascending colon. After initial treatment, budesonide is tapered over 2–4 weeks in 3 mg increments. In some patients, low-dose budesonide (6 mg/day) may be used for up to 1 year to maintain remission. Budesonide is superior to mesalamine but somewhat less effective than prednisone. However, because budesonide has markedly reduced acute and chronic steroid-related adverse effects, including smaller reductions of bone mineral density, it is preferred to other

systemic corticosteroids for the treatment of mild to moderate Crohn disease involving the terminal ileum or ascending colon.

Prednisone or methylprednisolone, 40–60 mg/day, is generally administered to patients with Crohn disease that is severe, that involves the distal colon or proximal small intestine, or that has failed treatment with budesonide. Remission or significant improvement occurs in greater than 80% of patients after 8–16 weeks of therapy. After improvement at 2 weeks, tapering proceeds at 5 mg/wk until a dosage of 20 mg/day is being given. Thereafter, slow tapering by 2.5 mg/wk is recommended. Approximately 20% of patients cannot be completely withdrawn from corticosteroids without experiencing a symptomatic flare-up. Furthermore, more than 50% of patients who achieve initial remission on corticosteroids will experience a relapse within 1 year. Use of long-term low corticosteroid doses (2.5–10 mg/day) should be avoided, because of associated complications (see above). Patients requiring long-term corticosteroid treatment should be given immunomodulatory drugs (as described below) in an effort to wean them from corticosteroids.

Patients with persisting symptoms despite oral corticosteroids or those with high fever, persistent vomiting, evidence of intestinal obstruction, severe weight loss, severe abdominal tenderness, or suspicion of an abscess should be hospitalized. In patients with a tender, palpable inflammatory abdominal mass, CT scan of the abdomen should be obtained prior to administering corticosteroids to rule out an abscess. If no abscess is identified, parenteral corticosteroids should be administered (as described for ulcerative colitis below).

4. Immunomodulating drugs: Azathioprine, mercaptopurine, or methotrexate—The two main indications for immunomodulators in Crohn disease are (1) for maintenance of remission after induction with corticosteroids; and (2) for the induction of remission, in combination with anti-TNF therapy, in patients with moderate to severe active Crohn disease (discussed in next section). In the United States, mercaptopurine or azathioprine are more commonly used than methotrexate. Immunomodulators are used in up to 60% of patients with Crohn disease for maintenance after induction of remission with corticosteroids. Although the magnitude of benefit is debated, metaanalysis of controlled trials suggest that patients treated with thiopurines are 2.3 times as likely to maintain remission as patients treated with placebo, reducing the 3-year relapse rate from more than 60% to less than 25%. Methotrexate (25 mg subcutaneously weekly for 12 weeks, followed by 12.5–15 mg once weekly) is used in patients who are unresponsive to, or intolerant of, mercaptopurine or azathioprine. Because oral absorption may be erratic, parenteral administration of methotrexate is preferred. Immunomodulators do not appear to be effective at inducing remission. Two 2013 randomized controlled trials in patients with newly diagnosed Crohn disease (treated with or without corticosteroids) found equivalent corticosteroid-free remissions rates in patients treated with thiopurines or placebo. A 2013 AGA guideline has recommended against the use of thiopurine monotherapy to induce remission.

5. Anti-TNF therapies—Infliximab, adalimumab, and certolizumab are used to induce and maintain remission in patients with moderate to severe Crohn disease,

including fistulizing disease. These agents are also used to treat extraintestinal manifestations of Crohn disease (except optic neuritis).

A. Acute induction therapy—Anti-TNF therapies are recommended as the preferred first-line agents to induce remission in patients with moderate to severe Crohn disease, either as monotherapy or in combination with thiopurines.

Currently, there are two major controversies about the use of anti-TNF agents: (1) whether anti-TNF agents should be reserved as second-line therapy in patients with moderate to severe Crohn disease who have not responded to prior therapy with corticosteroids and immunomodulators ("step-up" therapy) or whether it should be used early in the course of illness with the goal of inducing early remission and altering the natural history of the disease; (2) whether anti-TNF therapy should be used alone or in combination with an immunomodulator to enhance remission and reduce the development of antibodies to the anti-TNF agent. The best data support the use of anti-TNF agents early in the course of disease and suggest that "step-up therapy" (corticosteroids, followed by azathioprine, followed by infliximab) is obsolete. Furthermore, for most patients, anti-TNF therapy should be used in combination with an immunomodulator—at least during the first year of treatment. Data in support of use of early combination therapy come from a large 2010 trial (SONIC) that compared three treatment arms: combination therapy with infliximab and azathioprine versus infliximab alone or azathioprine alone in patients with moderate to severe Crohn disease who had not previously been treated with immunomodulators or anti-TNF agents. After 6 months, clinical remission (57%) and mucosal healing (44%) was significantly higher with combination therapy than with either agent alone. Combination therapy with anti-TNF and azathioprine may not be appropriate in men younger than 26 years of age in whom there is a higher risk of hepatosplenic T-cell lymphoma and in the elderly in whom there is a higher risk of lymphoma and infectious complications.

The doses for acute induction therapy are described above. Up to two-thirds of patients have significant clinical improvement during acute induction therapy.

B. Maintenance therapy—After initial clinical response, symptom relapse occurs in more than 80% of patients within 1 year in the absence of further maintenance therapy. Therefore, scheduled maintenance therapy is usually recommended (infliximab, 5 mg/kg infusion every 8 weeks; adalimumab, 40 mg subcutaneous injection every 2 weeks; certolizumab, 400 mg subcutaneous injection every 4 weeks). With long-term maintenance therapy, approximately two-thirds have continued clinical response and up to one-half have complete symptom remission. A gradual or complete loss of efficacy occurs over time in some patients, necessitating increased dosing (infliximab 10 mg/kg; adalimumab 80 mg), decreased dosing intervals (infliximab every 6 weeks; adalimumab every week), changing to the alternative agent, or discontinuation of anti-TNF therapy. In some cases, loss of efficacy is due to the development of antibodies to the anti-TNF agent. Concomitant therapy with anti-TNF agents and immunomodulating agents (azathioprine, mercaptopurine, or methotrexate) reduces the risk of development of antibodies to the anti-TNF agent but may increase the risk of complications (non-Hodgkin lymphoma and opportunistic infections). At this time, there is uncertainty

about whether combination therapy with anti-TNF agents and immunomodulators should be continued indefinitely or converted after 1–2 years to anti-TNF monotherapy.

6. Anti-integrins—Anti-integrins may offer a therapeutic option for patients who do not respond or who lose response to anti-TNF agents. Natalizumab, an antibody directed against the alpha4 integrin for the induction and maintenance of Crohn disease, demonstrated a 56% clinical response and 37% remission at 10 weeks. However, due to the subsequently recognized risk of reactivation of JC virus and development of PML and the advent of more gutspecific anti-integrins, natalizumab now has little use in inflammatory bowel disease.

Vedolizumab, a monoclonal antibody directed against the alpha4 beta7 heterodimer, was approved by the FDA in 2014 for the treatment of moderate to severe Crohn disease. Its purported specificity for gut leukocyte trafficking may mitigate the risk of PML. Pending further clinical studies, vedolizumab primarily is used in patients with moderate to severe Crohn disease in whom anti-TNF therapy has failed or is not tolerated. In a 2014 phase III trial among patients with Crohn disease who did not respond to prior anti-TNF therapy (due to loss of response or side effects), one-quarter (26.6%) of patients treated with vedolizumab (300 mg intravenously at weeks 0 and 2) were in clinical remission at week 10 versus 12.1% of placebo-treated patients. In another phase III trial, among patients demonstrating initial clinical improvement with vedolizumab induction therapy, 39% of patients treated with long-term vedolizumab (300 mg every 8 weeks) were in remission at 1 year compared with 21.6% of patients given placebo.

Indications for Surgery

Over 50% of patients will require at least one surgical procedure. The main indications for surgery are intractability to medical therapy, intra-abdominal abscess, massive bleeding, symptomatic refractory internal or perianal fistulas, and intestinal obstruction. Patients with chronic obstructive symptoms due to a short segment of ileal stenosis are best treated with resection or stricturoplasty (rather than longterm medical therapy), which promotes rapid return of wellbeing and elimination of corticosteroids. After surgery, endoscopic evidence of recurrence occurs in 60% within 1 year. Endoscopic recurrence precedes clinical recurrence by months to years; clinical recurrence occurs in 20% of patients within 1 year and 80% within 10–15 years. Therapy with metronidazole, 250 mg three times daily for 3 months, or long-term therapy with immunomodulators (mercaptopurine or azathioprine) has only been modestly effective in preventing clinical and endoscopic recurrence after ileocolic resection; however, small uncontrolled studies suggest that anti-TNF therapies may prevent endoscopic recurrence in up to 90% of patients. Clinicians may choose to perform endoscopy in high-risk patients 6–12 months after surgery in order to identify patients with early endoscopic recurrence who may benefit from anti-TNF therapy.

Prognosis

With proper medical and surgical treatment, the majority of patients are able

to cope with this chronic disease and its complications and lead productive lives. Few patients die as a direct consequence of the disease.

When to Refer

• For expertise in endoscopic procedures or capsule endoscopy.

• For follow-up of any patient requiring hospitalization.

• Patients with moderate to severe disease for whom therapy with immunomodulators or biologic agents is being considered.

• When surgery may be necessary

When to Admit

• An intestinal obstruction is suspected.

• An intra-abdominal or perirectal abscess is suspected.

• A serious infectious complication is suspected, especially in patients who are immunocompromised due to concomitant use of corticosteroids, immunomodulators, or anti-TNF agents.

• Patients with severe symptoms of diarrhea, dehydration, weight loss, or abdominal pain.

• Patients with severe or persisting symptoms despite treatment with corticosteroids.

Ulcerative Colitis

- ESSENTIALS OF DIAGNOSIS

- Bloody diarrhea.
- Lower abdominal cramps and fecal urgency.
- Anemia, low serum albumin.
- Negative stool cultures.
- Sigmoidoscopy is the key to diagnosis.

General Considerations

Ulcerative colitis is an idiopathic inflammatory condition that involves the mucosal surface of the colon, resulting in diffuse friability and erosions with bleeding. Approximately one-third of patients have disease confined to the rectosigmoid region (proctosigmoiditis); one-third have disease that extends to the splenic flexure (left-sided colitis); and one-third have disease that extends more proximally (extensive colitis). In patients with distal colitis, the disease progresses with time to more extensive involvement in 25–50%. There is some correlation between disease extent and symptom severity. In most patients, the disease is characterized by periods of symptomatic flareups and remissions. Ulcerative colitis is more common in nonsmokers and former smokers. Disease severity may be lower in active smokers and may worsen in patients who stop smoking. Appendectomy before the age of 20 years for acute appendicitis is associated with a reduced risk of developing ulcerative colitis.

Clinical Findings

A. Symptoms and Signs

The clinical profile in ulcerative colitis is highly variable. Bloody diarrhea is the hallmark. On the basis of several clinical and laboratory parameters, it is clinically useful to classify patients as having mild, moderate, or severe disease. Patients should be asked about stool frequency, the presence and amount of rectal bleeding, cramps, abdominal pain, fecal urgency, and tenesmus. Physical examination should focus on the patient's volume status as determined by orthostatic blood pressure and pulse measurements and by nutritional status. On abdominal examination, the clinician should look for tenderness and evidence of peritoneal inflammation. Red blood may be present on digital rectal examination.

1. Mild to moderate disease—Patients with mild disease have a gradual onset of infrequent diarrhea (less than four movements per day) with intermittent rectal bleeding and mucus. Stools may be formed or loose in consistency.

Because of rectal inflammation, there is fecal urgency and tenesmus. Left lower quadrant cramps relieved by defecation are common, but there is no significant abdominal tenderness. Patients with moderate disease have more severe diarrhea with frequent bleeding. Abdominal pain and tenderness may be present but are not severe. There may be mild fever, anemia, and hypoalbuminemia.

2. Severe disease—Patients with severe disease have more than six bloody bowel movements per day, resulting in severe anemia, hypovolemia, and impaired nutrition with hypoalbuminemia. Abdominal pain and tenderness are present. "Fulminant colitis" is a subset of severe disease characterized by rapidly worsening symptoms with signs of toxicity.

B. Laboratory Findings

The degree of abnormality of the hematocrit, sedimentation rate, and serum albumin reflects disease severity.

C. Endoscopy

In acute colitis, the diagnosis is readily established by sigmoidoscopy. The mucosal appearance is characterized by edema, friability, mucopus, and erosions. Colonoscopy should not be performed in patients with fulminant disease because of the risk of perforation. After patients have demonstrated improvement on therapy, colonoscopy is performed to determine the extent of disease.

D. Imaging

Plain abdominal radiographs are obtained in patients with severe colitis to look for significant colonic dilation. Barium enemas are of little utility in the evaluation of acute ulcerative colitis and may precipitate toxic megacolon in patients with severe disease.

Differential Diagnosis

The initial presentation of ulcerative colitis is indistinguishable from other

causes of colitis, clinically as well as endoscopically. Thus, the diagnosis of idiopathic ulcerative colitis is reached after excluding other known causes of colitis. Infectious colitis should be excluded by sending stool specimens for routine bacterial cultures (to exclude Salmonella, Shigella, and Campylobacter, as well as specific assays for E coli O157), ova and parasites (to exclude amebiasis), and stool toxin assay for C difficile. Mucosal biopsy can distinguish amebic colitis from ulcerative colitis. CMV colitis occurs in immunocompromised patients, including patients receiving prolonged corticosteroid therapy, and is diagnosed on mucosal biopsy. Gonorrhea, chlamydial infection, herpes, and syphilis are considerations in sexually active patients with proctitis. In elderly patients with cardiovascular disease, ischemic colitis may involve the rectosigmoid. A history of radiation to the pelvic region can result in proctitis months to years later. Crohn disease involving the colon but not the small intestine may be confused with ulcerative colitis. In 10% of patients, a distinction between Crohn disease and ulcerative colitis may not be possible.

Treatment

There are two main treatment objectives: (1) to terminate the acute, symptomatic attack and (2) to prevent recurrence of attacks. The treatment of acute ulcerative colitis depends on the extent of colonic involvement and the severity of illness.

Patients with mild to moderate disease should eat a regular diet but limit their intake of caffeine and gasproducing vegetables. Antidiarrheal agents should not be given in the acute phase of illness but are safe and helpful in patients with mild chronic symptoms. Oral loperamide (2 mg) or diphenoxylate with atropine (one tablet) may be given up to four times daily. Such remedies are particularly useful at nighttime and when taken prophylactically for occasions when patients may not have reliable access to toilet facilities.

A. Mild to Moderate Distal Colitis

Patients with disease confined to the rectum or rectosigmoid region generally have mild to moderate but distressing symptoms. Patients may be treated with topical mesalamine, topical corticosteroids, or oral aminosalicylates (5-ASA) according to patient preference and cost considerations. Topical mesalamine is the drug of choice and is superior to topical corticosteroids and 5-ASA. Mesalamine is administered as a suppository, 1000 mg once daily at bedtime for proctitis, and as an enema, 4 g at bedtime for proctosigmoiditis, for 4–12 weeks, with 75% of patients improving. Patients who either decline or are unable to manage topical therapy may be treated with oral 5-ASA, as discussed below. Topical corticosteroids are a less expensive alternative to mesalamine but are also less effective. Hydrocortisone suppository or foam is prescribed for proctitis and hydrocortisone enema (80–100 mg) for proctosigmoiditis. Systemic effects from short-term use are very slight. For patients with distal disease who do not improve with topical or oral mesalamine therapy, the following options may be considered: (1) a combination of a topical agent with an oral 5-ASA agent is more effective

than either drug alone; (2) combination topical therapy with a 5-ASA suppository or enema at bedtime and a corticosteroid enema or foam in the morning; or (3) a combination of oral 5-ASA agent, topical 5-ASA agent, and a topical corticosteroid. Patients with distal colitis who are refractory to all of these therapies or who have severe disease may require treatment with oral prednisone 40–60 mg/day or infliximab, as described below.

Patients whose acute symptoms resolve rapidly with immediate therapy may have prolonged periods of remission that are treated successfully with intermittent courses of therapy. Patients with early or frequent relapse should be treated with maintenance therapy with mesalamine suppositories (1000 mg) or enemas (4 g) nightly or every other night. For patients who have difficulty complying with topical therapies, oral 5-ASA agents are an acceptable, though possibly less effective, alternative (see below). Topical corticosteroids are ineffective for maintaining remission of distal colitis.

B. Mild to Moderate Colitis

1. 5-ASA Agents—Disease extending above the sigmoid colon is best treated with oral 5-ASA agents (mesalamine, balsalazide, or sulfasalazine), which result in symptomatic improvement in 50–75% of patients. The optimal dose for induction of remission of mild disease is 2.4 g daily and for moderate disease is 2.4–4.8 g daily. Most patients improve within 3–6 weeks, though some require 2–3 months. These agents achieve clinical improvement in 50–70% of patients and remission in 20–30%. Oral sulfasalazine is comparable in efficacy to mesalamine and because of its low cost is still commonly used as a first-line agent by many providers, though it is associated with greater side effects. To minimize side effects, sulfasalazine is begun at a dosage of 500 mg twice daily and increased gradually over 1–2 weeks to 2 g twice daily. Total doses of 5–6 g/day may have greater efficacy but are poorly tolerated. Folic acid, 1 mg/day orally, should be administered to all patients taking sulfasalazine.

2. Corticosteroids—Patients with mild to moderate disease who do not improve within 4 weeks of 5-ASA therapy should have corticosteroid therapy added. Prednisone and methylprednisolone are most commonly used. Depending on the severity of illness, the initial oral dose of prednisone is 40–60 mg daily. Rapid improvement is observed in most cases within 2 weeks. Thereafter, tapering of prednisone should proceed by 5–10 mg/wk. After tapering to 20 mg/day, slower tapering (2.5 mg/week) is sometimes required. Complete tapering without symptomatic flare-ups is possible in the majority of patients. Delayed-release budesonide (Uceris) 9 mg ER orally once daily has shown modest benefit in mild to moderate colitis, achieving remission in 17.5% of patients after 8 weeks compared with 12.5 % with placebo. In view of its low incidence of corticosteroidassociated side-effects, it may be considered in patients with mild colitis for whom other systemic corticosteroids are deemed high risk.

3. Immunomodulating agents—Approximately 30% of patients either do

not respond to corticosteroids or have symptomatic flares during attempts at corticosteroid tapering and develop steroid dependency. Patients with steroid dependency or frequent relapse while taking mesalamine may be treated with thiopurines (mercaptopurine or azathioprine), although rigorous controlled trials are lacking and their absolute benefit appears to be modest. The risks of these drugs must be weighed against the certainty of cure with surgical resection. There is less evidence that methotrexate is effective.

The anti-TNF agents infliximab, adalimumab, and golimumab are approved in the United States for the treatment of patients with moderate to severe ulcerative colitis who have had an inadequate response to conventional therapies (oral corticosteroids, mercaptopurine or azathioprine, and mesalamine). Following a three-dose induction regimen of infliximab 5 mg/kg administered at 0, 2, and 6 weeks, clinical response occurs in 65% and clinical remission in 35%. By comparison, phase III trials of adalimumab and golimumab reported clinical response rates of 50–59% and remission rates of 16–21% after 8 weeks. Although the response and remission rates appear lower with adalimumab and golimumab than infliximab, differences in study design and patient populations limit comparisons. Importantly, 40% of patients in the adalimumab trials were previously treated with other anti-TNF agents, in whom lower response rates were noted.

4. Anti-integrin therapy—Vedolizumab, a monoclonal antibody directed against the the alpha4 beta7 heterodimer, was approved in 2014 for the treatment of moderate to severe ulcerative colitis in patients who have not responded, lost response, or been intolerant of other therapies. In a phase III clinical trial of patients with moderate to severe ulcerative colitis, vedolizumab induction (300 mg intravenously at 0 and 2 weeks) led to clinical improvement at 6 weeks in 47.1% of patients compared with 25.5% who were given placebo. Among patients who demonstrated initial clinical improvement, 41.8% of those given long-term maintenance treatment with vedolizumab (300 mg intravenous every 8 weeks) were in clinical remission at 1 year compared with 15.9% of those given placebo. Pending further clinical studies, vedolizumab may be recommended for patients with moderate to severe ulcerative colitis who have not responded to therapy with anti-TNF or immunomodulator therapies or both.

5. Probiotics—VSL#3 (two packets twice daily), a probiotic compound containing eight different nonpathogenic strains of lactobacilli, bifidobacteria, and streptococci, has demonstrated significant benefit versus placebo in the treatment of mild to moderate ulcerative colitis in two randomized, controlled multicenter trials. Although its efficacy relative to other agents is unclear, it may be considered as an adjunctive therapy for mild to moderate disease.

C. Severe and Fulminant Colitis

About 15% of patients with ulcerative colitis have a more severe course. Of these, a small subset has a fulminant course with rapid progression of symptoms over 1–2 weeks and signs of severe toxicity. These patients appear quite ill, with

fever, prominent hypovolemia, hemorrhage requiring transfusion, and abdominal distention with tenderness. Toxic megacolon develops in less than 2% of cases of ulcerative colitis. It is characterized by colonic dilation of more than 6 cm on plain films with signs of toxicity.

1. General measures—Discontinue all oral intake for 24–48 hours or until the patient demonstrates clinical improvement. TPN is indicated only in patients with poor nutritional status or if feedings cannot be reinstituted within 7–10 days. All opioid or anticholinergic agents should be discontinued. Restore circulating volume with fluids, correct electrolyte abnormalities, and consider transfusion for significant anemia (hematocrit less than 25–28%). A plain abdominal radiograph should be ordered on admission to look for evidence of colonic dilation. Send stools for bacterial culture, C difficile toxin assay, and examination for ova and parasites. CMV superinfection should be considered in patients receiving long-term immunosuppressive therapy who are unresponsive to corticosteroid therapy. Due to a high risk of venous thromboembolic disease, prophylaxis should be administered to all hospitalized patients with inflammatory bowel disease. Surgical consultation should be sought for all patients with severe disease. Patients with fulminant disease are at higher risk for perforation or toxic megacolon and must be monitored closely. Abdominal examinations should be repeated to look for evidence of worsening distention or pain. Broadspectrum antibiotics should be administered to cover anaerobes and gram-negative bacteria. In addition to the therapies outlined above, nasogastric suction should be initiated. Patients should be instructed to roll from side to side and onto the abdomen in an effort to decompress the distended colon. Serial abdominal plain films should be obtained to look for worsening dilation or signs of ischemia. Patients with fulminant disease or toxic megacolon who worsen or do not improve within 48–72 hours should undergo surgery to prevent perforation. If the operation is performed before perforation, the mortality rate should be low.

2. Corticosteroid therapy—Methylprednisolone, 48–64 mg, or hydrocortisone, 300 mg, is administered intravenously in four divided doses or by continuous infusion over 24 hours. Higher or "pulse" doses are of no benefit. Hydrocortisone enemas (100 mg) may also be administered twice daily for treatment of urgency or tenesmus. Approximately 50–75% of patients achieve remission with systemic corticosteroids within 7–10 days. Once symptomatic improvement has occurred, oral fluids are reinstituted. If fluids are well tolerated, intravenous corticosteroids are discontinued and the patient is started on oral prednisone (as described for moderate disease). Patients without significant improvement within 3–5 days of intravenous corticosteroid therapy should be referred for surgery or considered for anti-TNF therapies or cyclosporine.

3. Anti-TNF therapies—A single infusion of infliximab, 5 mg/kg, has been shown in controlled and uncontrolled studies to be effective in treating severe colitis in patients who did not improve within 4–7 days of intravenous corticosteroid therapy. In a controlled study of patients hospitalized for ulcerative colitis, colectomy was required within 3 months in 69% who received placebo therapy, compared with 47% who received infliximab. Thus, infliximab therapy

should be considered in patients with severe ulcerative colitis who have not improved with intravenous corticosteroid therapy. (See Crohn Disease, above.)

4. Cyclosporine—Intravenous cyclosporine (2–4 mg/kg/day as a continuous infusion) benefits 60–75% of patients with severe colitis who have not improved after 7–10 days of corticosteroids, but it is associated with significant toxicity (nephrotoxicity, seizures, infection, hypertension). Up to two-thirds of responders may be maintained in remission with a combination of oral cyclosporine for 3 months and long-term therapy with mercaptopurine or azathioprine. A 2011 randomized study of patients with severe colitis refractory to intravenous corticosteroids found similar response rates (85%) with cyclosporine and infliximab therapy.

5. Surgical therapy—Patients with severe disease who do not improve after corticosteroid, infliximab, or cyclosporine therapy are unlikely to respond to further medical therapy, and surgery is recommended.

Maintenance of Remission

Without long-term therapy, 75% of patients who initially go into remission on medical therapy will experience a symptomatic relapse within 1 year. Long-term oral maintenance therapy with sulfasalazine, 1–1.5 g twice daily, or mesalamine, 1.6–2.4 g once daily, have been shown to reduce relapse rates to less than 35%. Mercaptopurine and azathioprine are useful in patients with frequent disease relapses (more than two per year) or corticosteroiddependent disease to maintain remission. The role of longterm infliximab therapy in the maintenance of remission is evolving. In two, large, controlled studies of patients with active moderate to severe colitis, initial induction therapy was followed by infliximab maintenance infusions (5 mg/kg) administered every 8 weeks for 30–54 weeks. At the end of the study (30 or 54 weeks), 35% were in clinical remission, (21% in corticosteroid-free remission), a modest but impressive response in patients with more refractory disease. In considering long-term infliximab therapy, patients and clinicians need to weigh the long-term risks of immunosuppression against colectomy.

Risk of Colon Cancer

In patients with ulcerative colitis with disease proximal to the rectum and in patients with Crohn colitis, there is a markedly increased risk of developing colon carcinoma. A large meta-analysis of observational studies reported a cumulative incidence of 2% at 10 years, 8% at 20 years, and 18% after 30 years of disease. Retrospective studies suggest that the risk of colon cancer may be reduced in patients treated with long-term 5-ASA therapy. Ingestion of folic acid, 1 mg/day, also is associated with a decreased risk of cancer development. Colonoscopies are recommended every 1–2 years in patients with colitis, beginning 8 years after diagnosis. Several prospective studies demonstrate that dye spraying with methylene blue or indigo carmine (“chromoendoscopy”) enhances the detection of subtle mucosal lesions, thereby significantly increasing the detection of dysplasia compared with standard colonoscopy. At colonoscopy, all adenoma-like polyps should be resected, when possible, and biopsies obtained of non-endoscopically

resectable mass lesions.

Surgery in Ulcerative Colitis

Surgery is required in 25% of patients. Severe hemorrhage, perforation, and documented carcinoma are absolute indications for surgery. Surgery is indicated also in patients with fulminant colitis or toxic megacolon that does not improve within 48–72 hours, in patients with flat dysplasia or nonendoscopically resectable dysplastic lesions on surveillance colonoscopy, and in patients with refractory disease requiring long-term corticosteroids to control symptoms.

Although total proctocolectomy (with placement of an ileostomy) provides complete cure of the disease, most patients seek to avoid it out of concern for the impact it may have on their bowel function, their self-image, and their social interactions. After complete colectomy, patients may have a standard ileostomy with an external appliance, a continent ileostomy, or an internal ileal pouch that is anastomosed to the anal canal (ileal pouch-anal anastomosis). The latter maintains intestinal continuity, thereby obviating an ostomy. Under optimal circumstances, patients have five to seven loose bowel movements per day without incontinence. Endoscopic or histologic inflammation in the ileal pouch ("pouchitis") develops in over 40% of patients, resulting in increased stool frequency, fecal urgency, cramping, and bleeding, but usually resolves with a 2-week course of oral metronidazole (250–500 mg three times daily) or ciprofloxacin (500 mg twice daily). Patients with frequently relapsing pouchitis may need continuous antibiotics. Probiotics containing nonpathogenic strains of lactobacilli, bifidobacteria, and streptococci (VSL#3) are effective in the maintenance of remission in patients with recurrent pouchitis. Bismuth subsalicylate (Pepto Bismol, 262 mg, two tablets four times daily) has demonstrated benefit in some series. Some clinicians report that topical corticosteroids or oral budesonide 9 mg/day are of benefit. Refractory cases of pouchitis can be disabling and may require conversion to a standard ileostomy.

Prognosis

Ulcerative colitis is a lifelong disease characterized by exacerbations and remissions. For most patients, the disease is readily controlled by medical therapy without need for surgery. The majority never require hospitalization. A subset of patients with more severe disease will require surgery, which results in complete cure of the disease. Properly managed, most patients with ulcerative colitis lead close to normal productive lives.

When to Refer

• Colonoscopy: for evaluation of activity and extent of active disease and for surveillance for neoplasia in patients with quiescent disease for more than 8–10 years.

• For follow-up of any patient requiring hospitalization.

• When surgical colectomy is indicated.

When to Admit

• Patients with severe disease manifested by frequent bloody stools, anemia, weight loss, and fever.

• Patients with fulminant disease manifested by rapid progression of symptoms, worsening abdominal pain, distention, high fever, tachycardia.

• Patients with moderate to severe symptoms that do not respond to oral corticosteroids and require a trial of bowel rest and intravenous corticosteroids.

HEMORRHOIDS

ESSENTIALS OF DIAGNOSIS

- Bright red blood per rectum.
- Protrusion, discomfort.
- Characteristic findings on external anal inspection and anoscopic examination.

General Considerations

Internal hemorrhoids are subepithelial vascular cushions consisting of connective tissue, smooth muscle fibers, and arteriovenous communications between terminal branches of the superior rectal artery and rectal veins. They are a normal anatomic entity, occurring in all adults, that contribute to normal anal pressures and ensure a water-tight closure of the anal canal. They commonly occur in *three primary locations—right anterior, right posterior, and left lateral*. *External hemorrhoids* arise from the inferior hemorrhoidal veins located below the dentate line and are covered with squamous epithelium of the anal canal or perianal region.

Hemorrhoids may become symptomatic as a result of activities that increase venous pressure, resulting in distention and engorgement. Straining at stool, constipation, prolonged sitting, pregnancy, obesity, and low-fiber diets all may contribute. With time, redundancy and enlargement of the venous cushions may develop and result in bleeding or protrusion.

Clinical Findings

A. Symptoms and Signs

Patients often attribute a variety of perianal complaints to “hemorrhoids.” However, the principal problems attributable to internal hemorrhoids are bleeding, prolapse, and mucoid discharge. Bleeding is manifested by bright red blood that may range from streaks of blood visible on toilet paper or stool to bright red blood that drips into the toilet bowl after a bowel movement. Uncommonly, bleeding is severe and prolonged enough to result in anemia. Initially, internal hemorrhoids are confined to the anal canal (stage I). Over time, the internal hemorrhoids may gradually enlarge and protrude from the anal opening. At first, this mucosal prolapse occurs during straining and reduces spontaneously (stage II). With progression over time, the prolapsed hemorrhoids may require manual reduction after bowel movements (stage III) or may remain chronically protruding (stage IV). Chronically prolapsed hemorrhoids may result in a sense of fullness or discomfort and mucoid perianal discharge, resulting in irritation and soiling of underclothes.

Pain is unusual with internal hemorrhoids, occurring only when there is extensive inflammation and thrombosis of irreducible tissue or with thrombosis of an external hemorrhoid (see below).

B. Examination

External hemorrhoids are readily visible on perianal inspection. Nonprolapsed internal hemorrhoids are not visible but may protrude through the anus with gentle straining while the clinician spreads the buttocks. Prolapsed hemorrhoids are visible as protuberant purple nodules covered by mucosa. The perianal region should also be examined for other signs of disease such as fistulas, fissures, skin tags, condyloma, anal cancer, or dermatitis. On digital examination, uncomplicated internal hemorrhoids are neither palpable nor painful. Anoscopic evaluation, best performed in the prone jackknife position, provides optimal visualization of internal hemorrhoids.

Differential Diagnosis

Small volume rectal bleeding may be caused by anal fissure or fistula, neoplasms of the distal colon or rectum, ulcerative colitis or Crohn colitis, infectious proctitis, or rectal ulcers. Rectal prolapse, in which a full thickness of rectum protrudes concentrically from the anus, is readily distinguished from mucosal hemorrhoidal prolapse. Proctosigmoidoscopy or colonoscopy should be performed in all patients with hematochezia to exclude disease in the rectum or sigmoid colon that could be misinterpreted in the presence of hemorrhoidal bleeding.

Treatment

A. Conservative Measures

Most patients with early (stage I and stage II) disease can be managed with conservative treatment. To decrease straining with defecation, patients should be given instructions for a high-fiber diet and told to increase fluid intake with meals. Dietary fiber may be supplemented with bran powder (1–2 tbsp twice daily added to food or in 8 oz of liquid) or with commercial bulk laxatives (eg, Benefiber, Metamucil, Citrucel). Suppositories and rectal ointments have no demonstrated utility in the management of mild disease. Mucoid discharge may be treated effectively by the local application of a cotton ball tucked next to the anal opening after bowel movements.

B. Medical Treatment

Patients with stage I, stage II, and stage III hemorrhoids and recurrent bleeding despite conservative measures may be treated without anesthesia with injection sclerotherapy, rubber band ligation, or application of electrocoagulation (bipolar cautery or infrared photocoagulation). The choice of therapy is dictated by operator preference, but rubber band ligation is preferred due to its ease of use and high rate of efficacy. Major complications occur in less than 2%, including pelvic sepsis, pelvic abscess, urinary retention, and bleeding. Recurrence is common

unless patients alter their dietary habits. Edematous, prolapsed (stage IV) internal hemorrhoids, may be treated acutely with topical creams, foams, or suppositories containing various combinations of emollients, topical anesthetics, (eg, pramoxine, dibucaine), vasoconstrictors (eg, phenylephrine), astringents (witch hazel) and corticosteroids. Common preparations include Preparation H (several formulations), Anusol HC, Proctofoam, Nupercainal, Tucks, and Doloproct (not available in the United States).

C. Surgical Treatment

Surgical excision (hemorrhoidectomy) is reserved for less than 5–10% of patients with chronic severe bleeding due to stage III or stage IV hemorrhoids or patients with acute thrombosed stage IV hemorrhoids with necrosis. Complications of surgical hemorrhoidectomy include postoperative pain (which may persist for 2–4 weeks) and impaired continence.

Thrombosed External Hemorrhoid

Thrombosis of the external hemorrhoidal plexus results in a perianal hematoma. It most commonly occurs in otherwise healthy young adults and may be precipitated by coughing, heavy lifting, or straining at stool. The condition is characterized by the relatively acute onset of an exquisitely painful, tense and bluish perianal nodule covered with skin that may be up to several centimeters in size. Pain is most severe within the first few hours but gradually eases over 2–3 days as edema subsides. Symptoms may be relieved with warm sitz baths, analgesics, and ointments. If the patient is evaluated in the first 24–48 hours, removal of the clot may hasten symptomatic relief. With the patient in the lateral position, the skin around and over the lump is injected subcutaneously with 1% lidocaine using a tuberculin syringe with a 30-gauge needle. An ellipse of skin is then excised and the clot evacuated. A dry gauze dressing is applied for 12–24 hours, and daily sitz baths are then begun.

When to Refer

• Stage I, II, or III: When conservative measures fail and expertise in medical procedures is needed (injection, banding, thermocoagulation).

• Stage IV: When surgical excision is required.

FECAL INCONTINENCE

There are five general requirements for bowel continence: (1) solid or semisolid stool (even healthy young adults have difficulty maintaining continence with liquid rectal contents); (2) a distensible rectal reservoir (as sigmoid contents empty into the rectum, the vault must expand to accommodate); (3) a sensation of rectal fullness (if the patient cannot sense this, overflow may occur before the patient can take appropriate action); (4) intact pelvic nerves and muscles; and (5) the ability to reach a toilet in a timely fashion.

Minor Incontinence

Many patients complain of inability to control flatus or slight soilage of undergarments that tends to occur after bowel movements or with straining or coughing. This may be due to local anal problems such as prolapsed hemorrhoids that make it difficult to form a tight anal seal or isolated weakness of the internal anal sphincter, especially if stools are somewhat loose. Patients should be treated with fiber supplements to provide greater stool bulk. Coffee and other caffeinated beverages should be eliminated. The perianal skin should be cleansed with moist, lanolincoated tissue (baby wipes) to reduce excoriation and infection. After wiping, loose application of a cotton ball near the anal opening may absorb small amounts of fecal leakage. Prolapsing hemorrhoids may be treated with band ligation or surgical hemorrhoidectomy. Control of flatus and seepage may be improved by Kegel perineal exercises. Conditions such as ulcerative proctitis that cause tenesmus and urgency, chronic diarrheal conditions, and irritable bowel syndrome may result in difficulty in maintaining complete continence, especially if a toilet is not readily available. Loperamide may be helpful to reduce urge incontinence in patients with loose stools and may be taken in anticipation of situations in which a toilet may not be readily available. The elderly may require more time or assistance to reach a toilet, which may lead to incontinence. Scheduled toileting and the availability of a bedside commode are helpful. Elderly patients with chronic constipation may develop stool impaction leading to “overflow” incontinence.

Major Incontinence

Complete uncontrolled loss of stool reflects a significant problem with central perception or neuromuscular function. Incontinence that occurs without awareness suggests a loss of central awareness (eg, dementia, cerebrovascular accident, multiple sclerosis) or peripheral nerve injury (eg, spinal cord injury, cauda equina syndrome, pudendal nerve damage due to obstetric trauma or pelvic floor prolapse, aging, or diabetes mellitus). Incontinence that occurs despite awareness and active efforts to retain stool suggests sphincteric damage, which may be caused by traumatic childbirth (especially forceps delivery), episiotomy, prolapse, prior anal surgery, and physical trauma.

Physical examination should include careful inspection of the perianal area for hemorrhoids, rectal prolapse, fissures, fistulas, and either gaping or a keyhole defect of the anal sphincter (indicating severe sphincteric injury or neurologic disorder). The perianal skin should be stimulated to confirm an intact anocutaneous reflex. Digital examination during relaxation gives valuable information about resting tone (due mainly to the internal sphincter) and contraction of the external sphincter and pelvic floor during squeezing. It also excludes fecal impaction. Anoscopy is required to evaluate for hemorrhoids, fissures, and fistulas. Proctosigmoidoscopy is useful to exclude rectal carcinoma or proctitis. Anal ultrasonography or pelvic MRI is the most reliable test for definition of anatomic defects in the external and internal anal sphincters. Anal manometry may also be useful to define the severity of weakness, to assess sensation, and to predict

response to biofeedback training. In special circumstances, surface electromyography is useful to document sphincteric denervation and proctography to document perineal descent or rectal intussusception.

Patients who are incontinent only of loose or liquid stools are treated with bulking agents and antidiarrheal drugs (eg, loperamide, 2 mg before meals and prophylactically before social engagements, shopping trips, etc). Patients with incontinence of solid stool benefit from scheduled toilet use after glycerin suppositories or tap water enemas. Biofeedback training with anal sphincteric strengthening (Kegel) exercises (alternating 5-second squeeze and 10-second rest for 10 minutes twice daily) may be helpful in motivated patients to lower the threshold for awareness of rectal filling—or to improve anal sphincter squeeze function—or both. In 2012, the FDA approved two interventions for fecal incontinence. The first is a sterile gel (containing dextranomer and sodium hyaluronate) for submucosal injection into the proximal anal canal for the treatment of anal incontinence for patients who have not responded to conservative therapies, such as fiber supplements and antidiarrheal agents. This treatment is hypothesized to reduce incontinence episodes by bulking and narrowing the anal canal. In clinical trials, more than onehalf of treated patients reported a greater than 50% reduction in the number of fecal incontinence episodes. The second is a sacral nerve stimulation device. In uncontrolled trials in selected patients, 83% of patients were improved with sacral stimulation. Further study is needed to determine optimal candidates and the true efficacy of these treatments. Operative management is seldom needed but should be considered in patients with major incontinence due to prior injury to the anal sphincter who have not responded to medical therapy.

When to Refer

•Conservative measures fail.

•Anorectal tests are deemed necessary (manometry, ultrasonography, electromyography).

•A surgically correctable lesion is suspected.

Control questions

1. Anatomy and physiology of the small intestine.
2. Anatomical-physiological features of the large intestine.
3. Subjective and objective methods of studying the intestines.
4. Laboratory methods of intestinal examination (coprological examination).
5. Instrumental methods of studying the intestines.
6. Acute enterocolitis - etiopathogenesis, clinical picture, treatment, prevention.
7. Chronic enterocolitis - etiology, pathogenesis, clinical picture, course, treatment, prevention.
8. Pharmacotherapy of chronic enteritis.
9. Etiology, pathogenesis, clinical picture, course, treatment, prevention of chronic colitis.

10. Pharmacotherapy of chronic colitis:
11. Complications of pharmacotherapy of chronic colitis.
12. Nonspecific ulcerative colitis - etiology, pathogenesis, clinical picture, complications.
13. Pharmacotherapy of nonspecific ulcerative colitis.
14. Crohn's disease - etiology, pathogenesis, clinical picture, pharmacotherapy, complications.
15. Urgent medical aid for intestinal colic.

List of practical works

A. Homework.

1. To know the classification and the clinic of diseases of the intestines.
2. To study the main directions of treatment of diseases of the intestine.
3. Be able to provide first aid to a patient with an intestinal plague.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data of laboratory and instrumental studies, examination of consultants, records of the attending physician) and the letter of medical appointments.
3. At examination of the patient to allocate subjective, physical, laboratory-instrumental signs of diseases of the intestines.
4. Write a clinical diagnosis:
5. a) the underlying disease; complications of the underlying disease;
6. b) concomitant diseases.
7. Determine a group of lesions necessary for correction of existing disorders.
8. On the basis of theoretical data and own observations, to make a choice of the specific drug of the examined patient.
9. To substantiate the duration of basic and supportive therapy.
10. To make a plan of urgent medical help at intestinal colic.

Control the level of knowledge

1. Fill in the table "Diagnostic capabilities of objective methods for the study of patients with intestinal diseases".

Parameters	Definition	Diagnostic value
1.Outlook		
2.Percussion		
3.Palpation		

4. Auscultation		

2. Fill in the table "Diagnostic value, essence of instrumental methods of intestinal studies".

Research methods	**Definition, the essence of the method**	**Diagnostic capabilities of the method**
Radiation: -radiography -radioscopy -tomography		
Instrumental: - irrigoscopy - colonoscopy - rectoromanoscopy		

3. To make a scheme of treatment of nonspecific ulcerative colitis indicating the directions of pharmacotherapy and the names of the means.

№	**Kind Pharmacotherapy**	**Pharmacotherapeutic groups**	**Medicine**
1.	Etiotropic therapy		
2.	Pathogenetic		
3.	Symptomatic		

4. To lay the scheme of pharmacotherapy for acute Crohn's disease:

№	**Kind pharmacotherapy**	**Pharmacotherapeutic Groups**	**Medicine**	**Direction and purpose of pharmacotherapy**
1.	Etiotropic therapy			
2.	Pathogenetic			
3.	Symptomatic			

5. To make the scheme of treatment of acute enterocolitis:

№	Kind pharmacotherapy	Direction and purpose	Medicine
1.	Etiotropic therapy		
2.	Pathogenetic		
3.	Symptomatic		

6. To make the scheme of treatment of chronic enterocolitis:

№	Kind Pharmacotherapy	Direction and purpose	Medicine
1.	Etiotropic therapy		
2.	Pathogenetic		
3.	Symptomatic		

7. To make the scheme of treatment of intestinal colic:

№	Pharmacotherapeutic groups	Direction and purpose	Medicine

Solution of situational tasks

1. In the admission department of the infectious disease hospital three patients were received within 6 hours with suspected food poisoning. Patients are concerned about thirst, diarrhea (up to 10-12 times a day), which began several hours ago. The diarrhea was initially fecal, then liquid watery, in the form of rice broth. One patient had a vomiting fountain without nausea and pain in the epigastrium. From anamnesis of the disease - all three used to eat fish caught from standing water 2-3 days ago. When examined by patients, attention is drawn to their difficult condition, dry skin, tongue, adynamia, inflamed stomach.

What can a previous diagnosis be? Directions of pharmacotherapy.

2. In the admission department of the infectious disease hospital, a patient with complaints of nausea, vomiting eaten food, abdominal pain, dizziness, weakness, body temperature up to 38^0C, diarrhea. The survey found that the patient 4-5 hours ago ate cakes with meat bought from a merchant on the beach.

What is the reason for such a patient's condition? Directions of pharmacotherapy.

3. In the patient for 45 years against the background of intensive antimicrobial therapy there were abdominal pain, frequent vaginal discharge. How to explain these symptoms? What is the correction of these complications?

4. A patient with 31 years diagnosed with non-specific ulcerative colitis. What is a disease clinic? Identify treatment tactics.

5. Assign treatment to a patient with chronic colitis, which is accompanied by a constipation.

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TOPIC 11, 12 Pharmacotherapy of diseases of the liver, gall bladder and pancreas.

Actuality of topic.

Diseases of the liver and gall bladder constitute a large section of the pathology faced by pharmacists and doctors of many specialties (infectionists, therapists, surgeons). The liver undergoes major transformations of the drug, undergo metabolism, their inactivation, the appearance of biological activity and even toxicity to the body. On the other hand, drugs themselves can cause liver damage (toxic hepatitis, chronic active and cholestatic hepatitis). Formation and allocation of bile, disorders of the gallbladder may be accompanied by diseases of the liver parenchyma, as well as cause a second time its damage. In the case of gall bladder disease, acute conditions (liver colic) occur when it is necessary to provide urgent care to the patient. The need for knowledge of the main groups of drugs that improve the function of the liver cells and affect the processes of biliary excretion, the ability to apply them to a particular patient, depending on the nature and course of the pathological process, determine the importance of this topic for future pharmacists.

Unnecessary prescription of a large number of drugs, self-medication, and ecological tension of the environment lead to an increased risk of toxic effects of exogenous chemicals on the human body. In the first place, this relates to the liver - the body of the "target", which plays a leading role in the biotransformation of xenobiotics, which can affect the liver and cause specific dose-dependent changes on the part of its function and morphological structure. In recent years, there is an increase in the incidence of liver viral etiology, which is more dangerous to its complications.

Pancreatitis - inflammatory and autoimmune diseases of the pancreas, which often occur as a serious pathology. Acute pancreatitis is one of the most difficult problems of urgent surgery of the abdominal cavity. Recent years are characterized by a steady increase in the incidence of acute pancreatitis, accounting for about 8% of the contingent of surgical inpatient facilities, and the frequency ranks third after acute appendicitis and acute cholecystitis. Pancreatitis chronic - chronic inflammation of the pancreas. Occasionally occurs in the middle and in the elderly, more often in women. Distinguish primary chronic pancreatitis and secondary, or related, developing against the background of other diseases of the digestive tract (chronic gastritis, cholecystitis, enteritis, etc.). Long-term acute pancreatitis can be chronic, but more often it is formed gradually against a background of chronic cholecystitis, gallstone disease or under the influence of unsystematic irregular nutrition, frequent use of acute and fatty foods, chronic alcoholism, especially when combined with a systematic deficiency in the diet of proteins and vitamins , penetration of ulcers of the stomach or duodenum into the pancreas, atherosclerotic lesion of the pancreas, infectious diseases (especially in infectious parotitis, abdominal typhus, viral hepatitis), some hepmintozah, chronic intoxication with lead, mercury, phosphorus, arsenic.

Purpose of the lesson. To learn etiopathogenetic factors of diseases of the liver, biliary tract; Requirements for medicinal products used to treat liver and gall bladder. Students should know: etiology, pathogenesis, clinical manifestations, methods of diagnosis of acute and chronic hepatitis, directions of pharmacotherapy; liver cirrhosis: etiology, pathogenesis, clinic, diagnostic methods, principles of treatment of acute and chronic cholecystitis: etiology, pathogenesis, clinic, diagnostic methods, principles of treatment; Functional diseases of the gallbladder: methods of diagnosis and treatment.

The student should know the features of the functions of the pancreas. To learn the etiopathogenetic factors of diseases of the pancreas, requirements for medicines used for the treatment of pancreatic diseases (acute and chronic pancreatitis).

LIVER STRUCTURE AND FUNCTION

The liver is the largest organ of the body, weighing 1–1.5 kg and representing 1.5–2.5% of the lean body mass. The size and shape of the liver vary and generally match the general body shape—long and lean or squat and square. This organ is located in the right upper quadrant of the abdomen under the right lower rib cage against the diaphragm and projects for a variable extent into the left upper quadrant. It is held in place by ligamentous attachments to the diaphragm, peritoneum, great vessels, and upper gastrointestinal organs. The liver receives a dual blood supply; ~20% of the blood flow is oxygen-rich blood from the hepatic artery, and 80% is nutrient-rich blood from the portal vein arising from the stomach, intestines, pancreas, and spleen.

The majority of cells in the liver are hepatocytes, which constitute two-thirds of the organ’s mass. The remaining cell types are Kupffer cells (members of the reticuloendothelial system), stellate (Ito or fatstoring) cells, endothelial and blood vessel cells, bile ductular cells, and cells of supporting structures. Viewed by light microscopy, the liver appears to be organized in lobules, with portal areas at the periphery and central veins in the center of each lobule. However, from a functional point of view, the liver is organized into acini, with both hepatic arterial and portal venous blood entering the acinus from the portal areas (zone 1) and then flowing through the sinusoids to the terminal hepatic veins (zone 3); the intervening hepatocytes constitute zone 2. The advantage of viewing the acinus as the physiologic unit of the liver is that this perspective helps to explain the morphologic patterns and zonality of many vascular and biliary diseases not explained by the lobular arrangement

Portal areas of the liver consist of small veins, arteries, bile ducts, and

lymphatics organized in a loose stroma of supporting matrix and small amounts of collagen. Blood flowing into the portal areas is distributed through the sinusoids, passing from zone 1 to zone 3 of the acinus and draining into the terminal hepatic veins ("central veins"). Secreted bile flows in the opposite direction—i.e., in a counter-current pattern from zone 3 to zone 1. The sinusoids are lined by unique endothelial cells that have prominent fenestrae of variable sizes, allowing the free flow of plasma but not of cellular elements. The plasma is thus in direct contact with hepatocytes in the subendothelial space of Disse.

Hepatocytes have distinct polarity. The basolateral side of the hepatocyte lines the space of Disse and is richly lined with microvilli; it exhibits endocytotic and pinocytotic activity, with passive and active uptake of nutrients, proteins, and other molecules. The apical pole of the hepatocyte forms the canalicular membranes through which bile components are secreted. The canaliculi of hepatocytes form a fine network, which fuses into the bile ductular elements near the portal areas. Kupffer cells usually lie within the sinusoidal vascular space and represent the largest group of fixed macrophages in the body. The stellate cells are located in the space of Disse but are not usually prominent unless activated, when they produce collagen and matrix. Red blood cells stay in the sinusoidal space as blood flows through the lobules, but white blood cells can migrate through or around endothelial cells into the space of Disse and from there to portal areas, where they can return to the circulation through lymphatics.

Hepatocytes perform numerous and vital roles in maintaining homeostasis and health. These functions include the synthesis of most essential serum proteins (albumin, carrier proteins, coagulation factors, many hormonal and growth factors), the production of bile and its carriers (bile acids, cholesterol, lecithin, phospholipids), the regulation of nutrients (glucose, glycogen, lipids, cholesterol, amino acids), and the metabolism and conjugation of lipophilic compounds (bilirubin, anions, cations, drugs) for excretion in the bile or urine. Measurement of these activities to assess liver function is complicated by the multiplicity and variability of these functions. The most commonly used liver "function" tests are measurements of serum bilirubin, serum albumin, and prothrombin time. The serum bilirubin level is a measure of hepatic conjugation and excretion; the serum albumin level and prothrombin time are measures of protein synthesis. Abnormalities of bilirubin, albumin, and prothrombin time are typical of hepatic dysfunction. Frank liver failure is incompatible with life, and the functions of the liver are too complex and diverse to be subserved by a mechanical pump; a dialysis membrane; or a concoction of infused hormones, proteins, and growth factors.

JAUNDICE & EVALUATION OF ABNORMAL LIVER BIOCHEMICAL TESTS

ESSENTIALS OF DIAGNOSIS

- Jaundice results from accumulation of bilirubin in body tissues; the cause may be hepatic or nonhepatic.
- Hyperbilirubinemia may be due to abnormalities in the formation, transport, metabolism, or excretion of bilirubin.

- Persistent mild elevations of the aminotransferase levels are common in clinical practice and caused most often by nonalcoholic fatty liver disease.
- Evaluation of obstructive jaundice begins with ultrasonography and is usually followed by cholangiography.

General Considerations

Jaundice (icterus) results from the accumulation of bilirubin—a product of heme metabolism—in body tissues. Hyperbilirubinemia may be due to abnormalities in the formation, transport, metabolism, or excretion of bilirubin. Total serum bilirubin is normally 0.2–1.2 mg/dL (3.42–20.52 mcmol/L). Mean levels are higher in men than women, higher in whites and Hispanics than blacks, and correlate with an increased risk of symptomatic gallstone disease and inversely with the risk of stroke, respiratory disease, cardiovascular disease, and mortality, presumably because of an antioxidant effect. Jaundice may not be recognizable until serum bilirubin levels are about 3 mg/dL (51.3 mcmol/L).

Jaundice is caused by predominantly unconjugated or conjugated bilirubin in the serum. Unconjugated hyperbilirubinemia may result from overproduction of bilirubin because of hemolysis; impaired hepatic uptake of bilirubin due to certain drugs; or impaired conjugation of bilirubin by glucuronide, as in Gilbert syndrome, due to mild decreases in uridine diphosphate (UDP) glucuronyl transferase, or Lawrence S. Friedman, MD 16 Liver, Biliary Tract, & Pancreas Disorders Crigler-Najjar syndrome, caused by moderate decreases or absence of UDP glucuronyl transferase. Hemolysis alone rarely elevates the serum bilirubin level to more than 7 mg/dL (119.7 mcmol/L). Predominantly conjugated hyperbilirubinemia may result from impaired excretion of bilirubin from the liver due to hepatocellular disease, drugs, sepsis, or hereditary hepatocanalicular transport defects (such as Dubin-Johnson syndrome, progressive familial intrahepatic cholestasis syndromes, and intrahepatic cholestasis of pregnancy) or from extrahepatic biliary obstruction. The term “cholestasis” denotes retention of bile in the liver, and the term “cholestatic jaundice” is often used when conjugated hyperbilirubinemia results from impaired bile flow. Mediators of pruritus due to cholestasis have been identified to be lysophosphatidic acid and autotaxin, the enzyme that forms lysophosphatidic acid.

Clinical Findings

A. Unconjugated Hyperbilirubinemia

Stool and urine color are normal, and there is mild jaundice and indirect (unconjugated) hyperbilirubinemia with no bilirubin in the urine. Splenomegaly occurs in all hemolytic disorders except in sickle cell disease.

B. Conjugated Hyperbilirubinemia

1. Hereditary cholestatic syndromes or intrahepatic cholestasis—The patient may be asymptomatic; cholestasis is often accompanied by pruritus, light-colored stools, and jaundice.

2. Hepatocellular disease—Malaise, anorexia, low-grade fever, and right upper

quadrant discomfort are frequent. Dark urine, jaundice, and, in women, amenorrhea occur. An enlarged tender liver, spider telangiectasias, palmar erythema, ascites, gynecomastia, sparse body hair, fetor hepaticus, and asterixis may be present, depending on the cause, severity, and chronicity of liver dysfunction.

E. Biliary Obstruction

There may be right upper quadrant pain, weight loss (suggesting carcinoma), jaundice, pruritus, dark urine, and light-colored stools. Symptoms and signs may be intermittent if caused by a stone, carcinoma of the ampulla, or cholangiocarcinoma. Pain may be absent early in pancreatic cancer. Occult blood in the stools suggests cancer of the ampulla. Hepatomegaly and a palpable gallbladder (Courvoisier sign) are characteristic, but neither specific nor sensitive, of a pancreatic head tumor. Fever and chills are more common in benign obstruction with associated cholangitis.

Diagnostic Studies

A. Laboratory Findings

Serum alanine and aspartate aminotransferase (ALT and AST) levels decrease with age and correlate with body mass index and mortality from liver disease and inversely with caffeine consumption and possibly serum vitamin D levels. There is controversy about whether an elevated ALT level is associated with mortality from coronary artery disease, cancer, diabetes mellitus, and all causes. Normal reference values for ALT and AST are lower than generally reported when persons with risk factors for fatty liver are excluded. Truncal fat and early-onset paternal obesity are risk factors for increased ALT levels. Levels are mildly elevated in more than 25% of persons with untreated celiac disease and in type 1 diabetic patients with so-called glycogenic hepatopathy and often rise transiently in healthy persons who begin taking 4 g of acetaminophen per day or experience rapid weight gain on a fast-food diet. Levels may rise strikingly but transiently in patients with acute biliary obstruction from choledocholithiasis. Nonalcoholic fatty liver disease is by far the most common cause of mildly to moderately elevated aminotransferase levels. Elevated ALT and AST levels, often greater than 1000 units/L (20 mckat/L), are the hallmark of hepatocellular necrosis or inflammation. Elevated alkaline phosphatase levels are seen in cholestasis or infiltrative liver disease (such as tumor, granulomas, or amyloidosis). Isolated alkaline phosphatase elevations of hepatic rather than bone, intestinal, or placental origin are confirmed by diagnosis of any liver test elevation includes toxicity caused by drugs, herbal remedies, and toxins.

Liver biochemical tests

Normal Values

Bilirubin

Direct 0.1–0.3 mg/dL (1.71–5.13 mcmol/L)

Indirect 0.2–0.7 mg/dL (3.42–11.97 mcmol/L)

Urine bilirubin None

Serum albumin 3.5–5.5 g/dL (35–55 g/L)

Alkaline phosphatase 30–115 units/L (0.6–2.3 mkat/L)

Prothrombin time INR (international normalized ratio) of 1.0–1.4. After vitamin K, 10% decrease in 24 hours

ALT (alanine aminotransferase) ≤ 30 units/L (0.6 mkat/L) (men), ≤ 19 units/L (0.38 mkat/L) (women)

AST (aspartate aminotransferase) 5–40 units/L (0.1–0.8 mkat/L)

Causes of serum aminotransferase elevations

(Almost any liver disease can cause moderate aminotransferase elevations (5–15 × normal)

Mild Elevations (5 × normal)

Hepatic: ALT-predominant

Chronic hepatitis B, C, and D

Acute viral hepatitis (A-E, EBV-Epstein-Barr virus, CMV-cytomegalovirus)

Steatosis/steatohepatitis

Hemochromatosis

Medications/toxins

Autoimmune hepatitis

Alpha-1-antitrypsin (alpha-1-antiprotease) deficiency Wilson disease

Celiac disease

Glycogenic hepatopathy

Hepatic: AST–predominant

Alcohol-related liver injury (AST:ALT >2:1)

Cirrhosis

Nonhepatic

Strenuous exercise

Hemolysis

Myopathy T

hyroid disease

Macro-AST

Severe Elevations (> 15 × normal)

Acute viral hepatitis (A–E, herpes)

Medications/toxins

Ischemic hepatitis

Autoimmune hepatitis

Wilson disease

Acute bile duct obstruction

Acute Budd-Chiari syndrome

Hepatic artery ligation

B. Imaging

Demonstration of dilated bile ducts by ultrasonography or CT indicates biliary obstruction (90–95% sensitivity). Ultrasonography, CT, and MRI may also demonstrate hepatomegaly, intrahepatic tumors, and portal hypertension. Use of color Doppler ultrasonography or contrast agents that produce microbubbles increases the sensitivity of transcutaneous ultrasonography for detecting small neoplasms. MRI is the most accurate technique for identifying isolated liver lesions such as hemangiomas, focal nodular hyperplasia, or focal fatty infiltration and for detecting hepatic iron overload. The most sensitive techniques for detection of individual small hepatic metastases in patients eligible for resection are multiphasic helical or multislice CT; CT arterial portography, in which imaging follows intravenous contrast infusion via a catheter placed in the superior mesenteric artery; MRI with use of gadolinium or ferumoxides as contrast agents; and intraoperative ultrasonography. Dynamic gadolinium-enhanced MRI and MRI following administration of superparamagnetic iron oxide show promise in visualizing hepatic fibrosis. Because of its much lower cost, ultrasonography is preferable to CT (~six times more expensive) or MRI (~seven times more expensive) as a screening test. Positron emission tomography (PET) can be used to detect small pancreatic tumors and metastases. Ultrasonography can detect gallstones with a sensitivity of 95%.

Magnetic resonance cholangiopancreatography (MRCP) is a sensitive, noninvasive method of detecting bile duct stones, strictures, and dilatation; however, it is less reliable than endoscopic retrograde cholangiopancreatography (ERCP) for distinguishing malignant from benign strictures. ERCP requires a skilled endoscopist and may be used to demonstrate pancreatic or ampullary causes of jaundice, carry out papillotomy and stone extraction, insert a stent through an obstructing lesion, or facilitate direct cholangiopancreatoscopy. Complications of ERCP include pancreatitis (5% or less) and, less commonly, cholangitis, bleeding, or duodenal perforation after papillotomy. Risk factors for post-ERCP pancreatitis include female sex, prior post-ERCP pancreatitis, suspected sphincter of Oddi dysfunction, and a difficult or failed cannulation. Percutaneous transhepatic cholangiography (PTC) is an alternative approach to evaluating the anatomy of the biliary tree. Serious complications of PTC occur in 3% and include fever, bacteremia, bile peritonitis, and intraperitoneal hemorrhage. Endoscopic ultrasonography (EUS) is the most sensitive test for detecting small lesions of the ampulla or pancreatic head and for detecting portal vein invasion by pancreatic cancer. It is also accurate in detecting or excluding bile duct stones.

C. Liver Biopsy

Percutaneous liver biopsy is the definitive study for determining the cause and histologic severity of hepatocellular dysfunction or infiltrative liver disease. In patients with suspected metastatic disease or a hepatic mass, it is performed under ultrasound or CT guidance. A transjugular route can be used in patients with coagulopathy or ascites. The risk of bleeding after a percutaneous liver biopsy is approximately 0.5% and is increased in persons with a platelet count of 60,000/mcL (60×10^9/mcL) or less. Panels of blood tests (eg, FibroSure) and ultrasound or

magnetic resonance elastography to measure liver stiffness are emerging approaches for estimating the stage of liver fibrosis and degree of portal hypertension without the need for liver biopsy.

When to Refer

Patients with jaundice should be referred for diagnostic procedures.

When to Admit

Patients with liver failure should be hospitalized.

DISEASES OF THE LIVER

ACUTE HEPATITIS A

ESSENTIALS OF DIAGNOSIS

- Prodrome of anorexia, nausea, vomiting, malaise, aversion to smoking.
- Fever, enlarged and tender liver, jaundice.
- Normal to low white cell count; markedly elevated aminotransferases.

General Considerations

Hepatitis can be caused by viruses, including the five hepatotropic viruses—A, B, C, D, and E—and many drugs and toxic agents; the clinical manifestations may be similar regardless of cause. Hepatitis A virus (HAV) is a 27-nm RNA hepatovirus (in the picornavirus family) that causes epidemics or sporadic cases of hepatitis. The virus is transmitted by the fecal-oral route, and its spread is favored by crowding and poor sanitation. Since introduction of the HAV vaccine in the United States in 1995, the incidence rate of HAV infection has declined from 14 to 1.3 per 100,000 population, with a corresponding decline of 32% in the mortality rate, and international travel has emerged as the leading risk factor, accounting for over 40% of cases, with another 18% of cases attributable to exposure to an international traveler. Common source outbreaks may still result from contaminated water or food, including inadequately cooked shellfish. In 2013, an outbreak in the United States resulted from frozen pomegranate arils imported from Turkey, and HAV has been described as a reemerging food-borne public health threat in Europe. Outbreaks among people who inject drugs and cases among international adoptees and their contacts also have been reported. The incubation period averages 30 days. HAV is excreted in feces for up to 2 weeks before clinical illness but rarely after the first week of illness. The mortality rate for hepatitis A is low, and fulminant hepatitis A is uncommon except for rare instances in which it occurs in a patient with concomitant chronic hepatitis C. There is no chronic carrier state. In the United States, about 30% of the population have serologic evidence of previous HAV infection.

Clinical Findings

A. Symptoms and Signs

Clinical illness is more severe in adults than in children, in whom it is usually

asymptomatic. The onset may be abrupt or insidious, with malaise, myalgia, arthralgia, easy fatigability, upper respiratory symptoms, and anorexia. A distaste for smoking, paralleling anorexia, may occur early. Nausea and vomiting are frequent, and diarrhea or constipation may occur. Fever is generally present but is lowgrade except in occasional cases in which systemic toxicity may occur. Defervescence and a fall in pulse rate often coincide with the onset of jaundice.

Abdominal pain is usually mild and constant in the right upper quadrant or epigastrium, often aggravated by jarring or exertion, and rarely may be severe enough to simulate cholecystitis. Jaundice occurs after 5–10 days but may appear at the same time as the initial symptoms. In many patients, jaundice never develops. With the onset of jaundice, prodromal symptoms often worsen, followed by progressive clinical improvement. Stools may be acholic during this phase.

The acute illness usually subsides over 2–3 weeks with complete clinical and laboratory recovery by 9 weeks. In some cases, clinical, biochemical, and serologic recovery may be followed by one or two relapses, but recovery is the rule. Acute cholecystitis occasionally complicates the course of acute hepatitis A.

Hepatomegaly—rarely marked—is present in over half of cases. Liver tenderness is usually present. Splenomegaly is reported in 15% of patients, and soft, enlarged lymph nodes—especially in the cervical or epitrochlear areas— may occur.

B. Laboratory Findings

The white blood cell count is normal to low, especially in the preicteric phase. Large atypical lymphocytes may occasionally be seen. Mild proteinuria is common, and bilirubinuria often precedes the appearance of jaundice. Strikingly elevated ALT or AST levels occur early, followed by elevations of bilirubin and alkaline phosphatase; in a minority of patients, the latter persist after aminotransferase levels have normalized. Cholestasis is occasionally marked. Antibody to hepatitis A (anti-HAV) appears early in the course of the illness. Both IgM and IgG anti-HAV are detectable in serum soon after the onset. Peak titers of IgM anti-HAV occur during the first week of clinical disease and disappear within 3–6 months. Detection of IgM anti-HAV is an excellent test for diagnosing acute hepatitis A but is not recommended for the evaluation of asymptomatic persons with persistently elevated serum aminotransferase levels because false-positive results occur. False-negative results have been described in a patient receiving rituximab for rheumatoid arthritis. Titers of IgG anti-HAV rise after 1 month of the disease and may persist for years. IgG anti-HAV (in the absence of IgM anti-HAV) indicates previous exposure to HAV, noninfectivity, and immunity.

Differential Diagnosis

The differential diagnosis includes other viruses that cause hepatitis, particularly hepatitis B and C, and diseases such as infectious mononucleosis, cytomegalovirus infection, herpes simplex virus infection, Middle East respiratory syndrome, and infections caused by many other viruses, including influenza and Ebola virus; spirochetal diseases such as leptospirosis and secondary syphilis;

brucellosis; rickettsial diseases such as Q fever; drug-induced liver injury; and ischemic hepatitis (shock liver). Occasionally, autoimmune hepatitis may have an acute onset mimicking acute viral hepatitis. Rarely, metastatic cancer of the liver, lymphoma, or leukemia may present as a hepatitis-like picture.

The prodromal phase of viral hepatitis must be distinguished from other infectious disease such as influenza, upper respiratory infections, and the prodromal stages of the exanthematous diseases. Cholestasis may mimic obstructive jaundice.

Prevention

Strict isolation of patients is not necessary, but hand washing after bowel movements is required. Unvaccinated persons who are exposed to HAV are advised to receive postexposure prophylaxis with a single dose of HAV vaccine or immune globulin (0.02 mL/kg) as soon as possible. The vaccine is preferred in healthy persons ages 1 year to 40 years, whereas immune globulin is preferred in those who are younger than 1 year or older than 40 years or who are immunocompromised or who have chronic liver disease.

Two effective inactivated hepatitis A vaccines are available in the United States and recommended for persons living in or traveling to endemic areas (including military personnel), patients with chronic liver disease upon diagnosis after prescreening for immunity (although the costeffectiveness of vaccinating all patients with concomitant chronic hepatitis C has been questioned), persons with clotting-factor disorders who are treated with concentrates, men who have sex with men, animal handlers, illicit drug users, sewage workers, food handlers, close personal contacts of international adoptees, and children and caregivers in day-care centers and institutions. For healthy travelers, a single dose of vaccine at any time before departure can provide adequate protection. Routine vaccination is advised for all children in states with an incidence of hepatitis A at least twice the national average and has been approved by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) for use in all children between ages 1 and 2 in the United States. HAV vaccine is also effective in the prevention of secondary spread to household contacts of primary cases. The recommended dose for adults is 1 mL (1440 ELISA units) of Havrix (GlaxoSmithKline) or 1 mL (50 units) of Vaqta (Merck) intramuscularly, followed by a booster dose at 6–18 months. A combined hepatitis A and B vaccine (Twinrix, GlaxoSmithKline) is available. HIV infection impairs the response to the HAV vaccine, especially in persons with a CD4 count less than 200/mcL.

Treatment

Bed rest is recommended only if symptoms are marked. If nausea and vomiting are pronounced or if oral intake is substantially decreased, intravenous 10% glucose is indicated.

Dietary management consists of palatable meals as tolerated, without overfeeding; breakfast is usually tolerated best. Strenuous physical exertion, alcohol, and hepatotoxic agents should be avoided. Small doses of oxazepam are safe because metabolism is not hepatic; morphine sulfate should be avoided.

Corticosteroids have no benefit in patients with viral hepatitis, including those with fulminant disease.

Prognosis

In most patients, clinical recovery is generally complete within 3 months. Laboratory evidence of liver dysfunction may persist for a longer period, but most patients recover completely. Hepatitis A does not cause chronic liver disease, although it may persist for up to 1 year, and clinical and biochemical relapses may occur before full recovery. The mortality rate is less than 0.6%.

When to Admit

- Encephalopathy is present.
- INR greater than 1.6.
- The patient is unable to maintain hydration.

ACUTE HEPATITIS B

ESSENTIALS OF DIAGNOSIS

- Prodrome of anorexia, nausea, vomiting, malaise, aversion to smoking.
- Fever, enlarged and tender liver, jaundice.
- Normal to low white blood cell count; markedly elevated aminotransferases early in the course.
- Liver biopsy shows hepatocellular necrosis and mononuclear infiltrate but is rarely indicated.

General Considerations

Hepatitis B virus (HBV) is a 42-nm hepadnavirus with a partially double-stranded DNA genome, inner core protein (hepatitis B core antigen, HBcAg), and outer surface coat (hepatitis B surface antigen, HBsAg). There are eight different genotypes (A–H), which may influence the course of infection and responsiveness to antiviral therapy. HBV is usually transmitted by inoculation of infected blood or blood products or by sexual contact and is present in saliva, semen, and vaginal secretions. HBsAg-positive mothers may transmit HBV at delivery; the risk of chronic infection in the infant is as high as 90%.

Since 1990, the incidence of HBV infection in the United States has decreased from 8.5 to 1.5 cases per 100,000 population. The prevalence is 0.27% in persons aged 6 or over. Because of universal vaccination since 1992, exposure to HBV is now very low among persons aged 18 or younger. HBV is prevalent in men who have sex with men and in people who inject drugs (about 7% of HIVinfected persons are coinfected with HBV), but the greatest number of cases result from heterosexual transmission. Other groups at risk include patients and staff at hemodialysis centers, physicians, dentists, nurses, and personnel working in clinical and pathology laboratories and blood banks. Half of all patients with acute hepatitis B in the United States have previously been incarcerated or treated for a sexually transmitted disease. The risk of HBV infection from a blood transfusion in the United States is no higher than 1 in 350,000 units transfused. Screening for HBV

infection is recommended for high-risk groups by the US Preventive Services Task Force.

The incubation period of hepatitis B is 6 weeks to 6 months (average 12–14 weeks). The onset of hepatitis B is more insidious and the aminotransferase levels are higher on average than in HAV infection. Fulminant hepatitis occurs in less than 1%, with a mortality rate of up to 60%. Following acute hepatitis B, HBV infection persists in 1–2% of immunocompetent adults but in a higher percentage of children and immunocompromised adults. There are as many as 2.2 million persons (including an estimated 1.32 million foreign-born persons from endemic areas) with chronic hepatitis B in the United States. Persons with chronic hepatitis B, particularly when HBV infection is acquired early in life and viral replication persists, are at substantial risk for cirrhosis and hepatocellular carcinoma (up to 25–40%); men are at greater risk than women.

Clinical Findings

A. Symptoms and Signs

The clinical picture of viral hepatitis is extremely variable, ranging from asymptomatic infection without jaundice to a fulminating disease and death in a few days. The onset may be abrupt or insidious, and the clinical features are similar to those for acute hepatitis A. Serum sickness may be seen early in acute hepatitis B. Fever is generally present and is lowgrade. Defervescence and a fall in pulse rate often coincide with the onset of jaundice. Infection caused by HBV may be associated with glomerulonephritis and polyarteritis nodosa.

The acute illness usually subsides over 2–3 weeks with complete clinical and laboratory recovery by 16 weeks. In 5–10% of cases, the course may be more protracted, but less than 1% will have a fulminant course. Hepatitis B may become chronic.

B. Laboratory Findings

The laboratory features are similar to those for acute hepatitis A, although serum aminotransferase levels are higher on average in acute hepatitis B, and marked cholestasis is not a feature. Marked prolongation of the prothrombin time in severe hepatitis correlates with increased mortality. There are several antigens and antibodies as well as HBV DNA that relate to HBV infection and that are useful in diagnosis.

1. HBsAg—The appearance of HBsAg in serum is the first evidence of infection, appearing before biochemical evidence of liver disease, and persisting throughout the clinical illness. Persistence of HBsAg more than 6 months after the acute illness signifies chronic hepatitis B.

2. Anti-HBs—Specific antibody to HBsAg (anti-HBs) appears in most individuals after clearance of HBsAg and after successful vaccination against hepatitis B. Disappearance of HBsAg and the appearance of anti-HBs signal recovery from HBV infection, noninfectivity, and immunity.

3. Anti-HBc—IgM anti-HBc appears shortly after HBsAg is detected. (HBcAg alone does not appear in serum.) In the setting of acute hepatitis, IgM anti-HBc indicates a diagnosis of acute hepatitis B, and it fills the serologic gap in rare patients who have cleared HBsAg but do not yet have detectable anti-HBs. IgM anti-HBc can persist for 3–6 months, and sometimes longer. IgM anti-HBc may also reappear during flares of previously inactive chronic hepatitis B. IgG anti-HBc also appears during acute hepatitis B but persists indefinitely, whether the patient recovers (with the appearance of anti-HBs in serum) or chronic hepatitis B develops (with persistence of HBsAg). In asymptomatic blood donors, an isolated anti-HBc with no other positive HBV serologic results may represent a falsely positive result or latent infection in which HBV DNA is detectable in serum only by polymerase chain reaction (PCR) testing.

4. HBeAg—HBeAg is a secretory form of HBcAg that appears in serum during the incubation period shortly after the detection of HBsAg. HBeAg indicates viral replication and infectivity. Persistence of HBeAg beyond 3 months indicates an increased likelihood of chronic hepatitis B. Its disappearance is often followed by the appearance of anti-HBe, generally signifying diminished viral replication and decreased infectivity.

5. HBV DNA—The presence of HBV DNA in serum generally parallels the presence of HBeAg, although HBV DNA is a more sensitive and precise marker of viral replication and infectivity. Very low levels of HBV DNA, detectable only by PCR testing, may persist in serum and liver long after a patient has recovered from acute hepatitis B, but the HBV DNA in serum is bound to IgG and is rarely infectious. In some patients with chronic hepatitis B, HBV DNA is present at high levels without HBeAg in serum because of development of a mutation in the core promoter or precore region of the gene that codes HBcAg; these mutations prevent synthesis of HBeAg in infected hepatocytes. When additional mutations in the core gene are present, the precore mutant enhances the severity of HBV infection and increases the risk of cirrhosis.

Differential Diagnosis

The differential diagnosis includes hepatitis A and the same disorders listed for the differential diagnosis of acute hepatitis A. In addition, coinfection with HDV must be considered.

Prevention

Strict isolation of patients is not necessary. Thorough hand washing by medical staff who may contact contaminated utensils, bedding, or clothing is essential. Medical staff should handle disposable needles carefully and not recap them. Screening of donated blood for HBsAg, anti-HBc, and anti-HCV has reduced the risk of transfusion-associated hepatitis markedly. All pregnant women should undergo testing for HBsAg. HBV-infected persons should practice safer sex. Cesarean section, in combination with immunoprophylaxis of the neonate (see

below), reduces the risk of perinatal transmission of HBV infection when the mother's serum HBV DNA level is 200,000 international units/mL or higher, although initiation of antiviral therapy of the mother in the third trimester is an alternative approach (see Chronic Hepatitis B & Chronic Hepatitis D). HBV-infected health care workers are not precluded from practicing medicine or dentistry if they follow CDC guidelines.

Hepatitis B immune globulin (HBIG) may be protective—or may attenuate the severity of illness—if given within 7 days after exposure (adult dose is 0.06 mL/kg body weight) followed by initiation of the HBV vaccine series. This approach is currently recommended for persons exposed to HBsAg-contaminated material via mucous membranes or through breaks in the skin and for individuals who have had sexual contact with a person with HBV infection (irrespective of the presence or absence of HBeAg in the source). HBIG is also indicated for newborn infants of HBsAg-positive mothers followed by initiation of the vaccine series.

The CDC recommends HBV vaccination of all infants and children in the United States and all adults who are at risk for hepatitis B (including persons under age 60 with diabetes mellitus) or who request vaccination. Over 90% of recipients of the vaccine mount protective antibody to hepatitis B; immunocompromised persons, including patients receiving dialysis (especially those with diabetes mellitus), respond poorly. Reduced response to the vaccine may have a genetic basis in some cases and has also been associated with age over 40 years and celiac disease. The standard regimen for adults is 10–20 mcg (depending on the formulation) repeated again at 1 and 6 months, but alternative schedules have been approved, including accelerated schedules of 0, 1, 2, and 12 months and of 0,7, and 21 days plus 12 months. For greatest reliability of absorption, the deltoid muscle is the preferred site of innoculation. Vaccine formulations free of the mercury-containing preservative thimerosal are given to infants under 6 months of age. When documentation of seroconversion is considered desirable, postimmunization anti-HBs titers may be checked. Protection appears to be excellent even if the titer wanes—at least for 20 years—and booster reimmunization is not routinely recommended but is advised for immunocompromised persons in whom anti-HBs titers fall below 10 milli-international units/mL. For vaccine nonresponders, three additional vaccine doses may elicit seroprotective anti-HBs levels in 30–50% of persons. Doubling of the standard dose may also be effective. Universal vaccination of neonates in countries endemic for HBV has reduced the incidence of hepatocellular carcinoma. Incomplete immunization is the most important predictor of liver disease among vaccinees.

Treatment

Treatment of acute hepatitis B is the same as that for acute hepatitis A. Encephalopathy or severe coagulopathy indicates acute liver failure, and hospitalization at a liver transplant center is mandatory. Antiviral therapy is generally unnecessary in patients with acute hepatitis B but is usually prescribed in cases of fulminant hepatitis B as well as in spontaneous reactivation of chronic hepatitis B presenting as acute-on-chronic liver failure.

Prognosis

In most patients, clinical recovery is complete in 3–6 months. Laboratory evidence of liver dysfunction may persist for a longer period, but most patients recover completely. The mortality rate for acute hepatitis B is 0.1–1% but is higher with superimposed hepatitis D.

Chronic hepatitis, characterized by elevated aminotransferase levels for more than 6 months, develops in 1–2% of immunocompetent adults with acute hepatitis B but in as many as 90% of infected neonates and infants and a substantial proportion of immunocompromised adults. Ultimately, cirrhosis develops in up to 40% of those with chronic hepatitis B; the risk of cirrhosis is even higher in HBV-infected patients coinfected with hepatitis C or HIV. Patients with cirrhosis are at risk for hepatocellular carcinoma at a rate of 3–5% per year. Even in the absence of cirrhosis, patients with chronic hepatitis B—particularly those with active viral replication—are at increased risk for hepatocellular carcinoma.

When to Refer

Refer patients with acute hepatitis who require liver biopsy for diagnosis. »

When to Admit

- Encephalopathy is present.
- INR greater than 1.6.
- The patient is unable to maintain hydration.

ACUTE HEPATITIS C & OTHER CAUSES OF ACUTE VIRAL HEPATITIS

Viruses other than HAV and HBV that can cause hepatitis are hepatitis C virus (HCV), hepatitis D virus (HDV) (delta agent), and hepatitis E virus (HEV) (an enterically transmitted hepatitis seen in epidemic form in Asia, the Middle East, and North Africa). Hepatitis G virus (HGV) rarely, if ever, causes frank hepatitis. A DNA virus designated the TT virus (TTV) has been identified in up to 7.5% of blood donors and found to be transmitted readily by blood transfusions, but an association between this virus and liver disease has not been established. A related virus known as SEN-V has been found in 2% of US blood donors, is transmitted by transfusion, and may account for some cases of transfusion-associated non-ABCDE hepatitis. In immunocompromised and rare immunocompetent persons, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus should be considered in the differential diagnosis of hepatitis. Severe acute respiratory syndrome (SARS) and influenza may be associated with marked serum aminotransferase elevations. Unidentified pathogens account for a small percentage of cases of acute viral hepatitis.

1. Hepatitis C

HCV is a single-stranded RNA virus (hepacivirus) with properties similar to those of flaviviruses. Seven major genotypes of HCV have been identified. In the

past, HCV was responsible for over 90% of cases of posttransfusion hepatitis, yet only 4% of cases of hepatitis C were attributable to blood transfusions. Over 50% of cases are transmitted by injection drug use, and both reinfection and superinfection of HCV are common in people who actively inject drugs. Body piercing, tattoos, and hemodialysis are risk factors. The risk of sexual and maternal– neonatal transmission is low and may be greatest in a subset of patients with high circulating levels of HCV RNA. Having multiple sexual partners may increase the risk of HCV infection, and HIV coinfection, unprotected receptive anal intercourse with ejaculation, and sex while high on methamphetamine increase the risk of HCV transmission in men who have sex with men. Transmission via breastfeeding has not been documented. An outbreak of hepatitis C in patients with immune deficiencies has occurred in some recipients of intravenous immune globulin. Hospital- and outpatient facility-acquired transmission has occurred via multidose vials of saline used to flush Portacaths; through reuse of disposable syringes (including drug "diversion" by an infected health care worker); through contamination of shared saline, radiopharmaceutical, and sclerosant vials; via inadequately disinfected endoscopy equipment; and between hospitalized patients on a liver unit. In the developing world, unsafe medical practices lead to a substantial number of cases of HCV infection. Covert transmission during bloody fisticuffs has even been reported, and incarceration in prison is a risk factor, with a frequency of 26% in the United States. In many patients, the source of infection is unknown. Coinfection with HCV is found in at least 30% of HIV-infected persons. HIV infection leads to an increased risk of acute liver failure and more rapid progression of chronic hepatitis C to cirrhosis; in addition, HCV increases the hepatotoxicity of highly active antiretroviral therapy. The number of cases of chronic HCV infections in the United States decreased from 3.2 million in 2001 to 2.3 million in 2013. The incidence of new cases of acute, symptomatic hepatitis C declined from 1992 to 2005, but an increase was observed in persons aged 15 to 24 from 2002 to 2006, as a result of injection drug use.

Clinical Findings

A. Symptoms and Signs

The incubation period for hepatitis C averages 6–7 weeks, and clinical illness is often mild, usually asymptomatic, and characterized by waxing and waning aminotransferase elevations and a high rate (greater than 80%) of chronic hepatitis. Spontaneous clearance of HCV following acute infection is more common (64%) in persons with the CC genotype of the IL28B gene than in those with the CT or TT genotype (24% and 6%, respectively). In persons with the CC genotype, jaundice is more likely to develop during the course of acute hepatitis C. Patients with the CC genotype and chronic hepatitis C are more likely to respond to therapy with pegylated interferon (see Chronic Viral Hepatitis). In pregnant patients with chronic hepatitis C, serum aminotransferase levels frequently normalize despite persistence of viremia, only to increase again after delivery.

B. Laboratory Findings

Diagnosis of hepatitis C is based on an enzyme immunoassay (EIA) that detects antibodies to HCV. Anti-HCV is not protective, and in patients with acute or chronic hepatitis, its presence in serum generally signifies that HCV is the cause. Limitations of the EIA include moderate sensitivity (falsenegatives) for the diagnosis of acute hepatitis C early in the course and low specificity (false-positives) in some persons with elevated gamma-globulin levels. In these situations, a diagnosis of hepatitis C may be confirmed by using an assay for HCV RNA. Occasional persons are found to have antiHCV in serum, without HCV RNA in serum, suggesting recovery from HCV infection in the past.

Complications

HCV is a pathogenetic factor in mixed cryoglobulinemia and membranoproliferative glomerulonephritis and may be related to lichen planus, autoimmune thyroiditis, lymphocytic sialadenitis, idiopathic pulmonary fibrosis, sporadic porphyria cutanea tarda, and monoclonal gammopathies. HCV infection confers a 20–30% increased risk of non-Hodgkin lymphoma. Hepatic steatosis is a particular feature of infection with HCV genotype 3 and may also occur in patients infected with other HCV genotypes who have risk factors for fatty liver. On the other hand, chronic HCV infection is associated with a decrease in serum cholesterol and low-density lipoprotein levels.

Prevention

Testing donated blood for HCV has helped reduce the risk of transfusion-associated hepatitis C from 10% in 1990 to about 1 case per 2 million units in 2011. Birth cohort screening of persons born between 1945 and 1965 (“baby boomers”) for HCV infection has been recommended by the CDC and the US Preventive Services Task Force and could identify over 900,000 new cases. HCV-infected persons should practice safe sex, but there is little evidence that HCV is spread easily by sexual contact or perinatally, and no specific preventive measures are recommended for persons in a monogamous relationship or for pregnant women. Vaccination against HAV (after prescreening for prior immunity) and HBV is recommended for patients with chronic hepatitis C, and vaccination against HAV is also recommended for patients with chronic hepatitis B.

Treatment

Treatment of patients with acute hepatitis C with peginterferon for 6–24 weeks appreciably decreases the risk of chronic hepatitis. In general, patients infected with HCV genotype 1 require a 24-week course of treatment, but a 12-week course is adequate if HCV RNA is undetectable in serum by 4 weeks. Those infected with genotypes 2, 3, or 4 generally require 8–12 weeks of therapy. Because 20% of patients with acute hepatitis C, particularly those who are symptomatic, clear the virus without such treatment, reserving treatment for patients in whom serum HCV RNA levels fail to clear after 3 months may be advisable. Ribavirin may be added if HCV RNA fails to clear after 3 months of peginterferon, but some authorities

recommend using ribavirin with peginterferon from the start of therapy. New oral direct-acting agents are likely to supplant interferon-based therapy (see Chronic Viral Hepatitis).

Prognosis

In most patients, clinical recovery is complete in 3–6 months. Laboratory evidence of liver dysfunction may persist for a longer period. The overall mortality rate is less than 1%, but the rate is reportedly higher in older people. Fulminant hepatitis C is rare in the United States.

Chronic hepatitis, which progresses very slowly in many cases, develops in as many as 85% of all persons with acute hepatitis C. Ultimately, cirrhosis develops in up to 30% of those with chronic hepatitis C; the risk of cirrhosis and hepatic decompensation is higher in patients coinfected with both HCV and HBV or HIV. Patients with cirrhosis are at risk for hepatocellular carcinoma at a rate of 3–5% per year. Long-term morbidity and mortality in patients with chronic hepatitis C is lower in black than in white patients and lowest in those infected with HCV genotype 2 and highest in those with HCV genotype 3.

2. Hepatitis D (Delta Agent)

HDV is a defective RNA virus that causes hepatitis only in association with HBV infection and specifically only in the presence of HBsAg; it is cleared when the latter is cleared.

HDV may coinfect with HBV or may superinfect a person with chronic hepatitis B, usually by percutaneous exposure. When acute hepatitis D is coincident with acute HBV infection, the infection is generally similar in severity to acute hepatitis B alone. In chronic hepatitis B, superinfection by HDV appears to carry a worse short-term prognosis, often resulting in fulminant hepatitis or severe chronic hepatitis that progresses rapidly to cirrhosis.

New cases of hepatitis D are now infrequent in the United States primarily because of the control of HBV infection, and cases seen today are usually from cohorts infected years ago who survived the initial impact of hepatitis D and now have cirrhosis. These patients are at risk for decompensation and have a threefold increased risk of hepatocellular carcinoma. New cases are primarily seen in immigrants from endemic areas, including Africa, central Asia, Eastern Europe, and the Amazon region of Brazil. More than 15 million people are infected worldwide. The diagnosis of hepatitis D is made by detection of antibody to hepatitis D antigen (anti-HDV) and, where available, hepatitis D antigen (HDAg) or HDV RNA in serum.

3. Hepatitis E

HEV is a 29- to 32-nm RNA hepevirus (in the Hepeviridae family) that is a major cause of acute hepatitis throughout Central and Southeast Asia, the Middle East, and North Africa, where it is responsible for waterborne hepatitis outbreaks. It is uncommon in the United States but should be considered in patients with acute hepatitis after a trip to an endemic area. In industrialized countries, it may be spread

by swine, and having a pet in the home and consuming undercooked organ meats are risk factors. Illness generally is self-limited (no carrier state), but instances of chronic hepatitis with rapid progression to cirrhosis attributed to HEV have been reported in transplant recipients (particularly when tacrolimus rather than cyclosporine is used as the main immunosuppressant) and, rarely, in persons with HIV infection, preexisting liver disease, or cancer undergoing chemotherapy. The diagnosis of acute hepatitis E is made most readily by testing for IgM anti-HEV in serum, although available tests may not be reliable. Reported extrahepatic manifestations include arthritis; pancreatitis; monoclonal gammopathy; thrombocytopenia; and a variety of neurologic complications, including Guillain-Barré syndrome and peripheral neuropathy. In endemic regions, the mortality rate is high (10–20%) in pregnant women and correlates with high levels of HEV RNA in serum and gene mutations that lead to reduced expression of progesterone receptors, and the risk of hepatic decompensation is increased in patients with underlying chronic liver disease. A 3-month course of treatment with oral ribavirin has been reported to induce sustained clearance of HEV RNA from the serum in 78% of patients. Improved public hygiene reduces the risk of HEV infection in endemic areas. Recombinant vaccines against HEV have shown promise in clinical trials.

CHRONIC VIRAL HEPATITIS

ESSENTIALS OF DIAGNOSIS

- Defined by chronic infection (HBV, HCV, HDV) for longer than 3–6 months.
- Diagnosis is usually made by antibody tests and viral nucleic acid in serum.

General Considerations

Chronic hepatitis is defined as chronic necroinflammation of the liver of more than 3–6 months' duration, demonstrated by persistently elevated serum aminotransferase levels or characteristic histologic findings. In many cases, the diagnosis of chronic hepatitis may be made on initial presentation. The causes of chronic hepatitis include HBV, HCV, and HDV as well as autoimmune hepatitis; alcoholic and nonalcoholic steatohepatitis; certain medications, such as isoniazid and nitrofurantoin; Wilson disease; alpha-1-antiprotease deficiency; and, rarely, celiac disease. Mortality from chronic HBV and HCV infection has been rising in the United States, and HCV has surpassed HIV as a cause of death. Chronic hepatitis is categorized on the basis of etiology; the grade of portal, periportal, and lobular inflammation (minimal, mild, moderate, or severe); and the stage of fibrosis (none, mild, moderate, severe, cirrhosis). In the absence of advanced cirrhosis, patients are often asymptomatic or have mild nonspecific symptoms.

1. Chronic Hepatitis B & Chronic Hepatitis D

Clinical Findings & Diagnosis Chronic hepatitis B afflicts 400 million people

worldwide (2 billion overall have been infected; endemic areas include Asia and sub-Saharan Africa) and up to 2.2 million (predominantly males) in the United States. It may be noted as a continuum of acute hepatitis B or diagnosed because of repeated detection of HBsAg in serum, often with elevated aminotransferase levels.

Four phases of HBV infection are recognized: immune tolerant phase, immune clearance phase, inactive HBsAg carrier state, and reactivated chronic hepatitis B phase. In the **immune tolerant phase**, HBeAg and HBV DNA are present in serum, which is indicative of active viral replication, and serum aminotransferase levels are normal, with little necroinflammation in the liver. This phase is common in infants and young children whose immature immune system fails to mount an immune response to HBV. Persons in the **immune tolerant phase** and those who acquire HBV infection later in life may enter an immune clearance phase, in which aminotransferase levels are elevated and necroinflammation is present in the liver, with a risk of progression to cirrhosis (at a rate of 2–5.5% per year) and of hepatocellular carcinoma (at a rate of more than 2% per year in those with cirrhosis); low-level IgM anti-HBc is present in serum in about 70%.

Patients enter the **inactive HBsAg carrier state** when biochemical improvement follows immune clearance. This improvement coincides with disappearance of HBeAg and reduced HBV DNA levels (less than 10^5 copies/mL, or less than 20,000 international units/mL) in serum, appearance of anti-HBe, and integration of the HBV genome into the host genome in infected hepatocytes. Patients in this phase are at a low risk for cirrhosis (if it has not already developed) and hepatocellular carcinoma, and those with persistently normal serum aminotransferase levels infrequently have histologically significant liver disease, especially if the HBsAg level is low.

The **reactivated chronic hepatitis B phase** may result from infection by a pre-core mutant of HBV or spontaneous mutation of the pre-core or core promoter region of the HBV genome during the course of chronic hepatitis caused by wild-type HBV. So-called HBeAg-negative chronic hepatitis B accounts for less than 10% of cases of chronic hepatitis B in the United States, up to 50% in southeast Asia, and up to 90% in Mediterranean countries, reflecting in part differences in the frequencies of HBV genotypes. In reactivated chronic hepatitis B, there is a rise in serum HBV DNA levels and possible progression to cirrhosis (at a rate of 8–10% per year), particularly when additional mutations in the core gene of HBV are present. Risk factors for reactivation include male sex and HBV genotype C. In patients with either HBeAg-positive or HBeAg-negative chronic hepatitis B, the risk of cirrhosis and of hepatocellular carcinoma correlates with the serum HBV DNA level. Other risk factors include advanced age, male sex, alcohol use, cigarette smoking, HBV genotype C, and coinfection with HCV or HDV. HIV coinfection is also associated with an increased frequency of cirrhosis when the CD4 count is low.

Acute **hepatitis D** infection superimposed on chronic HBV infection may result in severe chronic hepatitis, which may progress rapidly to cirrhosis and may be fatal. Patients with long-standing chronic hepatitis D and B often have inactive cirrhosis and are at risk for decompensation and hepatocellular carcinoma. The

diagnosis is confirmed by detection of anti-HDV or HDAg (or HDV RNA) in serum.

Treatment

Patients with active viral replication (HBeAg and HBV DNA [105 copies/mL or more, or 20,000 international units/mL or more] in serum and elevated aminotransferase levels) may be treated with a nucleoside or nucleotide analog or with pegylated interferon. Nucleoside and nucleotide analogs are preferred because they are better tolerated and can be taken orally. For patients who are HBeAg-negative, the threshold for treatment is a serum HBV DNA level of 104 copies/mL or more, or 2000 international units/mL or more. If the threshold HBV DNA level for treatment is met but the serum ALT level is normal, treatment may still be considered in patients over age 35–40 if liver biopsy demonstrates a fibrosis stage of 2 of 4 (moderate) or higher. Therapy is aimed at reducing and maintaining the serum HBV DNA level to the lowest possible levels, thereby leading to normalization of the ALT level and histologic improvement. An additional goal in HBeAg-positive patients is seroconversion to anti-HBe, and some responders eventually clear HBsAg. Although nucleoside and nucleotide analogs generally have been discontinued 6–12 months after HBeAg-to-anti-HBe seroconversion, some patients serorevert to HBeAg after discontinuation, have a rise in HBV DNA levels and recurrence of hepatitis activity, and require long-term therapy, which also is required when seroconversion does not occur. All HBeAg-negative patients with chronic hepatitis B also require long-term therapy.

The available nucleoside and nucleotide analogs—entecavir, tenofovir, lamivudine, adefovir, and telbivudine— differ in efficacy and rates of resistance; however, in HBeAg-positive patients, they all achieve an HBeAg-toanti-HBe seroconversion rate of about 20% at 1 year, with higher rates after more prolonged therapy. The preferred first-line oral agents are entecavir and tenofovir. Entecavir is rarely associated with resistance unless a patient is already resistant to lamivudine. The daily dose is 0.5 mg orally for patients not resistant to lamivudine and 1 mg for patients who previously became resistant to lamivudine. Histologic improvement is observed in 70% of treated patients and suppression of HBV DNA in serum in nearly all patients. Entecavir has been reported to cause lactic acidosis when used in patients with decompensated cirrhosis. Tenofovir is equally effective and is used as a firstline agent or when resistance to a nucleoside analog has developed. Like entecavir, tenofovir has a low rate of resistance when used as initial therapy. Long-term use may lead to an elevated serum creatinine level and reduced serum phosphate level (Fanconi-like syndrome) that is reversible with discontinuation of the drug.

The first available nucleoside analog was lamivudine, 100 mg orally daily. By the end of 1 year of therapy with lamivudine, however, 15–30% of responders experience a relapse (and occasionally frank decompensation). The rate of resistance reaches 70% by 5 years of therapy, and the drug is no longer considered first-line therapy in the United States but may be used in countries in which cost is a deciding factor. Adefovir dipivoxil has activity against wild-type and lamivudine-

resistant HBV but is the least potent of the oral antiviral agents for HBV. The standard dose is 10 mg orally once a day for at least 1 year. As with lamivudine, only a small number of patients achieve sustained suppression of HBV replication with adefovir, and long-term suppressive therapy is often required. Resistance to adefovir is less frequent than with lamivudine but is seen in up to 29% of patients treated for 5 years. Patients with underlying kidney dysfunction are at risk for nephrotoxicity from adefovir. Telbivudine, given in a daily dose of 600 mg orally, is more potent than either lamivudine or adefovir. Resistance to this drug may develop, however, particularly in patients who are resistant to lamivudine, and elevated creatine kinase levels are common in patients treated with telbivudine. Other antiviral agents are under study, and strategies using multiple drugs are being investigated.

Nucleoside and nucleotide analogs are well tolerated even in patients with decompensated cirrhosis (for whom the treatment threshold may be an HBV DNA level less than 104 copies/mL) and may be effective in patients with rapidly progressive hepatitis B ("fibrosing cholestatic hepatitis") following organ transplantation. Although therapy with these agents leads to biochemical, virologic, and histologic improvement in patients with HBeAg-negative chronic hepatitis B and baseline HBV DNA levels of 10^4 copies/mL or more (2000 international units/mL or more), relapse is frequent when therapy is stopped, and long-term treatment is often required. Resistance is most likely to develop to lamivudine and may develop to adefovir and telbivudine, but these drugs are no longer used as first-line agents in the United States. The development of resistance occasionally results in hepatic decompensation. Sequential addition of a second antiviral agent is usually effective after resistance to the first agent has developed. Combined use of peginterferon and a nucleoside or nucleotide analog has not been shown convincingly to have a substantial advantage over the use of either type of drug alone.

Nucleoside analogs are also recommended for inactive HBV carriers prior to the initiation of immunosuppressive therapy (including rituximab or anti-tumor necrosis factor antibody therapy) or cancer chemotherapy to prevent reactivation; entecavir has been shown to be more effective than lamivudine. In patients infected with both HBV and HIV, antiretroviral therapy, including two drugs active against both viruses (eg, tenofovir plus lamivudine or emtricitabine), has been recommended when treatment of HIV infection is indicated. Telbivudine and tenofovir are classified as pregnancy category B drugs, and lamivudine, a category C drug, has been shown to be safe in pregnant women with HIV infection. Antiviral therapy has been recommended, beginning in the third trimester, when the mother's serum HBV DNA level is 200,000 international units/mL or higher to reduce levels at the time of delivery

Peginterferon alfa-2a is still an alternative to the oral agents in selected cases. A dose of 180 mcg subcutaneously once weekly for 48 weeks leads to sustained normalization of aminotransferase levels, disappearance of HBeAg and HBV DNA from serum, appearance of anti-HBe, and improved survival in up to 40% of treated patients. A response is most likely in patients with a low baseline HBV DNA level

and high aminotransferase levels and is more likely in those who are infected with HBV genotype A than with other genotypes (especially genotype D). Moreover, most complete responders eventually clear HBsAg and develop anti-HBs in serum, and are thus cured. Relapses are uncommon in complete responders who seroconvert from HBeAg to anti-HBe. Peginterferon may be considered in order to avoid long-term therapy with an oral agent, as in young women who may want to become pregnant in the future. Patients with HBeAg-negative chronic hepatitis B have a response rate of 60% after 48 weeks of therapy with peginterferon, but the response may not be durable once peginterferon is stopped. A rapid decline in serum HBsAg titers predicts a sustained response and ultimate clearance of HBsAg. The response to peginterferon is poor in patients with HIV coinfection.

In **chronic hepatitis D**, peginterferon alfa-2b (1.5 mcg/ kg/wk for 48 weeks) may lead to normalization of serum aminotransferase levels, histologic improvement, and elimination of HDV RNA from serum in 20–50% of patients, but relapse may occur and tolerance is poor. Nucleoside and nucleotide analogs are not effective in treating chronic hepatitis D.

Prognosis

The course of chronic hepatitis B is variable. The sequelae of chronic hepatitis secondary to hepatitis B include cirrhosis, liver failure, and hepatocellular carcinoma. The 5-year mortality rate is 0–2% in those without cirrhosis, 14–20% in those with compensated cirrhosis, and 70–86% following decompensation. The risk of cirrhosis and hepatocellular carcinoma correlates with serum HBV DNA levels, and a focus of therapy is to suppress HBV DNA levels below 300 copies/mL (60 international units/mL). HBV genotype C is associated with a higher risk of cirrhosis and hepatocellular carcinoma than other genotypes. Antiviral treatment improves the prognosis in responders, prevents (or leads to regression of) cirrhosis, and decreases the frequency of liver-related complications (although the risk of hepatocellular carcinoma does not become as low as that in inactive HBV carriers).

2. Chronic Hepatitis C

Clinical Findings & Diagnosis

Chronic hepatitis C develops in up to 85% of patients with acute hepatitis C. It is clinically indistinguishable from chronic hepatitis due to other causes and may be the most common. Worldwide, 170 million people are infected with HCV, with 1.8% of the US population infected. In approximately 40% of cases, serum aminotransferase levels are persistently normal. The diagnosis is confirmed by detection of anti-HCV by EIA. In rare cases of suspected chronic hepatitis C but a negative EIA, HCV RNA is detected by PCR testing. Progression to cirrhosis occurs in 20% of affected patients after 20 years, with an increased risk in men, those who drink more than 50 g of alcohol daily, and those who acquire HCV infection after age 40 years. The rate of fibrosis progression accelerates after age 50. African Americans have a higher rate of chronic hepatitis C but lower rates of fibrosis progression and response to therapy than whites. Immunosuppressed persons—including patients with hypogammaglobulinemia or HIV infection with a

low CD4 count or those receiving immunosuppressants—appear to progress more rapidly to cirrhosis than immunocompetent persons with chronic hepatitis C. Tobacco and cannibis smoking and hepatic steatosis also appear to promote progression of fibrosis, but coffee consumption appears to slow progression. Persons with chronic hepatitis C and persistently normal serum aminotransferase levels usually have mild chronic hepatitis with slow or absent progression to cirrhosis; however, cirrhosis is present in 10% of these patients. Serum FibroSure testing or ultrasound elastography may be used to identify the absence of fibrosis or presence of cirrhosis.

Treatment

The introduction of direct-acting and host-targeting antiviral agents is rapidly expanding the therapeutic armamentarium against HCV. Standard therapy for HCV infection from the late 1990s to the early 2010s was a combination of peginterferon plus ribavirin, and ribavirin continues to be used in some all-oral regimens. Sustained virologic response rates (negative HCV RNA in serum at 24 weeks after completion of therapy) to peginterferon plus ribavirin were 45% in patients with HCV genotype 1 infection and 70–80% in those with genotype 2 or 3 infection. Response of genotype 1 infection to peginterferon plus ribavirin was associated most strongly with the CC genotype of the IL28B gene, with sustained response rates as high as 80%, compared to 40% for the CT genotype and 30% for the TT genotype.

Higher rates of response were achieved in persons infected with HCV genotype 1 when one of two firstgeneration direct-acting antiviral agents—telaprevir and boceprevir, which are nonstructural (NS) 3/4A serine protease inhibitors approved by the FDA in 2011—was added to peginterferon plus ribavirin. Sustained response rates were as high as 75% for HCV genotype 1 with a standard three-drug regimen. With the addition of one of these two protease inhibitors, the treatment duration for HCV genotype 1 infection could be shortened to 24 weeks, depending on the rapidity of clearance of HCV RNA from serum—socalled response-guided therapy. The definition of clearance of HCV RNA requires use of a sensitive real-time reverse transcriptase-PCR assay to monitor HCV RNA during treatment (the lower limit of quantification should be 25 international units/mL or less, and the limit of detection should be 10–15 international units/mL). The criterion for a sustained virologic response has been shortened from 24 to 12 weeks after the completion of treatment with newer regimens.

Peginterferon-based therapy has been shown to be beneficial in the treatment of cryoglobulinemia associated with chronic hepatitis C; an acute flare of cryoglobulinemia may first require treatment with rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange. Patients with both HCV and HIV infections have also been shown to benefit from treatment of HCV. Moreover, in persons coinfected with HCV and HIV, long-term liver disease–related mortality increases as HIV infection–related mortality is reduced by highly active antiretroviral therapy.

Treatment with peginterferon-based therapy is associated with frequent, often distressing, side effects, and discontinuation rates have been as high as 15–30%. Peginterferon alfa is contraindicated in pregnant or breast-feeding women and those with decompensated cirrhosis, profound cytopenias, severe psychiatric disorders, autoimmune diseases, or an inability to self-administer or comply with treatment. On the other hand, peginterferon-based HCV treatment has been used in carefully selected people who continue to inject illicit drugs if they are managed by a multidisciplinary team. Men and women taking ribavirin must practice strict contraception until 6 months after the conclusion of therapy because of its teratogenic effects in animals. Ribavirin should be used with caution in persons over 65 years of age and in others in whom hemolysis could pose a risk of angina or stroke.

HCV protease inhibitors ("...previrs") generally have high antiviral potency but differ with respect to the development of resistance. Most of the compounds show better response rates in HCV genotype 1b than in genotype 1a infection. The first two protease inhibitors approved by the FDA in 2011 were boceprevir and telaprevir, and simeprevir became available in 2014. These drugs were used initially in combination with peginterferon and ribavirin for HCV genotype 1 infection, although simeprevir was less effective in patients with genotype 1a and a nonstructural protein Q80K mutation than in those without the mutation.

NS5A inhibitors ("...asvirs") are characterized by high antiviral potency at picomolar doses. The cross-genotype efficacy of these agents varies. Ledipasvir was the first NS5A inhibitor approved by the FDA in 2014.

HCV polymerase inhibitors ("…buvirs") are categorized as nucleoside or nucleotide analog and non-nucleoside polymerase inhibitors. Non-nucleoside polymerase inhibitors are the weakest class of compounds against HCV because of a low barrier to resistance. Most drugs in this class are more active against HCV genotype 1b than HCV genotype 1a. They are being developed to be used only in combination with the other direct-acting antiviral agents, mainly protease inhibitors and NS5A inhibitors. Nucleoside analogs are active across all HCV genotypes and have a high barrier to resistance; nucleoside analog-resistant variants may emerge but have very low fitness and do not expand rapidly. The first approved HCV NS5B nucleotide polymerase inhibitor was sofosbuvir in 2013.

Sofosbuvir was initially approved for use in combination with peginterferon and ribavirin in patients with HCV genotype 1 infection and with ribavirin alone in patients with HCV genotype 2 or 3 infection . Most patients with HCV genotypes 2 or 3 infection are cured with 12 or 24 weeks of therapy, respectively. HCV genotype 2 responds much better to interferon-free sofosbuvir-based therapy than HCV genotype 3, but the sustained virologic response is 20–30% lower in patients with cirrhosis. Importantly, no sofosbuvir-resistant variants have been selected during therapy. The combination of sofosbuvir and simeprevir has been found to be effective in HCV genotype 1 infection and was approved by the FDA in 2014.

Ledipasvir, an NS5A inhibitor with potent activity against genotype 1 HCV, has been formulated in combination with sofosbuvir and is highly effective in both treatment-naive and treatment-experienced patients, even those with cirrhosis. The

combination was approved by the FDA in 2014 for HCV genotype 1 infection in a fixed dose of ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks in treatment-naive patients and treatment-experienced patients without cirrhosis and for 24 weeks in treatmentexperienced patients with cirrhosis. In treatment-naive patients without cirrhosis, the duration of treatment can be shortened to 8 weeks if the baseline HCV RNA level is less than 6 million international units/mL. Sustained virologic response rates are well above 90%, and this regimen has emerged as a first-line therapy for HCV genotype 1. Side effects are mild and include fatigue and headache.

The combination of paritaprevir (an NS3/4A protease inhibitor), boosted by ritonavir, plus ombitasvir (an NS5A inhibitor) and dasabuvir (an NS5B non-nucleoside polymerase inhibitor) is effective in both HCV genotype-1 treatment-naive and prior nonresponders to interferonbased therapy, with or without cirrhosis, and was approved by the FDA in late 2014. Daclatasvir in combination with sofosbuvir has proved effective in genotype 1-, 2-, and 3-infected patients. The combination of daclatasvir and asunaprevir is highly effective in genotype 1b-infected patients and also in genotype 4-, 5-, and 6-infected patients but less effective in genotype 1a-infected patients; neither drug is available in the United States.

Numerous other antiviral agents with various, often novel, mechanisms of action are under study, and several regimens have become commercially available, although not all are approved yet by the US FDA. However, despite the efficacy of the new regimens, their cost is high and insurance coverage is often a barrier to their use. Newer agents include other NS3/4A protease inhibitors (eg, asunaprevir, danoprevir, faldaprevir, grazoprevir, paritaprevir, simeprevir, vaniprevir); NS5A inhibitors (eg, daclatasvir, elbasvir, ledipasvir, ombitasvir); NS5B non-nucleos(t)ide polymerase inhibitors (eg, dasabuvir, beclabuvir); polymerase inhibitors (eg, mericitabine, sofosbuvir); virus entry, assembly, and secretion inhibitors; microRNA-122 antisense oligonucleotides (eg, miravirsen); cyclophilin A inhibitors (eg, alisporivir); interferon lambda-3; and therapeutic vaccines. HCV genotype 1 has become easy to cure with oral direct-acting agents, with expected sustained virologic response rates above 90%, and virtually all HCV genotype 2 infection is curable with all-oral regimens. Treatment of HCV genotype 3 infection, particularly in association with cirrhosis, remains a challenge because few alternative compounds are available. Interferon is now rarely required, and the need for ribavirin will likely decline.

Prognosis

Chronic hepatitis C is an indolent, often subclinical disease that may lead to cirrhosis and hepatocellular carcinoma after decades. The overall mortality rate in patients with transfusion-associated hepatitis C may be no different from that of an age-matched control population. Nevertheless, mortality or transplantation rates clearly rise to 5% per year once cirrhosis develops, and mortality from cirrhosis and hepatocellular carcinoma due to hepatitis C is rising. There is some evidence that HCV genotype 1b is associated with a higher risk of hepatocellular carcinoma than

other genotypes. Antiviral therapy has a beneficial effect on mortality and quality of life, is cost-effective, appears to retard and even reverse fibrosis, and reduces the risk of decompensated cirrhosis and hepatocellular carcinoma in responders. Even patients who achieve a sustained virologic response remain at an increased risk for mortality compared with the general population. The risk of mortality from drug addiction is higher than that for liver disease in patients with chronic hepatitis C.

When to Refer

• For liver biopsy.
• For antiviral therapy.

When to Admit

For complications of decompensated cirrhosis.

AUTOIMMUNE HEPATITIS

ESSENTIALS OF DIAGNOSIS

- Usually young to middle-aged women.
- Chronic hepatitis with high serum globulins and characteristic liver histology.
- Positive antinuclear antibody (ANA) and/or smooth muscle antibody in most common type.
- Responds to corticosteroids.

General Considerations

Although autoimmune hepatitis is usually seen in young women, it can occur in either sex at any age. The incidence, which has been rising, and prevalence are estimated to be 8.5 and 107 per million population, respectively.

Clinical Findings A. Symptoms and Signs

The onset is usually insidious, but up to 40% of cases present with acute (occasionally fulminant) hepatitis and some cases follow a viral illness (such as hepatitis A, Epstein-Barr infection, or measles) or exposure to a drug or toxin (such as nitrofurantoin, minocycline, or infliximab). Exacerbations may occur postpartum. Amenorrhea may be a presenting feature, and the frequency of depression appears to be increased. Thirty-four percent of patients, and particularly elderly patients, are asymptomatic. Typically, examination reveals a healthy-appearing young woman with multiple spider telangiectasias, cutaneous striae, acne, hirsutism, and hepatomegaly. Extrahepatic features include arthritis, Sjögren syndrome, thyroiditis, nephritis, ulcerative colitis, and Coombs-positive hemolytic anemia. Patients, especially elderly patients, with autoimmune hepatitis are at increased risk for cirrhosis, which, in turn, increases the risk of hepatocellular carcinoma (at a rate of about 1% per year).

B. Laboratory Findings

Serum aminotransferase levels may be greater than 1000 units/L, and the total

bilirubin is usually increased. In type I (classic) autoimmune hepatitis, ANA or smooth muscle antibodies (either or both) are usually detected in serum. Serum gamma-globulin levels are typically elevated (up to 5–6 g/dL [0.05–0.06 g/L]); in such patients, the EIA for antibody to HCV may be falsely positive. Other antibodies, including atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) and antibodies to histones and F-actin, may be found. Antibodies to soluble liver antigen (anti-SLA) characterize a variant of type I that is marked by severe disease, a high relapse rate after treatment, and absence of the usual antibodies (ANA and smooth muscle antibodies). Type II, seen more often in girls under age 14 in Europe, is characterized by circulating antibodies to liver-kidney microsome type 1 (anti-LKM1) without antismooth muscle antibodies or ANA. In some cases, antiliver cytosol type 1, directed against formiminotransferase cyclodeaminase, is detected. This type of autoimmune hepatitis can be seen in patients with autoimmune polyglandular syndrome type 1. Concurrent primary biliary cirrhosis or primary sclerosing cholangitis ("overlap syndrome") has been recognized in 7–13% and 6–11% of patients with autoimmune hepatitis, respectively. Liver biopsy is indicated to help establish the diagnosis (interface hepatitis is the hallmark), evaluate disease severity, and determine the need for treatment.

Simplified diagnostic criteria based on the detection of autoantibodies (1 point for a titer of > 1:40 or 2 points for a titer of > 1:80), elevated IgG levels (1 point for IgG level ≥ upper limit of normal or 2 points for level ≥ 1.1 times upper limit of normal), and characteristic histologic features (1 or 2 points depending on how typical the features are) and exclusion of viral hepatitis (2 points) can be useful for diagnosis; a score of 6 indicates probable and a score of 7 indicates definite autoimmune hepatitis with a high degree of specificity but moderate sensitivity. Diagnostic criteria for an overlap of autoimmune hepatitis and primary biliary cirrhosis ("Paris criteria") have been proposed.

Treatment

Prednisone with or without azathioprine improves symptoms; decreases the serum bilirubin, aminotransferase, and gamma-globulin levels; and reduces hepatic inflammation. Symptomatic patients with aminotransferase levels elevated tenfold (or fivefold if the serum globulins are elevated at least twofold) are optimal candidates for therapy, and asymptomatic patients with modest enzyme elevations may be considered for therapy depending on the clinical circumstances and histologic severity; however, asymptomatic patients usually remain asymptomatic, have either mild hepatitis or inactive cirrhosis on liver biopsy specimens, and have a good long-term prognosis without therapy.

Prednisone is given initially in a dose of 30 mg orally daily with azathioprine, 50 mg orally daily, which is generally well tolerated and permits the use of lower corticosteroid doses than a regimen beginning with prednisone 60 mg orally daily alone. Prednisone, 60 mg orally daily, is recommended for patients with acute severe autoimmune hepatitis. Budesonide, 6–9 mg orally daily, may be at least as effective as prednisone in noncirrhotic autoimmune hepatitis and associated with

fewer side effects. Whether patients should undergo testing for the genotype or level of thiopurine methyltransferase prior to treatment with azathioprine to predict toxicity is debated. Blood counts are monitored weekly for the first 2 months of therapy and monthly thereafter because of the small risk of bone marrow suppression. The dose of prednisone is lowered from 30 mg/day after 1 week to 20 mg/day and again after 2 or 3 weeks to 15 mg/day. Ultimately, a maintenance dose of 10 mg/day is achieved. While symptomatic improvement is often prompt, biochemical improvement is more gradual, with normalization of serum aminotransferase levels after several months in many cases. Histologic resolution of inflammation lags biochemical remission by 3–8 months, and repeat liver biopsy is recommended after 18 months of treatment. Failure of aminotransferase levels to normalize invariably predicts lack of histologic resolution.

The response rate to therapy with prednisone and azathioprine is 80%. Older patients and those with HLA genotype DRB1*04 are more likely to respond than younger patients and those with HLA DRB1*03, hyperbilirubinemia or a high MELD score (12 or higher). Fibrosis may reverse with therapy and rarely progresses after apparent biochemical and histologic remission. Once complete remission is achieved, therapy may be withdrawn, but the subsequent relapse rate is 50–80%. Relapses may again be treated in the same manner as the initial episode, with the same remission rate. After successful treatment of a relapse, the patient may continue taking azathioprine (up to 2 mg/kg) or the lowest dose of prednisone needed to maintain aminotransferase levels as close to normal as possible; another attempt at withdrawing therapy may be considered in patients remaining in remission long term (eg, 4 years or longer). Prednisone can be used to treat rare flares during pregnancy, and maintenance azathioprine does not have to be discontinued.

Nonresponders to corticosteroids and azathioprine (failure of serum aminotransferase levels to decrease by 50% after 6 months) may be considered for a trial of cyclosporine, tacrolimus, sirolimus, everolimus, methotrexate, rituximab, or infliximab. Mycophenolate mofetil, 1 g twice daily, is an effective alternative to azathioprine in patients who cannot tolerate it but is less effective in nonresponders to azathioprine. Bone density should be monitored— particularly in patients receiving maintenance corticosteroid therapy—and measures undertaken to prevent or treat osteoporosis. Liver transplantation may be required for treatment failures and patients with a fulminant presentation, but the outcome may be worse than that for primary biliary cirrhosis because of an increased rate of infectious complications, and the disease has been recognized to recur in up to 40% of transplanted livers (and rarely to develop de novo) as immunosuppression is reduced; sirolimus can be effective in such cases. Overall long-term mortality of patients with autoimmune hepatitis appears to be twofold higher than that of the general population despite response to immunosuppressive therapy. Factors that predict the need for liver transplantation or that predict liver-related death include the following: (1) age 20 years or younger or older than 60 years at presentation, (2) low serum albumin level at diagnosis, and (3) incomplete normalization of the serum ALT level after 6 months of treatment. Histologic severity is not a predictor.

When to Refer

• For liver biopsy.
• For immunosuppressive therapy.

When to Admit

• Hepatic encephalopathy.
• INR greater than 1.6.

ALCOHOLIC LIVER DISEASE

ESSENTIALS OF DIAGNOSIS

- Chronic alcohol intake usually exceeds 80 g/day in men and 30–40 g/day in women with alcoholic hepatitis or cirrhosis.
- Fatty liver is often asymptomatic.
- Fever, right upper quadrant pain, tender hepatomegaly, and jaundice characterize alcoholic hepatitis, but the patient may be asymptomatic.
- AST is usually elevated but usually not above 300 units/L (6 mckat/L); AST is greater than ALT, usually by a factor of 2 or more.
- Alcoholic hepatitis is often reversible but it is the most common precursor of cirrhosis in the United States.

General Considerations

Excessive alcohol intake can lead to fatty liver, hepatitis, and cirrhosis. Alcoholic hepatitis is characterized by acute or chronic inflammation and parenchymal necrosis of the liver induced by alcohol. Alcoholic hepatitis is often a reversible disease but the most common precursor of cirrhosis in the United States. It is associated with four to five times the number of hospitalizations and deaths as hepatitis C, which is the second most common cause of cirrhosis.

The frequency of alcoholic cirrhosis is estimated to be 10–15% among persons who consume over 50 g of alcohol (4 oz of 100-proof whiskey, 15 oz of wine, or four 12-oz cans of beer) daily for over 10 years (although the risk of cirrhosis may be lower for wine than for a comparable intake of beer or spirits). The risk of cirrhosis is lower (5%) in the absence of other cofactors such as chronic viral hepatitis and obesity. Genetic factors may also account for differences in susceptibility to and severity of liver disease. Women appear to be more susceptible than men, in part because of lower gastric mucosal alcohol dehydrogenase levels.

Clinical Findings

A. Symptoms and Signs

The clinical presentation of alcoholic liver disease can vary from asymptomatic hepatomegaly to a rapidly fatal acute illness or end-stage cirrhosis. A recent period of heavy drinking, complaints of anorexia and nausea, and the demonstration of hepatomegaly and jaundice strongly suggest the diagnosis. Abdominal pain and tenderness, splenomegaly, ascites, fever, and encephalopathy may be present. Infection, including invasive aspergillosis, is common in patients

with severe alcoholic hepatitis.

B. Laboratory Findings

In patients with steatosis, mild liver enzyme elevations may be the only laboratory abnormality. Anemia (usually macrocytic) may be present. Leukocytosis with a shift to the left is common in patients with severe alcoholic hepatitis. Leukopenia is occasionally seen and resolves after cessation of drinking. About 10% of patients have thrombocytopenia related to a direct toxic effect of alcohol on megakaryocyte production or to hypersplenism. AST is usually elevated but infrequently above 300 units/L (6 mckat/L).

AST is greater than ALT, usually by a factor of 2 or more. Serum alkaline phosphatase is generally elevated, but seldom more than three times the normal value. Serum bilirubin is increased in 60–90% of patients with alcoholic hepatitis.

Serum bilirubin levels greater than 10 mg/dL (171 mcmol/L) and marked prolongation of the prothrombin time (6 seconds or more above control) indicate severe alcoholic hepatitis with a mortality rate as high as 50%. The serum albumin is depressed, and the gamma-globulin level is elevated in 50–75% of individuals, even in the absence of cirrhosis. Increased transferrin saturation, hepatic iron stores, and sideroblastic anemia are found in many alcoholic patients. Folic acid deficiency may coexist.

C. Imaging

Imaging studies can detect moderate to severe hepatic steatosis reliably but not inflammation or fibrosis. Ultrasonography helps exclude biliary obstruction and identifies subclinical ascites. CT with intravenous contrast or MRI may be indicated in selected cases to evaluate patients for collateral vessels, space-occupying lesions of the liver, or concomitant disease of the pancreas.

D. Liver Biopsy

Liver biopsy, if done, demonstrates macrovesicular fat and, in patients with alcoholic hepatitis, polymorphonuclear infiltration with hepatic necrosis, Mallory (or MalloryDenk) bodies (alcoholic hyaline), and perivenular and perisinusoidal fibrosis. Micronodular cirrhosis may be present as well. The findings are identical to those of nonalcoholic steatohepatitis.

Differential Diagnosis

Alcoholic hepatitis may be closely mimicked by cholecystitis and cholelithiasis and by drug toxicity. Other causes of hepatitis or chronic liver disease may be excluded by serologic or biochemical testing, imaging studies, or liver biopsy. A formula based on the AST/ALT ratio, body mass index, mean corpuscular volume, and sex has been reported to reliably distinguish alcoholic liver disease from nonalcoholic fatty liver disease (NAFLD).

Treatment

A. General Measures

Abstinence from alcohol is essential. Naltrexone, acamprosate, or baclofen may be considered in combination with counseling to reduce the likelihood of recidivism. Fatty liver is quickly reversible with abstinence. Every effort should be made to provide sufficient amounts of carbohydrates and calories in anorectic patients to reduce endogenous protein catabolism, promote gluconeogenesis, and prevent hypoglycemia. Nutritional support (40 kcal/kg with 1.5–2 g/kg as protein) improves liver disease, but not necessarily survival, in patients with malnutrition. Use of liquid formulas rich in branched-chain amino acids does not improve survival beyond that achieved with less expensive caloric supplementation. The administration of micronutrients, particularly folic acid, thiamine, and zinc, is indicated, especially when deficiencies are noted; glucose administration increases the thiamine requirement and can precipitate Wernicke-Korsakoff syndrome if thiamine is not coadministered.

B. Pharmacologic Measures

Methylprednisolone, 32 mg/day orally, or the equivalent, for 1 month, may reduce short-term mortality in patients with alcoholic hepatitis and encephalopathy or a Maddrey discriminant function index (defined by the patient's prothrombin time minus the control prothrombin time times 4.6 plus the total bilirubin in mg/dL) of 32 or more, or a MELD score of 18 or more. No benefit has been demonstrated in patients with concomitant gastrointestinal bleeding, but infection should not preclude treatment with corticosteroids if otherwise indicated.

Pentoxifylline, 400 mg orally three times daily for 4 weeks, may reduce 1-month mortality rates in patients with severe alcoholic hepatitis, primarily by decreasing the risk of hepatorenal syndrome. It is often used when corticosteroids are contraindicated. The combination of corticosteroids and N-acetylcysteine has been reported to improve 1-month but not 6-month survival and reduce the risk of hepatorenal syndrome and infections.

Prognosis

A. Short-Term

The overall mortality rate is 34% (20% within 1 month) without corticosteroid therapy. Individuals in whom the prothrombin time prohibits liver biopsy have a 42% mortality rate at 1 year. Other unfavorable prognostic factors are older age, a serum bilirubin greater than 10 mg/dL (171 mcmol/L), hepatic encephalopathy, coagulopathy, azotemia, leukocytosis, sepsis and other infections, lack of response to corticosteroid therapy, and possibly a paucity of steatosis on a liver biopsy specimen and reversal of portal blood flow by Doppler ultrasonography. Failure of the serum bilirubin level to decline after 7 days of treatment with corticosteroids predicts nonresponse and poor longterm survival, as does the Lille model (which includes age, serum creatinine, serum albumin, prothrombin time [or INR], serum bilirubin on admission, and serum bilirubin on day 7). The MELD score used for cirrhosis and the Glasgow alcoholic hepatitis score (based on age, white blood cell

count, blood urea nitrogen, prothrombin time ratio, and bilirubin level) also correlate with mortality from alcoholic hepatitis and have higher specificities than the discriminant function and Lille score. A scoring system based on age, serum bilirubin, INR, and serum creatinine (ABIC) has been proposed, and one study has shown that the development of acute kidney injury is the most accurate predictor of 90-day mortality. Histologic features associated with 90-day mortality include the degree of fibrosis and neutrophil infiltration, presence of metamitochondria, and pattern of bilirubinostasis.

B. Long-Term

Overall mortality from alcoholic liver disease has declined slightly in the United States since 1980. Nevertheless, the 3-year mortality rate of persons who recover from acute alcoholic hepatitis is ten times greater than that of control individuals of comparable age; the 5-year mortality rate is as high as 85%. Histologically, severe disease is associated with continued excessive mortality rates after 3 years, whereas the death rate is not increased after the same period in those whose liver biopsies show only mild alcoholic hepatitis. Complications of portal hypertension (ascites, variceal bleeding, hepatorenal syndrome), coagulopathy, and severe jaundice following recovery from acute alcoholic hepatitis also suggest a poor long-term prognosis. Alcoholic cirrhosis is a risk factor for hepatocellular carcinoma, and the risk is highest in carriers of the C282Y mutation for hemochromatosis or those with increased hepatic iron.

The most important prognostic consideration is continued excessive drinking. A 6-month period of abstinence is generally required before liver transplantation is considered, although this requirement has been questioned and early liver transplantation has been performed in selected patients with alcoholic hepatitis, with good outcomes. Optimal candidates have adequate social support, do not smoke, have no psychosis or personality disorder, are adherent to therapy, and have regular appointments with a psychiatrist or psychologist who specializes in addiction treatment. Patients with alcoholic liver disease are at higher risk for posttransplant malignancy than those with other types of liver disease because of alcohol and tobacco use.

When to Refer

Refer patients with alcoholic hepatitis who require liver biopsy for diagnosis.

When to Admit

- Hepatic encephalopathy.
- INR greater than 1.6.
- Total bilirubin 10 mg/dL or more.
- Inability to maintain hydration.

DRUG- & TOXIN-INDUCED LIVER INJURY

ESSENTIALS OF DIAGNOSIS

- Drug-induced liver injury can mimic viral hepatitis, biliary tract

obstruction, or other types of liver disease.

- Clinicians must inquire about the use of many widely used therapeutic agents, including overthe-counter “natural” and herbal products, in any patient with liver disease.

General Considerations

Many therapeutic agents may cause drug-induced liver injury, and up to 10% of patients with drug-induced liver injury die or undergo liver transplantation within 6 months of onset. The medications most commonly implicated are nonsteroidal anti-inflammatory drugs and antibiotics because of their widespread use. In any patient with liver disease, the clinician must inquire carefully about the use of potentially hepatotoxic drugs or exposure to hepatotoxins, including over-the-counter “natural” and herbal products. In some cases, coadministration of a second agent may increase the toxicity of the first (eg, isoniazid and rifampin, acetaminophen and alcohol). A relationship between increased serum ALT levels in premarketing clinical trials and postmarketing reports of hepatotoxicity has been identified. Except for drugs used to treat tuberculosis and HIV infection, the risk of hepatotoxicity is not increased in patients with preexisting cirrhosis. Drug toxicity may be categorized on the basis of pathogenesis or predominant histologic appearance. Drug-induced liver injury can mimic viral hepatitis, biliary tract obstruction, or other types of liver disease.

Categorization by Pathogenesis

A. Direct Hepatotoxicity

Liver toxicity caused by this group of drugs is characterized by: (1) dose-related severity, (2) a latent period following exposure, and (3) susceptibility in all individuals. Examples include acetaminophen (toxicity is enhanced by fasting and chronic alcohol use because of depletion of glutathione and induction of cytochrome P450 2E1 and possibly reduced by statins, fibrates, and nonsteroidal anti-inflammatory drugs), alcohol, carbon tetrachloride, chloroform, heavy metals, mercaptopurine, niacin, plant alkaloids, phosphorus, pyrazinamide, tetracyclines, tipranavir, valproic acid, and vitamin A.

B. Idiosyncratic Reactions

Except for acetaminophen, most severe hepatotoxicity is idiosyncratic. Reactions of this type are (1) sporadic, (2) not related to dose above a general threshold of 100 mg/day, and (3) occasionally associated with features suggesting an allergic reaction, such as fever and eosinophilia, which may be associated with a favorable outcome. In many instances, the drug is lipophilic, and toxicity results directly from a metabolite that is produced only in certain individuals on a genetic basis. Drug-induced liver injury may be observed only during post-marketing surveillance and not during preclinical trials. Examples include abacavir, amiodarone, aspirin, carbamazepine, chloramphenicol, diclofenac, disulfiram, duloxetine, ezetimibe, flavocoxid (a “medical food”), fluoroquinolones (moxifloxacin and levofloxacin, in particular), flutamide, halothane, isoniazid,

ketoconazole, lamotrigine, methyldopa, natalizumab, nevirapine, oxacillin, phenytoin, pyrazinamide, quinidine, rivaroxaban, streptomycin, thiazolidinediones, tolvaptan, and perhaps tacrine. Statins, like all cholesterol-lowering agents, may cause serum aminotransferase elevations but rarely cause true hepatitis, and even more rarely cause acute liver failure, and are no longer considered contraindicated in patients with liver disease.

Categorization by Histopathology

A. Cholestasis

1. Noninflammatory—Drug-induced cholestasis results from inhibition or genetic deficiency of various hepatobiliary transporter systems. The following drugs cause cholestasis: anabolic steroids containing an alkyl or ethinyl group at carbon 17, azathioprine, cetirizine, cyclosporine, diclofenac, estrogens, indinavir (increased risk of indirect hyperbilirubinemia in patients with Gilbert syndrome), mercaptopurine, methyltestosterone, tamoxifen, temozolomide, and ticlopidine.

2. Inflammatory—The following drugs cause inflammation of portal areas with bile duct injury (cholangitis), often with allergic features such as eosinophilia: amoxicillinclavulanic acid (among the most common causes of druginduced liver injury), azathioprine, azithromycin, captopril, celecoxib, cephalosporins, chlorothiazide, chlorpromazine, chlorpropamide, erythromycin, mercaptopurine, penicillamine, prochlorperazine, semisynthetic penicillins (eg, cloxacillin), and sulfadiazine. Ketamine abuse may cause secondary biliary cirrhosis. Cholestatic and mixed cholestatic hepatocellular toxicity is more likely than pure hepatocellular toxicity to lead to chronic liver disease.

B. Acute or Chronic Hepatitis

Medications that may result in acute or chronic hepatitis that is histologically and in some cases clinically similar to autoimmune hepatitis include minocycline and nitrofurantoin, most commonly, as well as aspirin, isoniazid (increased risk in HBV and HCV carriers), methyldopa, nonsteroidal antiinflammatory drugs, propylthiouracil, terbinafine, and tumor necrosis factor inhibitors. Histologic features that favor a drug cause include portal tract neutrophils and hepatocellular cholestasis. Hepatitis also can occur in patients taking cocaine, diclofenac, methylenedioxymethamphetamine (MDMA; Ecstasy), efavirenz, imatinib mesylate, ipilimumab, nafazodone (has a black box warning for a potential to cause liver failure), nevirapine (like other protease inhibitors, increased risk in HBV and HCV carriers), pioglitazone, ritonavir (greater rate than other protease inhibitors), rosiglitazone, saquinavir, sulfonamides, telithromycin, and zafirlukast, as well as a variety of alternative remedies (eg, chaparral, germander, green tea extracts, Herbalife products, Hydroxycut, jin bu huan, kava, skullcap, possibly black cohosh and other traditional Chinese herbal preparations), as well as dietary supplements (eg, 1, 3-dimethylamylamine in OxyELITE Pro, a weight loss supplement now withdrawn from the US market). In patients with jaundice due to druginduced hepatitis, the mortality rate without liver transplantation is at least 10%.

C. Other Reactions

1. Fatty liver

A. Macrovesicular—This type of liver injury may be produced by alcohol, amiodarone, corticosteroids, irinotecan, methotrexate, tamoxifen, vinyl chloride (in exposed workers), zalcitabine, and possibly oxaliplatin.

B. Microvesicular—Often resulting from mitochondrial injury, this condition is associated with didanosine, stavudine, tetracyclines, valproic acid, and zidovudine.

2. Granulomas—Allopurinol, phenytoin, pyrazinamide, quinidine, and quinine can lead to granulomas.

3. Fibrosis and cirrhosis—Methotrexate and vitamin A are associated with fibrosis and cirrhosis.

4. Sinusoidal obstruction syndrome (veno-occlusive disease)—This disorder may result from treatment with antineoplastic agents (eg, pre-bone marrow transplant, oxaliplatin), and pyrrolizidine alkaloids (eg, Comfrey).

5. Peliosis hepatis (blood-filled cavities)—Peliosis hepatis may be caused by anabolic steroids and oral contraceptive steroids as well as azathioprine and mercaptopurine, which may also cause nodular regenerative hyperplasia.

6. Neoplasms—Neoplasms may result from therapy with oral contraceptive steroids, including estrogens (hepatic adenoma but not focal nodular hyperplasia), and vinyl chloride (angiosarcoma).

When to Refer

Refer patients with drug- and toxin-induced hepatitis who require liver biopsy for diagnosis.

When to Admit

Patients with liver failure should be hospitalized.

NONALCOHOLIC FATTY LIVER DISEASE

ESSENTIALS OF DIAGNOSIS

- Often asymptomatic.
- Elevated aminotransferase levels and/or hepatomegaly.
- Predominantly macrovesicular steatosis with or without inflammation and fibrosis on liver biopsy.

General Considerations

Nonalcoholic fatty liver disease (NAFLD) is estimated to affect 20–45% of the US population. The principal causes of NAFLD are obesity (present in 40% or more of affected patients), diabetes mellitus (in 20% or more), and hypertriglyceridemia (in 20% or more) in association with insulin resistance as part of the metabolic syndrome. The risk of NAFLD in persons with metabolic syndrome is 4 to 11 times higher than that of persons without insulin resistance. Other causes of fatty liver include corticosteroids, amiodarone, diltiazem, tamoxifen, irinotecan, oxaliplatin, highly active antiretroviral therapy, toxins (vinyl

chloride, carbon tetrachloride, yellow phosphorus), endocrinopathies such as Cushing syndrome and hypopituitarism, polycystic ovary syndrome, hypothyroidism, hypobetalipoproteinemia and other metabolic disorders, obstructive sleep apnea (with chronic intermittent hypoxia), excessive dietary fructose consumption, starvation and refeeding syndrome, and total parenteral nutrition. Genetic factors may account in part for an increased risk in Hispanics. The risk of NAFLD is increased in persons with psoriasis and appears to correlate with the activity of psoriasis. Soft drink consumption and cholecystectomy have been reported to be associated with NAFLD. Physical activity protects against the development of NAFLD. In addition to macrovesicular steatosis, histologic features may include focal infiltration by polymorphonuclear neutrophils and Mallory hyalin, a picture indistinguishable from that of alcoholic hepatitis and referred to as nonalcoholic steatohepatitis (NASH), which affects 3–5% of the US population. In patients with NAFLD, older age, obesity, and diabetes mellitus are risk factors for advanced hepatic fibrosis and cirrhosis, whereas coffee consumption appears to reduce the risk. Cirrhosis caused by NASH appears to be uncommon in African Americans. Persons with NAFLD appear to be at increased risk for cardiovascular disease, chronic kidney disease, and colorectal cancer.

Microvesicular steatosis is seen with Reye syndrome, didanosine or stavudine toxicity, valproic acid toxicity, high-dose tetracycline, or acute fatty liver of pregnancy and may result in fulminant hepatic failure. Women in whom fatty liver of pregnancy develops often have a defect in fatty acid oxidation due to reduced long-chain 3-hydroxyacylCoA dehydrogenase activity.

Clinical Findings

A. Symptoms and Signs

Most patients with NAFLD are asymptomatic or have mild right upper quadrant discomfort. Hepatomegaly is present in up to 75% of patients, but stigmata of chronic liver disease are uncommon. Rare instances of subacute liver failure caused by previously unrecognized NASH have been described. Signs of portal hypertension generally signify advanced liver fibrosis or cirrhosis but occasionally occur in patients with mild and no fibrosis and severe steatosis.

B. Laboratory Findings

Laboratory studies may show mildly elevated aminotransferase and alkaline phosphatase levels; however, laboratory values may be normal in up to 80% of persons with hepatic steatosis. In contrast to alcoholic liver disease, the ratio of ALT to AST is almost always greater than 1 in NAFLD, but it decreases to less than 1 as advanced fibrosis and cirrhosis develop. Antinuclear or smooth muscle antibodies and an elevated serum ferritin level may each be detected in onefourth of patients with NASH. Elevated serum ferritin levels may signify so-called dysmetabolic iron overload syndrome and mildly increased body iron stores, which may play a causal role in insulin resistance and oxidative stress in hepatocytes and correlate with advanced fibrosis; the frequency of mutations in the HFE gene for hemochromatosis is not increased in patients with NAFLD. Iron deficiency is also

common and associated with female sex, obesity, increased waist circumference, diabetes mellitus, and black or Native American race.

C. Imaging

Macrovascular steatosis may be demonstrated on ultrasonography, CT, or MRI. However, imaging does not distinguish steatosis from steatohepatitis or detect fibrosis.

D. Liver Biopsy

Percutaneous liver biopsy is diagnostic and is the standard approach to assessing the degree of inflammation and fibrosis. The risks of the procedure must be balanced against the impact of the added information on management decisions and assessment of prognosis. Liver biopsy is generally not recommended in asymptomatic persons with unsuspected hepatic steatosis detected on imaging but normal liver biochemistry test results. The histologic spectrum of NAFLD includes fatty liver, isolated portal fibrosis, steatohepatitis, and cirrhosis. A risk score for predicting advanced fibrosis, known as BARD, is based on body mass index more than 28, AST/ALT ratio 0.8 or more, and diabetes mellitus; it has a 96% negative predictive value (ie, a low score reliably excludes advanced fibrosis). Another risk score for advanced fibrosis, the NAFLD Fibrosis Score (http://nafldscore.com) based on age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio, has a positive predictive value of over 80% and identifies patients at increased risk for liver-related complications and death. A clinical scoring system to predict the likelihood of NASH in morbidly obese persons includes six predictive factors: hypertension, type 2 diabetes mellitus, sleep apnea, AST greater than 27 units/L (0.54 mckat/L), ALT greater than 27 units/L (0.54 mckat/L), and non-black race.

Treatment

Treatment consists of lifestyle changes to remove or modify the offending factors. Weight loss, dietary fat restriction, and exercise (through reduction of abdominal obesity) often lead to improvement in liver biochemical tests and steatosis in obese patients with NAFLD. Loss of 3–5% of body weight appears necessary to improve steatosis, but loss of up to 10% may be needed to improve necroinflammation. Exercise may reduce liver fat with minimal or no weight loss and no reduction in ALT levels. Resistance training and aerobic exercise are equally effective in reducing hepatic fat content in patients with NAFLD and type 2 diabetes mellitus. Various drugs are under study. Vitamin E 800 international units/day (to reduce oxidative stress) appears to be of benefit. Thiazolidinediones reverse insulin resistance and, in most relevant studies, have improved both serum aminotransferase levels and histologic features of steatohepatitis but lead to weight gain. Metformin, which reduces insulin resistance, improves abnormal liver chemistries but may not reliably improve liver histology. Pentoxifylline improves liver biochemical test levels but is associated with a high rate of side effects, particularly nausea. Ursodeoxycholic acid, 12–15 mg/kg/day, has not consistently

resulted in biochemical and histologic improvement in patients with NASH but may be effective when given in combination with vitamin E. Hepatic steatosis due to total parenteral nutrition may be ameliorated—and perhaps prevented—with supplemental choline. Statins are not contraindicated in persons with NAFLD. Gastric bypass may be considered in patients with a body mass index greater than 35 and leads to improvement in hepatic steatosis. Liver transplantation is indicated in appropriate candidates with advanced cirrhosis caused by NASH, now the third most common (and most rapidly increasing) indication for liver transplantation in the United States. Liver transplantation for NASH with advanced cirrhosis may be associated with increased mortality from cardiovascular disease and sepsis compared with liver transplantation for other indications.

Prognosis

Fatty liver often has a benign course and is readily reversible with discontinuation of alcohol (or no more than one glass of wine per day, which may actually reduce the frequency of NASH in persons with NAFLD), or treatment of other underlying conditions; if untreated, cirrhosis develops in 1–3% of patients. In patients with NAFLD, the likelihood of NASH is increased by the following factors: obesity, older age, non–African American ethnicity, female sex, diabetes mellitus, hypertension, higher ALT or AST level, higher AST/ALT ratio, low platelet count, elevated fasting C-peptide level, and an ultrasound steatosis score. NASH may be associated with hepatic fibrosis in 40% of cases; cirrhosis develops in 9–25%; and decompensated cirrhosis occurs in 30–50% of cirrhotic patients over 10 years. The course may be more aggressive in diabetic persons than in nondiabetic persons. Mortality is increased in patients with NAFLD and is more likely to be the result of malignancy and ischemic heart disease than liver disease. Risk factors for mortality are older age, male sex, white race, higher body mass index, hypertension, diabetes mellitus, and cirrhosis. Steatosis is a cofactor for the progression of fibrosis in patients with other causes of chronic liver disease, such as hepatitis C. Hepatocellular carcinoma is a complication of cirrhosis caused by NASH as it is for other causes of cirrhosis. NASH accounts for a substantial percentage of cases labeled as cryptogenic cirrhosis and can recur following liver transplantation. Central obesity is an independent risk factor for death from cirrhosis of any cause.

When to Refer

Refer patients with NAFLD who require liver biopsy for diagnosis.

CIRRHOSIS

ESSENTIALS OF DIAGNOSIS

- End result of injury that leads to both fibrosis and regenerative nodules.
- May be reversible if cause is removed.
- The clinical features result from hepatic cell dysfunction, portosystemic shunting, and portal hypertension.

General Considerations

Cirrhosis, the twelfth leading cause of death in the United States, is the end result of hepatocellular injury that leads to both fibrosis and regenerative nodules throughout the liver. Hospitalization rates for cirrhosis and portal hypertension are rising in the United States. Causes include chronic viral hepatitis, alcohol, drug toxicity, autoimmune and metabolic liver diseases, and miscellaneous disorders. Celiac disease appears to be associated with an increased risk of cirrhosis. Many patients have more than one risk factor (eg, chronic hepatitis and alcohol use). Mexican Americans and African Americans have a higher frequency of cirrhosis than whites because of a higher rate of risk factors. In persons at increased risk for liver injury (eg, heavy alcohol use, obesity, iron overload), higher coffee and tea consumption has been reported to reduce the risk of cirrhosis. The risk of hospitalization or death due to cirrhosis has been reported to correlate with protein and cholesterol consumption and with hyperuricemia and inversely with carbohydrate consumption.

Clinically, cirrhosis is considered to progress through three stages: compensated, compensated with varices, and decompensated (ascites, variceal bleeding, encephalopathy, or jaundice) that correlate with the thickness of fibrous septa.

Clinical Findings

A. Symptoms and Signs

The clinical features of cirrhosis result from hepatocyte dysfunction, portosystemic shunting, and portal hypertension. Patients may have no symptoms for long periods. The onset of symptoms may be insidious or, less often, abrupt. Fatigue, disturbed sleep, muscle cramps, and weight loss are common. In advanced cirrhosis, anorexia is usually present and may be extreme, with associated nausea and occasional vomiting, as well as reduced muscle strength and exercise capacity. Abdominal pain may be present and is related either to hepatic enlargement and stretching of Glisson capsule or to the presence of ascites. Menstrual abnormalities (usually amenorrhea), erectile dysfunction, loss of libido, sterility, and gynecomastia in men may occur. Hematemesis is the presenting symptom in 15–25%.

Skin manifestations consist of spider telangiectasias (invariably on the upper half of the body), palmar erythema (mottled redness of the thenar and hypothenar eminences), and Dupuytren contractures. Evidence of vitamin deficiencies (glossitis and cheilosis) is common. Weight loss, wasting (due to sarcopenia), and the appearance of chronic illness are present. Jaundice—usually not an initial sign—is mild at first, increasing in severity during the later stages of the disease. In 70% of cases, the liver is enlarged, palpable, and firm if not hard and has a sharp or nodular edge; the left lobe may predominate. Splenomegaly is present in 35–50% of cases and is associated with an increased risk of complications of portal hypertension. The superficial veins of the abdomen and thorax are dilated, reflecting the intrahepatic obstruction to portal blood flow, as do rectal varices. The abdominal wall veins fill from below when compressed. Ascites, pleural effusions, peripheral

edema, and ecchymoses are late findings. Encephalopathy characterized by day-night reversal, asterixis, tremor, dysarthria, delirium, drowsiness, and ultimately coma also occurs late except when precipitated by an acute hepatocellular insult or an episode of gastrointestinal bleeding or infection. Fever is present in up to 35% of patients and usually reflects associated alcoholic hepatitis, spontaneous bacterial peritonitis, or intercurrent infection.

B. Laboratory Findings

Laboratory abnormalities are either absent or minimal in early or compensated cirrhosis. Anemia, a frequent finding, is often macrocytic; causes include suppression of erythropoiesis by alcohol as well as folate deficiency, hemolysis, hypersplenism, and occult or overt blood loss from the gastrointestinal tract. The white blood cell count may be low, reflecting hypersplenism, or high, suggesting infection. Thrombocytopenia, the most common cytopenia in cirrhotic patients, is secondary to alcoholic marrow suppression, sepsis, folate deficiency, or splenic sequestration. Prolongation of the prothrombin time may result from reduced levels of clotting factors (except factor VIII). However, bleeding risk correlates poorly with the prothrombin time because of concomitant abnormalities of fibrinolysis, and among hospitalized patients under age 45, cirrhosis is associated with an increased risk of venous thromboembolism.

Blood chemistries reflect hepatocellular injury and dysfunction, manifested by modest elevations of AST and alkaline phosphatase and progressive elevation of the bilirubin. Serum albumin decreases as the disease progresses; gamma-globulin levels are increased and may be as high as in autoimmune hepatitis. The risk of diabetes mellitus is increased in patients with cirrhosis, particularly when associated with HCV infection, alcoholism, hemochromatosis, or NAFLD. Vitamin D deficiency has been reported in as many as 91% of patients with cirrhosis. Patients with alcoholic cirrhosis may have elevated serum cardiac troponin I and B-type natriuretic peptide (BNP) levels. Blunted cardiac inotropic and chronotropic responses to exercise, stress, and drugs, as well as systolic and diastolic ventricular dysfunction in the absence of other known causes of cardiac disease (“cirrhotic cardiomyopathy”), and prolongation of the QT interval in the setting of a hyperkinetic circulation, are common in cirrhosis of all causes, but overt heart failure is rare in the absence of alcoholism. Relative adrenal insufficiency appears to be common in patients with advanced cirrhosis, even in the absence of sepsis, and may relate in part to reduced synthesis of cholesterol and increased levels of proinflammatory cytokines.

C. Imaging

Ultrasonography is helpful for assessing liver size and detecting ascites or hepatic nodules, including small hepatocellular carcinomas. Together with a Doppler study, it may establish patency of the splenic, portal, and hepatic veins. Hepatic nodules are characterized further by contrastenhanced CT or MRI. Nodules suspicious for malignancy may be biopsied under ultrasound or CT guidance.

D. Liver Biopsy

Liver biopsy may show inactive cirrhosis (fibrosis with regenerative nodules) with no specific features to suggest the underlying cause. Alternatively, there may be additional features of alcoholic liver disease, chronic hepatitis, NASH, or other specific causes of cirrhosis. Liver biopsy may be performed by laparoscopy or, in patients with coagulopathy and ascites, by a transjugular approach. Combinations of routine blood tests (eg, AST, platelet count), including the FibroSure test, and serum markers of hepatic fibrosis (eg, hyaluronic acid, amino-terminal propeptide of type III collagen, tissue inhibitor of matrix metalloproteinase 1) are potential alternatives to liver biopsy for the diagnosis or exclusion of cirrhosis. In persons with chronic hepatitis C, for example, a low FibroSure score reliably excludes advanced fibrosis, a high score reliably predicts advanced fibrosis, and intermediate scores are inconclusive.

E. Other Tests

Esophagogastroduodenoscopy confirms the presence of varices and detects specific causes of bleeding in the esophagus, stomach, and proximal duodenum. In selected cases, wedged hepatic vein pressure measurement may establish the presence and cause of portal hypertension. *Ultrasound elastography* and *magnetic resonance elastography* to measure liver stiffness are available in a limited number of centers as noninvasive tests for cirrhosis and portal hypertension.

Differential Diagnosis

The most common causes of cirrhosis are alcohol, chronic hepatitis C infection, NAFLD, and hepatitis B infection. Hemochromatosis is the most commonly identified genetic disorder that causes cirrhosis. Other diseases associated with cirrhosis include Wilson disease, alpha-1-antitrypsin (alpha-1-antiprotease) deficiency, and celiac disease. Primary biliary cirrhosis occurs more frequently in women than men. Secondary biliary cirrhosis may result from chronic biliary obstruction due to a stone, stricture, or neoplasm. Heart failure and constrictive pericarditis may lead to hepatic fibrosis (“cardiac cirrhosis”) complicated by ascites. Hereditary hemorrhagic telangiectasia can lead to portal hypertension because of portosystemic shunting and nodular transformation of the liver as well as high-output heart failure. Many cases of cirrhosis are “cryptogenic,” in which unrecognized NAFLD may play a role.

Complications

Upper gastrointestinal tract *bleeding* may occur from *varices, portal hypertensive gastropathy, or gastroduodenal ulcer.* Varices may also result from portal vein thrombosis, which may complicate cirrhosis. *Liver failure* may be precipitated by alcoholism, surgery, and infection. Hepatic Kupffer cell (reticuloendothelial) dysfunction and decreased opsonic activity lead to an increased risk of *systemic infection* (which may be increased further by the use of proton pump inhibitors), and which increase mortality fourfold. These infections include *nosocomial infections*, which may be classified as spontaneous bloodstream

infections, urinary tract infections, pulmonary infections, spontaneous bacterial peritonitis, Clostridium difficile infection, and intervention-related infections. These nosocomial infections are increasingly caused by multidrug-resistant bacteria. *Osteoporosis* occurs in 12–55% of patients with cirrhosis. The risk of *hepatocellular carcinoma* is increased greatly in persons with cirrhosis.

Treatment

A. General Measures

Most important is abstinence from alcohol. The diet should be palatable, with adequate calories (25–35 kcal/kg body weight per day in those with compensated cirrhosis and 35–45 kcal/kg/day in those with malnutrition) and protein (1–1.5 g/kg/day in those with compensated cirrhosis and 1.5 g/kg/day in those with malnutrition) and, if there is fluid retention, sodium restriction. In the presence of hepatic encephalopathy, protein intake should be reduced to no less than 60–80 g/day. Specialized supplements containing branched-chain amino acids to prevent or treat hepatic encephalopathy or delay progressive liver failure are generally unnecessary. Vitamin supplementation is desirable, but optimal treatment of muscle cramps is uncertain. Patients with cirrhosis should receive the HAV, HBV, and pneumococcal vaccines and a yearly influenza vaccine. Liver transplantation in appropriate candidates is curative.

B. Treatment of Complications

1. Ascites and edema—Diagnostic paracentesis is indicated for patients who have new ascites or who have been hospitalized for a complication of cirrhosis; it reduces mortality, especially if performed within 12 hours of admission. Serious complications of paracentesis, including bleeding, infection, or bowel perforation, occur in 1.6% of procedures and are associated with therapeutic (vs diagnostic) paracentesis and possibly with Child-TurcottePugh class C, platelet counts less than 50,000/mcL (50×10^9/L), and alcoholic cirrhosis. In patients with coagulopathy, however, pre-paracentesis prophylactic transfusions do not appear to be necessary. In addition to a cell count and culture, the ascitic albumin level should be determined: a serum-ascites albumin gradient (serum albumin minus ascitic fluid albumin) greater than or equal to 1.1 suggests portal hypertension. An elevated ascitic adenosine deaminase level is suggestive of tuberculous peritonitis. Occasionally, cirrhotic ascites is chylous (rich in triglycerides); other causes of chylous ascites are malignancy, tuberculosis, and recent abdominal surgery or trauma

Ascites in patients with cirrhosis results from portal hypertension (increased hydrostatic pressure); hypoalbuminemia (decreased oncotic pressure); peripheral vasodilation, perhaps mediated by endotoxin-induced release of nitric oxide from splanchnic and systemic vasculature, with resulting increases in renin and angiotensin levels and sodium retention by the kidneys; impaired hepatic inactivation of aldosterone; and increased aldosterone secretion secondary to increased renin production. In individuals with ascites, the urinary sodium concentration is often less than 10 mEq/L (10 mmol/L). Free water excretion is also

impaired in cirrhosis, and hyponatremia may develop.

In all patients with cirrhotic ascites, dietary sodium intake may initially be restricted to 2000 mg/day; the intake of sodium may be liberalized slightly after diuresis ensues. Nonsteroidal anti-inflammatory drugs are contraindicated, and angiotensin-converting enzyme inhibitors and angiotensin II antagonists should be avoided. In some patients, ascites diminishes promptly with bed rest and dietary sodium restriction alone. Fluid intake (800– 1000 mL/day) is often restricted in patients with hyponatremia. Treatment of severe hyponatremia (serum sodium less than 125 mEq/L [125 mmol/L]) with vasopressin receptor antagonists (eg, intravenous conivaptan, 20 mg daily) can be considered but such treatment is expensive, causes thirst, and does not improve survival; oral tolvaptan is contraindicated in patients with liver disease because of potential hepatotoxicity

A. Diuretics—Spironolactone, generally in combination with furosemide, should be used in patients who do not respond to salt restriction. An initial trial of furosemide 80 mg intravenously demonstrating a rise in urine sodium to 750 mmol in 8 hours may predict response to diuretic therapy. The dose of spironolactone is initially 100 mg orally daily and may be increased by 100 mg every 3–5 days (up to a maximal conventional daily dose of 400 mg/day, although higher doses have been used) until diuresis is achieved, typically preceded by a rise in the urinary sodium concentration. A “spot” urine sodium concentration that exceeds the potassium concentration correlates with a 24-hour sodium excretion greater than 78 mmol/ day, which predicts diuresis in patients adherent to a saltrestricted diet. Monitoring for hyperkalemia is important. In patients who cannot tolerate spironolactone because of side effects, such as painful gynecomastia, amiloride (another potassium-sparing diuretic) may be used in a starting dose of 5–10 mg orally daily. Diuresis is augmented by the addition of a loop diuretic such as furosemide. This potent diuretic, however, will maintain its effect even with a falling glomerular filtration rate, with resulting prerenal azotemia. The dose of oral furosemide ranges from 40 mg/day to 160 mg/day, and the drug should be administered while blood pressure, urinary output, mental status, and serum electrolytes (especially potassium) are monitored. The goal of weight loss in the ascitic patient without associated peripheral edema should be no more than 1–1.5 lb/day (0.5–0.7 kg/day).

B. Large-volume paracentesis—In patients with massive ascites and respiratory compromise, ascites refractory to diuretics (“diuretic resistant”), or intolerable diuretic side effects (“diuretic intractable”), large-volume paracentesis (more than 5 L) is effective. Intravenous albumin concomitantly at a dosage of 6–8 g/L of ascites fluid removed protects the intravascular volume and may prevent postparacentesis circulatory dysfunction, although the usefulness of this practice is debated and the use of albumin is expensive. Large-volume paracentesis can be repeated daily until ascites is largely resolved and may decrease the need for hospitalization. If possible, diuretics should be continued in the hope of preventing recurrent ascites.

C. Transjugular intrahepatic portosystemic shunt (TIPS)—TIPS is an effective treatment of variceal bleeding refractory to standard therapy (eg, endoscopic band ligation [or, now less commonly, sclerotherapy]) and has shown

benefit in the treatment of severe refractory ascites. The technique involves insertion of an expandable metal stent between a branch of the hepatic vein and the portal vein over a catheter inserted via the internal jugular vein. Increased renal sodium excretion and control of ascites refractory to diuretics can be achieved in about 75% of selected cases. The success rate is lower in patients with underlying chronic kidney disease. TIPS appears to be the treatment of choice for refractory hepatic hydrothorax (translocation of ascites across the diaphragm to the pleural space); video-assisted thoracoscopy with pleurodesis using talc may be effective when TIPS is contraindicated. Complications of TIPS include hepatic encephalopathy in 20–30% of cases, infection, shunt stenosis in up to 60% of cases, and shunt occlusion in up to 30% of cases when bare stents are used; polytetrafluoroethylene-covered stents are associated with long-term patency rates of 80–90%. Longterm patency often requires periodic shunt revisions. In most cases, patency can be maintained by balloon dilation, local thrombolysis, or placement of an additional stent. TIPS is particularly useful in patients who require shortterm control of variceal bleeding or ascites until liver transplantation can be performed. In patients with refractory ascites, TIPS results in lower rates of ascites recurrence and hepatorenal syndrome but a higher rate of hepatic encephalopathy than occurs with repeated large-volume paracentesis; a benefit in survival has been demonstrated in one study and a meta-analysis. Chronic kidney disease, diastolic cardiac dysfunction, refractory encephalopathy, and hyperbilirubinemia (greater than 5 mg/dL [85.5 mcmol/L]) are associated with mortality after TIPS.

2. Spontaneous bacterial peritonitis—Spontaneous bacterial peritonitis is heralded by abdominal pain, increasing ascites, fever, and progressive encephalopathy in a patient with cirrhotic ascites; symptoms are typically mild. (Analogously, spontaneous bacterial empyema may complicate hepatic hydrothorax and is managed similarly.) Risk factors in cirrhotic patients with ascites include gastroesophageal variceal bleeding and possibly use of a proton pump inhibitor. Paracentesis reveals an ascitic fluid with, most commonly, a total white cell count of up to 500 cells/mcL with a high percentage of polymorphonuclear cells (PMNs) (250/mcL or more) and a protein concentration of 1 g/dL (10 g/L) or less, corresponding to decreased ascitic opsonic activity. Rapid diagnosis of bacterial peritonitis can be made with a high degree of specificity with rapid reagent strips ("dipsticks") that detect leukocyte esterase in ascitic fluid, but the sensitivity is too low for routine use. Cultures of ascites give the highest yield—80–90% positive—using specialized culture bottles inoculated at the bedside. Common isolates are Escherichia coli and Streptococcus spp. Gram-positive cocci are the most common isolates in patients who have undergone an invasive procedure such as central venous line placement, and the frequency of enterococcal isolates is increasing. Anaerobes are uncommon. Pending culture results, if there are 250 or more PMNs/mcL or symptoms or signs of infection, intravenous antibiotic therapy should be initiated with cefotaxime, 2 g every 8–12 hours for at least 5 days. Ceftriaxone and amoxicillin-clavulanic acid are alternative choices. Oral ofloxacin, 400 mg twice daily for 7 days, or, in a patient not already taking a fluoroquinolone

for prophylaxis against bacterial peritonitis, a 2-day course of intravenous ciprofloxacin, 200 mg twice daily, followed by oral ciprofloxacin, 500 mg twice daily for 5 days, may be effective alternative regimens in selected patients. A carbapenem has been recommended for patients with hospital-acquired spontaneous bacterial peritonitis. Supplemental administration of intravenous albumin (which may have anti-inflammatory effects in addition to expanding plasma volume) prevents further renal impairment and reduces mortality, particularly in patients with a serum creatinine greater than 1 mg/dL (83.3 mcmol/L), blood urea nitrogen greater than 30 mg/dL (10.8 mmol/L), or total bilirubin greater than 4 mg/dL (68.4 mcmol/L). Response to therapy can be documented, if necessary, by a decrease in the PMN count of at least 50% on repeat paracentesis 48 hours after initiation of therapy. The overall mortality rate is high—up to 30% during hospitalization and up to 70% by 1 year. Mortality may be predicted by the 22/11 model: MELD score greater than 22 and peripheral white blood cell count higher than 11,000/mcL (11 $\times 10^9$/L). Patients with cirrhosis and septic shock have a high frequency of relative adrenal insufficiency, which if present requires administration of hydrocortisone. In survivors of bacterial peritonitis, the risk of recurrent peritonitis may be decreased by long-term norfloxacin, 400 mg orally daily; ciprofloxacin (eg, 500 mg orally once or twice a day), although with recurrence the causative organism is often resistant to fluoroquinolones; or trimethoprim-sulfamethoxazole (eg, one doublestrength tablet five times a week). In high-risk cirrhotic patients without prior peritonitis (eg, those with an ascitic protein less than 1.5 g/dL and serum bilirubin greater than 3 mg/dL (51.3 mcmol/L), serum creatinine greater than 1.2 mg/dL (99.96 mcmol/L), blood urea nitrogen 25 mg/dL or more (9 mmol/L or more), or sodium 130 mEq/L or less [130 mmol/L or less]), the risk of peritonitis, hepatorenal syndrome, and mortality for at least 1 year may be reduced by prophylactic norfloxacin, 400 mg orally once a day. In patients hospitalized for acute variceal bleeding, oral norfloxacin (400 mg orally twice a day) or intravenous ceftriaxone (1 g per day), which may be preferable, for 7 days reduces the risk of bacterial peritonitis.

3. Hepatorenal syndrome—Hepatorenal syndrome occurs in up to 10% of patients with advanced cirrhosis and ascites and is characterized by azotemia (serum creatinine greater than 1.5 mg/dL [124.95 mcmol/L]) in the absence of parenchymal kidney disease or shock and by failure of kidney function to improve following 2 days of diuretic withdrawal and volume expansion with albumin, 1 g/kg up to a maximum of 100 g/day. Oliguria, hyponatremia, and a low urinary sodium concentration are typical features. Hepatorenal syndrome is diagnosed only when other causes of acute kidney injury (including prerenal azotemia and acute tubular necrosis) have been excluded. Urinary neutrophil gelatinase-associated lipocalin levels (normal, 20 ng/mL) and other biomarkers may help distinguish hepatorenal syndrome (105 ng/mL) from chronic kidney disease (50 ng/mL) and acute kidney injury (325 ng/mL). Type I hepatorenal syndrome is characterized by doubling of the serum creatinine to a level greater than 2.5 mg/dL (208.25 mcmol/L) or by halving of the creatinine clearance to less than 20 mL/min (0.34 mL/s/1.73 m2

BSA) in less than 2 weeks. Type II hepatorenal syndrome is more slowly progressive and chronic. An acute decrease in cardiac output is often the precipitating event. In addition to discontinuation of diuretics, clinical improvement and an increase in short-term survival may follow intravenous infusion of albumin in combination with one of the following vasoconstrictor regimens for 7–14 days: oral midodrine plus octreotide, subcutaneously or intravenously; intravenous terlipressin (not yet available in the United States but perhaps the preferred agent where available); or intravenous norepinephrine. Oral midodrine, 7.5 mg three times daily, added to diuretics, to increase blood pressure has also been reported to convert refractory ascites to diuretic-sensitive ascites. Prolongation of survival has been associated with use of MARS, a modified dialysis method that selectively removes albumin-bound substances. Improvement and sometimes normalization of kidney function may also follow placement of a TIPS; survival after 1 year is reported to be predicted by the combination of a serum bilirubin level less than 3 mg/dL (50 mcmol/L) and a platelet count greater than 75,000/mcL (75×10^9/L). Continuous venovenous hemofiltration and hemodialysis are of uncertain value in hepatorenal syndrome. Liver transplantation is the treatment of choice, but many patients die before a donor liver can be obtained. Mortality correlates with the MELD score and presence of a systemic inflammatory response. Type 1 hepatorenal syndrome is often irreversible in patients with a systemic infection. The 3-month probability of survival in cirrhotic patients with hepatorenal syndrome (15%) is lower than that for renal failure associated with infections (31%), hypovolemia (46%), and parenchymal kidney disease (73%).

4. Hepatic encephalopathy—Hepatic encephalopathy is a state of disordered central nervous system function resulting from failure of the liver to detoxify noxious agents of gut origin because of hepatocellular dysfunction and portosystemic shunting. The clinical spectrum ranges from day-night reversal and mild intellectual impairment to coma. Patients with covert (formerly minimal) hepatic encephalopathy have no recognizable clinical symptoms but demonstrate mild cognitive and psychomotor deficits and attention deficit on standardized psychometric tests and an increased rate of traffic accidents. The stages of overt encephalopathy are: (1) mild confusion, (2) drowsiness, (3) stupor, and (4) coma. A revised staging system known as SONIC (spectrum of neurocognitive impairment in cirrhosis) encompasses absent, covert, and stages 2 to 4 encephalopathy. Ammonia is the most readily identified and measurable toxin but is not solely responsible for the disturbed mental status. Bleeding into the intestinal tract may significantly increase the amount of protein in the bowel and precipitate encephalopathy. Other precipitants include constipation, alkalosis, and potassium deficiency induced by diuretics, opioids, hypnotics, and sedatives; medications containing ammonium or amino compounds; paracentesis with consequent hypovolemia; hepatic or systemic infection; and portosystemic shunts (including TIPS). The diagnosis is based primarily on detection of characteristic symptoms and signs, including asterixis. The role of neuroimaging studies (eg, cerebral PET, magnetic resonance spectroscopy) in the diagnosis of hepatic encephalopathy is

evolving.

Protein is withheld during acute episodes if the patient cannot eat. When the patient resumes oral intake, protein intake should be 60–80 g/day as tolerated; vegetable protein is better tolerated than meat protein. Gastrointestinal bleeding should be controlled and blood purged from the gastrointestinal tract. This can be accomplished with 120 mL of magnesium citrate by mouth or nasogastric tube every 3–4 hours until the stool is free of gross blood, or by administration of lactulose. The value of treating patients with covert hepatic encephalopathy is uncertain; probiotic agents may have some benefit.

Lactulose, a nonabsorbable synthetic disaccharide syrup, is digested by bacteria in the colon to short-chain fatty acids, resulting in acidification of colon contents. This acidification favors the formation of ammonium ion in the $NH4 + \leftrightarrow NH3 + H+$ equation; NH4 + is not absorbable, whereas NH3 is absorbable and thought to be neurotoxic. Lactulose also leads to a change in bowel flora so that fewer ammonia-forming organisms are present. When given orally, the initial dose of lactulose for acute hepatic encephalopathy is 30 mL three or four times daily. The dose should then be titrated so that the patient produces 2–3 soft stools per day. When given rectally because the patient is unable to take medicines orally, the dose is 300 mL of lactulose in 700 mL of saline or sorbitol as a retention enema for 30–60 minutes; it may be repeated every 4–6 hours. Bowel cleansing with a polyethylene glycol colonoscopy preparation is also effective in patients with acute overt hepatic encephalopathy. Continued use of lactulose after an episode of acute encephalopathy reduces the frequency of recurrences.

The ammonia-producing intestinal flora may also be controlled with an oral antibiotic. The nonabsorbable agent rifaximin, 550 mg orally twice daily, is preferred and has been shown as well to maintain remission from and reduce the risk of rehospitalization for hepatic encephalopathy over a 24-month period, with or without the concomitant use of lactulose. Metronidazole, 250 mg orally three times daily, has also shown benefit. Patients who do not respond to lactulose alone may improve with a course of an antibiotic added to treatment with lactulose.

Opioids and sedatives metabolized or excreted by the liver should be avoided. If agitation is marked, oxazepam, 10–30 mg, which is not metabolized by the liver, may be given cautiously by mouth or by nasogastric tube. Zinc deficiency should be corrected, if present, with oral zinc sulfate, 600 mg/day in divided doses. Sodium benzoate, 5 g orally twice daily, ornithine aspartate, 9 g orally three times daily, and L-acyl-carnitine (an essential factor in the mitochrondrial transport of long-chain fatty acids), 4 g orally daily, may lower blood ammonia levels, but there is less experience with these drugs than with lactulose. Flumazenil is effective in about 30% of patients with severe hepatic encephalopathy, but the drug is short-acting and intravenous administration is required. Use of special dietary supplements enriched with branched-chain amino acids is usually unnecessary except in occasional patients who are intolerant of standard protein supplements.

5. Coagulopathy—Hypoprothrombinemia caused by malnutrition and vitamin K deficiency may be treated with vitamin K (eg, phytonadione, 5 mg orally or

intravenously daily); however, this treatment is ineffective when synthesis of coagulation factors is impaired because of hepatic disease. In such cases, correcting the prolonged prothrombin time requires large volumes of fresh frozen plasma. Because the effect is transient, plasma infusions are not indicated except for active bleeding or before an invasive procedure, and even then, their value has been questioned because of concomitant alterations in antihemostatic factors and because bleeding risk does not correlate with the INR. Recombinant activated factor VIIa may be an alternative but is expensive and poses a 1–2% risk of thrombotic complications. Eltrombopag reduces the need for platelet transfusions in patients with cirrhosis and a platelet count less than 50,000/mcL (50×10^9/L) who undergo invasive procedures, but eltrombopag is associated with an increased risk of portal vein thrombosis and arterial thromboembolism.

6. Hemorrhage from esophageal varices.

7. Hepatopulmonary syndrome and portopulmonary hypertension—Shortness of breath in patients with cirrhosis may result from pulmonary restriction and atelectasis caused by massive ascites or hepatic hydrothorax. The hepatopulmonary syndrome—the triad of chronic liver disease, an increased alveolar-arterial gradient while the patient is breathing room air, and intrapulmonary vascular dilatations or arteriovenous communications that result in a right-to-left intrapulmonary shunt—occurs in 5–32% of patients with cirrhosis. Patients often have greater dyspnea (platypnea) and arterial deoxygenation (orthodeoxia) in the upright than in the recumbent position. The diagnosis should be suspected in a cirrhotic patient with a pulse oximetry level of 96% or less.

Contrast-enhanced echocardiography is a sensitive screening test for detecting pulmonary vascular dilatations, whereas macroaggregated albumin lung perfusion scanning is more specific and may be used to confirm the diagnosis. High-resolution CT may be useful for detecting dilated pulmonary vessels that may be amenable to embolization in patients with severe hypoxemia (Po2 less than 60 mm Hg [7.8 kPa]) who respond poorly to supplemental oxygen.

Medical therapy has been disappointing; experimentally, intravenous methylene blue, oral garlic powder, oral norfloxacin, and mycophenolate mofetil may improve oxygenation by inhibiting nitric oxide-induced vasodilatation and angiogenesis, and pentoxifylline may prevent hepatopulmonary syndrome by inhibiting production of tumor necrosis factor. Long-term oxygen therapy is recommended for severely hypoxemic patients. The syndrome may reverse with liver transplantation, although postoperative mortality is increased in patients with a preoperative arterial Po2 less than 44 mm Hg (5.9 kPa) or with substantial intrapulmonary shunting. TIPS may provide palliation in patients with hepatopulmonary syndrome awaiting transplantation. Portopulmonary hypertension occurs in 0.7% of patients with cirrhosis. Female sex and autoimmune hepatitis have been reported to be risk factors, and large spontaneous portosystemic shunts are present in many affected patients and are associated with a lack of response to treatment. In cases confirmed by right-sided heart catheterization, treatment with

the prostaglandin epoprostenol, the endothelin-receptor antagonists bosentan or ambrisentan, or the phosphodiesterase-5 inhibitors sildenafil or tadalafil may reduce pulmonary hypertension and thereby facilitate liver transplantation; beta-blockers worsen exercise capacity and are contraindicated, and calcium channel blockers should be used with caution because they may worsen portal hypertension. Liver transplantation is contraindicated in patients with moderate to severe pulmonary hypertension (mean pulmonary pressure greater than 35 mm Hg).

C. Liver Transplantation

Liver transplantation is indicated in selected cases of irreversible, progressive chronic liver disease, acute liver failure, and certain metabolic diseases in which the metabolic defect is in the liver. Absolute contraindications include malignancy advanced cardiopulmonary disease (except hepatopulmonary syndrome), and sepsis. Relative contraindications include age over 70 years, morbid obesity, portal and mesenteric vein thrombosis, active alcohol or drug abuse, severe malnutrition, and lack of patient understanding. With the emergence of effective antiretroviral therapy for HIV disease, a major cause of mortality in these patients has shifted to liver disease caused by HCV and HBV infection; experience to date suggests that the outcome of liver transplantation is comparable to that for non–HIV-infected liver transplant recipients. Patients with alcoholism should be abstinent for 6 months. Liver transplantation should be considered in patients with worsening functional status, rising bilirubin, decreasing albumin, worsening coagulopathy, refractory ascites, recurrent variceal bleeding, or worsening encephalopathy; prioritization is based on the MELD score. Combined liver-kidney transplantation is indicated in patients with associated kidney failure presumed to be irreversible. The major impediment to more widespread use of liver transplantation is a shortage of donor organs. Adult living donor liver transplantation is an option for some patients, and extended-criteria donors are beingused. Five-year survival rates as high as 80% are now reported. Hepatocellular carcinoma, hepatitis B and C, and some cases of Budd-Chiari syndrome and autoimmune liver disease may recur in the transplanted liver. The incidence of recurrence of hepatitis B can be reduced by preoperative and postoperative treatment with a nucleoside or nucleotide analog and perioperative administration of HBIG. Immunosuppression is achieved with combinations of cyclosporine, tacrolimus or sirolimus, corticosteroids, azathioprine, and mycophenolate mofetil and may be complicated by infections, advanced chronic kidney disease, neurologic disorders, and drug toxicity as well as graft rejection, vascular occlusion, or bile leaks. Patients taking these drugs are at risk for obesity, diabetes mellitus, and hyperlipidemia.

Prognosis

Prognostic scoring systems for cirrhosis include the ChildTurcotte-Pugh score and MELD score. The MELD score, which incorporates the serum bilirubin and creatinine levels and the INR, is also a measure of mortality risk in patients with end-stage liver disease and is particularly useful for predicting short- and intermediate-term survival and complications of cirrhosis (eg, bacterial peritonitis)

as well as determining allocation priorities fordonor livers. Additional (MELD-exception) points are given for patients with conditions such as hepatopulmonary syndrome and hepatocellular carcinoma that may benefit from liver transplantation. A MELD score of greater than 14 is required for liver transplant listing. In patients with a relatively low MELD score (less than 21) and a low priority for liver transplantation, a low serum sodium concentration (below 130 mEq/L [130 mmol/L]), an elevated hepatic venous pressure gradient, persistent ascites, and a low health-related quality of life appear to be additional independent predictors of mortality, and modifications of the MELD score, including one that incorporates the serum sodium (MELDNa), are under consideration. Only 50% of patients with severe hepatic dysfunction (serum albumin less than 3 g/dL [30 g/L]), bilirubin greater than 3 mg/dL [51.3 mcmol/L]), ascites, encephalopathy, cachexia, and upper gastrointestinal bleeding) survive 6 months without transplantation. The risk of death in this subgroup of patients with advanced cirrhosis is associated with muscle wasting, age 65 years or older, mean arterial pressure 82 mm Hg or less, renal failure, cognitive dysfunction, ventilatory insufficiency, and prothrombin time 16 seconds or longer, delayed and suboptimal treatment of sepsis, and second infections. For cirrhotic patients admitted to an intensive care unit, the Royal Free Hospital score, consisting of the serum bilirubin, INR, serum lactate, alveolar-arterial oxygen gradient, and blood urea nitrogen, has been reported to predict mortality. Renal failure increases mortality in patients with cirrhosis up to sevenfold. Obesity and diabetes mellitus appear to be risk factors for clinical deterioration and cirrhosis-related mortality, as is continued alcohol use in patients with alcoholic cirrhosis. The use of beta-blockers for portal hypertension is beneficial early in the course but is associated with reduced survival in patients with refractory ascites or spontaneous bacterial peritonitis because of their negative effect on cardiac compensatory reserve. Patients with cirrhosis are at risk for the development of hepatocellular carcinoma, with rates of 3–5% per year for alcoholic and viral hepatitis-related cirrhosis. Liver transplantation has markedly improved the outlook for patients with cirrhosis who are candidates and are referred for evaluation early. Patients with compensated cirrhosis are given additional priority for liver transplantation if they are found to have a lesion larger than 2 cm in diameter consistent with hepatocellular carcinoma. In-hospital mortality from variceal bleeding in patients with cirrhosis has declined from over 40% in 1980 to 15% in 2000.

When to Refer

- For liver biopsy.
- When the MELD score is 14 or higher.
- For upper endoscopy to screen for gastroesophageal varices.

When to Admit

- Gastrointestinal bleeding.
- Stage 3–4 hepatic encephalopathy.
- Worsening kidney function.

• Severe hyponatremia.
• Serious infection.
• Profound hypoxia.

DISEASES OF THE BILIARY TRACT CHOLELITHIASIS (Gallstones)

ESSENTIALS OF DIAGNOSIS

- Often asymptomatic.
- Classic biliary pain ("episodic gallbladder pain") characterized by infrequent episodes of steady severe pain in epigastrium or right upper quadrant with radiation to right scapula.
- Detected on ultrasonography.

General Considerations

Gallstones are more common in women than in men and increase in incidence in both sexes and all races with age. In the United States, the prevalence of gallstones is 8.6% in women and 5.5% in men, with the highest rates in persons over age 60 and higher rates in Mexican-Americans than in non-Hispanic whites and African Americans, and gallstone disease is associated with increased overall, cardiovascular, and cancer mortality. Although cholesterol gallstones are less common in black people, cholelithiasis attributable to hemolysis occurs in over a third of individuals with sickle cell disease. Native Americans of both the Northern and Southern hemispheres have a high rate of cholesterol cholelithiasis, probably because of a predisposition resulting from "thrifty" (LITH) genes that promote efficient calorie utilization and fat storage. As many as 75% of Pima and other American Indian women over the age of 25 years have cholelithiasis. Other genetic mutations that predispose persons to gallstones have been identified. Obesity is a risk factor for gallstones, especially in women. Rapid weight loss, as occurs after bariatric surgery, also increases the risk of symptomatic gallstone formation. Diabetes mellitus, glucose intolerance, and insulin resistance are risk factors for gallstones, and a high intake of carbohydrate and high dietary glycemic load increase the risk of cholecystectomy in women. Hypertriglyceridemia may promote gallstone formation by impairing gallbladder motility. The prevalence of gallbladder disease is increased in men (but not women) with cirrhosis and hepatitis C virus infection. Moreover, cholecystectomy has been reported to be associated with an increased risk of NAFLD and cirrhosis, possibly because gallstones and liver disease have some risk factors in common. A lowcarbohydrate diet, physical activity, and cardiorespiratory fitness may help prevent gallstones. Consumption of caffeinated coffee appears to protect against gallstones in women, and a high intake of magnesium and of polyunsaturated and monounsaturated fats reduces the risk of gallstones in men. A diet high in fiber, a diet rich in fruits and vegetables, and statin use reduce the risk of cholecystectomy, particularly in women. The incidence of gallstones is high in individuals with Crohn disease; approximately one-third of those with inflammatory involvement of the terminal ileum have gallstones due to disruption of bile salt resorption that results in decreased solubility of the bile. Drugs such as clofibrate, octreotide, and ceftriaxone can cause gallstones. In

contrast, aspirin and other nonsteroidal anti-inflammatory drugs may protect against gallstones. Prolonged fasting (over 5–10 days) can lead to formation of biliary "sludge" (microlithiasis), which usually resolves with refeeding but can lead to gallstones or biliary symptoms. Pregnancy, particularly in obese women and those with insulin resistance, is associated with an increased risk of gallstones and of symptomatic gallbladder disease. Hormone replacement therapy appears to increase the risk of gallbladder disease and need for cholecystectomy; the risk is lower with transdermal than oral therapy. Gallstones are classified according to their predominant chemical composition as cholesterol or calcium bilirubinate stones. The latter comprise less than 20% of the gallstones found in patients in Europe or the United States but 30–40% of gallstones found in patients in Japan.

Clinical Findings

Cholelithiasis is frequently asymptomatic and is discovered in the course of routine radiographic study, operation, or autopsy. Symptoms (biliary [or "episodic gallbladder"] pain) develop in 10–25% of patients (1–4% annually), and acute cholecystitis develops in 20% of these symptomatic persons over time. Occasionally, small intestinal obstruction due to "gallstone ileus" (or Bouveret syndrome when the obstructing stone is in pylorus or duodenum) presents as the initial manifestation of cholelithiasis.

Diseases of the biliary tract

Gallstones:
Clinical Features - Asymptomatic
Laboratory Features - Normal
Diagnosis - Ultrasonography
Treatment – None
or
Gallstones + Biliary pain
Laboratory Features - Normal
Diagnosis - Ultrasonography
Treatment – Laparoscopic cholecystectomy

Cholesterolosis of gallbladder:
Clinical Features - Usually asymptomatic
Laboratory Features - Normal
Diagnosis - Oral cholecystography
Treatment – None

Adenomyomatosis:
Clinical Features - May cause biliary pain
Laboratory Features - Normal
Diagnosis - Oral cholecystography
Treatment – Laparoscopic cholecystectomy if symptomatic

Porcelain gallbladder:
Clinical Features - Usually asymptomatic
Laboratory Features - high risk of gallbladder cancer
Diagnosis - Normal Radiograph or CT
Treatment – Laparoscopic cholecystectomy

Acute cholecystitis:
Clinical Features - Epigastric or right upper quadrant pain, nausea, vomiting, fever, Murphy sign
Laboratory Features - high risk of gallbladder cancer
Diagnosis - Leukocytosis
Treatment – HIDA scan Antibiotics, laparoscopic cholecystectomy

Chronic cholecystitis:
Clinical Features - Biliary pain, constant epigastric or right upper quadrant pain, nausea
Laboratory Features - Normal
Diagnosis - Ultrasonography (stones), oral cholecystography (nonfunctioning gallbladder)
Treatment – Laparoscopic cholecystectomy

Choledocholithiasis:
Clinical Features - Asymptomatic or biliary pain, jaundice, fever; gallstone pancreatitis
Laboratory Features - Cholestatic liver biochemical tests; leukocytosis and positive blood cultures in cholangitis; elevated amylase and lipase in pancreatitis
Diagnosis - Ultrasonography (dilated ducts), EUS, MRCP, ERCP
Treatment – Endoscopic sphincterotomy and stone extraction; antibiotics for cholangitis

Treatment

Nonsteroidal anti-inflammatory drugs (eg, diclofenac 50–75 mg intramuscularly) can be used to relieve biliary pain. Laparoscopic cholecystectomy is the treatment of choice for symptomatic gallbladder disease. Pain relief after cholecystectomy is most likely in patients with episodic pain (generally once a month or less), pain lasting 30 minutes to 24 hours, pain in the evening or at night, and the onset of symptoms 1 year or less before presentation. Patients may go home within 1 day of the procedure and return to work within days (instead of weeks for those undergoing open cholecystectomy). The procedure is often performed on an outpatient basis and is suitable for most patients, including those with acute cholecystitis. Conversion to a conventional open cholecystectomy may be necessary in 2–8% of cases (higher for acute cholecystitis than for uncomplicated cholelithiasis). Bile duct injuries occur in 0.1% of cases done by experienced surgeons. There is generally no need for prophylactic cholecystectomy in an asymptomatic person unless the gallbladder is calcified, gallstones are 3 cm or

greater in diameter, or the patient is a Native American or a candidate for bariatric surgery or cardiac transplantation. Cholecystectomy may increase the risk of esophageal, proximal small intestinal, and colonic adenocarcinomas because of increased duodenogastric reflux and changes in intestinal exposure to bile. In pregnant patients a conservative approach to biliary pain is advised, but for patients with repeated attacks of biliary pain or acute cholecystitis, cholecystectomy can be performed—even by the laparoscopic route—preferably in the second trimester. Enterolithotomy alone is considered adequate treatment in most patients with gallstone ileus. Cholecystectomy via natural orifice translumenal endoscopic surgery (NOTES) has been performed and is under study. Ursodeoxycholic acid is a bile salt that when given orally for up to 2 years dissolve some cholesterol stones and may be considered in occasional, selected patients who refuse cholecystectomy. The dose is 8–13 mg/kg in divided doses daily. It is most effective in patients with a functioning gallbladder, as determined by gallbladder visualization on oral cholecystography, and multiple small "floating" gallstones (representing not more than 15% of patients with gallstones). In half of patients, gallstones recur within 5 years after treatment is stopped.

Ursodeoxycholic acid, 500–600 mg daily, and diets higher in fat reduce the risk of gallstone formation with rapid weight loss. Lithotripsy in combination with bile salt therapy for single radiolucent stones smaller than 20 mm in diameter was an option in the past but is no longer generally used in the United States.

When to Refer

Patients should be referred when they require surgery.

ACUTE CHOLECYSTITIS

ESSENTIALS OF DIAGNOSIS

- Steady, severe pain and tenderness in the right hypochondrium or epigastrium.
- Nausea and vomiting.
- Fever and leukocytosis

General Considerations

Cholecystitis is associated with gallstones in over 90% of cases. It occurs when a stone becomes impacted in the cystic duct and inflammation develops behind the obstruction. Acalculous cholecystitis should be considered when unexplained fever or right upper quadrant pain occurs within 2–4 weeks of major surgery or in a critically ill patient who has had no oral intake for a prolonged period; multiorgan failure is often present. Acute cholecystitis may be caused by infectious agents (eg, cytomegalovirus, cryptosporidiosis, or microsporidiosis) in patients with AIDS or by vasculitis (eg, polyarteritis nodosa, Henoch-Schönlein purpura).

Clinical Findings

A. Symptoms and Signs

The acute attack is often precipitated by a large or fatty meal and is characterized by the sudden appearance of steady pain localized to the epigastrium or right hypochondrium, which may gradually subside over a period of 12–18 hours. Vomiting occurs in about 75% of patients and in half of instances affords variable relief. Fever is typical. Right upper quadrant abdominal tenderness (often with a Murphy sign, or inhibition of inspiration by pain on palpation of the right upper quadrant) is almost always present and is usually associated with muscle guarding and rebound tenderness. A palpable gallbladder is present in about 15% of cases. Jaundice is present in about 25% of cases and, when persistent or severe, suggests the possibility of choledocholithiasis.

B. Laboratory Findings

The white blood cell count is usually high (12,000–15,000/mcL [12–15×10^9/L]). Total serum bilirubin values of 1–4 mg/dL (17.1–68.4 mcmol/L) may be seen even in the absence of bile duct obstruction. Serum aminotransferase and alkaline phosphatase levels are often elevated—the former as high as 300 units/mL, and even higher when associated with ascending cholangitis. Serum amylase may also be moderately elevated.

B. Imaging

Plain films of the abdomen may show radiopaque gallstones in 15% of cases. 99mTc hepatobiliary imaging (using iminodiacetic acid compounds), also known as the hepatic iminodiacetic acid (HIDA) scan, is useful in demonstrating an obstructed cystic duct, which is the cause of acute cholecystitis in most patients. This test is reliable if the bilirubin is under 5 mg/dL (85.5 mcmol/L) (98% sensitivity and 81% specificity for acute cholecystitis). False-positive results can occur with prolonged fasting, liver disease, and chronic cholecystitis, and the specificity can be improved by intravenous administration of morphine, which induces spasm of the sphincter of Oddi. Right upper quadrant abdominal ultrasonography, which is often performed first, may show gallstones but is not as sensitive for acute cholecystitis (67% sensitivity, 82% specificity); findings suggestive of acute cholecystitis are gallbladder wall thickening, pericholecystic fluid, and a sonographic Murphy sign. CT may show complications of acute cholecystitis, such as perforation or gangrene.

Differential Diagnosis

The disorders most likely to be confused with acute cholecystitis are perforated peptic ulcer, acute pancreatitis, appendicitis in a high-lying appendix, perforated colonic carcinoma or diverticulum of the hepatic flexure, liver abscess, hepatitis, pneumonia with pleurisy on the right side, and even myocardial ischemia. Definite localization of pain and tenderness in the right upper quadrant, with radiation around to the infrascapular area, strongly favors the diagnosis of acute cholecystitis. True cholecystitis without stones suggests acalculous cholecystitis.

Complications

A. Gangrene of the Gallbladder

Continuation or progression of right upper quadrant abdominal pain, tenderness, muscle guarding, fever, and leukocytosis after 24–48 hours suggests severe inflammation and possible gangrene of the gallbladder, resulting from ischemia due to splanchnic vasoconstriction and intravascular coagulation. Necrosis may occasionally develop without specific signs in the obese, diabetic, elderly, or immunosuppressed patient. Gangrene may lead to gallbladder perforation, usually with formation of a pericholecystic abscess, and rarely to generalized peritonitis. Other serious acute complications include emphysematous cholecystitis (secondary infection with a gas-forming organism) and empyema.

B. Chronic Cholecystitis and Other Complications

Chronic cholecystitis results from repeated episodes of acute cholecystitis or chronic irritation of the gallbladder wall by stones and is characterized pathologically by varying degrees of chronic inflammation of the gallbladder. Calculi are usually present. In about 4–5% of cases, the villi of the gallbladder undergo polypoid enlargement due to deposition of cholesterol that may be visible to the naked eye ("strawberry gallbladder," cholesterolosis). In other instances, hyperplasia of all or part of the gallbladder wall may be so marked as to give the appearance of a myoma (adenomyomatosis). Hydrops of the gallbladder results when acute cholecystitis subsides but cystic duct obstruction persists, producing distention of the gallbladder with a clear mucoid fluid. Occasionally, a stone in the neck of the gallbladder may compress the common hepatic duct and cause jaundice (Mirizzi syndrome). Xanthogranulomatous cholecystitis is a rare variant of chronic cholecystitis characterized by grayish-yellow nodules or streaks, representing lipid-laden macrophages, in the wall of the gallbladder. Cholelithiasis with chronic cholecystitis may be associated with acute exacerbations of gallbladder inflammation, bile duct stone, fistulization to the bowel, pancreatitis and, rarely, carcinoma of the gallbladder. Calcified (porcelain) gallbladder is associated with gallbladder carcinoma and is generally an indication for cholecystectomy; the risk of gallbladder cancer may be higher when calcification is mucosal rather than intramural.

Treatment

Acute cholecystitis will usually subside on a conservative regimen (withholding of oral feedings, intravenous alimentation, analgesics, and intravenous antibiotics—generally a second- or third-generation cephalosporin such as cefoperazone, 1–2 g intravenously every 12 hours, with the addition of metronidazole, 500 mg intravenously every 6 hours; in severe cases, a fluoroquinolone such as ciprofloxacin, 250 mg intravenously every 12 hours, plus metronidazole may be given). Morphine or meperidine may be administered for pain. Because of the high risk of recurrent attacks (up to 10% by 1 month and over 30% by 1 year), cholecystectomy—generally laparoscopically—should generally

be performed within 24 hours of admission to the hospital for acute cholecystitis. Compared with delayed surgery, surgery within 24 hours is associated with a reduced risk of major bile duct injury and death. If nonsurgical treatment has been elected, the patient (especially if diabetic or elderly) should be watched carefully for recurrent symptoms, evidence of gangrene of the gallbladder, or cholangitis. In high-risk patients, ultrasound-guided aspiration of the gallbladder, if feasible, percutaneous cholecystostomy, or endoscopic insertion of a stent or nasobiliary drain into the gallbladder may postpone or even avoid the need for surgery. Immediate cholecystectomy is mandatory when there is evidence of gangrene or perforation. Surgical treatment of chronic cholecystitis is the same as for acute cholecystitis. If indicated, cholangiography can be performed during laparoscopic cholecystectomy. Choledocholithiasis can also be excluded by either preoperative or postoperative ERCP or MRCP.

Prognosis

The overall mortality rate of cholecystectomy is less than 0.2%, but hepatobiliary tract surgery is a more formidable procedure in the elderly, in whom mortality rates are higher; mortality rates are also higher in persons with diabetes mellitus. A technically successful surgical procedure in an appropriately selected patient is generally followed by complete resolution of symptoms.

When to Admit

All patients with acute cholecystitis should be hospitalized.

CHOLEDOCHOLITHIASIS & CHOLANGITIS

ESSENTIALS OF DIAGNOSIS

- Often a history of biliary pain, which may be accompanied by jaundice.
- Occasional patients present with painless jaundice.
- Nausea and vomiting.
- Cholangitis should be suspected with fever followed by hypothermia and gram-negative shock, jaundice, and leukocytosis.
- Stones in bile duct most reliably detected by ERCP or EUS.

General Considerations

About 15% of patients with gallstones have choledocholithiasis (bile duct stones). The percentage rises with age, and the frequency in elderly people with gallstones may be as high as 50%. Bile duct stones usually originate in the gallbladder but may also form spontaneously in the bile duct after cholecystectomy. The risk is increased twofold in persons with a juxtapapillary duodenal diverticulum. Symptoms, including cholangitis, result if there is obstruction.

Clinical Findings A. Symptoms and Signs A history of biliary pain or jaundice may be obtained. Biliary pain results from rapid increases in bile duct pressure due to obstructed bile flow. The features that suggest the presence of a bile duct stone are: (1) frequently recurring attacks of right upper abdominal pain that is

severe and persists for hours; (2) chills and fever associated with severe pain; and (3) a history of jaundice associated with episodes of abdominal pain. The combination of pain, fever (and chills), and jaundice represents Charcot triad and denotes the classic picture of acute cholangitis. The addition of altered mental status and hypotension (Reynolds pentad) signifies acute suppurative cholangitis and is an endoscopic emergency. According to the Tokyo guidelines (2006), the diagnosis of acute cholangitis is established by the presence of (1) the Charcot triad; or (2) two elements of the Charcot triad plus laboratory evidence of an inflammatory response (eg, elevated white blood cell count, C-reactive protein), elevated liver biochemical test levels, and imaging evidence of biliary dilatation or a cause of obstruction.

Hepatomegaly may be present in calculous biliary obstruction, and tenderness is usually present in the right upper quadrant and epigastrium. Bile duct obstruction lasting more than 30 days results in liver damage leading to cirrhosis. Hepatic failure with portal hypertension occurs in untreated cases. In a population-based study from Denmark, acute cholangitis was reported to be a marker of occult gastrointestinal cancer.

B. Laboratory Findings

Acute obstruction of the bile duct typically produces a transient albeit striking increase in serum aminotransferase levels (often greater than 1000 units/L [20 mckat/L]). Bilirubinuria and elevation of the serum bilirubin are present if the bile duct remains obstructed; levels commonly fluctuate. Serum alkaline phosphatase levels rise more slowly. Not uncommonly, serum amylase elevations are present because of secondary pancreatitis. When extrahepatic obstruction persists for more than a few weeks, differentiation of obstruction from chronic cholestatic liver disease becomes more difficult. Leukocytosis is present in patients with acute cholangitis. Prolongation of the prothrombin time can result from the obstructed flow of bile to the intestine. In contrast to hepatocellular dysfunction, hypoprothrombinemia due to obstructive jaundice will respond to 10 mg of intravenous vitamin K or water-soluble oral vitamin K (phytonadione, 5 mg) within 24–36 hours.

C. Imaging

Ultrasonography and CT may demonstrate dilated bile ducts, and radionuclide imaging may show impaired bile flow. EUS, helical CT, and magnetic resonance cholangiography are accurate in demonstrating bile duct stones and may be used in patients thought to be at intermediate risk for choledocholithiasis (age older than 55 years, cholecystitis, bile duct diameter greater than 6 mm on ultrasonography, serum bilirubin 1.8–4 mg/dL [30.78–68.4 mcmol/L], elevated serum liver enzymes, pancreatitis). ERCP (occasionally with intraductal ultrasonography) or percutaneous transhepatic cholangiography provides the most direct and accurate means of determining the cause, location, and extent of obstruction, but in patients at intermediate risk of choledocholithiasis, initial cholecystectomy and intraoperative cholangiography result in a shorter length of hospital stay, fewer bile duct investigations, and no increase in morbidity. If the

likelihood that obstruction is caused by a stone is high (bile duct diameter greater than 6 mm, bile duct stone seen on ultrasonography, serum bilirubin greater than 4 mg/dL [68.4 mcmol/L]) or acute cholangitis is present, ERCP with sphincterotomy and stone extraction or stent placement is the procedure of choice. Meticulous technique is required to avoid causing acute cholangitis.

Differential Diagnosis

The most common cause of obstructive jaundice is a bile duct stone. Next in frequency are neoplasms of the pancreas, ampulla of Vater, or bile duct or an obstructed stent placed previously for decompression of an obstructing tumor. Extrinsic compression of the bile duct may result from metastatic carcinoma (usually from the gastrointestinal tract or breast) involving porta hepatis lymph nodes or, rarely, from a large duodenal diverticulum. Gallbladder cancer extending into the bile duct often presents as obstructive jaundice. Chronic cholestatic liver diseases (primarily biliary cirrhosis, sclerosing cholangitis, druginduced) must be considered. Hepatocellular jaundice can usually be differentiated by the history, clinical findings, and liver biochemical tests, but liver biopsy is necessary on occasion. Recurrent pyogenic cholangitis should be considered in persons from Asia (and occasionally elsewhere) with intrahepatic biliary stones (particularly in the left ductal system) and recurrent cholangitis.

Treatment

In general, bile duct stones, even small ones, should be removed, even in an asymptomatic patient. A bile duct stone in a patient with cholelithiasis or cholecystitis is usually treated by endoscopic sphincterotomy and stone extraction followed by laparoscopic cholecystectomy within 72 hours in patients with cholecystitis and within 2 weeks in those without cholecystitis. An alternative approach, which is associated with a shorter duration of hospitalization in patients at intermediate risk for choledocholithiasis, is laparoscopic cholecystectomy and bile duct exploration. For patients older than 70 years or the poorrisk patient with cholelithiasis and choledocholithiasis, cholecystectomy may be deferred after endoscopic sphincterotomy because the risk of subsequent cholecystitis is low. ERCP with sphincterotomy should be performed before cholecystectomy in patients with gallstones and cholangitis, jaundice (serum total bilirubin greater than 4 mg/dL [68.4 mcmol/L]), a dilated bile duct (greater than 6 mm), or stones in the bile duct seen on ultrasonography or CT. (Stones may ultimately recur in up to 12% of patients, particularly in the elderly, when the bile duct diameter is 15 mm or greater or when brown pigment stones are found at the time of the initial sphincterotomy.) Endoscopic balloon dilation of the sphincter of Oddi may be associated with a higher rate of pancreatitis than endoscopic sphincterotomy unless adequate dilation for more than 1 min is carried out. This procedure is generally reserved for patients with coagulopathy because the risk of bleeding is lower with balloon dilation than with sphincterotomy. Endoscopic ultrasound-guided biliary drainage and PTC with drainage are second-line approaches if ERCP fails or is not possible. In patients with biliary pancreatitis that resolves rapidly, the stone usually passes into the

intestine, and ERCP prior to cholecystectomy is not necessary if an intraoperative cholangiogram is planned.

Choledocholithiasis discovered at laparoscopic cholecystectomy may be managed via laparoscopic or, if necessary, open bile duct exploration or by postoperative endoscopic sphincterotomy. Operative findings of choledocholithiasis are palpable stones in the bile duct, dilatation or thickening of the wall of the bile duct, or stones in the gallbladder small enough to pass through the cystic duct. Laparoscopic intraoperative cholangiography (or intraoperative ultrasonography) should be done at the time of cholecystectomy in patients with liver enzyme elevations but a bile duct diameter of less than 5 mm; if a ductal stone is found, the duct should be explored. In the post-cholecystectomy patient with choledocholithiasis, endoscopic sphincterotomy with stone extraction is preferable to transabdominal surgery. Lithotripsy (endoscopic or external), direct choledoscopy (cholangioscopy), or biliary stenting may be a therapeutic consideration for large stones. For the patient with a T tube and bile duct stone, the stone may be extracted via the T tube.

Postoperative antibiotics are not administered routinely after biliary tract surgery. Cultures of the bile are always taken at operation. If biliary tract infection was present preoperatively or is apparent at operation, ampicillin (500 mg every 6 hours intravenously) with gentamicin (1.5 mg/kg intravenously every 8 hours) and metronidazole (500 mg intravenously every 6 hours) or ciprofloxacin (250 mg intravenously every 12 hours) or a third-generation cephalosporin (eg, cefoperazone, 1–2 g intravenous every 12 hours) is administered postoperatively until the results of sensitivity tests on culture specimens are available. A T-tube cholangiogram should be done before the tube is removed, usually about 3 weeks after surgery. A small amount of bile frequently leaks from the tube site for a few days.

Urgent ERCP with sphincterotomy and stone extraction is generally indicated for choledocholithiasis complicated by acute cholangitis and is preferred to surgery. Before ERCP, liver function should be evaluated thoroughly. The prothrombin time should be restored to normal by intravenous administration of vitamin K. For mild-to-moderately severe community-acquired acute cholangitis, ciprofloxacin, 500 mg intravenously every 12 hours, penetrates well into bile and is effective treatment, with the possible addition of metronidazole, 500 mg every 6–8 hours. Alternative regimens include intravenous cefoxitin, 1–2 g every 6 hours, ampicillin, 2 g every 6 hours, plus gentamicin, 1.7 mg/kg every 8 hours, or ceftriaxone 1–2 g daily, among others. Regimens for severe or hospitalacquired acute cholangitis include intravenous piperacillin and tazobactam, 3.375 g every 6 hours; ticarcillin and clavulanate, 3.1 g every 6 hours; ceftriaxone, 1–2 g daily, plus metronidazole, 500 mg every 6–8 hours; or, in patients at high risk for harboring antibiotic-resistant pathogens, meropenem, 1 g every 8 hours. Aminoglycosides should not be given for more than a few days because the risk of aminoglycoside nephrotoxicity is increased in patients with cholestasis. Regimens that include drugs active against anaerobes are required when a biliary-enteric communication is present. Emergent decompression of the bile duct, generally by ERCP, is required for patients who are

septic or fail to improve on antibiotics within 12–24 hours. Medical therapy alone is most likely to fail in patients with tachycardia, serum albumin less than 3 g/dL (30 g/L), marked hyperbilirubinemia, high serum ALT level, high white blood cell count, and prothrombin time greater than 14 seconds on admission. If sphincterotomy cannot be performed, the bile duct can be decompressed by a biliary stent or nasobiliary catheter. Once decompression is achieved, antibiotics are generally continued for at least another 3 days. Elective cholecystectomy can be undertaken after resolution of cholangitis, unless the patient remains unfit for surgery. Mortality from acute cholangitis has been reported to correlate with a high total bilirubin level, prolonged partial thromboplastin time, presence of a liver abscess, and unsuccessful ERCP.

When to Refer

All symptomatic patients with choledocholithiasis should be referred.

When to Admit

All patients with acute cholangitis should be hospitalized.

Control questions

1. Anatomy and physiology of the liver and gall bladder.
2. Subjective methods of studying the liver and gall bladder.
3. Objective research methods: review:
4. Objective research methods: palpation of the liver and gall bladder: superficial palpation of the liver; deep palpation on the Obraztsov and Strazhetsko method (in a standing position, in a position lying on the back, and on the left side);
5. Objective research methods: percussion:
   - definition of the upper boundary of absolute dullness of the liver;
   - definition of the lower boundary of absolute dullness of the liver;
   - percutaneous determination of the size and configuration of the liver.
6. Objective methods of research: auscultation (noise of peritoneal friction).
7. Laboratory methods of liver and gall bladder examination.
8. Instrumental methods for liver and gall bladder examination.
9. Acute viral hepatitis, classification:
   - acute viral hepatitis A;
   - acute viral hepatitis B;
   - acute viral hepatitis C;
   - acute viral hepatitis E - close to hepatitis A;
   - acute viral hepatitis D;
   - hepatitis, caused by cytomegalovirus,
   - Hepatitis caused by Epstein-Barr virus;
   - hepatitis caused by herpes virus;
   - toxic hepatitis.
10. Pathogenesis of acute hepatitis.
11. Clinical picture of viral hepatitis.

12. Pharmacotherapy of viral hepatitis.
13. Chronic hepatitis – classification.
14. Etiology, pathogenesis, clinical picture, course of chronic hepatitis.
15. Pharmacotherapy for chronic hepatitis.
16. Alcoholic liver damage - pathogenesis, clinical picture, pharmacotherapy.
17. Liver cirrhosis, classification.
18. Etiology, pathogenesis, clinical picture, progression of cirrhosis.
19. Pharmacotherapy of cirrhosis of the liver.
20. Complications and prognosis of liver cirrhosis.
21. To prepare in recipes: holosas, hofitol, papaverin, drotaverin, hepabene, essentiale, karlsil.

List of practical works

A. Homework.

1. To study the anatomical and physiological features of the hepatotoxic biliary system
2. To know the classification and clinic of diseases of the gall bladder and liver.
3. To study the main directions of treatment of these diseases.
4. Be able to provide first aid to a patient with a liver colic.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data laboratory-instrumental research, examination consultants, records of the doctor) and a letter of medical appointments.
3. At examination of the patient to allocate subjective, physical, laboratory-instrumental signs of diseases of the liver and gall bladder.
4. Write a clinical diagnosis:
a) the underlying disease; complications of the underlying disease;
b) concomitant diseases.
5. Determine the group of drugs needed to correct the existing violations.
6. On the basis of theoretical data and own observations, make a choice of a specific drug to this patient.
7. To substantiate duration of basic and maintenance therapy.
8. To draw up a plan of urgent medical aid for liver colic.

Control the level of knowledge

1. Fill in the table "Differential diagnosis of jaundice".

Kind of jaundice	The mechanism of occurrence	Clinical examples

1. Hemolytic (superhepatic) 2.Parenchymal (hepatocellular) 3.Mechanical (Pephechinkova)		

2. Fill in the table "Groups of drugs for the treatment of cirrhosis of the liver".

Pharmacological groups	**Medical Drugs**	**Way of administration, dose**
1. Cystostatics 2.Disotoksikatory means 3. Vitamins 4. Amino acids 5. Glucocorticoids 6. Hepatoprotectors 7. Diuretics		

3. Fill in the table "Groups of drugs for the treatment of chronic hepatitis".

Pharmacological groups	**Medical Drugs**	**The mechanism of action**	**Way of administration, dose**
1.Anabolic steroid hormones 2. Detoxification means 3. Vitamins 4. Glucocorticoids 5. Hepatoprotectors 6. Antivirus drugs			

4. Fill in the table "Groups of drugs for the treatment of acute cholecystitis."

Pharmacological groups	**Medical Drugs**	**Way of administration, dose**

1.Antibiotics 2. Anesthetizing 3. Spasmolytics 4. Medications that stimulate bile ducts 5. Detoxification means		

5. Fill in the table "Groups of medicines for the treatment of chronic cholecystitis".

Pharmacological groups	**Medical Drugs**
Antibiotics Cholinergic drugs Choleratics: - *drugs containing bile acids* - *vegetable origin* - *synthetic* - *hydrocollections* Cholecinetics Spasmolytics	

Solution of situational tasks

1. The pharmacist asked the patient to recommend her a drug for "blind" sensing. Tactics of the pharmacist.

How to conduct this treatment?

2. Patient D., 56 years old, notes pain in the right hypochondrium, dull aching pain throughout the abdomen, which increases after a meal, especially oily food, after physical work. Appetite decreased, nausea, sometimes vomiting, flatulence. Performance is reduced. There is weakness, fatigue, sleep disturbance. Objectively: sub-ethics of sclera and skin, the abdomen is enlarged in size, dilated veins on the anterior abdominal wall. On the skin of the anterior chest and on the back vascular "sprockets", erythema palms. Edema of the legs, ascites. The liver is enlarged, with palpation dense, the lower edge is sharp. Palpable enlarged spleen.

Your previous diagnosis. What other survey methods should I use in this case? Your treatment recommendations. Type recipes.

3. Patient A., 36 years old, entered the clinic with complaints of dull pain in the right hypochondrium, which appears after violations of diet, a sense of bitterness in the mouth, nausea. When palpation, pain in the right hypochondrium is noted. In blood - leukocytosis, accelerated rate of erythrocyte sedimentation.

Which disease is the given clinical case? Your recommendations on the

tactics of medical treatment (the direction of pharmacotherapy, drugs).

4. In a patient with portal cirrhosis of the liver developed a non-clinical right-sided non-neoplastic pneumonia. The use of penicillin, a dose of 1 million 6 times a day, did not produce an effect and for the third day the doctor decided to start treatment with erythromycin phosphate at a dose of 0.2 g 2 times daily intravenously.

Give an assessment of the situation.

5. Choose a drug for the treatment of severe community-acquired staphylococcal pneumonia in a patient with chronic hepatitis: benzylpenicillin sodium salt in a daily dose of 20 million; benzylpenicillin sodium salt in a daily dose of 40 million; doxycycline; rifampicin cefazolin

Give explanations for your actions.

6. The patient is 20 years old, a student, a year ago suffered from Botkin's disease, complains about pain in the right hypochondrium. Objectively: sharply expressed pain in palpation of the gall bladder. In cholecysticization, enlargement of the gall bladder and slowdown of evacuation have been noted. With the ultrasound examination of the abdominal cavity, the gall bladder showed that after a trial breakfast, the gall bladder emptyed by 20% of the initial volume.

Your diagnosis? Option of the disease. What are the drugs that affect the function of the gallbladder shown by the patient?

7. A 56-year-old patient, who was overweight, appealed to a therapist at a clinic with complaints of pain in the epigastrium and right hypochondrium, which increased after fried food, burping, and dry mouth in the morning. Objectively: the heart, lungs - without peculiarities. The abdomen moderately swollen, soft when palpated. Ortner's symptom is negative. A positive symptom of Kerat and frenicus is a symptom. No edema.

Your previous diagnosis? What is the most important examination to be prescribed by the patient and for what purpose. Plan a treatment plan and explain its stages.

8. Patient 23 years old, with chronic stoneless cholecystitis, cholecystography was performed with the definition of function. Hypomotor hypokinetic dyskinesia of the gall bladder was detected.

Assign treatment.

9. The surgical department received a woman 59 years with acute pain syndrome against the background of exacerbation of pancreatitis.

Which analgesic should be prescribed for the treatment of an attack?

10. A 55-year-old patient complains of stupid pain in the right hypochondrium, bitterness in the mouth. With 35 years suffering from chronic cholecystitis. A year ago, during the ultrasonic examination in the gallbladder, isolated concretions were

found - 4-5 mm.

What is a cholecinetic drug contraindicated in a patient?

11. A 53 year old patient has suffered from chronic cholecystitis for the past 15 years. Currently, due to the exacerbation of the course of the disease (bitterness in the mouth, nausea, dull pain in the right hypochondrium), a control ultrasound examination of the gall bladder was performed. The concrement is found up to 6 mm in size. From surgery refuses.

What remedy is recommended for the patient?

12. After suffering acute viral hepatitis in the patient for 46 years, pain and heaviness in the right hypochondrium, increase in liver size, increase in serum ALT and AST levels remain as markers for the presence of hepatocyte cytolysis syndrome.

Choose the patient's desired drug to stabilize the membrane permeability.

Test tasks

1. In a patient, after eating, there is nausea, pain in the upper abdomen ("under the spoon"), heartburn, pain and heartburn decreases after taking soda. What is the probable diagnosis of this patient?
A. Gastrit
B. Pancreatitis.
C. Hepatitis.
D. Gallstone disease.
E. Cholecystitis.

2. A 34-year-old patient complains of pulling, aching pain in the right hypochondrium, the severity of the right side after fatty foods, and worries constipation. What is the most likely illness in a patient?
A. Gastrit
B. Stomach ulcer.
C. Pulmonary disease of the 12th digestive tract.
D. Pancreatitis.
E. Cholecystitis.

3. For a man 32 years old, who is irregularly taking food due to the nature of work, there were pains in the upper abdomen that appear on an empty stomach, at night, worrying nausea, pain disappears after eating. What are the most likely causes of a patient's complaints?
A. Peptic ulcer disease of the 12th digestive tract.
B. Acute cholecystitis.
C. Acute pancreatitis.
D. Chronic hepatitis.
E. Gallstone disease.

4. The patient complains of pain in the right hypochondrium of intense nature, nausea, an increase in body temperature to 37.6^0C, jaundice, light feces and dark urine, became ill acutely. Her words also got her girlfriend sick, with whom she rested three weeks ago. What is the most likely illness in a patient?
A. Acute pancreatitis.
B. Acute cholecystitis.
C. Acute hepatitis.
D. Stomach ulcers of the 12th digestive tract.
E. Stomach ulcer

5. In a patient who for a long time suffers from chronic hepatitis, there was a yellowish sclera and mucous membranes, small "stars" on the skin, ascites, swelling of the legs and feet, nausea, vomiting. What was the reason for this condition?
A. Acute hepatitis.
B. Development of heart failure.
C. Formation of liver cirrhosis.
D. Acute pancreatitis.
E. Development of gastric ulcer.

6. Among choleretic drugs, choose choleratics:
1. 1. Magnesium sulfate.
2. Leobil.
3. Sorbitol.
4. Xylitol
5. Olive oil.

7. In the treatment of exacerbation of chronic hepatitis include the following groups of drugs, except:
1. Antibacterial agents.
2. Hepatoprotectors.
3. Disinfectants.
4. Vitamins.
5. Glucocorticoids.

8. Among the choleretic, select a remedy that has an antibacterial effect:
1.Holenzim.
2.Sorbide
3. Nicodyn.
4. Leobol.
5. Xylitol

9. The hepatoprotectors include the following drugs:
1.Tiotriazolin.
2. No-sha
3. Leobil.

4. Pansinorm.
5. Alochol.

10. Nausea, vomiting, bitterness in the mouth, appetite disturbance - characteristic signs of the syndrome:
A. Cholestasis.
B. Portal hypertension.
C. Dyspepsia.
D. Violation of external secretion of the pancreas.
E. Cytolysis.

11. When informing doctors about the presence of choleretic drugs in the pharmacy, note which of the drugs is characterized by cholecinetic action?

A. Deholin
D. Nikodin
C. Sodium salicylate.
D. Holagol
E. Magnesium sulfate.

12. When informing the patient about the presence of cholagogue in the pharmacy, note which of the drugs is characterized by choleretic action?

A. Sorbitol
V. Eufilin.
S. Holecistokinin.
D. Holenzim
E. Magnesium sulfate.

DISEASES OF THE PANCREAS
ACUTE PANCREATITIS

ESSENTIALS OF DIAGNOSIS

- Abrupt onset of deep epigastric pain, often with radiation to the back.
- History of previous episodes, often related to alcohol intake.
- Nausea, vomiting, sweating, weakness.
- Abdominal tenderness and distention and fever.
- Leukocytosis, elevated serum amylase, elevated serum lipase.

General Considerations

Most cases of acute pancreatitis are related to biliary tract disease (a passed gallstone, usually 5 mm or less in diameter) or heavy alcohol intake. The exact pathogenesis is not known but may include edema or obstruction of the ampulla of Vater, reflux of bile into pancreatic ducts, and direct injury of pancreatic acinar cells by prematurely activated pancreatic enzymes. Among the numerous other

causes or associations are hypercalcemia, hyperlipidemias (chylomicronemia, hypertriglyceridemia, or both), abdominal trauma (including surgery), drugs (including azathioprine, mercaptopurine, asparaginase, pentamidine, didanosine, valproic acid, tetracyclines, dapsone, isoniazid, metronidazole, estrogen and tamoxifen [by raising serum triglycerides], sulfonamides, mesalamine, sulindac, leflunomide, thiazides, simvastatin, fenofibrate, enalapril, methyldopa, procainamide, sitagliptin, exenatide, possibly corticosteroids, and others), vasculitis, infections (eg, mumps, cytomegalovirus, M avium intracellulare complex), peritoneal dialysis, cardiopulmonary bypass, and ERCP. Genetic mutations also predispose to chronic pancreatitis, particularly in persons younger than 30 years of age if no other cause is evident and a family history of pancreatic disease is present. In patients with pancreas divisum, a congenital anomaly in which the dorsal and ventral pancreatic ducts fail to fuse, acute pancreatitis may result from stenosis of the minor papilla with obstruction to flow from the accessory pancreatic duct, although concomitant genetic mutations, particularly in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, have also been reported to account for acute pancreatitis in some patients with pancreas divisum. Acute pancreatitis may also result from the anomalous union of the pancreaticobiliary duct. Rarely, acute pancreatitis may be the presenting manifestation of a pancreatic or ampullary neoplasm. Celiac disease appears to be associated with an increased risk of acute and chronic pancreatitis. Apparently "idiopathic" acute pancreatitis is often caused by occult biliary microlithiasis and may be caused by sphincter of Oddi dysfunction involving the pancreatic duct. Between 15% and 25% of cases are truly idiopathic. Smoking, high dietary glycemic load, and abdominal adiposity increase the risk of pancreatitis, and older age and obesity increase the risk of a severe course; vegetable consumption and use of statins may reduce the risk of pancreatitis. The incidence of pancreatitis has increased since 1990.

Clinical Findings

A. Symptoms and Signs

Epigastric abdominal pain, generally abrupt in onset, is steady, boring, and severe and often made worse by walking and lying supine and better by sitting and leaning forward. The pain usually radiates into the back but may radiate to the right or left. Nausea and vomiting are usually present. Weakness, sweating, and anxiety are noted in severe attacks. There may be a history of alcohol intake or a heavy meal immediately preceding the attack or a history of milder similar episodes or biliary pain in the past.

The abdomen is tender mainly in the upper part, most often without guarding, rigidity, or rebound. The abdomen may be distended, and bowel sounds may be absent with associated ileus. Fever of 38.4–39°C, tachycardia, hypotension (even shock), pallor, and cool clammy skin are present in severe cases. Mild jaundice may be seen. Occasionally, an upper abdominal mass due to the inflamed pancreas or a pseudocyst may be palpated. Acute kidney injury (usually prerenal) may occur early in the course of acute pancreatitis.

B. Laboratory Findings

Serum amylase and lipase are elevated—usually more than three times the upper limit of normal—within 24 hours in 90% of cases; their return to normal is variable depending on the severity of disease. Lipase remains elevated longer than amylase and is slightly more accurate for the diagnosis of acute pancreatitis. Leukocytosis (10,000–30,000/mcL), proteinuria, granular casts, glycosuria (10–20% of cases), hyperglycemia, and elevated serum bilirubin may be present. Blood urea nitrogen and serum alkaline phosphatase may be elevated and coagulation tests abnormal. An elevated serum creatinine level (greater than 1.8 mg/dL [149.94 mcmol/L]) at 48 hours is associated with the development of pancreatic necrosis. In patients with clear evidence of acute pancreatitis, a serum ALT level of more than 150 units/L (3 mkat/L) suggests biliary pancreatitis. A decrease in serum calcium may reflect saponification and correlates with severity of the disease. Levels lower than 7 mg/dL (1.75 mmol/L) (when serum albumin is normal) are associated with tetany and an unfavorable prognosis. Patients with acute pancreatitis caused by hypertriglyceridemia generally have fasting triglyceride levels above 1000 mg/dL (10 mmol/L); in some cases, the serum amylase is not elevated substantially because of an inhibitor in the serum of patients with marked hypertriglyceridemia that interferes with measurement of serum amylase. An early rise in the hematocrit value above 44% suggests hemoconcentration and predicts pancreatic necrosis. An elevated C-reactive protein concentration (greater than 150 mg/L [1500 mg/L]) at 48 hours suggests severe disease.

Other diagnostic tests that offer the possibility of simplicity, rapidity, ease of use, and low cost—including urinary trypsinogen-2, trypsinogen activation peptide, and carboxypeptidase B—are not widely available. In patients in whom ascites or a left pleural effusion develops, fluid amylase content is high. Electrocardiography may show ST–T wave changes.

C. Assessment of Severity

In addition to the individual laboratory parameters noted above, the severity of acute alcoholic pancreatitis can be assessed using several scoring systems, including the **Ranson criteria**. The **Sequential Organ Failure Assessment (SOFA)** score or **modified Marshall scoring system** can be used to assess injury to other organs, and the **Acute Physiology and Chronic Health Evaluation (APACHE II)** score is another tool for assessing severity. A simple 5-point clinical scoring system (the **Bedside Index for Severity in Acute Pancreatitis,** or **BISAP**) based on blood urea nitrogen above 25 mg/dL (9 mmol/L), impaired mental status, systemic inflammatory response syndrome, age older than 60 years, and pleural effusion during the first 24 hours (before the onset of organ failure) identifies patients at increased risk for mortality. More simply, the presence of a systemic inflammatory response alone and an elevated blood urea nitrogen level on admission as well as a rise in blood urea nitrogen within the first 24 hours of hospitalization are independently associated with increased mortality; the greater the rise in blood urea nitrogen after admission, the greater the mortality rate. An

early rise in serum levels of neutrophil gelatinase-associated lipocalin has also been proposed as a marker of severe acute pancreatitis. The absence of rebound abdominal tenderness or guarding, a normal hematocrit value, and a normal serum creatinine level (the "**harmless acute pancreatitis score**," or **HAPS**) predicts a nonsevere course with 98% accuracy. The **revised Atlanta classification** of the severity of acute pancreatitis uses the following three categories: (1) mild disease is the absence of organ failure and local ([peri] pancreatic necrosis or fluid collections) or systemic complications; (2) moderate disease is the presence of transient (under 48 hours) organ failure or local or systemic complications, or both; and (3) severe disease is the presence of persistent (48 hours or more) organ failure. A similar "determinant-based" classification includes a category of critical acute pancreatitis characterized by both persistent organ failure and infected peripancreatic necrosis.

Ranson criteria for assessing the severity of acute pancreatitis

Three or more of the following predict a severe course complicated by pancreatic necrosis with a sensitivity of 60–80%

Age over 55 years
White blood cell count > 16×10^3 /mcL (> 16×10^9 /L)
Blood glucose > 200 mg/dL (> 11 mmol/L)
Serum lactic dehydrogenase > 350 units/L (> 7 mkat/L)
Aspartate aminotransferase > 250 units/L (> 5 mkat/L)

Development of the following in the first 48 hours indicates a worsening prognosis

Hematocrit drop of more than 10 percentage points
Blood urea nitrogen rise > 5 mg/dL (> 1.8 mmol/L)
Arterial Po2 of < 60 mm Hg (< 7.8 kPa)
Serum calcium of < 8 mg/dL (< 0.2 mmol/L)
Base deficit over 4 mEq/L
Estimated fluid sequestration of > 6 L

D. Imaging

Plain radiographs of the abdomen may show gallstones (if calcified), a "sentinel loop" (a segment of air-filled small intestine most commonly in the left upper quadrant), the "colon cutoff sign"—a gas-filled segment of transverse colon abruptly ending at the area of pancreatic inflammation— or focal linear atelectasis of the lower lobe of the lungs with or without pleural effusion. Ultrasonography is often not helpful in diagnosing acute pancreatitis because of intervening bowel gas but may identify gallstones in the gallbladder. Unenhanced CT is useful for demonstrating an enlarged pancreas when the diagnosis of pancreatitis is uncertain, differentiating pancreatitis from other possible intra-abdominal catastrophes, and providing an initial assessment of prognosis but is often unnecessary early in the course. Rapid-bolus intravenous contrast-enhanced CT following aggressive

volume resuscitation is of particular value after the first 3 days of severe acute pancreatitis for identifying areas of necrotizing pancreatitis and assessing the degree of necrosis, although the use of intravenous contrast may increase the risk of complications of pancreatitis and of acute kidney injury and should be avoided when the serum creatinine level is above 1.5 mg/dL (124.95 mcmol/L). MRI appears to be a suitable alternative to CT. Perfusion CT on day 3 demonstrating areas of ischemia in the pancreas has been reported to predict the development of pancreatic necrosis. The presence of a fluid collection in the pancreas correlates with an increased mortality rate. CT-guided needle aspiration of areas of necrotizing pancreatitis after the third day may disclose infection, usually by enteric organisms, which typically requires debridement. The presence of gas bubbles on CT implies infection by gas-forming organisms. EUS is useful in identifying occult biliary disease (eg, small stones, sludge, microlithiasis), which is present in a majority of patients with apparently idiopathic acute pancreatitis, and is indicated in persons over age 40 to exclude malignancy. ERCP is generally not indicated after a first attack of acute pancreatitis unless there is associated cholangitis or jaundice or a bile duct stone is known to be present, but EUS or MRCP should be considered, especially after repeated attacks of idiopathic acute pancreatitis. In selected cases, aspiration of bile for crystal analysis may confirm the suspicion of microlithiasis, and manometry of the pancreatic duct sphincter may detect sphincter of Oddi dysfunction as a cause of recurrent pancreatitis.

Differential Diagnosis

Acute pancreatitis must be differentiated from an acutely perforated duodenal ulcer, acute cholecystitis, acute intestinal obstruction, leaking aortic aneurysm, renal colic, and acute mesenteric ischemia. Serum amylase may also be elevated in high intestinal obstruction, in gastroenteritis, in mumps not involving the pancreas (salivary amylase), in ectopic pregnancy, after administration of opioids, and after abdominal surgery. Serum lipase may also be elevated in many of these conditions.

Complications

Intravascular volume depletion secondary to leakage of fluids in the pancreatic bed and ileus with fluid-filled loops of bowel may result in prerenal azotemia and even acute tubular necrosis without overt shock. This sequence usually occurs within 24 hours of the onset of acute pancreatitis and lasts 8–9 days. Some patients require renal replacement therapy.

According to the revised Atlanta classification, fluid collections and necrosis may be acute (within the first 4 weeks) or chronic (after 4 weeks) and sterile or infected. Chronic collections, including pseudocysts and walled-off necrosis, are characterized by encapsulation. Sterile or infected necrotizing pancreatitis may complicate the course of 5–10% of cases and accounts for most of the deaths. The risk of infection does not correlate with the extent of necrosis. Pancreatic necrosis is often associated with fever, leukocytosis, and, in some cases, shock and is associated with organ failure (eg, gastrointestinal bleeding, respiratory failure, acute kidney injury) in 50% of cases. Because infected pancreatic necrosis is often an

indication for debridement, fine-needle aspiration of necrotic tissue under CT guidance should be performed (if necessary, repeatedly) for Gram stain and culture.

A serious complication of acute pancreatitis is *acute respiratory distress syndrome (ARDS)*; *cardiac dysfunction* may be superimposed. It usually occurs 3–7 days after the onset of pancreatitis in patients who have required large volumes of fluid and colloid to maintain blood pressure and urinary output. Most patients with ARDS require intubation, mechanical ventilation, and supplemental oxygen.

Pancreatic abscess (also referred to as infected or suppurative pseudocyst) is a suppurative process characterized by rising fever, leukocytosis, and localized tenderness and an epigastric mass usually 6 or more weeks into the course of acute pancreatitis. The abscess may be associated with a left-sided pleural effusion or an enlarging spleen secondary to splenic vein thrombosis. In contrast to infected necrosis, the mortality rate is low following drainage.

Pseudocysts, encapsulated fluid collections with high amylase content, commonly appear in pancreatitis when CT is used to monitor the evolution of an acute attack. Pseudocysts that are smaller than 6 cm in diameter often resolve spontaneously. They most commonly are within or adjacent to the pancreas but can present almost anywhere (eg, mediastinal, retrorectal) by extension along anatomic planes. Multiple pseudocysts are seen in 14% of cases. Pseudocysts may become secondarily infected, necessitating drainage as for an abscess. Pancreatic ascites may present after recovery from acute pancreatitis as a gradual increase in abdominal girth and persistent elevation of the serum amylase level in the absence of frank abdominal pain. Marked elevations in ascitic protein (greater than 3 g/dL) and amylase (greater than 1000 units/L [20 mkat/L]) concentrations are typical. The condition results from disruption of the pancreatic duct or drainage of a pseudocyst into the peritoneal cavity

Rare complications of acute pancreatitis include *hemorrhage* caused by erosion of a blood vessel to form a pseudoaneurysm and colonic necrosis. *Portosplenomesenteric venous thrombosis* frequently develops in patients with necrotizing acute pancreatitis but rarely leads to complications. Chronic pancreatitis develops in about 10% of cases. Permanent diabetes mellitus and exocrine pancreatic insufficiency occur uncommonly after a single acute episode.

Treatment

A. Treatment of Acute Disease

1. Mild disease—In most patients, acute pancreatitis is a mild disease (“nonsevere acute pancreatitis”) that subsides spontaneously within several days. The pancreas is “rested” by a regimen of withholding food and liquids by mouth, bed rest, and, in patients with moderately severe pain or ileus and abdominal distention or vomiting, nasogastric suction. Early fluid resuscitation (one-third of the total 72-hour fluid volume administered within 24 hours of presentation, 250–500 mL/h initially) may reduce the frequency of systemic inflammatory response syndrome and organ failure in this group of patients, and lactated Ringer solution may be preferable to normal saline; however, overly aggressive fluid resuscitation may lead to morbidity as well. Pain is controlled with meperidine, up to 100–150

mg intramuscularly every 3–4 hours as necessary. In those with severe liver or kidney dysfunction, the dose may need to be reduced. Morphine has been thought to cause sphincter of Oddi spasm but is now considered an acceptable alternative and, given the potential side effects of meperidine, may even be preferable. Oral intake of fluid and foods can be resumed when the patient is largely free of pain and has bowel sounds (even if the serum amylase is still elevated). Clear liquids are given first (this step may be skipped in patients with mild acute pancreatitis), followed by gradual advancement to a low-fat diet, guided by the patient's tolerance and by the absence of pain. Pain may recur on refeeding in 20% of patients. Following recovery from acute biliary pancreatitis, laparoscopic cholecystectomy is generally performed, preferably during the same hospital admission, although in selected cases endoscopic sphincterotomy alone may be done. In patients with recurrent pancreatitis associated with pancreas divisum, insertion of a stent in the minor papilla (or minor papilla sphincterotomy) may reduce the frequency of subsequent attacks, although complications of such therapy are frequent. In patients with recurrent acute pancreatitis attributed to pancreatic sphincter of Oddi dysfunction, biliary sphincterotomy alone is as effective as combined biliary and pancreatic sphincterotomy in reducing the frequency of recurrent acute pancreatitis, but chronic pancreatitis may still develop in treated patients. Hypertriglyceridemia with acute pancreatitis has been treated with insulin, heparin, or apheresis, but the benefit of these approaches has not been proven.

2. Severe disease—In more severe pancreatitis—particularly necrotizing pancreatitis—there may be considerable leakage of fluids, necessitating large amounts of intravenous fluids (eg, 500–1000 mL/h for several hours, then 250–300 mL/h) to maintain intravascular volume. Risk factors for high levels of fluid sequestration include younger age, alcohol etiology, higher hematocrit value, higher serum glucose, and systemic inflammatory response syndrome in the first 48 hours of hospital admission. Hemodynamic monitoring in an intensive care unit is required, and the importance of aggressive intravenous hydration cannot be overemphasized targeted to result in adequate urinary output, stabilization of blood pressure and heart rate, restoration of central venous pressure, and a modest decrease in hematocrit value. Calcium gluconate must be given intravenously if there is evidence of hypocalcemia with tetany. Infusions of fresh frozen plasma or serum albumin may be necessary in patients with coagulopathy or hypoalbuminemia. With colloid solutions, there may be an increased risk of developing ARDS. If shock persists after adequate volume replacement (including packed red cells), pressors may be required. For the patient requiring a large volume of parenteral fluids, central venous pressure and blood gases should be monitored at regular intervals. Enteral nutrition via a nasojejunal or possibly nasogastric feeding tube is preferable to parenteral nutrition in patients who will otherwise be without oral nutrition for at least 7–10 days but may not be tolerated in some patients with an ileus and does not reduce the rates of infection and death compared with the introduction of an oral diet after 72 hours. Parenteral nutrition (including lipids) should be considered in patients who have severe pancreatitis and

ileus. The routine use of antibiotics to prevent conversion of sterile pancreatic necrosis to infected necrosis is still controversial and generally is not indicated in those with less than 30% pancreatic necrosis. Imipenem (500 mg every 8 hours intravenously) and possibly cefuroxime (1.5 g intravenously three times daily, then 250 mg orally twice daily) administered for no more than 14 days to patients with sterile pancreatic necrosis has been reported in some studies to reduce the risk of pancreatic infection and mortality; meropenem and the combination of ciprofloxacin and metronidazole do not appear to reduce the frequency of infected necrosis, multiorgan failure, or mortality. When infected necrosis is confirmed, imipenem or meropenem should be continued. In occasional cases, a fungal infection is found, and appropriate antifungal therapy should be prescribed. The role of intravenous somatostatin in severe acute pancreatitis is uncertain, and octreotide is thought to have no benefit. To date, probiotic agents have not been shown to reduce infectious complications of severe pancreatitis and may increase mortality. Nonsteroidal anti-inflammatory drugs (eg, indomethacin administered rectally), allopurinol, ulinastatin, and aggressive hydration with lactated Ringer solution have been reported to reduce the frequency and severity of postERCP pancreatitis in persons at high risk. There is conflicting evidence about whether the risk of pancreatitis after ERCP can be reduced by the administration of somatostatin, octreotide, gabexate mesilate and other protease inhibitors, or nitroglycerin. Placement of a stent across the pancreatic duct or orifice has been shown to reduce the risk of post-ERCP pancreatitis and is also a common practice but has not been compared directly with rectal indomethacin.

B. Treatment of Complications and Follow-Up

A surgeon should be consulted in all cases of severe acute pancreatitis. If the diagnosis is in doubt and investigation indicates a strong possibility of a serious surgically correctable lesion (eg, perforated peptic ulcer), exploratory laparotomy is indicated. When acute pancreatitis is found unexpectedly, it is usually wise to close without intervention. If the pancreatitis appears mild and cholelithiasis or microlithiasis is present, cholecystectomy or cholecystostomy may be justified. When severe pancreatitis results from choledocholithiasis and jaundice (serum total bilirubin above 5 mg/dL [85.5 mcmol/L]) or cholangitis is present, ERCP with endoscopic sphincterotomy and stone extraction is indicated. MRCP may be useful in selecting patients for therapeutic ERCP. Endoscopic sphincterotomy does not appear to improve the outcome of severe pancreatitis in the absence of cholangitis or jaundice.

Necrosectomy may improve survival in patients with necrotizing pancreatitis and clinical deterioration with multiorgan failure or lack of resolution by 4 weeks and is often indicated for infected necrosis, although a select group of relatively stable patients with infected pancreatic necrosis may be managed with antibiotics alone. The goal is to debride necrotic pancreas and surrounding tissue and establish adequate drainage. Outcomes are best if necrosectomy is delayed until the necrosis has organized, usually about 4 weeks after disease onset. A “step-up” approach in which nonsurgical drainage of walled-off pancreatic necrosis under radiologic

guidance with subsequent open surgical necrosectomy if necessary has been shown to reduce mortality and resource utilization in selected patients with necrotizing pancreatitis and confirmed or suspected secondary infection. Endoscopic (transgastric or transduodenal) drainage combined with percutaneous drainage and, in some cases, laparoscopic guidance are additional options, depending on local expertise. Treatment is labor intensive, and multiple procedures are often required. Peritoneal lavage has not been shown to improve survival in severe acute pancreatitis, in part because the risk of late septic complications is not reduced.

The development of a pancreatic abscess is an indication for prompt percutaneous or surgical drainage. Chronic pseudocysts require endoscopic, percutaneous catheter, or surgical drainage when infected or associated with persisting pain, pancreatitis, or bile duct obstruction. For pancreatic infections, imipenem, 500 mg every 8 hours intravenously, is a good choice of antibiotic because it achieves bactericidal levels in pancreatic tissue for most causative organisms. Pancreatic duct leaks and fistulas may require endoscopic or surgical therapy.

Prognosis

Mortality rates for acute pancreatitis have declined from at least 10% to around 5% since the 1980s, but the mortality rate for severe acute pancreatitis (more than three Ranson criteria) remains at least 20%, with rates of 10% and 25% in those with sterile and infected necrosis, respectively. Severe acute pancreatitis is predicted by features of the systemic inflammatory response on admission; a persistent systemic inflammatory response is associated with a mortality rate of 25% and a transient response with a mortality rate of 8%. Half of the deaths occur within the first 2 weeks, usually from multiorgan failure. Multiorgan failure is associated with a mortality rate of at least 30%, and if it persists beyond the first 48 hours, the mortality rate is over 50%. Later deaths occur because of complications of infected necrosis. The risk of death doubles when both organ failure and infected necrosis are present. Moreover, hospital-acquired infections increase the mortality of acute pancreatitis, independent of severity. Readmission to the hospital for acute pancreatitis within 30 days may be predicted by a scoring system based on five factors during the index admission: eating less than a solid diet at discharge; nausea, vomiting, or diarrhea at discharge; pancreatic necrosis; use of antibiotics at discharge; and pain at discharge. Male sex, an alcohol etiology, and severe acute disease are risk factors. Recurrences are common in alcoholic pancreatitis but can be reduced by repeated, regularly scheduled interventions to eliminate alcohol consumption after discharge from the hospital. The risk of chronic pancreatitis following an episode of acute alcoholic pancreatitis is 13% in 10 years and 16% in 20 years, and the risk of diabetes mellitus is increased more than twofold over 5 years.

When to Admit

Nearly all patients with acute pancreatitis should be hospitalized.

CHRONIC PANCREATITIS

ESSENTIALS OF DIAGNOSIS

- Chronic or intermittent epigastric pain, steatorrhea, weight loss, abnormal pancreatic imaging.
- A mnemonic for the predisposing factors of chronic pancreatitis is TIGAR-O: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive.

General Considerations

Chronic pancreatitis occurs most often in patients with alcoholism (45–80% of all cases). The risk of chronic pancreatitis increases with the duration and amount of alcohol consumed, but pancreatitis develops in only 5–10% of heavy drinkers. Tobacco smoking is a risk factor for idiopathic chronic pancreatitis and has been reported to accelerate progression of alcoholic chronic pancreatitis. About 2% of patients with hyperparathyroidism develop pancreatitis. In tropical Africa and Asia, tropical pancreatitis, related in part to malnutrition, is the most common cause of chronic pancreatitis. A stricture, stone, or tumor obstructing the pancreas can lead to obstructive chronic pancreatitis. Autoimmune pancreatitis is associated with hypergammaglobulinemia (IgG4 in particular), and often with autoantibodies and other autoimmune diseases, and is responsive to corticosteroids. Affected persons are at increased risk for various cancers. Type 1 autoimmune pancreatitis is a multisystem disease characterized by lymphoplasmacytic sclerosing pancreatitis on biopsy, associated bile duct strictures, retroperitoneal fibrosis, renal and salivary gland lesions, and a high rate of relapse after treatment. Type 2 affects the pancreas alone and is characterized by idiopathic duct-centric pancreatitis on biopsy, lack of systemic IgG4 involvement, an association with inflammatory bowel disease, often a tumor-like mass, and a lower rate of relapse after treatment. Between 10% and 30% of cases of chronic pancreatitis are idiopathic, with either early onset (median age 23) or late onset (median age 62). Genetic factors may predispose to chronic pancreatitis in some of these cases and include mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the pancreatic secretory trypsin inhibitory gene (PSTI, serine protease inhibitor, SPINK1), and possibly the gene for uridine 5′-diphosphate glucuronosyltransferase. Mutation of the cationic trypsinogen gene on chromosome 7 (serine protease 1, PRSS1) is associated with hereditary pancreatitis, transmitted as an autosomal dominant trait with variable penetrance. A useful mnemonic for the predisposing factors to chronic pancreatitis is TIGAR-O: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive.

The pathogenesis of chronic pancreatitis may be explained by the SAPE (sentinel acute pancreatitis event) hypothesis by which the first (sentinel) acute pancreatitis event initiates an inflammatory process that results in injury and later fibrosis (“necrosis-fibrosis”). In many cases, chronic pancreatitis is a self-perpetuating disease characterized by chronic pain or recurrent episodes of acute pancreatitis and ultimately by pancreatic exocrine or endocrine insufficiency (sooner in alcoholic pancreatitis than in other types). After many years, chronic

pain may resolve spontaneously or as a result of surgery tailored to the cause of pain. Over 80% of adults develop diabetes mellitus within 25 years after the clinical onset of chronic pancreatitis.

Clinical Findings

A. Symptoms and Signs

Persistent or recurrent episodes of epigastric and left upper quadrant pain are typical. The pain results in part from impaired inhibitory pain modulation by the central nervous system. Anorexia, nausea, vomiting, constipation, flatulence, and weight loss are common. During attacks, tenderness over the pancreas, mild muscle guarding, and ileus may be noted. Attacks may last only a few hours or as long as 2 weeks; pain may eventually be almost continuous. Steatorrhea (as indicated by bulky, foul, fatty stools) may occur late in the course.

B. Laboratory Findings

Serum amylase and lipase may be elevated during acute attacks; however, normal values do not exclude the diagnosis. Serum alkaline phosphatase and bilirubin may be elevated owing to compression of the bile duct. Glycosuria may be present. Excess fecal fat may be demonstrated on chemical analysis of the stool. Pancreatic insufficiency generally is confirmed by response to therapy with pancreatic enzyme supplements; the secretin stimulation test can be used if available (and has a high negative predictive factor for ruling out early acute chronic pancreatitis), as can detection of decreased fecal chymotrypsin or elastase levels, although the latter tests lack sensitivity and specificity. Vitamin B12 malabsorption is detectable in about 40% of patients, but clinical deficiency of vitamin B12 and fat-soluble vitamins is rare. Accurate diagnostic tests are available for the major trypsinogen gene mutations, but because of uncertainty about the mechanisms linking heterozygous CFTR and PSTI mutations with pancreatitis, genetic testing for mutations in these two genes is not currently recommended. Elevated IgG4 levels, ANA, and antibodies to lactoferrin and carbonic anhydrase II are often found in patients with autoimmune pancreatitis (especially type 1). Pancreatic biopsy, if necessary, shows a lymphoplasmacytic inflammatory infiltrate with characteristic IgG4 immunostaining, which is also found in biopsy specimens of the major papilla, bile duct, and salivary glands, in type 1 autoimmune pancreatitis.

C. Imaging

Plain films show calcifications due to pancreaticolithiasis in 30% of affected patients. CT may show calcifications not seen on plain films as well as ductal dilatation and heterogeneity or atrophy of the gland. Occasionally, the findings raise suspicion of pancreatic cancer (“tumefactive chronic pancreatitis”). ERCP is the most sensitive imaging study for chronic pancreatitis and may show dilated ducts, intraductal stones, strictures, or pseudocyst, but is infrequently used for diagnosis alone; moreover, the results may be normal in patients with so-called minimal change pancreatitis. MRCP (including secretin-enhanced MRCP) and EUS (with

pancreatic tissue sampling) are less invasive alternatives to ERCP. Endoscopic ultrasonographic ("Rosemont") criteria for the diagnosis of chronic pancreatitis include hyperechoic foci with shadowing indicative of calculi in the main pancreatic duct and lobularity with honeycombing of the pancreatic parenchyma. Characteristic imaging features of autoimmune pancreatitis include diffuse enlargement of the pancreas, a peripheral rim of hypoattenuation, and irregular narrowing of the main pancreatic duct. In the United States, the diagnosis of autoimmune pancreatitis is based on the HISORt criteria: histology, imaging, serology, other organ involvement, and response to corticosteroid therapy

Complications

Opioid addiction is common. Other frequent complications include often brittle diabetes mellitus, pancreatic pseudocyst or abscess, cholestatic liver enzymes with or without jaundice, bile duct stricture, steatorrhea, malnutrition, osteoporosis, and peptic ulcer. Pancreatic cancer develops in 4% of patients after 20 years; the risk may relate to tobacco and alcohol use. In patients with hereditary pancreatitis, the risk of pancreatic cancer rises after age 50 years and reaches 19% by age 70 years.

Treatment Correctable coexistent biliary tract disease should be treated surgically.

A. Medical Measures

A low-fat diet should be prescribed. Alcohol is forbidden because it frequently precipitates attacks. Opioids should be avoided if possible. Preferred agents for pain are acetaminophen, nonsteroidal anti-inflammatory drugs, and tramadol, along with pain-modifying agents such as tricyclic antidepressants, selective serotonin uptake inhibitors, and gabapentin or pregabalin. Steatorrhea is treated with pancreatic supplements that are selected on the basis of their high lipase activity. A total dose of at least 40,000 units of lipase in capsules is given with each meal (during and after the meal). Doses of 90,000 units or more of lipase per meal may be required in some cases. The tablets should be taken at the start of, during, and at the end of a meal. Concurrent administration of a H2-receptor antagonist (eg, ranitidine, 150 mg orally twice daily), a proton pump inhibitor (eg, omeprazole, 20–60 mg orally daily), or sodium bicarbonate, 650 mg orally before and after meals, decreases the inactivation of lipase by acid and may thereby further decrease steatorrhea. In selected cases of alcoholic pancreatitis and in cystic fibrosis, entericcoated microencapsulated preparations may offer an advantage. However, in patients with cystic fibrosis, high-dose pancreatic enzyme therapy has been associated with strictures of the ascending colon. Pain secondary to idiopathic chronic pancreatitis may be alleviated in some cases by the use of pancreatic enzymes (not enteric-coated) or octreotide, 200 mcg subcutaneously three times daily. Antioxidant therapy to inhibit electrophilic stress on key macromolecules in the pancreas by toxic metabolites has shown promise in some, but not all, studies. Associated diabetes mellitus should be treated. Autoimmune pancreatitis is treated with prednisone 40 mg/day orally for 1–2 months, followed by a taper of 5 mg

every 2–4 weeks. Nonresponse or relapse occurs in 45% of cases (particularly in those with concomitant IgG4 -associated cholangitis); azathioprine appears to reduce the risk of relapse. Other immunomodulators and biologic agents, including rituximab, are under study.

FDA (US Food and Drug Administration) - approved pancreatic enzyme (pancrelipase) preparations

Medications contain enzymes: Lipase Amylase Protease

Immediate-Release Capsule

Nonenteric-coated

Viokace 10,440; 20,880

Delayed-Release Capsules

Enteric-coated minimicrospheres

Creon 3000; 6000;12,00; 24,000; 36,000

Enteric-coated minitablets

Ultresa 13,800; 20,700; 23,000

Enteric-coated beads

Zenpep 3000; 5000; 10,000; 15,000; 20,000; 25,000

Enteric-coated microtablets

Pancreaze 4200; 10,500; 16,800; 21,000

Bicarbonate-buffered enteric-coated microspheres Peptyze 8000; 16,000

C. **Endoscopic and Surgical Treatment**

Endoscopic therapy or surgery may be indicated in chronic pancreatitis to treat underlying biliary tract disease, ensure free flow of bile into the duodenum, drain persistent pseudocysts, treat other complications, eliminate obstruction of the pancreatic duct, attempt to relieve pain, or exclude pancreatic cancer. Liver fibrosis may regress after biliary drainage. Distal bile duct obstruction may be relieved by endoscopic placement of multiple bile duct stents. When obstruction of the duodenal end of the pancreatic duct can be demonstrated by ERCP, dilation of or placement of a stent in the duct and pancreatic duct stone lithotripsy or surgical resection of the tail of the pancreas with implantation of the distal end of the duct by pancreaticojejunostomy may be performed. Endoscopic therapy is successful in about 50% of cases. In patients who do not respond to endoscopic therapy, surgery is successful in about 50%. When the pancreatic duct is diffusely dilated, anastomosis between the duct after it is split longitudinally and a defunctionalized limb of jejunum (modified Puestow procedure), in some cases combined with resection of the head of the pancreas (Beger or Frey procedure), is associated with relief of pain in 80% of cases. In advanced cases, subtotal or total pancreatectomy may be considered as a last resort but has variable efficacy and causes pancreatic insufficiency and diabetes mellitus. Perioperative administration of somatostatin or octreotide may reduce the risk of postoperative pancreatic fistulas. Endoscopic or surgical (including laparoscopic) drainage is indicated for symptomatic pseudocysts and, in many cases, those over 6 cm in diameter. EUS may facilitate selection of an optimal site for endoscopic drainage. Pancreatic ascites or pancreaticopleural

fistulas due to a disrupted pancreatic duct can be managed by endoscopic placement of a stent across the disrupted duct. Pancreatic sphincterotomy or fragmentation of stones in the pancreatic duct by lithotripsy and endoscopic removal of stones from the duct may relieve pain in selected patients. For patients with chronic pain and nondilated ducts, a percutaneous celiac plexus nerve block may be considered under either CT or endoscopic ultrasound guidance, with pain relief (albeit often short-lived) in approximately 50% of patients. A single session of radiation therapy to the pancreas has been reported to relieve otherwise refractory pain.

Prognosis

Chronic pancreatitis often leads to disability and reduced life expectancy; pancreatic cancer is the main cause of death. The prognosis is best in patients with recurrent acute pancreatitis caused by a remediable condition, such as cholelithiasis, choledocholithiasis, stenosis of the sphincter of Oddi, or hyperparathyroidism, and in those with autoimmune pancreatitis. Medical management of hyperlipidemia, if present, may also prevent recurrent attacks of pancreatitis. In alcoholic pancreatitis, pain relief is most likely when a dilated pancreatic duct can be decompressed. In patients with disease not amenable to decompressive surgery, addiction to opioids is a frequent outcome of treatment. The quality of life is poorer in patients with constant pain than in those with intermittent pain.

When to Refer

All patients with chronic pancreatitis should be referred for diagnostic and therapeutic procedures.

When to Admit

- Severe pain.
- New jaundice.
- New fever.

Control questions

1. Anatomy, structure and physiology of the pancreas.
2. Subjective methods of studying the pancreas.
3. Objective research methods: review.
4. Objective research methods: palpation of the pancreas:
5. Laboratory methods for the study of the pancreas.
6. Instrumental methods of studying the pancreas.
7. Major clinical syndromes:
8. Treatment and prevention.
9. Acute pancreatitis - etiology, pathogenesis, clinical picture, course, pharmacotherapy.
10. Chronic pancreatitis - etiology, pathogenesis, clinical picture, course, pharmacotherapy, prophylaxis.
11. To write recipes for drugs: panzinorm, kreon, mezim, festal, contrikal, sandostatin, gordox, omeprazole, reosorbilact, neogemodez, aminocaproic acid.

12. The role of pharmacist in the prevention of complications of pharmacotherapy of diseases of the digestive system.

List of practical works

A. Homework.

1. To study anatomical and physiological pancreas.
2. To know the classification and clinic of diseases of the pancreas.
3. To study the main directions of treatment of diseases of the pancreas.
4. To be able to provide first aid to a patient with acute pancreatitis.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data laboratory-instrumental research, examination consultants, records of the doctor) and a letter of medical appointments.
3. At examination of the patient to allocate subjective, physical, laboratory-instrumental signs of diseases of the pancreas.
4. Write a clinical diagnosis:
5. a) the underlying disease; complications of the underlying disease;
6. b) concomitant diseases.
7. Determine a group of lesions necessary for correction of existing disorders.
8. On the basis of theoretical data and own observations, to select a specific drug for this patient.
9. To substantiate duration of basic and maintenance therapy.
10. Make a plan for urgent medical assistance in acute pancreatitis.

Control the level of knowledge

1. Fill in the table "Directions of Pharmacotherapy of Chronic Pancreatitis"

Directions of pharmacotherapy	Groups of medicines
1. Correction of exocrine insufficiency 2. Correction of endocrine insufficiency 3. Anesthetizing 4. Decrease of secretory function	

2. Fill in the table "Directions of pharmacotherapy of acute pancreatitis"

Directions of pharmacotherapy	Groups of medicines
1. Decreased secretory function of the pancreas (anti-enzyme preparations) 2. Detoxification therapy 3. Anesthetics 3. Decrease of the secretory function of the stomach 4.	

Solution of situational tasks

1. Patient A., 34, entered the clinic with complaints of pain in the left hypochondrium, which appear after a violation of the diet. The pain has an enveloping character, accompanied by nausea, vomiting, diarrhea with constipation, a general weakness. Palpation of the abdomen shows pain in the left hypochondrium. Attacks are accompanied by an increase in blood amylase and urinary diastase, leukocytosis and elevated ESR.

Which disease most likely corresponds to the described clinical picture? Your recommendations on the tactics of the examination and treatment of this patient. Type recipes.

2. A patient, 38 years of age, 65 kg of body weight, was admitted to the therapeutic department in connection with the exacerbation of chronic cholecystitis-pancreatitis. The patient is concerned with pain in the epigastrium, repeated vomiting with bile, sharp weakness, dizziness. Objectively: pale, cold, sticky sweat. Breathing is frequent, superficial. AT - 100/50 mm Hg. st .. heart rate - 92 for 1 min. The abdomen is painful in the upper half, symptoms of peritoneal irritation are absent, peristalsis is preserved. Another doctor prescribed treatment with cholinolytics, anesthetics, non-narcotic analgesics (all drugs are administered parenterally), in addition, 200 ml of 4% solution of sodium bicarbonate is injected intravenously. Contrary to the hopes of the doctor after the events, the patient's condition deteriorated. Increased nausea, vomiting, weakness, dizziness, BP - 90/50 mm Hg. st., heart rate 106 for 1 min.

Explain the cause of deterioration. What did the doctor do not take into account? Tactics of treatment?

Test tasks

1. A patient with a diagnosis of "acute pancreatitis" is hospitalized in a hospital. The choice of which drug is pathogenetically substantiated?

A. Acetylsalicylic acid.
B. Aktilise.
C. Acid ascorbic acid.
D. Trental.
E. Contrical.

2. You were referred to a patient with chronic pancreatitis with severe manifestations of insufficiency of the external secretory function of the pancreas. Which of the following drugs is best suited in this case?

A. Acidine-pepsin.
B. Omeprazole.
C. Pancreatin
D. Drotaverin (No-Shpa).
E. De nol

3. Choose the most effective enzyme preparation:

1.Festal
2. Pansinorm.
3.Kreon.
4.Digestal.
5.Pankreatin

4. The introduction of which pathogenetically justified methods for chronic pancreatitis?

1. Antianginal.
2. Antihistamines
3.Ferent preparations.
4. Glucocorticoids.
5. Winter boots.

5. Which of the following drugs refers to pancreatic enzyme inhibitors?

1.Festal
2. Mesim-forte.
3. Aminocaproic acid.
4. Karsil.
5. Gastrotrazine.

6. Choose an anti-enzyme drug:

1.Festal

2.Panzinorm.
3.Kreon.
4.Contrical.
5.Pankreatin

7. Anti-enzyme preparations include all but:

1. Amben
2.Kontrical
3.Kreon.
4. Aminocaproic Acid.
5.Gordox.

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TOPIC 13. Principles of pharmacotherapy for diseases of the kidneys and the urinary system.

Actuality of topic.

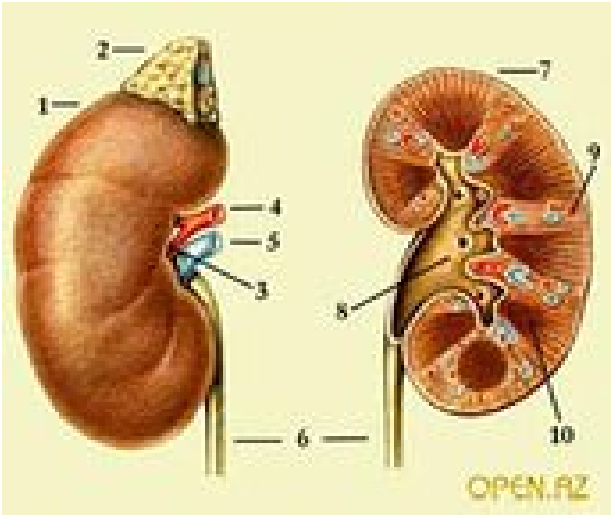
The kidney maintains the composition and quantity of body fluids, and its failure is manifested by dysfunction of multiple organs. Chronic kidney disease is approaching epidemic proportions worldwide, and acute kidney injury in the inpatient setting affects a very high percentage of hospital admissions with a high mortality rate. The etiologies of these conditions are very diverse. In addition to loss of glomerular filtration, kidney diseases include hypertension, urolithiasis, and a host of electrolyte disorders that do not affect the glomerular filtration rate (GFR) but nonetheless cause significant morbidity and mortality. To understand these conditions, a thorough knowledge of the anatomy and function of the kidney is requisite. Approximately 25% of the cardiac output is distributed to the kidneys, where the blood is continuously cleansed. In addition to excretion, the kidney is an important metabolic organ and a source of endocrine molecules. Renal failure represents a disruption of all three of these functions.

Purpose of the lesson: The student must know the anatomical and physiological features of the kidneys and the urinary system; etiology, pathogenesis, symptoms and syndromes in diseases of the urinary system and kidneys; diagnostic methods; principles of treatment. To study acute and chronic pyelonephritis, acute and chronic glomerulonephritis, urolithiasis, acute and chronic cystitis.

RENAL STRUCTURE

Macroscopic Anatomy

The kidneys are seated against the posterior wall of the abdomen in the retroperitoneal space, making them readily accessible for percutaneous biopsy. The lower poles may be palpable on deep inspiration in a lean individual. Each human kidney weighs about 120 to 170 g; is about 11 cm long, 6 cm wide, and 3 cm thick; and is endowed with approximately 1 million nephrons. There are interindividual variations. The “kidney size” commonly referred to in clinical sonographic reports is actually the cephalocaudal renal length, which is not a perfect surrogate for renal volume and mass.



The kidney is surrounded by a fibrous capsule. The renal arteries enter the kidney and the renal vein and ureters leave the kidney in the renal pelvis. The bisected surface consists of the lighter-colored outer cortex and the darker inner medulla. A sample from a clinical biopsy typically originates from the cortex in the lower pole. The medulla is divided into outer and inner regions, and the outer medulla is subdivided into outer and inner stripes. The medulla has multiple conical contours, called pyramids, with their apices abutting on the renal pelvis as papillae. The contact points of the renal pelvis with the renal papillae are cup-like structures called calyces. Interpolated between the pyramids are centripetal extensions of cortical tissue called columns of Bertin.

Renal Circulation

Each kidney receives blood from a single renal artery, although supernumerary arteries are present in up to one third of individuals. Just before or after the renal artery enters the kidney, it divides into interlobar arteries that pass between the pyramids of the kidney radially up the columns of Bertin. The interlobar arteries further divide into arcuate arteries which arch along the corticomedullary junction. Arcuate arteries give rise to cortical ascending arteries, which bring blood to the glomeruli. Afferent arterioles ramify into glomerular capillaries, distributing blood to individual glomeruli.

The glomerular capillary is the site for glomerular ultrafiltration. Even though the efferent arteriole is downstream from the glomerular capillary, it is not a venule because it has arteriolar walls and is upstream of the second capillary system surrounding the tubules. The peritubular capillaries provide oxygen and nutrients for the kidney, collect the fluid and solutes reabsorbed by tubules to return into the circulation, and deliver the solutes to be secreted by tubule into the tubule fluid. The peritubular capillaries surrounding the cortical and juxtamedullary nephrons originate from the efferent arterioles of cortical and juxtamedullary glomeruli, respectively.

The vessels that run parallel to loops of Henle are called vasa recta because of their long, straight structures. Blood from the peritubular capillaries is returned to the circulation by a venous system that mirrors the architectural structure of the arterial supply: interlobular vein, arcuate vein, interlobar vein, and renal vein. The parallel countercurrent nature of the vasculature provides the basis for the very high

medullar tonicity, which allows urine concentration but also direct arteriovenous diffusion of oxygen, giving rise to the very low oxygen tension in the medulla. This low oxygen tension renders the kidney prone to ischemic injury, which is one of the most common causes of acute kidney injury.

Renal Nerves

The capsules of the kidney and the ureters have pain fibers derived from splanchnic nerves. This explains the costovertebral angle pain that occurs when the kidneys are inflamed and during renal colic. The renal parenchyma does not have pain fibers but is richly innervated with sympathetic nerves that enter the renal parenchyma with the renal artery. The sympathetic nerves abut on the arterioles, stimulate renin release, decrease renal blood flow, and promote renal retention of sodium (Na+). Renal sympathetic denervation has been proposed as a novel treatment of resistant hypertension using radiofrequency energy delivered via an intrarenal arterial catheter radially to disrupt the nerve fibers on the renal artery.

Walk the Nephron

The functional unit of the kidney is the nephron. Each human kidney has approximately 1 million nephrons. Approximately 30% of these have their glomeruli situated deep in the cortex and are referred to as juxtamedullary nephrons; the rest are in the outer cortex and are referred to as superficial nephrons. Each nephron isa glomerulus followed by a tubule. The surrounding capillaries and the interstitial space are also important functional components of the nephron.

Glomerulus

The glomerulus consists of the glomerular vasculature (arterioles and capillaries) supported by the mesangium (mesangial cells and matrix) inside Bowman's capsule (parietal and visceral epithelial cells). The visceral cells of Bowman's capsule are the podocytes, so named because of their numerous "foot processes." The smooth muscle layers of the afferent and efferent arterioles are critical in determining arteriolar tone. The glomerular capillary contacts the mesangium on one side and is separated from the foot processes of the podocyte on the opposite side by the glomerular basement membrane (GBM). The glomerulus filters large volumes of water and solutes while retaining most of the proteins and all of the cells in the blood. The glomerular filtration barrier is composed of the capillary endothelium, the GBM, and the podocyte slit diaphragm.

Lining the inside of the GBM is a single layer of fenestrated endothelial cells. The fenestrations (50 to 100 nm in diameter) provide a barrier to negatively charged large molecules in the blood. The GBM contains laminin, type IV collagen, nidogen, and proteoglycans that restrict movement of large molecules (e.g., albumin) from the capillary into Bowman's space. The GBM contains dense negative charges due to glycoproteins with sialic acid residues that restrict the passage of anionic plasma solutes. It can be the site of deposition of immunocomplexes that cause glomerulonephritis (e.g., membranous glomerulonephritis, lupus nephritis). Autoantibodies to the GBM cause severe inflammation and loss of filtration. The epithelial layer consists of podocytes and the parietal epithelium, which is flat and squamous with very few organelles. At the

vascular pole, the parietal epithelium is contiguous with a completely different epithelium— the proximal convoluted tubule.

On the visceral side of Bowman's space are the podocytes, which constitute the outermost layer of the filtration barrier. These cells have a highly interdigitating system of foot processes that rest against the basement membrane. The podocyte cell bodies lie within the extracellular matrix. The spaces between foot processes are filtration slits approximately 40 nm in diameter; they are bridged by slit diaphragms, which are also negatively charged, contributing to the containment of middle-size negatively charged particles in the capillary. In the last decade, there have been momentous advances in identifying the components of the slit diaphragm complex and understanding their functions. A full discussion is not possible here, but major slit diaphragm– associated proteins include nephrin, podocin, neph-1/2/3, FAT-1, R-cadherin, catenin, CD2AP, ZO-1, and α-actinin 4. Mutations of many of these genes cause congenital nephrotic syndrome

Tubules

The parietal epithelium of Bowman's capsule becomes the renal tubule as it leaves the glomerulus. The renal tubule is a prototypical polarized epithelium. A simple cylinder would not suffice in terms of surface area for transport. In theluminal apical membrane, surface amplification is achieved either by protrusions or by a more extensive form of protrusions called the brush border in the proximal tubule. Between cells are structures called tight junctions. Although they are called tight junctions, some are truly tight (with high resistance to solute and charge movement), whereas others can be quite leaky to solutes. In addition to resistance, these complexes also regulate whether the junction is more permeable to one ion type compared with another (relative and selective permeability). On the other side of the tight junction is the intercellular space, which is contiguous with the interstitial space. The basolateral cell membrane on the interstitial-capillary side amplifies its surface area by infoldings into the cell and interdigitations between two cells.

The movement of a solute can be through a cell (transcellular transport) or around the cell (paracellular transport). Solute transport is an energy-consuming process that requires metabolic fuels. There are many kinds of transport proteins. ATPases directly couple hydrolysis of adenosine triphosphate (ATP) to transport. Cotransporters (symporters) move two solutes in the same direction, and countertransporters (antiporters) move two different solutes in opposite directions. Channels function as protein-lined "holes" that allows specific solutes to permeate. Different transporters can also be coupled together to form a new transport system. Finally, there are proteins that protrude outside the cell in the junctional area to provide a conduit for paracellular transport.

Specialized Structures

Interstitium

The space between the tubules and peritubular capillaries constitutes about 5% to 10% of renal volume and harbors interstitial fibroblasts and dendritic cells. In diseases such as interstitial nephritis, the interstitium is full of inflammatory cells, which elaborate cytokines and chemokines that profoundly affect filtration and

tubular function. The resident fibroblasts are stellate cells with projections that physically contact tubules and capillaries, provide scaffold support, and secrete and maintain matrix. In pathologic conditions, these cells, when stimulated by cytokines, can transform into myofibroblasts and contribute to interstitial fibrosis. Some specialized fibroblasts in the deep cortex are sensors of oxygen and producers of circulating erythropoietin. The dendritic cells are antigen-presenting cells that express major histocompatibility complex (MHC) class II molecules. They are in intimate communication with the renal parenchyma, constantly sampling and responding to the local antigenic environment. Dendritic cells are involved with innate and adaptive immunity and are major players in immunologic homeostasis and diseases of the renal parenchyma.

Juxtaglomerular Apparatus

A unique feature of the nephron is that each thick ascending limb traverses back to and engages in physical contact with its parent glomerulus. The tubular cell at the point of contact is different from the rest of the thick ascending limb and is called the macula densa. The tripartite structure comprising the macula densa, the afferent and efferent glomerular arterioles, and the extraglomerular mesangium, a special part of the mesangium that protrudesoutside the glomerulus, is called the juxtaglomerular apparatus (JGA). The JGA is an important structure in the maintenance of GFR by tubuloglomerular feedback and is the site of endocrine renin production.

RENAL VASCULAR ANATOMY

The renal arteries arise directly from the aorta and enter the renal hilum. The right renal artery passes anterior to the inferior vena cava (IVC) and is longer than the left renal artery. In up to 30% of the population, accessory renal arteries arise from the aorta to provide blood to portions of one or both kidneys, which may become important when evaluating patients for renovascular hypertension. The renal arteries give rise to segmental, interlobar, and arcuate arteries. Arcuate arteries course along the corticomedullary junction and give rise to interlobular arterioles, which extend outward into the cortex before branching into afferent arterioles, from which the glomerular capillary tufts arise. The postglomerular efferent arterioles from more superficial glomeruli form a capillary network in the renal cortex, and those extending from glomeruli nearer the cortical-medullary junction (i.e., juxtamedullary glomeruli) form capillaries that extend deeper into the medulla in association with thin, descending and ascending loops of Henle as the vasa recta. The vasa recta provide the sole blood supply for the renal medulla, making this portion of the kidney particularly susceptible to ischemic injury. Venules from the ascending vasa recta and the cortical capillary network empty into the renal veins. The left renal vein returns to the IVC anterior to the aorta and inferior to the inferior mesenteric artery, which may rarely cause compression of this vein. The left gonadal vein also empties into the left renal vein, and a left varicocele may be evident if the renal vein is occluded by thrombosis or tumor involvement. The right renal vein is much shorter and empties directly into the IVC.

The right gonadal vein empties directly into the IVC rather than into the right renal vein.

RENAL FUNCTION

Excretory Function

Renal excretion of a substance can be mediated and modified by one or a combination of three processes: filtration, secretion, and reabsorption.

Filtration occurs exclusively at the glomerulus. The GFR, measured as volume per unit time, has been the standard quantitative surrogate for overall kidney function, although there are many disturbances of renal function that are not associated with a decrease in GFR (e.g., nephrotic syndrome, tubulointerstitial disorders, kidney stones).

Reabsorption High GFR, which is required to maintain a high metabolic rate, can be sustained only if there is high reclamation to maintain intravascular volume and prevent circulatory collapse. Tubular reabsorption thwarts the loss of valuable solutes and allows for finer tuning of the water and solutes not reabsorbed. The resulting tubular contents are excreted. In the mammalian kidney, tubular reabsorption assumes critical roles in the regulation of excretion of many solutes. A universal mechanism of reabsorption is energy-dependent transepithelial transport, which is mostly Na+ dependent but can be Na+ independent. The proximal tubules participate in the reabsorption of all solutes, but some solutes are sequentially reabsorbed by the proximal and distal segments; in these cases, the generic design tends to be high-capacity reabsorption proximally and more of a highgradient reabsorption for fine tuning distally. The axial differencecan occur within the same nephron segment (e.g., early vs. late proximal tubule) or across different segments (e.g., proximal vs. distal nephron segments).

Secretion Secretion is an ancient mode of excretion that is found in lowerorder organisms. Although the human nephron is not primarily secretory in nature, a number of solutes are still handled by secretion. For example, the renal excretion of potassium (K^+) and hydrogen (H^+) ions is largely achieved by secretion. Many organic cations and anions are secreted by the proximal tubule, and so are many exogenous toxins such as xenobiotics. The secretion of creatinine by organic cation transporters in the proximal tubule is the reason why creatinine clearance overestimates GFR.

Endocrine Function

In addition to the prominent and more obvious roles in solute and water balance, the kidney also is an important endocrine organ. The autocrine and paracrine substances elaborated by the kidney are important for both intrarenal and systemic regulation. Although this subject is not addressed fully here, three of these substances are highlighted because they represent important pharmacologic targets.

Renin As the initiating component of the renin-angiotensin-aldosterone system (RAAS), renin is important for maintenance of the integrity of the circulation. The RAAS permits the kidney to have a constant GFR in the face of low and fluctuating salt intake, a property that is vital for terrestrial existence.

Renin is produced by the JGA (see earlier discussion). Despite the benefits and importance of the RAAS in physiology, its activation in many disease states appears to be maladaptive and contributes to kidney and cardiovascular injury. Pharmacologic blockade of RAAS pathways at various levels has proved beneficial in animal disease models and human clinical studies, and agents to block RAAS signaling are now in clinical use, with others under development..

Vitamin D 1α-Hydroxylase (cytochrome P-450 isoenzyme 27B1) is found in the proximal tubule, where the major body defense for maintaining phosphate homeostasis is localized. Lesser expression of the same enzyme is also found in the rest of the nephron segments. The kidney is one of the most important organs for maintaining calcium and phosphate homeostasis, not just as the major controller of external balance but as an elaborator of systemicfactors such as vitamin D and the Klotho protein. Conversion of the precursor 25(OH)-hydroxyvitamin D to its active form, 1,25(OH)2dihydroxyvitamin D, is achieved not exclusively but substantially in the kidney and is mediated by 1α-hydroxylase. Vitamin D deficiency is an important complication in chronic kidney disease. Replacement of vitamin D is efficacious in reducing the complications of chronic kidney disease and may even improve survival.

Erythropoietin Erythropoietin, which is produced mainly in the kidney, stimulates erythropoiesis. The erythropoietin-producing cells are strategically located in the cortical interstitium to sense the balance between oxygen delivery and consumption. The current model suggests that upregulation of renal erythropoietin production (mainly by anemia and hypoxia) occurs via an increase in the number of latent erythropoietin-producing cells. The mechanism of erythropoietin deficiency in kidney disease is not definitively known, although it does not involve destruction of renal erythropoietin-producing interstitial cells. One possible mechanism is decreased renal oxygen consumption as a consequence of reduced GFR; this results in higher renal tissue oxygen tension and suppression of erythropoietin production. Resetting of theoxygen-sensing mechanism has also been conjectured. Another theory is direct inhibition of the erythropoietin-producing cells by inflammatory cytokines. Others have proposed transdifferentiation of erythropoietin-producing cells into myofibroblasts and a decrease in the number of interstitial cells that can be recruited to produce erythropoietin.

The use of erythropoiesis-stimulating agents (ESAs) has revolutionized the treatment of anemia associated with chronic kidney disease, but because of incomplete understanding of erythropoietin and erythropoietin receptor biology, the clinical outcome is far from ideal due to inability to tailor the optimal hematocrit for individual patients and uncertainty about possible extra-erythropoietic effects of erythropoietin.

CLINICAL SYNDROMES

The major clinical syndromes associated with glomerular injury are discussed in this section. In each case, general recognition and management should be pursued in parallel with efforts to define the specific mechanisms of injury.

Nephrotic Syndrome

Nephrotic syndrome is defined as persistent urinary total protein excretion greater than 3.5 g/24h, accompanied by a serum albumin concentration less than 3.5 g/dL. Edema, hyperlipidemia, and lipiduria (i.e., doubly refractile fat bodies) are common but are not required for the diagnosis.

Complications of the nephrotic syndrome include hypogammaglobulinemia, vitamin D deficiency due to loss of vitamin D–binding protein, and iron deficiency anemia due to hypotransferrinemia. Thrombotic complications such as renal vein thrombosis are more common, especially in patients with greater protein loss (>10 g/24h) and serum albumin levels less than 2 g/dL. Patients with severe nephrotic syndrome may also have acute renal failure when there is superimposed volume depletion, sepsis, interstitial nephritis, or use of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs (NSAIDs).

Management of patients with nephrotic syndrome includes diuretics to control edema, regulation of blood pressure (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin-receptor blockers [ARBs] are preferred), limitation of the intake of protein to between 0.8 and 1 g/kg/day and sodium to less than 4 g/day, and control of lipid levels. Anticoagulation should be considered for patients at increased risk, especially if the nephrotic syndrome is caused by membranous nephropathy or amyloidosis.

Nephritic Syndrome

The nephritic syndrome is defined by oliguria, edema, hypertension, proteinuria (usually < 3.5 g/24h), and abnormal urinalysis with dysmorphic red blood cells or casts on microscopic examination.

Uremic Syndrome

Kidney disease commonly manifests first as abnormalities on laboratory or other diagnostic tests. Patients with CKD may not have symptoms until advanced stages, in which the GFR is less than 15 mL/minute. Uremia is a systemic syndrome that negatively affects every organ system. Uremic syndrome is likely the consequence of many factors, including retained molecules, deficiencies of important hormones, and metabolic abnormalities, rather than the effect of a single uremic toxin. Excess urea can cause symptoms of fatigue, nausea, vomiting, and headaches. Its breakdown product (cyanate) can result in carbamylation of lipoproteins and peptides, leading to multiple organ dysfunctions. Guanidines, byproducts of protein metabolism, are increased and can inhibit α1-hydroxylase activity within the kidney, leading to secondary hyperparathyroidism. β2-Microglobulin accumulation in patients with ESRD has been associated with

neuropathy, carpal tunnel syndrome, and amyloid infiltration of the joints. Specific roles for other accumulated metabolites are under investigation.

GLOMERULONEPHRITIS

ESSENTIALS OF DIAGNOSIS

- Hematuria, dysmorphic red cells, red cell casts, and mild proteinuria.
- Dependent edema and hypertension.
- Acute kidney injury.

General Considerations

Acute glomerulonephritis is a relatively uncommon cause of acute kidney injury, accounting for about 5% of cases. Pathologically, inflammatory glomerular lesions are seen. These include mesangioproliferative, focal and diffuse proliferative, and crescentic lesions. The larger the percentage of glomeruli involved and the more severe the lesion, the more likely it is that the patient will have a poor clinical outcome.

Categorization of acute glomerulonephritis can be done by serologic analysis. Markers include anti-GBM antibodies, antineutrophil cytoplasmic antibodies (ANCAs), and other immune markers of disease.

Immune complex deposition usually occurs when moderate antigen excess over antibody production occurs. Complexes formed with marked antigen excess tend to remain in the circulation. Antibody excess with large antigen–antibody aggregates usually results in phagocytosis and clearance of the precipitates by the mononuclear phagocytic system in the liver and spleen. Causes include IgA nephropathy (Berger disease), peri-infectious or postinfectious glomerulonephritis, endocarditis, lupus nephritis, cryoglobulinemic glomerulonephritis (often associated with hepatitis C virus [HCV]), and MPGN.

Anti-GBM–associated acute glomerulonephritis is either confined to the kidney or associated with pulmonary hemorrhage. The latter is termed "Goodpasture syndrome." Injury is related to autoantibodies aimed against type IV collagen in the GBM rather than to immune complex deposition.

Pauci-immune acute glomerulonephritis is a form of small-vessel vasculitis associated with ANCAs, causing primary and secondary kidney diseases that do not have direct immune complex deposition or antibody binding. Tissue injury is believed to be due to cell-mediated immune processes. An example is granulomatosis with polyangiitis, a systemic necrotizing vasculitis of small arteries and veins associated with intravascular and extravascular granuloma formation. In addition to glomerulonephritis, these patients can have upper airway, pulmonary, and skin manifestations of disease. Cytoplasmic ANCA (c-ANCA) is the common pattern. Microscopic polyangiitis is another pauci-immune vasculitis causing acute glomerulonephritis. Perinuclear staining (p-ANCA) is the common pattern in this scenario. ANCA-associated and anti-GBM-associated acute glomerulonephritis can evolve to crescentic glomerulonephritis and often have poor outcomes unless treatment is started early. Both are described more fully below.

Other vascular causes of acute glomerulonephritis include hypertensive emergencies and the thrombotic microangiopathies such as hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura.

Clinical Findings

A. Symptoms and Signs

Patients with acute glomerulonephritis are often hypertensive and edematous, and have an abnormal urinary sediment. The edema is found first in body parts with low tissue tension, such as the periorbital and scrotal regions.

B. Laboratory Findings

Serum creatinine can rise over days to months, depending on the rapidity of the underlying process. The BUN:creatinine ratio is not a reliable marker of kidney function and is more reflective of the underlying volume status of the patient. Dipstick and microscopic evaluation will reveal evidence of hematuria, moderate proteinuria (usually less than 3 g/day), and cellular elements such as red cells, red cell casts, and white cells. Red cell casts are specific for glomerulonephritis, and a detailed search is warranted. Either spot urinary protein-creatinine ratios or 24-hour urine collections can quantify protein excretion; the latter can quantify creatinine clearance when renal function is stable. However, in cases of rapidly changing serum creatinine values, the urinary creatinine clearance is an unreliable marker of GFR. The Fena is usually low unless the renal tubulo-interstitial space is affected, and renal dysfunction is marked.

Further tests include complement levels (C3, C4, CH50) that are low in immune complex glomerulonephritis aside from IgA nephropathy and normal in pauci immune and anti-GBM related glomerulonephritis. Other tests include ASO titers, anti-GBM antibody levels, ANCAs, antinuclear antibody titers, cryoglobulins, hepatitis serologies, blood cultures, renal ultrasound, and kidney biopsy in the appropriate setting.

Treatment

Depending on the nature and severity of disease, treatment can consist of high-dose corticosteroids and cytotoxic agents such as cyclophosphamide. Plasma exchange can be used in Goodpasture syndrome and pauci-immune glomerulonephritis as a temporizing measure until chemotherapy can take effect. Treatment and prognosis for specific diseases are discussed more fully below.

Postinfectious Glomerulonephritis

ESSENTIALS OF DIAGNOSIS

- Proteinuria.
- Glomerular hematuria.
- Symptoms 1–3 weeks after infection (often pharyngitis or impetigo).

General Considerations

Postinfectious glomerulonephritis is most often due to infection with nephritogenic group A beta-hemolytic streptococci. It can occur sporadically or in clusters and during epidemics. It commonly appears after pharyngitis or impetigo with onset 1–3 weeks after infection (average 7–10 days).

Other infections have been associated with postinfectious glomerulonephritis including bacteremic states (especially with S aureus), bacterial pneumonias, deep-seated abscesses, gram-negative infections, infective endocarditis, and shunt infections. Viral, fungal, and parasitic causes of postinfectious glomerulonephritis pattern of glomerular injury include hepatitis B or C, HIV, cytomegalovirus infection, infectious mononucleosis, coccidioidomycosis, malaria, mycobacteria, syphilis, and toxoplasmosis.

Clinical Findings

A. Symptoms and Signs

Disease presentation can vary widely across the nephritic spectrum from asymptomatic glomerular hematuria (especially in epidemic cases) to nephritic syndrome with hypertension, oliguria, edema, and perhaps gross glomerular hematuria (smokey-colored urine).

B. Laboratory Findings Serum complement levels are low; in postinfectious glomerulonephritis due to group A streptococcal infection, anti-streptolysin O (ASO) titers can be high unless the immune response has been blunted with previous antibiotic treatment. Glomerular hematuria and subnephrotic proteinuria are present; severe cases may demonstrate elevated serum creatinine and urinary red blood cell casts. Kidney biopsy shows a diffuse proliferative pattern of injury on light microscopy. Immunofluorescence demonstrates granular deposition of IgG and C3 in the mesangium and along the capillary basement membrane. Electron microscopy shows large, dense subepithelial deposits or “humps.”

Treatment

The underlying infection should be identified and treated appropriately; otherwise, treatment for postinfectious glomerulonephritis is supportive. Antihypertensives, salt restriction, and diuretics should be used if needed. Corticosteroids have not been shown to improve outcome. Prognosis depends on the severity of the glomerular injury and age of the patient. Children are more likely to fully recover; adults are more prone to the development of severe disease (RPGN with crescent formation) and CKD.

Anti-Glomerular Basement Membrane Glomerulonephritis & Goodpasture Syndrome

Goodpasture syndrome is defined by the clinical constellation of glomerulonephritis and pulmonary hemorrhage; injury to both the kidneys and the lungs is mediated by antibodies to epitopes in the GBM. Up to one-third of patients with anti-GBM glomerulonephritis have no evidence of concomitant lung injury

(anti-GBM disease). Anti-GBM–associated glomerulonephritis accounts for 10–20% of patients with acute RPGN. The incidence peaks in the second and third decades of life during which time males are predominantly affected and lung involvement is more common, and again in the sixth and seventh decades with less male sex predominance. Lung involvement has been associated with pulmonary infection, tobacco use, and hydrocarbon solvent exposure; HLA-DR2 and -B7 antigens may predispose as well.

Clinical Findings

A. Symptoms and Signs

The onset of disease may be preceded by an upper respiratory tract infection; hemoptysis, dyspnea, and possible respiratory failure may ensue. Other findings are consistent with an RPGN, although some cases may present with much milder forms of the nephritic spectrum of disease (eg, glomerular hematuria and proteinuria with minimal renal dysfunction).

B. Laboratory Findings

Chest radiographs may demonstrate pulmonary infiltrates if pulmonary hemorrhage is present. Serum complement levels are normal. Circulating anti-GBM antibodies are present in over 90% of patients. A small percentage of patients also have elevated ANCA titers; these patients should be treated with plasma exchange as for anti-GBM disease. Kidney biopsy typically shows crescent formation on light microscopy, with linear IgG staining along the GBM on immunofluorescence.

Treatment

Treatment is a combination of plasma exchange therapy to remove circulating antibodies, and administration of immunosuppressive drugs to prevent formation of new antibodies and control the inflammatory response. Corticosteroids are typically given initially in pulse doses of methylprednisolone, 1–2 g/day for 3 days, then prednisone orally 1 mg/kg/day. Cyclophosphamide is administered intravenously at a dose of 0.5–1 g/m2 per month or orally at a dosage of 2–3 mg/kg/day. Daily plasma exchange is performed for up to 2 weeks. Patients with oliguria and a serum creatinine greater than 6–7 mg/dL, or who require dialysis upon presentation have a poor prognosis. AntiGBM antibody titers should decrease as the clinical course improves.

Cryoglobulin-Associated Glomerulonephritis

Essential (mixed) cryoglobulinemia is a vasculitis associated with cold-precipitable immunoglobulins (cryoglobulins). The most common underlying etiology is HCV infection; in these cases, there is clonal expansion of B lymphocytes, which produce IgM rheumatoid factor. Rheumatoid factor, HCV antigen and polyclonal anti-HCV IgG form complexes that deposit in vessels and incite inflammation. Other overt or occult infections (eg, viral, bacterial, and fungal) as well as some connective tissue diseases can also be causative.

Patients exhibit purpuric and necrotizing skin lesions in dependent areas, arthralgias, fever, and hepatosplenomegaly. Serum complement levels are depressed. Rheumatoid factor is often elevated when cryoglobulins are present. Kidney biopsy may show several different patterns of injury; there may be crescent formation, glomerular capillary thrombi, or MPGN.

Treatment consists of aggressively targeting the causative infection. Pulse corticosteroids, plasma exchange, rituximab and cytotoxic agents have been used when risk of exacerbating the underlying infection is resolved, or when no infection is present. See also section on Hepatitis C Virus–Associated Renal Disease.

Membranoproliferative Glomerulonephritis & C3 Glomerulopathies

MPGN is a relatively rare pattern of glomerular injury that can be caused by a wide range of known etiologies or can be idiopathic. Clinically, it can present anywhere along the nephritic spectrum from asymptomatic glomerular hematuria to acute nephritic syndrome with bouts of gross hematuria to RPGN; nephrotic syndrome can also be seen. Traditionally, MPGN has been classified into several histologic subtypes; this classification is now in evolution. Type I is relatively more common and can be idiopathic (especially in children and young adults) or secondary to chronic infection (most commonly HCV), a paraproteinemia, or an underlying autoimmune disease such as lupus. The pathogenesis is likely a chronic antigenemia leading to classical complement pathway activation with immune complex deposition; however, it is now recognized that some cases may result from alternative complement pathway dysregulation. Type II MPGN is caused by several inherited or acquired abnormalities in the alternative complement pathway. Both types result in low circulating C3 complement; immune complex type I also has low C4. Light microscopy of both types shows varying degrees of mesangial hypercellularity, endocapillary proliferation and capillary wall remodeling resulting in double contours of the GBM (“tram track” appearance). Immunofluorescence and electron microscopy provide distinguishing information. Type II MPGN reveals C3 deposition without immunoglobulin staining on immunofluorescence, and electron microscopy demonstrates thick ribbon-like electron dense deposits along the GBM; thus, type II disease is also known as “dense deposit disease.” Conversely, type I MPGN has scattered subendothelial and subepithelial deposits on electron microscopy. When there is immunoglobulin and C3 staining on immunofluorescence in type I MPGN, it is also called immune complex MPGN (more common type); when a type I case demonstrates only C3 staining on immunofluorescence, it is now termed C3 glomerulonephritis (C3 GN). Together, dense deposit disease (type II) and C3 GN are now termed “C3 glomerulopathies”; both result from inherited or acquired alternative complement dysregulation/activation.

Treatment of type I immune complex MPGN should be directed at the underlying cause, if such is found. Treatment of idiopathic immune complex

disease is controversial and controlled trial data are lacking. For those with nephrotic syndrome and declining GFR, a combination of oral cyclophosphamide or mycophenolate mofetil plus corticosteroids could be considered; patients with RPGN and crescents on biopsy may be treated the same as those with ANCA-associated disease provided secondary causes have been ruled out. Despite therapy, most will progress to ESRD. Treatment for the C3 glomerulopathies is in evolution as novel therapies to target the dysregulated alternative complement cascade are being explored. Less favorable prognostic findings include type II/dense deposit disease, early decline in GFR, hypertension, and persistent nephrotic syndrome. All types of MPGN recur with high frequency after renal transplantation; however, type II recurs more commonly. Plasma exchange has been used with mixed results to treat posttransplant recurrence of MPGN.

Urinary tract infection

The term urinary tract infection (UTI) refers to significant bacteriuria in a patient with symptoms or signs attributable to the urinary tract and no alternative diagnosis. UTI includes asymptomatic bacteriuria, urethritis, cystitis, pyelonephritis, catheterassociated UTI, prostatitis, and urosepsis. This chapter focuses primarily on the two major forms of UTI, cystitis and pyelonephritis.

A practical classification divides these infections into uncomplicated and complicated UTI. Uncomplicated UTIs are episodes of cystitis and mild pyelonephritis occurring in healthy, premenopausal, sexually active, nonpregnant women with no history suggestive of abnormalities in the urinary tract. All other episodes of UTI are deemed to be potentially complicated and deserving of further evaluation.

The presence of dysuria, increased frequency of urination, suprapubic tenderness, and hematuria associated with bacteriuria or pyuria on urinalysis is unequivocally consistent with the diagnosis of cystitis. Back or flank pain, nausea, vomiting, and the presence of fever or rigors suggest infection of the upper urinary tract, although it is not easy to distinguish cystitis from pyelonephritis on clinical grounds alone. The diagnosis of UTI gets more difficult when patients cannot ascribe symptoms to the urinary tract (e.g., patients with paraplegia or neurogenic bladder, confused elderly or sedated patients) or when they have atypical symptoms, such as changes in mental status, agitation, or hypotension. Sometimes patients have urinary symptoms without bacteriuria (the pyuria-dysuria or “urethral syndrome” commonly caused by Chlamydia trachomatis or other difficult-toculture genitourinary pathogens).

Bacteriuria is the hallmark of UTI. In women, asymptomatic bacteriuria is defined as two consecutive voided midstream urine specimens with isolation of the same bacterial strain at levels of at least 10^5 colony-forming units (CFU) per milliliter from patients without genitourinary symptoms. In men, a single cleancatch, midstream voided urine specimen with one bacterial species at a concentration greater than 10^5CFU/mL defines asymptomatic bacteriuria. The diagnosis of asymptomatic bacteriuria is also established in both women and men

from a single catheterized urine specimen (not an indwelling catheter) with one bacterial species isolated at concentrations greater than 10^2 CFU/mL.

To increase the sensitivity of the tests, significant bacteriuria is defined as greater than 10^2CFU/mL of urine in a woman with symptoms of uncomplicated cystitis and pyuria (≥5 white blood cells per milliliter of urine per high-power field). Among women with symptoms of uncomplicated pyelonephritis and men with UTI, significant bacteriuria is defined as greater than 10^4CFU/ mL plus pyuria. In patients with complicated UTI, a concentration of 10^5 CFU/mL or higher is required for the definition of significant bacteriuria independently of pyuria.

In order for these definitions to be valid, the urine must remain in the bladder for at least 2 hours, and after urine collection the sample should be incubated immediately. If urine is not incubated immediately, it can be refrigerated for up to 8 hours before proper incubation.

The presence of asymptomatic bacteriuria is not equivalent to UTI except for pregnant women, neutropenic patients, and individuals with anatomic or functional defects in the urinary tract. The presence of white blood cell casts indicates pyelonephritis, and this finding suggests a complicated UTI with obstructive lesions of the kidney or collecting system (e.g., papillary necrosis). It is difficult to define asymptomatic bacteriuria in the patient who has undergone renal transplantation, and bacteriuria in such patients often indicates the need to treat for UTI.

Acute Pyelonephritis

ESSENTIALS OF DIAGNOSIS

- Fever.
- Flank pain.
- Irritative voiding symptoms.
- Positive urine culture.

General Considerations

Acute pyelonephritis is an infectious inflammatory disease involving the kidney parenchyma and renal pelvis. Gramnegative bacteria are the most common causative agents including E coli, Proteus, Klebsiella, Enterobacter, and Pseudomonas. Gram-positive bacteria are less commonly seen but include Enterococcus faecalis and Staphylococcus aureus. The infection usually ascends from the lower urinary tract—with the exception of S aureus, which usually is spread by a hematogenous route.

Clinical Findings

A. Symptoms and Signs

Symptoms include fever, flank pain, shaking chills, and irritative voiding symptoms (urgency, frequency, dysuria). Associated nausea and vomiting, and diarrhea are common. Signs include fever and tachycardia. Costovertebral angle tenderness is usually pronounced.

B. Laboratory Findings

Complete blood count shows leukocytosis and a left shift. Urinalysis shows pyuria, bacteriuria, and varying degrees of hematuria. White cell casts may be seen. Urine culture demonstrates heavy growth of the offending organism, and blood culture may also be positive.

C. Imaging

In complicated pyelonephritis, renal ultrasound may show hydronephrosis from a stone or other source of obstruction.

Differential Diagnosis

Acute intra-abdominal disease such as appendicitis, cholecystitis, pancreatitis, or diverticulitis must be distinguished from pyelonephritis. A normal urinalysis is usually seen in gastrointestinal disorders; however, on occasion, inflammation from adjacent bowel (appendicitis or diverticulitis) may result in hematuria or sterile pyuria. Abnormal liver biochemical tests or elevated amylase levels may assist in the differentiation. Lower-lobe pneumonia is distinguishable by the abnormal chest radiograph.

In males, the main differential diagnosis for acute pyelonephritis includes acute epididymitis, acute prostatitis, and acute cystitis. Physical examination and the location of the pain should permit this distinction.

Complications

Sepsis with shock can occur with acute pyelonephritis. In diabetic patients, emphysematous pyelonephritis resulting from gas-producing organisms may be life threatening if not adequately treated. Healthy adults usually recover complete kidney function, yet if coexistent kidney disease is present, scarring or chronic pyelonephritis may result. Inadequate therapy could result in abscess formation.

Treatment

Urine and blood cultures are obtained to identify the causative agent and to determine antimicrobial sensitivity. In the inpatient setting, intravenous ampicillin and an aminoglycoside are initiated prior to obtaining sensitivity results. In the outpatient setting, a quinolone may be initiated. Antibiotics are adjusted according to sensitivities. Fevers may persist for up to 72 hours; failure to respond warrants imaging (CT or ultrasound) to exclude complicating factors that may require intervention. Catheter drainage may be necessary in the face of urinary retention and nephrostomy drainage if there is ureteral obstruction. In inpatients, intravenous antibiotics are continued for 24 hours after the fever resolves, and oral antibiotics are then given to complete a 14-day course of therapy. However, a shorter 7-day course may be just as effective with fewer side effects, such as mucosal candidiasis. Follow-up urine cultures are mandatory following the completion of treatment.

Antibiotic:

- Ampicillin, 1 g every 6 hours, and gentamicin, 1 mg/kg every 8 hours,

I ntravenous,14 days

- Ciprofloxacin, 750 mg every 12 hours, Oral, 7–14 days
- Ofloxacin, 200–300 mg every 12 hours, Oral, 7–14 days
- Trimethoprim-sulfamethoxazole, 160/800 mg every 12 hours, Oral, 10–14 days

Treatment Chronic pyelonephritis Same as for acute pyelonephritis 3–6 months.

Prognosis

With prompt diagnosis and appropriate treatment, acute pyelonephritis carries a good prognosis. Complicating factors, underlying kidney disease, and increasing patient age may lead to a less favorable outcome.

When to Refer

• Evidence of complicating factors (urolithiasis, obstruction).
• Absence of clinical improvement in 48 hours.

When to Admit

• Severe infections or complicating factors, evidence of sepsis or need for parenteral antibiotics.
• Need for radiographic imaging or drainage of urinary tract obstruction.

Acute Cystitis

ESSENTIALS OF DIAGNOSIS

- Irritative voiding symptoms.
- Patient usually afebrile.
- Positive urine culture; blood cultures may also be positive.

General Considerations

Acute cystitis is an infection of the bladder most commonly due to the coliform bacteria (especially Escherichia coli) and occasionally gram-positive bacteria (enterococci). The route of infection is typically ascending from the urethra. Viral cystitis due to adenovirus is sometimes seen in children but is rare in adults. Uncomplicated cystitis in men is rare and implies a pathologic process such as infected stones, prostatitis, or chronic urinary retention requiring further investigation.

Clinical Findings

A. Symptoms and Signs

Irritative voiding symptoms (frequency, urgency, dysuria) and suprapubic discomfort are common. Women may experience gross hematuria, and symptoms may often appear following sexual intercourse. Physical examination may elicit suprapubic tenderness, but examination is often unremarkable. Systemic toxicity is absent.

B. Laboratory Findings

Urinalysis shows pyuria, bacteriuria, and varying degrees of hematuria. The degree of pyuria and bacteriuria does not necessarily correlate with the severity of symptoms. Urine culture is positive for the offending organism, but colony counts exceeding 10^5/mL are not essential for the diagnosis.

D. Imaging

Because uncomplicated cystitis is rare in men, elucidation of the underlying problem with appropriate investigations, such as abdominal ultrasonography or cystoscopy (or both), is warranted. Follow-up imaging using CT scanning is warranted if pyelonephritis, recurrent infections, or anatomic abnormalities are suspected.

Differential Diagnosis

In women, infectious processes such as vulvovaginitis and pelvic inflammatory disease can usually be distinguished by pelvic examination and urinalysis. In men, urethritis and prostatitis may be distinguished by physical examination (urethral discharge or prostatic tenderness).

Noninfectious causes of cystitis-like symptoms include pelvic irradiation, chemotherapy (cyclophosphamide), bladder carcinoma, interstitial cystitis, voiding dysfunction disorders, and psychosomatic disorders.

Prevention

Women who have more than three episodes of cystitis per year are considered candidates for prophylactic antibiotic therapy to prevent recurrence after treatment of urinary tract infection. Prior to institution of therapy, a thorough urologic evaluation is warranted to exclude any anatomic abnormality (eg, stones, reflux, fistula). The three most commonly used oral agents for prophylaxis are trimethoprimsulfamethoxazole (40 mg/200 mg), nitrofurantoin (100 mg), and cephalexin (250 mg). Single dosing at bedtime or at the time of intercourse is the recommended schedule.

The risk of acquiring a catheter-associated urinary tract infection in hospitalized patients can be minimized by using indwelling catheters only when necessary, implementing systems to ensure removal of catheters when no longer needed, using antimicrobial catheters in high-risk patients, using external collection devices in select men, identifying significant postvoid residuals by ultrasound, maintaining proper insertion techniques, and utilizing alternatives such as intermittent catheterization.

Treatment

Uncomplicated cystitis in women can be treated with short-term antimicrobial therapy, which consists of single-dose therapy or 1–9 days of therapy. Cephalexin, nitrofurantoin, and fluoroquinolones are the drugs of choice for uncomplicated cystitis. Trimethoprim-sulfamethoxazole can be ineffective because of the emergence of resistant organisms. A review of the literature proposed that

acute uncomplicated cystitis in women can be diagnosed without office evaluation or urine culture, and that appropriate first-line therapies include trimethoprim-sulfamethoxazole (100 mg twice daily for 3 days), nitrofurantoin (100 mg twice daily for 5–7 days), and fosfomycin trometamol (3 g single dose). In men, uncomplicated urinary tract infection is rare, and thus, the duration of antibiotic therapy depends on the underlying etiology. Hot sitz baths or urinary analgesics (phenazopyridine, 200 mg orally three times daily) may provide symptomatic relief.

Antibiotic:

- Cephalexin, 250–500 mg every 6 hours, Oral, 3 days
- Nitrofurantoin (macrocrystals), 100 mg every 12 hours, Oral, 7 days
- Ciprofloxacin, 250–500 mg every 12 hours, Oral, 3 days
- Norfloxacin, 400 mg every 12 hours, Oral,3 days
- Ofloxacin, 200 mg every 12 hours, Oral, 3 days
- Trimethoprim-sulfamethoxazole, 160/800 mg, two tablets, Oral, Single dose.

Prognosis

Infections typically respond rapidly to therapy, and failure to respond suggests resistance to the selected drug or anatomic abnormalities requiring further investigation.

When to Refer

• Suspicion or radiographic evidence of anatomic abnormality.
• Evidence of urolithiasis.
• Recurrent cystitis due to bacterial persistence.

URINARY STONE DISEASE

ESSENTIALS OF DIAGNOSIS

- Severe flank pain.
- Nausea and vomiting.
- Identification on noncontrast CT or ultrasonography
-

General Considerations

Urinary stone disease is exceeded in frequency as a urinary tract disorder only by infections and prostatic disease and is estimated to afflict 240,000–720,000 Americans per year. While men are more frequently affected by urolithiasis than women, with a ratio of 2.5:1, the incidence in women appears to be rising over time. Initial presentation predominates between the third and fifth decade.

Urinary calculi are polycrystalline aggregates composed of varying amounts of crystalloid and a small amount of organic matrix. Stone formation requires saturated urine that is dependent on pH, ionic strength, solute concentration, and complexation. There are five major types of urinary stones: calcium oxalate, calcium phosphate, struvite (magnesium ammonium phosphate), uric acid, and cystine. The most common types are composed of calcium, and for that reason most urinary stones (85%) are radiopaque on plain abdominal radiographs. Uric acid

stones frequently are composed of a combination of uric acid and calcium oxalate and thus are frequently radiopaque, though pure uric acid stones are radiolucent. Cystine stones frequently have a smooth-edged ground-glass appearance and are radiolucent.

Geographic factors contribute to the development of stones. Areas of high humidity and elevated temperatures appear to be contributing factors, and the incidence of symptomatic ureteral stones is greatest during hot summer months. Persons with sedentary lifestyles have a higher incidence of stones and increasing evidence demonstrates that urinary stone disease may be a precursor to subsequent cardiovascular disease.

High protein and salt intake as well as inadequate hydration appear to be the most important factors in the development of urinary stones.

Genetic factors may contribute to urinary stone formation. While approximately 50% of calcium-based stones are thought to have a heritable component, other stone types are better characterized genetically. For example, cystinuria is an autosomal recessive disorder. Homozygous individuals have markedly increased excretion of cystine and frequently have numerous recurrent episodes of urinary stones. Distal renal tubular acidosis may be transmitted as a hereditary trait, and urolithiasis occurs in up to 75% of affected patients.

Clinical Findings

A. Symptoms and Signs

Obstructing urinary stones usually present with acute and severe colic. Pain usually occurs suddenly and may awaken patients from sleep. It is localized to the flank, is usually severe, unremitting, and may be associated with nausea and vomiting. Patients are constantly moving trying to find a comfortable position—in sharp contrast to those with an acute abdomen. The pain may occur episodically and may radiate anteriorly over the abdomen. As the stone progresses down the ureter, the pain may be referred into the ipsilateral groin. If the stone becomes lodged at the uretero-vesicular junction, patients will complain of marked urinary urgency and frequency and in men, pain may radiate to the tip of the penis. After the stone passes into the bladder, there typically is minimal pain with passage through the urethra. Stone size does not correlate with the severity of the symptoms.

B. Laboratory Findings

In patients with either symptomatic or asymptomatic kidney stones, urinalysis usually reveals microscopic or gross hematuria (~90%). However, the absence of microhematuria does not exclude urinary stones. Urinary pH is a valuable clue to the cause of the possible stone. Normal urine pH is 5.8–5.9. Numerous dipstick measurements are valuable in the complete work-up of a patient in whom urinary stones are suspected. Persistent urinary pH < 5.5 is suggestive of uric acid or cystine stones. In contrast, a persistent urinary pH > 7.2 is suggestive of a struvite infection stone or calcium phosphate stone (when above 7.5). Patients with calcium oxalate–based stones typically have a urinary pH between 5.5 and 6.8.

Metabolic Evaluation

Patients should strain their urine through cheesecloth or a urine strainer during a symptomatic episode. This facilitates stone analysis on recovered stones. Controversy exists in deciding which patients need a thorough metabolic evaluation for stone disease. Patients with uncomplicated first-time stones should undergo dietary counseling as outlined below and can be offered metabolic evaluation

Complete metabolic evaluation is required in patients who have recurrent stones or those with a family history of nephrolithiasis. Patients are encouraged to change their diet to reduce sodium intake, reduce their animal protein intake during individual meals, and to ingest adequate fluid to achieve a voided volume of 1.5–2.0 L/day of urine. After these dietary changes have been initiated, a 24-hour urine collection should be obtained to ascertain urinary volume, pH, calcium, uric acid, oxalate, phosphate, sodium, and citrate excretion. Serum parathyroid hormone (PTH), calcium, uric acid, electrolytes (including bicarbonate), creatinine, and BUN should also be obtained.

D. Imaging

A plain abdominal radiograph (kidneys-ureters-bladder [KUB]) and renal ultrasound examination will diagnose most stones. More than 60% of patients with acute renal colic will have a stone in the distal 4 cm of the ureter; attention should be directed to that region when examining plain radiographs and abdominal ultrasonographic studies. Spiral CT is frequently the first-line tool in evaluating flank pain given its increased sensitivity and specificity over other tests. CT scans should be obtained in the prone position to help differentiate distal ureterovesicular stones from those that have already passed into the urinary bladder. Repeated CT scans should be avoided due to the substantial radiation exposure to these patients with recurrent stones. Stone density can be estimated with Hounsfield units (HU) on CT scans to help determine stone type. Stones with low HU (less than 450) are typically composed of uric acid, while those with high HU (greater than 1200) are typically composed of calcium oxalate monohydrate. All stones whether radiopaque or radiolucent on plain abdominal radiographs will be visible on noncontrast CT except the rare calculi due to protease inhibitors (classically indinavir).

Medical Treatment & Prevention

To reduce the recurrence rate of urinary stones, one must attempt to achieve a stone-free status. Small stone fragments may serve as a nidus for future stone development. Metabolic evaluation often identifies a modifiable risk factor that can reduce stone recurrence rates. If no medical treatment is provided after surgical stone removal, stones will generally recur in 50% of patients within 5 years. Some stone types (eg, uric acid, cystine) are more prone to rapid recurrence than others. Of greatest importance in reducing stone recurrence is an increased fluid intake. Absolute volumes are not established, but increasing fluid intake to ensure a voided volume of 1.5–2.0 L/day is recommended (normal average voided volume is 1.6 L/day). Patients are encouraged to ingest fluids during meals, 2 hours after each meal (when the body is most dehydrated), and prior to going to sleep in the

evening—enough to awaken the patient to void—and to ingest additional fluids during the night. Increasing fluids only during daylight hours may not dilute a supersaturated urine overnight and thus initiate a new stone.

A. Diet

Sodium intake should be restricted to keep urinary sodium levels less than 150 mEq/day. Increased sodium intake will increase renal sodium and calcium excretion, increase urinary monosodium urates (that can act as a nidus for stone growth), increase the relative saturation of calcium phosphate, and decrease urinary citrate excretion. All of these factors encourage stone growth. Animal protein intake should be spread out through the day and not consumed during any individual meal and is best limited to 1 g/kg/day. An increased protein load during an individual meal can also increase calcium, oxalate, and uric acid excretion and decrease urinary citrate excretion.

Excessive intake of oxalate and purines can increase the incidence of stones in predisposed individuals. Dietary calcium or calcium supplements should not be routinely decreased. In fact, decreased calcium consumption has been found to increase stone recurrence. Only type II absorptive hypercalciuric patients (see below and Table 23–3) benefit from a low-calcium diet.

B. Calcium Nephrolithiasis

1. Hypercalciuric — Hypercalciuric calcium nephrolithiasis (greater than 250 mg/24 h; greater than 4 mg/kg/24 h) can be caused by absorptive, resorptive, and renal disorders.

Absorptive hypercalciuria is secondary to increased absorption of calcium at the level of the small bowel, predominantly in the jejunum, and can be further subdivided into types I, II, and III. Type I absorptive hypercalciuria is independent of calcium intake. There is increased urinary calcium on a regular or even a calcium-restricted diet. Thiazide diuretics decrease renal calcium and result in increased bone density of approximately 1% per year. Thiazides have limited long-term utility (less than 5 years) since they may lose their hypocalciuric effect with continued therapy. Decreasing bowel absorption of calcium with a chelating agent, such as cellulose phosphate (10–15 g in three divided doses), is another treatment modality. It binds to the calcium and impedes small bowel absorption due to its increased bulk. Cellulose phosphate does not change the intestinal transport mechanism. It should be given with meals so it will be available to bind to the dietary calcium. Taking this chelating agent prior to bedtime is ineffective. Postmenopausal women should be treated with caution. Inappropriate use may result in a negative calcium balance and a secondary parathyroid stimulation and consequent bone reabsorption. However, there is generally no enhanced decline in bone density with long-term use. Long-term use without follow-up metabolic surveillance may result in hypomagnesuria and secondary hyperoxaluria and recurrent calculi. Routine follow-up every 6–8 months will help encourage medical compliance and permit adjustments in medical therapy based on repeat metabolic studies.

Type II absorptive hypercalciuria is diet-dependent and fortunately rare. Decreasing calcium intake by 50% (approximately 400 mg/day) will decrease the hypercalciuria to normal values (150–200 mg/24 h). There is no specific medical therapy.

Type III absorptive hypercalciuria is secondary to a renal phosphate leak. This results in increased vitamin D synthesis and secondarily increased small bowel absorption of calcium. This can be readily reversed by orthophosphates (250 mg orally three to four times per day), presently available without need for a prescription. Orthophosphates do not change intestinal absorption but rather inhibit vitamin D synthesis.

Resorptive hypercalciuria is secondary to hyperparathyroidism. Hypercalcemia, hypophosphatemia, hypercalciuria, and an elevated serum PTH value are found. Appropriate surgical resection of the parathyroid adenoma cures the disease, although recurrent urinary stones can still occur in 10% of patients after parathyroidectomy. Medical management invariably fails.

Renal hypercalciuria occurs when the renal tubules are unable to efficiently reabsorb filtered calcium, and hypercalciuria results. Spilling calcium in the urine results in secondary hyperparathyroidism. Serum calcium typically is normal. Thiazides are an effective long-term therapy in patients with this disorder.

2. Hyperuricosuric — Hyperuricosuric calcium nephrolithiasis is secondary to dietary purine excess or endogenous uric acid metabolic defects. Most cases (85%) can be treated with purine dietary restrictions; those that are not reversed with dietary modification are successfully treated with allopurinol. In contrast to uric acid nephrolithiasis, patients with hyperuricosuric calcium stones typically maintain a urinary pH > 5.5. Monosodium urates absorb and adsorb inhibitors and promote heterogeneous nucleation. Hyperuricosuric calcium nephrolithiasis is initiated with epitaxy, or heterogeneous nucleation. In such situations, similar crystal structures (ie, uric acid and calcium oxalate) can grow together with the aid of a protein matrix infrastructure.

3. Hyperoxaluric — Hyperoxaluric calcium nephrolithiasis (greater than 40 mg oxalate/24h urine) is usually due to primary intestinal disorders. Patients often have a history of chronic diarrhea frequently associated with inflammatory bowel disease. In these situations, increased bowel fat or bile (or both) combine with intraluminal calcium to form a soap-like product. Calcium is therefore unavailable to bind to oxalate in the gut, which is then freely and rapidly absorbed. A small increase in oxalate absorption will significantly increase stone formation. If the diarrhea or steatorrhea cannot be effectively curtailed, oral calcium should be taken with meals, either by ingesting milk products or taking calcium carbonate supplements (250–500 mg). This helps to bind dietary oxalate in the gut and oxalate movement into the kidneys. Excess ascorbic acid (greater than 2 g/day) will substantially increase urinary oxalate levels. Rare enzymatic liver defects can lead to primary hyperoxaluria that is routinely fatal without a combined liver and kidney transplantation.

4. Hypocitraturic — Hypocitraturic calcium nephrolithiasis may be secondary to chronic diarrhea, type I (distal) renal tubular acidosis, chronic

hydrochlorothiazide treatment, or in any condition that results in a metabolic acidosis. The metabolic acidosis enhances citrate transport into the proximal tubular cells where it is consumed by the citric acid cycle in their mitochondria, resulting in hypocitraturia (less than 450 mg/24h). Hypocitraturia is frequently associated with calcium stone formation. Urinary citrate binds to calcium in solution, thereby decreasing available calcium for precipitation and subsequent stone formation. Potassium citrate supplements are usually effective treatment in these situations. Urinary citrate is decreased in acidosis and is increased during alkalosis. The potassium will supplement the frequently associated hypokalemic states, and citrate will help correct the acidosis. A typical dose is 60 mEq total daily intake, divided either into three times daily as tablets or twice daily as the crystal formulations dissolved in water (it is also available as a solution). Alternatively, oral lemonade has been shown to increase urinary citrate by about 150 mg/24h.

C. Uric Acid Calculi

The average normal urinary pH is 5.8–5.9. Urinary pH is consistently less than 5.5 in persons who form uric acid stones. Increasing the urinary pH to > 6.2 dramatically increases uric acid solubility, can effectively dissolve large calculi at a rate of 1 cm per month, and effectively prevents future uric acid stone formation. Urinary alkalinization with potassium citrate or an equivalent agent is the key to stone dissolution and prophylaxis. The goal is a urinary pH > 6.2 and < 6.5 (to avoid calcium phosphate precipitation). Other precipitating factors include hyperuricemia, myeloproliferative disorders, malignancy with increased uric acid production, abrupt and dramatic weight loss, and uricosuric medications. If hyperuricemia is present, allopurinol (300 mg/day orally) may be given. Although pure uric acid stones are relatively radiolucent, most have some calcium components and can be visualized on plain abdominal radiographs.

D. Struvite Calculi

Struvite stones are radiodense magnesium-ammoniumphosphate stones. They are most common in women with recurrent urinary tract infections with urease-producing organisms, including Proteus, Pseudomonas, Providencia and, less commonly, Klebsiella, Staphylococcus, and Mycoplasma (but not E coli). They rarely present as ureteral stones with colic without prior upper tract endourologic intervention. Frequently, a struvite stone is discovered as a large staghorn calculus forming a cast of the renal collecting system. Urinary pH is high, routinely above 7.2. Struvite stones are relatively soft and amenable to percutaneous removal. Appropriate perioperative antibiotics are required. They can recur rapidly, and efforts should be taken to render the patient stone-free. Acetohydroxamic acid is an effective urease inhibitor that can dissolve and prevent struvite stones, but it is poorly tolerated by most patients because of gastrointestinal side effects.

E. Cystine Calculi

Cystine stones are a result of abnormal excretion of cystine. These stones are particularly difficult to manage medically. Prevention is centered around marked

increased fluid intake during the day and evening to achieve a urinary volume of 3–4 L/day, urinary alkalinization with a urinary pH > 7.0 (monitored with Nitrazine pH paper), and disulfide inhibitors such as tiopronin (alpha-mercaptoproprionylglycine) or penicillamine. There are no known Surgical Treatment In the acute setting, forced intravenous fluids will not push stones down the ureter. Forced diuresis can be counterproductive and exacerbate the pain; instead, a euvolemic state should be achieved. Signs of infection, including associated fever, tachycardia, or elevated white blood cell count may indicate a urinary tract infection behind the obstructing stone. Any obstructing stone with associated infection is a medical emergency requiring prompt drainage by a ureteral catheter or a percutaneous nephrostomy tube. Antibiotics alone are inadequate unless the obstruction is drained.inhibitors of cystine calculi.

Surgical Treatment

In the acute setting, forced intravenous fluids will not push stones down the ureter. Forced diuresis can be counterproductive and exacerbate the pain; instead, a euvolemic state should be achieved. Signs of infection, including associated fever, tachycardia, or elevated white blood cell count may indicate a urinary tract infection behind the obstructing stone. Any obstructing stone with associated infection is a medical emergency requiring prompt drainage by a ureteral catheter or a percutaneous nephrostomy tube. Antibiotics alone are inadequate unless the obstruction is drained.

A. Ureteral Stones

Impediment to urine flow by ureteral stones usually occurs at three sites: the ureteropelvic junction, the crossing of the ureter over the iliac artery, or the ureterovesicular junction. Prediction of spontaneous stone passage is difficult. Stones smaller than 5–6 mm in diameter on a plain abdominal radiograph usually pass spontaneously. Medical expulsive therapy with alpha-blockers (such as tamsulosin, 0.4 mg orally once daily) in combination with a nonsteroidal antiinflammatory agent (such as ibuprofen 600 mg orally three times per day with a full stomach), with or without a short course of a low-dose oral corticosteroid (such as prednisone 10 mg orally daily for 3–5 days) dramatically increases the rate of spontaneous stone passage. Medical expulsive therapy with appropriate pain medications is appropriate for the first few weeks. If the stone fails to pass within 4 weeks, the patient has fever, intolerable pain or persistent nausea or vomiting, or the patient must return to work or anticipates travel, then therapeutic intervention is indicated.

Ureteral stones are best managed with ureteroscopic stone extraction or in situ extracorporeal shock wave lithotripsy (SWL). Ureteroscopic stone extraction involves placement of a small endoscope through the urethra and into the ureter. Under direct vision, basket extraction or stone laser fragmentation followed by extraction is performed. Complications during endoscopic retrieval increase if medical expulsive therapy has been attempted for more than 6 weeks.

In situ SWL utilizes an external energy source focused on the stone with the aid of fluoroscopy or ultrasonography. SWL can be performed under anesthesia as

an outpatient procedure and results in a high rate of stone fragmentation. Most stone fragments then pass uneventfully within 2 weeks, but those that have not passed within 6 weeks are unlikely to do so without intervention. Decreased SWL success rates are associated with lower pole and distal stone location, as well as larger stone burden. Women of childbearing age with a stone in the lower ureter are best not treated with SWL because its impact on the ovary is unknown.

Proximal and midureteral stones—those above the inferior margin of the sacroiliac joint—as well as intrarenal stones can be treated with SWL or ureteroscopy. SWL is delivered directly to the stone in situ. Occasionally, stone fragments will obstruct the ureter after SWL. Conservative management will usually result in spontaneous resolution with eventual passage of the stone fragments. In rare instances, ureteroscopic extraction will be required.

B. Renal Calculi

Patients with renal calculi but without pain, urinary tract infection, or obstruction may not warrant surgical treatment. If surveillance is elected, they should be monitored with serial abdominal radiographs or renal ultrasonographic examinations. If calculi are growing or become symptomatic, intervention should be undertaken. Renal calculi smaller than 1.5 cm in diameter are best treated with SWL or ureteroscopic extraction. Calculi located in the inferior calix and of larger diameter are best treated via percutaneous nephrolithotomy. Percutaneous nephrolithotomy is performed by inserting a needle into the appropriate renal calyx and dilating a tract large enough to allow a nephroscope to pass directly into the kidney. In this fashion, larger and more complex renal stones can be inspected, fragmented, and removed. Perioperative antibiotic coverage for any stone procedure should be given, ideally based on preoperative urine culture.

When to Refer

- Evidence of urinary obstruction.
- Urinary stone with associated flank pain.
- Anatomic abnormalities or solitary kidney.
- Concomitant pyelonephritis or recurrent infection.

When to Admit

- Intractable nausea and vomiting or pain.
- Obstructing stone with signs of infection.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as persistent, progressive, and irreversible loss of renal function. The spectrum of CKD includes earlier stages of kidney damage (characterized by proteinuria, electrolyte abnormalities, and elevated serum creatinine) that represent a decrease in the glomerular filtration rate (GFR) and extends to complete loss of kidney function—that is, kidney failure or end-stage renal disease (ESRD). Markers of kidney damage or GFR less than 60 mL/min/1.73 m2 must be present to meet the diagnostic criteria of CKD. In

addition, these must be present and persistent for at least 3 months to differentiate CKD from acute kidney injury. There are six GFR categories, ranging from normal or high (G1, ≥90 mL/min/1.73 m^2) to kidney failure (G5, < 15 mL/ min/1.73 m^2), and three albuminuria categories based on severity. Most of these patients are seen in the outpatient setting, and the focus of their care is on determination of the cause of renal injury, preservation of kidney and cardiovascular function, prevention of the long-term complications of kidney disease, and provision of renal replacement therapy once kidney function deteriorates to the extent that it can no longer sustain an appropriate quality of life. In contrast, most patients with acute kidney injury (AKI) are hospitalized. The focus of their care also starts with accurate determination of the cause of renal failure, but over a period of days to weeks it is important to reverse the kidney failure if possible, replace kidney function if needed, and manage the many potential adverse consequences of AKI.

Because of the widespread use of automated systems for serum chemistry analysis, an elevated serum creatinine concentration is the most common initial manifestation of kidney disease. This test is performed as a screen for renal function abnormalities in most metabolic panels; in most cases, an elevated serum creatinine concentration reflects reduced filtration function of the kidney. After ensuring that intravascular volume is appropriate, the approach to the patient depends on whether renal insufficiency is thought to be acute or chronic. Accordingly, the initial step in evaluating an elevated serum creatinine level is to assess the time course and duration of the changes so as to distinguish AKI from CKD.

A careful history, physical examination, and laboratory evaluation, including imaging studies, are all fundamental to this process. The highest priority is to address acute dehydration, bleeding, and other causes of intravascular volume loss. Evidence of preceding kidney disease may be discovered by searching the records for prior abnormalities of serum creatinine, proteinuria, abnormal urine sediment, or anatomic features such as the presence of multiple cysts in both kidneys. Similarly, a call to the primary care doctor may provide clues to suggest the presence of kidney disease at an earlier time.

Small kidney size, as assessed by ultrasound, can be highly suggestive of CKD. The size of the kidney depends on the height of the patient, but in general, a kidney length on ultrasound images of less than 9 cm in an adult male is considered small. The presence of normal-sized or even large kidneys does not exclude the diagnosis of CKD. In fact, it is common in patients with diabetic nephropathy for kidneys to be 11 or 12 cm long. Radiography of clavicles or hands is not commonly performed but may demonstrate renal osteodystrophy and suggest the presence of CKD. Anemia is common in both AKI and CKD and therefore is not a differentiating feature. Rarely, if the initial evaluation is unrevealing, a kidney biopsy may be required to distinguish AKI from CKD and to define the etiology of injury.

Microscopic Urinalysis

Microscopic urinalysis at initial evaluation and on an ongoing basis can reveal vital information about the health of the kidney. Evaluation should be

performed by centrifugation of at least 12 mL of a freshly voided specimen. Cells, casts, crystals, and other elements can corroborate the diagnosis of the cause of CKD.

Renal Imaging

Bladder ultrasonography is a tool that can be used to assess residual urine volume. The wide availability of this tool allows diagnosis of bladder outlet obstruction without the need to catheterize the patient.

Renal ultrasonography is the most accurate way of determining kidney size. It is commonly performed to detect renal masses, cysts, and evidence of obstruction characterized by dilatation of the pelvicalyceal system and to evaluate the size and shape of the kidneys. The presence of small kidneys (i.e., < 9 cm on both sides) suggests the presence of scarring and therefore CKD. However, kidneys that are larger, typically in the range of 11 to 13 cm, are often seen in conjunction with CKD due to diabetes mellitus, amyloidosis, and multiple myeloma. Therefore, the presence of small kidneys is not needed to make a diagnosis of CKD.

The echogenicity of the kidneys is compared with that of liver parenchyma. Typically, the kidneys are less echogenic than the liver. Increased echogenicity of the kidneys suggests the presence of scarring and therefore CKD. Renal ultrasonography can also easily detect the presence of cysts in the kidneys and therefore is a useful technique to detect polycystic kidney disease. Pulsed Doppler imaging is often used to calculate the resistive index by estimating the systolic and diastolic Doppler velocities in the renal cortex. A resistive index greater than 0.8 suggests that interventional procedures to revascularize the kidney would be unlikely to benefit the patient in terms of improving blood pressure or protecting the long-term decline in kidney function. If the two kidneys differ in size by 1.5 cm, it suggests the presence of renovascular disease in an adult. In children, reflux nephropathy or congenital abnormalities are more common causes.

Computed tomography (CT) of the kidney is often helpful to evaluate complex cysts. In contrast to simple cysts, complex cysts are suspicious for the presence of malignancy, and CT can evaluate them better than ultrasonography. Likewise, CT is important for evaluating renal masses, stones, retroperitoneal conditions (e.g., hemorrhage, tumor, abscess), and renal vein thrombosis. In morbidly obese people, CT is often used to guide kidney biopsy. The use of contrast agents to assess vascular lesions of the kidney may be not be possible if kidney function is compromised due to fear of precipitating AKI. Limiting the volume of the contrast agent and volume repletion before radiocontrast administration may minimize renal injury.

Although *intravenous pyelography* can image the structures in the kidney, contrast CT has taken the place of classic intravenous pyelography in many centers because of the risk of inducing nephrotoxicity in patients with CKD. In contrast, retrograde pyelography is often used by urologists to define the site and nature of obstruction within the ureter and the pelvis. In addition, during the procedure, ureteric stones can be removed with the use of a basket device.

Magnetic resonance imaging (MRI) is useful for imaging of the vasculature and therefore for the diagnosis of renal vein thrombosis and renal artery stenosis.

Gadolinium-based contrast agents are often used for MRI because of their paramagnetic properties. These agents should be avoided if the GFR is less than 30 mL/min/1.73 m2 , because in such patients they have been implicated in causing a disabling and untreatable condition called nephrogenic systemic fibrosis. Two other MRI contrast agents (one containing iron and another containing manganese) may be used in such patients but are approved by the U.S. Food and Drug Administration only for the evaluation of lesions in the liver. MRI cannot be performed in patients who have metallic implanted devices such as pacemakers, artificial joints, or aneurysmal clips

After injection of a small amount of radioactive substance, radionuclide imaging can be performed to assess renal perfusion and function of the kidneys. One advantage of this technique is that it can assess kidney function and perfusion simultaneously for each kidney. It therefore allows diagnosis of renal artery stenosis, especially when it is performed before and after administration of angiotensin-converting enzyme (ACE) inhibitors.

Renal arteriography is the reference standard for the diagnosis of renal artery stenosis. It involves direct injection of a radiocontrast dye into the renal arteries. In patients with CKD, contrast injection can be limited and carbon dioxide can be injected to avoid nephrotoxicity. This technique is also useful for assessing vascular malformations in the kidney and for making a diagnosis of polyarteritis nodosa. In the latter condition, renal arteriography can detect the presence of microaneurysms.

TREATMENT

Prevention of Progression

In addition to treatment of the specific underlying cause of kidney disease, it is important to consider methods to slow the progression of CKD once it is diagnosed. These methods include optimal control of hypertension, diabetes, and other cardiovascular disease risk factors (e.g., tobacco cessation); use of medications that block the RAAS pathway; diet modifications; avoidance of nephrotoxins; and identification of reversible causes of acute kidney injury in the setting of CKD.

Management of Hypertension and Diabetes

Several controlled trials have demonstrated that treatment of hypertension attenuates the rate of progression of kidney disease. The present recommendation is to target blood pressure to lower than 140/90 mm Hg in patients with diabetes or kidney disease. However, the evidence supporting this recommendation in CKD is limited, and there is debate as to whether a higher target may be acceptable. Medications that block the production or effect of angiotensin II further prevent progression of CKD, beyond control of hypertension, in patients with proteinuria. Dihydropyridine calcium channel blockers have not been shown to be as beneficial as ACE inhibitors or ARBs in slowing CKD progression.

For patients with diabetes mellitus, adequate glycemic control also slows progression of CKD. The recommended goal is to maintain glycosylated hemoglobin (hemoglobin A1c) values less than 7%, irrespective of a concurrent

diagnosis of CKD, although this level of glycemic control warrants caution due to hypoglycemic risk. ACE inhibitors and ARBs may be considered, in patients with diabetes and proteinuria who do not have hypertension, to slow CKD progression.

Diet

Dietary protein restriction is advocated to slow progression of CKD. Several meta-analyses have indicated that reduced-protein diets are modestly beneficial to slow CKD progression, but the largest clinical trial, the MDRD study, did not show a significant benefit. The recommended dietary protein intake in advanced CKD is 0.60 g/kg/day with at least 50% of the protein being of high biologic value. The present consensus is that aggressive dietary management in patients with CKD, including proper restriction of sodium, potassium, phosphorus, and protein intake under the supervision of a dietician, may reduce progression of CKD, albeit to a small extent.

Avoidance of Toxic Drug Effects

Many drugs that are excreted by the kidney should be avoided, or their doses should be reduced. Drugs may injure the kidney in many ways, including direct toxicity leading to acute tubular necrosis, induction of interstitial nephritis, and development of urinary crystals that obstruct the kidney. Common classes of medications that injure the kidney include antibiotics, specifically aminoglycosides; nonsteroidal antiinflammatory drugs, including cyclooxygenase 2 (COX2) inhibitors; and antiretroviral medications. Certain over-the-counter herbal medications, including aristolochic acids, can cause CKD. Others, such as St. John’s wort, may interact with kidney transplant medications and should be avoided.

Iodinated radiocontrast agents can cause acute worsening of kidney function, especially in patients with CKD. Iso-osmolar contrast agents are less toxic than high-osmolar agents. Patients who are at high risk for contrast-induced kidney injury should receive adequate hydration, and the volume of the contrast agent should be minimized. The magnetic resonance imaging contrast agent gadolinium has been associated with the severe fibrotic skin condition of nephrogenic systemic fibrosis in patients with advanced CKD.

Reversible Causes of Acute Deterioration in Kidney Function

The rate of decline in GFR for individual patients is generally log-linear over time. Accordingly, a plot of the reciprocal of the plasma creatinine concentration against time usually predicts the rate at which a specific patient will reach ESRD. When such a patient suddenly shows acute worsening of kidney function, the differential diagnosis should be considered and investigated.

Care for the Patient with End-Stage Renal Disease

As CKD progresses to kidney failure, preparation is needed for RRT. Patients with moderate CKD should be referred to a nephrologist for comanagement, including evaluation of risk for CKD progression, estimation of timing until kidney

failure, and education related to RRT. Late referral (< 3 months before ESRD) is associated with a higher risk for death after initiation of RRT.

Renal Replacement Therapies

For those progressing to ESRD, discussions about available RRT options should occur early and should be paired with an assessment of the expectations and values of the patient and other family members. Options include kidney transplantation, dialysis, and medical management without dialysis, sometimes referred to as conservative care. In medically eligible patients, kidney transplantation is encouraged because it allows a better quality of life, increased survival rate, and greater chance for rehabilitation. Kidney transplants may be obtained from deceased or living donors. In the United States in 2011, new kidney transplantations were performed in 15,652 people, although most of these patients (83%) received dialysis before transplantation.

There are two types of dialysis, hemodialysis and peritoneal dialysis. The distribution of patients receiving various modalities differs in other countries. Chronic dialysis is initiated when the patient displays signs of uremia, usually when eGFR is 10 mL/ minute or less and there are no apparent reversible causes of kidney failure. However, chronic dialysis may be started at any time when complications of ESRD (e.g., fluid balance, potassium levels) cannot be controlled medically.

Hemodialysis

Blood is pumped from a vascular access into tubing that leads to a large number of capillary fibers bundled together in a dialyzer. These capillaries are made up of semisynthetic materials that are semipermeable and therefore capable of allowing exchange of small molecules between blood and a dialysate solution, permitting countercurrent exchange. The solution contains sodium chloride, bicarbonate, and varying concentrations of potassium. Diffusion through the membrane allows low-molecular-weight substances such as urea and organic acids to move across according to the concentration gradient. Fluid is removed by ultrafiltration, which is achieved by applying transmembrane hydrostatic pressure across the dialyzer.

In the setting of ESRD, an average patient undergoing intermittent chronic hemodialysis requires 4 hours of dialysis three times a week. Common complications include hypotension and muscle cramping. Avoiding excessive fluid weight gain can minimize these complications.

An arteriovenous fistula (AVF) or arteriovenous graft (AVG) is recommended for permanent vascular access for hemodialysis, rather than an indwelling catheter. Although the goal is for more than 74% of prevalent hemodialysis patients to use an AVF or AVG for dialysis access, many patients continue to use catheters, especially at the time of initiation of chronic hemodialysis. Temporary catheters are placed into the internal jugular, subclavian, or femoral vein, similar to other central venous lines. Permanent catheters have a cuff around the outer wall of the tubing and tunnel under the chest wall skin for

some distance before entering the internal jugular vein. Catheters have a higher rate of infection and a higher risk for mortality compared with AVF or AVG.

Peritoneal Dialysis

In peritoneal dialysis, the peritoneal capillaries act as a semipermeable membrane similar to a hemodialysis dialyzer. This technique has several advantages over hemodialysis: it allows independence from the long time spent in dialysis units; it may not require as stringent dietary restrictions compared with hemodialysis; and it allows more patients to return to full-time employment. In continuous ambulatory peritoneal dialysis, dialysate of 2- to 3-L volumes is instilled through a peritoneal catheter into the peritoneal cavity for varying amounts of time and exchanged four to six times daily. In continuous cyclic peritoneal dialysis, the patient is connected to a machine, referred to as a cycler, that allows inflow of smaller volumes of dialysate with shorter dwell time overnight while the patient sleeps. Modifications to this regimen can be made to fit a patient's lifestyle and still achieve adequate clearance of toxins and removal of fluid. Ultrafiltration is achieved through increasing the dextrose concentration in the dialysate.

Two major drawbacks of peritoneal dialysis are peritonitis and difficulty in achieving adequate clearances in patients with excess body mass. Peritonitis can be treated with intraperitoneal antibiotics. Additionally, a slow deterioration occurs in the permeability of the peritoneal membrane, especially after one or more peritonitis episodes, leading to inadequate dialysis and, ultimately, the need to change the modality of RRT.

Kidney Transplantation

Kidney transplantation is the preferred modality of RRT. The variety of available immunosuppressive drugs, including rapamycin, mycophenylate mofetil, anti–interleukin-2 receptor antibodies, and novel agents such as belatacept have resulted in excellent graft survival.

Types of Kidney Transplants

Kidney transplant donors may be deceased or living and related or unrelated to the patient. The 1-year and 5-year graft survival rates are 91% and 71% with a deceased donor, and 97% and 85%, respectively, with a living donor.

There is an effort to increase living donation because the deceased donor supply is inadequate. The main advantages of a living related donor transplant are less ischemic injury and better histocompatibility matching. However, with procedures to reduce antibodies, including plasmapheresis and pretransplantation immunosuppressive therapy, it is possible to successfully perform kidney transplantations in patients with high levels of antibodies or even ABO blood group incompatibility with the donor.

Immunosuppressant Drug Therapy

Prophylaxis against and treatment of graft rejection are at the heart of the success of kidney transplantation. All protocols for immunosuppression aim to

disrupt the lymphocyte cell cycle, and many include some period of exposure to corticosteroids.

The hepatic cytochrome P-450 system is essential for metabolism of cyclosporine, tacrolimus, and rapamycin. Significant changes in the levels of these drugs may occur when patients start or discontinue taking any of several drugs that can induce or inhibit this system. Therefore, evaluation for drug-drug interactions is critical to prevent toxic or even subtherapeutic effects of either the immunosuppressant drug or the other prescribed therapy.

Cyclosporine exerts its activity by inhibiting immunocompetent lymphocytes in the G0 and G1 phases of the cell cycle. Side effects of cyclosporine include hematologic suppression, hyperkalemia, seizures, exacerbation of gout, dyslipidemia, and gingival hypertrophy. The most significant of these effects is nephrotoxicity, and this is often related to decreased glomerular blood flow. Tacrolimus has a mechanism of action and side-effect profile similar to those of cyclosporine but with the additional problems of hyperglycemia and an increased tendency toward neurotoxicity. Both cyclosporine and tacrolimus can cause calcineurin inhibitor nephrotoxicity, which may contribute to chronic allograft nephropathy and, ultimately, graft loss.

Mycophenolate mofetil (also called mycophenolic acid) specifically inhibits proliferation of T and B lymphocytes by interfering with purine synthesis and thus DNA synthesis. Side effects include anemia and leucopenia as well as gastrointestinal symptoms.

Rapamycin is a macrolide antibiotic produced by the fungus Streptomyces hygroscopicus. Rapamycin binds to the mTOR (mammalian target of rapamycin) receptor, thus blocking the phosphorylation of p70 S6 kinase (RBS6KB1) and the eukaryotic initiation factor 4E–binding protein 1 (EIF4EBP1, also known as phosphorylated heat- and acid-stable protein regulated by insulin 1 [PHAS-1]). This action leads to the dampening of cytokine and growth factor activity on T, B, and nonimmune cells.

The major side effects are thrombocytopenia and dyslipidemia. Because of the persistence of episodes of rejection and graft loss over time, novel immunosuppressive agents continue to be developed. Most recently, *belatacept*, a fusion protein that inhibits T-cell activation by blocking the CD80 and CD86 sites on antigen-presenting cells. Clinical trials have established its efficacy and demonstrated a side effect profile similar to those of existing immunosuppression options, leading to its approval for use in the United States and other regions.

Acute Rejection

T lymphocytes recognize foreign antigens, especially when they are presented in association with class II major histocompatibility complex (MHC) antigens. This prompts lymphocyte activation. Activated cytotoxic lymphocytes invade the tubular interstitial region of the transplanted kidney, with resulting tubulitis. Clinically, acute rejection is detected by graft tenderness, a rise in serum creatinine levels, oliguria, and, in some instances, fever. Acute humoral rejection involves the intrarenal arteries and leads to vasculitis, carrying a poor prognosis.

This type of rejection is often resistant to steroids, necessitating antilymphocyte and possibly plasmapheresis therapy.

Post-transplantation Infection

Infection is second only to cardiovascular disease as the leading cause of mortality in kidney transplant recipients. Prophylaxis therapies are often used immediately after kidney transplantation to prevent infectious diseases that are of particularly high risk, including Pneumocystis jirovecii pneumonia, urinary tract infections, and cytomegalovirus infection. In addition to common community-acquired bacterial and viral infections, kidney transplant recipients are susceptible to numerous viral, fungal, and other opportunistic infections that usually do not cause severe illness in an immunocompetent host.

Post-transplantation Malignant Disease

Immunosuppression increases the risk of developing malignant disease; this is thought to be, in part, the result of impaired immune surveillance. Skin cancer (mostly squamous cell) has the highest incidence of any type of malignancy among transplant recipients. With continuous surveillance and aggressive management, metastasis from skin cancers is rare. Transplant recipients are also at high risk for development of non-Hodgkin's lymphoma and Kaposi's sarcoma. In addition to age-appropriate screening, cancer surveillance should be an essential part of posttransplantation care.

PROGNOSIS

The prognosis of CKD varies depending on the underlying cause, severity at presentation, and response to therapy. Moreover, CKD in general is a significant risk factor for cardiovascular disease and death. Mortality from cardiovascular disease in CKD patients, especially those with stage 3 to stage 5 disease, is 3.5 times that of an age-matched population, accounting for more than 50% of the deaths in ESRD patients. Research to understand the underlying mechanisms and final pathway, as well as those effects specific to patients with unique characteristics, are necessary to advance efforts to reduce related risks and cure kidney disease.

Control questions

1. Anatomy of the urinary system:
2.Physiological features of the kidneys.
3. Causes of renal dysfunction.
4. Subjective methods of studying the kidneys and urinary tract.
5. Objective research methods: review.
6. Objective methods of research: palpation.
7. Objective methods of research - a method of sneezing (a symptom of Pasternatsky).
8. Laboratory methods for the study of kidneys and urinary tract.
9. Instrumental methods for the study of the kidneys.
10. The main symptoms and syndromes in kidney diseases.

11. Etiology, pathogenesis, clinical picture, course of acute pyelonephritis.
12. Etiology, pathogenesis, clinical picture, course of chronic pyelonephritis.
13. Pharmacotherapy of acute pyelonephritis.
14. Pharmacotherapy of chronic pyelonephritis.
15. Etiology, pathogenesis, clinical picture, course of acute glomerulonephritis.
16. Pharmacotherapy of acute glomerulonephritis.
17. Etiology, pathogenesis, clinical picture, progression of chronic glomerulonephritis.
18. Pharmacotherapy of chronic glomerulonephritis.
19. Pharmacotherapy of renal colic.
20. Pharmacotherapy of renal failure.
21. To write prescriptions for the preparations: canephrons, cystone, nitroxoline, furoamag, farbodonin, ciprofloxacin, moxifloxacin, blemarene, monural.

List of practical works

A. Homework.

1. To know the anatomy and physiology of the urinary tract.
2. To study the research methods of the urinary system.
3. To study the basic symtoms and syndromes of diseases of kidneys and urinary tract.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To study the history of the disease (data laboratory-instrumental research, examination consultants, records of the doctor) and a letter of medical appointments.
3. When examining the patient, identify the subjective, physical, laboratory-instrumental signs of diseases of the urinary tract.
4. To write a clinical diagnosis and to make a pharmacotherapy to this patient:
a) the underlying disease; complications of the underlying disease;
b) concomitant diseases.

Control the level of knowledge

1. Fill in the table "Pharmacotherapy of pyelonephritis".

Types of pharmacotherapy	Pharmacological groups of medicines	Drugs, dose, way introduction
1.Ethiological 2.Pathogenetic		

3.Symptomatic 4. Phytotherapy		

2. Fill in the table "Directions of pharmacotherapy of chronic glomerulonephritis".

Types of pharmacotherapy	Pharmacological groups of medicines	Drugs, dose, way introduction
1. Immunosuppression 2.Protizapalnaya therapy 3. Influence on coagulation processes 4. Antimicrobial therapy 5.Symptomatic therapy: - edema - antihypertensiv		

3. Fill in the table "Pharmacotherapy of the renal colic".

Types of pharmacotherapy	Pharmacological groups of medicines	Drugs, dose, way introduction
1.Ethiological 2.Pathogenetic 3.Symptomatic 4. Phytotherapy		

4. Definition of terms in the study of urine analysis. Match the terms.

1. Proteinuria.
2. Microhematuria.
3. Macro-hematuria.
4. Glucosuria.
5. Ketonuria.
6. Urobilinuria.
7. Leukocyturia.

A. The appearance of erythrocytes in urine revealed by macroscopic examination.

A. Increase in the number of leukocytes in the urine.
B. Isolation of urobillinoids with urine in large numbers.

G. Appearance of protein in urine.
D. The appearance of erythrocytes in the urine, is detected microscopically.
E. Detection in the urine of acetone bodies.
J. Appearance of sugar in urine.

Solution of situational tasks

1. A student B., 18 years old, considers himself healthy, passes medical examination. In 9 years suffered quinine, after which found changes in urine tests. After that, it was not examined. Urine analysis: relative density - 1,024; protein - 0,066 g / l; erythrocytes - 10 - 15 in the field of view; leukocytes - 4 - 6 in the field of view.

Your previous diagnosis. What is the treatment tactic? Type recipes.

2. Patient R., 28 years old, during the dispensary examination revealed proteinuria (3.3 g / l), increased blood pressure to 160/90 mm Hg. After 2 months, the patient suffered an influenza, after which he had swelling on his legs. At examination of blood pressure - 180/100 mm Hg, in urine tests - proteinuria (6.3 - 11.5 g / day), erythrocytes - 25 - 50 in the field of view.

Which disease is most likely to meet this clinical description? What other additional survey methods should I use? Tactics of therapy.

3. A man 25 years sick acutely a few days ago: the body temperature increased to 39^0C, there was general weakness, pain in the lumbar and at the time of urination. In the general analysis of urine - pyuria, bacteriuria (E. coli).

Your previous diagnosis. Directions of pharmacotherapy.

4. A man, 47 years old, entered the nephrology department with complaints of general weakness, fatigue, drowsiness, dizziness, apathy, increased blood pressure (180/100 mm Hg), itching of the skin, lack of appetite, diarrhea, nasal bleeding In blood tests: azotemia, increased urea, creatinine.

Which disease, most likely, corresponds to the description of the clinical picture? Your recommendations on the tactics of examination and treatment of this patient.

5. Patient A., 17 years old, during the medical commission in the urine revealed the following changes: protein - 6.6 g / l, red blood cells - 30 - 40 in the field of view. There are no complaints, no edema, changes from the internal organs were not detected. In childhood often suffered sore throats. In repeated urine tests proteinuria and hematuria persist.

Which disease most likely corresponds to the above described clinical picture? Your recommendations on the tactics of further examination and treatment of this patient? Write recipes for the proposed medicines.

Test tasks

1. Name the basic principle of treating pyelonephritis:
1. Stimulation of the immune system.
2. Anti-inflammatory therapy.
3. Antibacterial therapy.
4. Diuretic therapy.
5. Antihypertensive therapy.

2. Name the basic principle of treatment of chronic nasal congestion:
1. Immunosuppression.
2. Anti-inflammatory therapy.
3. Antibacterial therapy.
4. Antihypertensive therapy.
5. Antianginal therapy.

3. In the treatment of acute pyelonephritis, the following groups of drugs are shown:
1.Spazmolitiki myotropic action.
2.Glucocorticoids.
3.Pohodnye nalidixic acid.
4.Nontracts of prolonged action.
5. Beta-adrenoblockers.

4. In the treatment of chronic GH shows the following groups of drugs:
1. Glucocorticoids.
2.Antibiotics of a wide spectrum of action.
3.Phadnoj nalidixic acid.
4.Nitrofurans
5.Sulphanilamides.

5. The most shown group of lesions for the treatment of hypertension with AR:
1. Dopamine receptor antagonists.
2.ACE inhibitors.
3.Serece glycosides.
4.Spamoliths of myotropic action.
5.Ganglioblokatory.

6. In the pharmacotherapy of chronic GN, the following groups of drugs are not used, except:
1. Glucocorticoids.
2. Anticoagulants.
3.Cystostatics.
4.Antigregants
5.Fluquinolones.

7. In the pharmacotherapy of chronic pyelonephritis the following groups of drugs are used, except:
1.Antibiotics.
2.Sulphanilamides.
3.Nitrofurans
4.Glucocorticoids.
5.Phadnoj nalidixic acid.

8. To treat an attack of the renal colic, it is most advisable to recommend:
1. Diabazole parenterally.
2.No-shpa inside.
3.Eufillin parenterally.
4.Tramadol parenterally.
5.Validol sublingual.

9. The appearance of protein in the urine of a healthy person:
1.It is possible at heavy physical activity.
2.It is possible at a psychoemotional load.
3.Impossible.

10. Symptomatic renal hypertension occurs in the following diseases, except:
1. Chronic glomerulonephritis.
2. Chronic pyelonephritis.
3. Cystitis
4. Nephropathy of pregnant women.
5. Acute glomerulonephritis.

11. With chronic renal failure in the body, the following changes are observed:
1. Packaging nitrogen exchange products.
2. Violation water-electrolyte exchange.
3. Violation of acid-base equilibrium.
4. Anemia.
5. All are listed above.

12. The appointment of glucocorticoids in chronic CNS is an example:
1.Etiotropic therapy.
2.Pathogenetic therapy.
3.Symptomatic therapy.
4.Medicinal therapy.
5.Stimulation therapy.

13. For a chronic GN with a urinary syndrome characterized by:
1. Edema.
2. Magrohematuria.

3. Increase of blood pressure.
4. Hypercholesterolemia.
5.Oliguria.

14. For chronic GN with a nephrotic syndrome characterized by:
1 .Cilindruria.
2. Reduction of blood pressure.
3. Hematuria.
4. Swelling
5. Dizuria

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TOPIC 14. Pharmacotherapy of diffuse diseases of the connective tissue and joints.

Actuality of topic.

Diseases of the connective tissue represent a large section of the pathology faced by doctors of many specialties, as with an independent disease or the consequence of the pathology of other systems. A special group of systemic lesions of connective tissues, bones, joints, muscles are so-called collagen diseases - a group of diseases with an allergic-lesion of connective tissue. Among the diseases of the bone and articular apparatus there are inflammatory arthritis, arthritis, arthrosis, spondylitis, etc., mainly metabolic-disastrophic (arthrosis, spondylosis), tumors, congenital anomalies of development and diffuse diseases of the connective tissue (systemic lupus erythematosus, systemic scleroderma, dermatomyositis).

Purpose of the lesson. The student should know the diagnostic methods of patients with systemic connective tissue diseases: diarrhea - complaints, data of anamnesis; examination, laboratory diagnosis, X-ray examination, biopsy; etiopathogenetic factors of connective tissue diseases, requirements for drugs used for the treatment of connective tissue and joints, as well as to master the general principles of pharmacotherapy for connective tissue diseases.

Some points to note in a rheumatological history

In the assessment of an arthritic presentation, pay particular attention to the distribution of joint involvement (including spine) and the presence of symmetry. Also look for disruption of joint anatomy, limitation of movement (by pain or contracture), joint eff usions and peri-articular involvement. Ask about, and examine for, extra-articular features: skin and nail involvement (include scalp, hairline, umbilicus, genitalia, and natal cleft—psoriasis can easily be missed); eye signs; lungs (eg fibrosis); kidneys; heart; GI (eg mouth ulcers, diarrhoea); GU (eg urethritis, genital ulcers); and CNS.

3 screening questions for musculo-skeletal disease:

1 Are you free of any pain or stiff ness in your joints, muscles or back?

2 Can you dress yourself without too much diffi culty?

3 Can you manage walking up and down stairs?

If yes to all 3, serious infl ammatory muscle/joint disease is unlikely.

Presenting symptoms:

• Pattern of involved joints

• Symmetry (or not)

• Morning stiff ness >30min (eg RA)

• Pain, swelling, loss of function, erythema, warmth

Related diseases:

• Crohn’s/UC (in ank yl osing spondylitis), gonorrhoea, psoriasis

Current and past drugs*:*

• NSAIDS, DMARDS

• Biological agents (eg TNF inhibitors)

Family history:

• Arthritis, psoriasis, autoimmune disease

Social history:

• Age
• Occupation
• Sexual history
• Ethnicity (eg SLE is commoner in AfricanCaribbeans and Asians)
• Ability to function, eg dressing, grooming, writing, walking • Domestic situation, social support, home adaptations
• Smoking (may worsen RA)

Extra-articular features:

• Rashes, photosensitivity (eg SLE)
• Raynaud's (SLE; CREST; polymyositis and dermatomyositis)
• Dry eyes or mouth (Sjögren's)
• Red eyes, iritis (eg AS)
• Diarrhoea/urethritis (Reiter's)
• Nodules or nodes (eg RA; TB; gout)
• Mouth/genital ulcers (eg Behçet's)
• Weight loss (eg malignancy, any systemic infl ammatory disease).

Patterns of presentation of arthritis

Monoarthritis:

Septic arthritis
Crystal arthritis (gout, CPPD)
Osteoarthritis
Trauma, eg haemarthrosis

Oligoarthritis (≤ 5 joints)

Crystal arthritis
Psoriatic arthritis
Reactive arthritis, *eg Yersinia, Salmonella, Campylobacter*
Ankylosing spondylitis
Osteoarthritis

Polyarthritis (> 5 joints involved)

<u>*Symmetrical:*</u>

Rheumatoid arthritis
Osteoarthritis
Viruses (eg hepatitis A, B & C; mumps)
Systemic conditions1 (can be either)

<u>*Asymmetrical:*</u>

Reactive arthritis
Psoriatic arthritis

- Exclude septic arthritis in any acutely inflamed joint, as it can destroy a joint in under 24h. Infl ammation may be less overt if immunocompromised (eg from the many immunosuppressive drugs used in rheumatological

conditions) or if there is underlying joint disease. Joint aspiration is the key investigation, and if you are unable to do it, fi nd someone who can.

Assessing the locomotor system

This aims to screen for rheumatological conditions primarily aff ecting mobility (as a consequence of underlying joint disease). It is based on the **GALS** locomotor screen (**Gait, Arms, Legs, Spine**).

Essence 'Look, feel and move' (active and passive). If a joint looks normal to you, feels normal to the patient, and has full range of movement, it usu ally is normal. Make sure the patient is comfortable, and obtain their consent before examination. The GALS screening examination should be done in light underwear.

Spine: Observe from behind: Is muscle bulk normal (buttocks, shoulders)? Is the spine straight? Are paraspinal muscles symmetrical? Any swellings/deformities? Observe from the side: Is cervical and lumbar lordosis normal? Any kyphosis? "*Touch your toes, please"*: Is lumbar spine fl exion normal, eg Schober's test? Observe from in front: "*Tilt your head"* (without moving the shoulders)—tests lateral neck fl exion. Palpate for typical fibromyalgia tender points.

Arms: "*Try putting your hands behind your head*"—tests functional shoulder movement. "*Arms out straight*"—tests elbow extension and forearm supination/pronation. Examine the hands. Any deformity, wasting, or swellings? Squeeze across 2nd–5th metacarpophalangeal joints. Pain may denote joint or tendon synovitis. "*Put your index fi nger on your thumb*"—tests pincer grip. Assess dexterity, eg fastening a button or picking up a coin.

Legs: Observe legs: Normal quadriceps bulk? Any swelling or deformity? *With patient lying supine:* Any leg length discrepancy? *Internally/externally rotate each hip in fl exion. Passively fl ex knee and hip to the full extent.* Is movement limited? Any crepitus? Find any knee effusion using the patella tap test. If there is fl uid, consider aspirating and testing for crystals or infection. With patient standing: Observe feet: Any deformity? Are arches high or fl at? Any callosities? These may indicate an abnormal gait of some chronicity. *Squeeze across metatarsophalangeal joints:* see above. Also: although not in the GALS system, *palpate the heel and Achilles tendon* to identify plantar fasciitis and Achilles tendonitis often associated with seronegative rheumatological conditions. *Examine the patient's shoes* for signs of uneven wear.

Gait*: Observe walking:* Is the gait smooth? Good arm swing? Stride length OK? Normal heel strike and toe off ? Can they turn quickly?

Range of joint movement is noted in degrees, with anatomical position being the neutral position—eg elbow fl exion 0°–150° normally, but with fi xed fl exion and limited movement, range may be reduced to 30°–90°. A valgus deformity deviates laterally (away from the mid-line, fi g 1); a varus deformity points towards the mid-line.

Some important rheumatological investigations

Joint aspiration is the most important investigation in any monoarthritic

presentation (see also OHCS). Send synovial fl uid for urgent white cell count, Gram stain, polarized light microscopy (for crystals) and culture. The risk of inducing septic arthritis, using sterile precautions, is < 1:10000. Look for blood1 , pus, and crystals (gout or CPPD crystal arthropathy. Do not attempt joint aspiration through infl amed and potentially infected skin (eg through a psoriatic plaque).

Blood tests FBC, ESR, urate, U&E, CRP. Blood culture for septic arthritis. Consider rheumatoid factor, anti-CCP, ANA, other auto antibodies, and HLA B27 — as guided by presentation. Consider causes of reactive arthritis, eg viral serology, urine chlamydia PCR, hepatitis and HIV serology if risk factors are present.

Radiology Look for erosions, calcification, widening or loss of joint space, changes in underlying bone of aff ected joints (eg periarticular osteopenia, sclerotic areas, osteophytes). Irregularity of the lower half of the sacroiliac joints is seen in spondyloarthritis. Ultrasound and MRI are more sensitive in identifying eff usions, synovitis, enthesitis and infection than plain radiographs—discuss further investigations with a radiologist. Do a CXR for RA, vasculitis, TB and sarcoid.

Back pain

Back pain is very common, and often self-limiting, but be alert to sinister causes, ie malignancy, infection or infl ammatory causes. See below for red-fl ag symptoms, and BOX opposite for neurosurgical emergencies.

Red flags for sinister causes of back pain

Aged 55yrs old
Acute onset in elderly people
Constant or progressive pain
Nocturnal pain
Worse pain on being supine
Fever, night sweats, weight loss
History of malignancy
Abdominal mass
Thoracic back pain
Morning stiff ness
Bilateral or alternating leg pain
Neurological disturbance (incl sciatica)
Sphincter disturbance
Current or recent infection
Immunosuppression, eg steroids/HIV
Leg claudication or exercise-related leg weakness/numbness (spinal stenosis).

Examination

1 With the patient standing, gauge the extent and smoothness of lumbar forward/ lateral flexion and extension.

2 ***Clinical tests for sacroiliitis:*** direct pressure, lateral compression, sacroiliac stretch test (pain on adduction of the hip, with the hip and knee flexed).

3 Neurological deficits: test lower limb sensation, power, and deep tendon and plantar refl exes. Digital rectal examination for perianal tone and sensation.

4 Examine for nerve root pain: this is distributed in relevant dermatomes, and is worsened by coughing or bending forward. *Straight leg test* (L4, L5, S1): positive if raising the leg with the knee extended causes pain below the knee, which increases on foot dorsifl exion (Lasègue's sign). It suggests irritation to the sciatic nerve. The main cause is lumbar disc prolapse. *Also femoral stretch test* (L4 and above): pain in front of thigh on lifting the hip into extension with the patient lying face downwards and the knee fl exed.

5 Signs of generalized disease—eg malignancy. Examine other systems (eg abdomen) as pain may be referred.

Causes Age determines the most likely causes:

15–30yrs: Prolapsed disc, trauma, fractures, ankylosing spondylitis (AS), spondylolisthesis (a forward shift of one vertebra over another, which is congenital or due to trauma), pregnancy.

30–50yrs: Degenerative spinal disease, prolapsed disc, malignancy (primary or secondary from lung, breast, prostate, thyroid or kidney ca).

>50yrs: Degenerative, osteoporotic vertebral collapse, Paget's, malignancy, myeloma, spinal stenosis.

Rarer: Cauda equina tumours, psoas abscess, spinal infection (eg discitis, usually staphylococcal but also Proteus, E. coli, S. typhi and TB—there are often no systemic signs).

Investigations Arrange relevant tests if you suspect a specifi ccause, or ifred flag symptoms: FBC, ESR and CRP (myeloma, infection, tumour), U&E, ALP (Paget's), serum/urine electrophoresis (myeloma), PSA. X-rays can exclude bony abnormality but are generally not indicated. MRI is the image of choice and can detect disc prolapse, cord compression, cancer, infection or infl ammation (eg sacroiliitis).

Management

Urgent neurosurgical referral if any neurological defi cit. Keep the diagnosis under review. For non-specific back pain, focus on education and self-management. Advise patients to continue with normal activites and be active. Manage pain to allow this—regular paracetamol ± NSAIDS ± codeine. Consider low dose amitriptyline if these fail (do not use SSRIS for treating pain). Offer physiotherapy, acupuncture or an exercise programme if not improving. Address psychosocial issues, which may predispose to developing chronic pain and disability. Surgical options may be considered in selected patients with intractable symptoms who fail to respond to other measures.

Osteoarthritis

Osteoarthritis (OA) is the commonest joint condition, onset typically >50yrs.

It is usually primary (generalized), but may be secondary to joint disease or other conditions (eg haemochromatosis, obesity, occupational).

Signs and symptoms Localized disease (usually knee or hip): pain on movement and crepitus, worse at end of day; background pain at rest; joint gelling—stiff ness after rest up to ~30min; joint instability. Generalized disease (primary OA): with Heb erden's nodes ('nodal OA', seen mainly in post-menopausal), commonly aff ected joints are the DIP joints, thumb carpo-metacarpal joints and the knees. There may be joint tenderness, derangement and bony swelling (Heberden's nodes at DIP, Bouchard's nodes at PIP), range of movement and mild synovitis. Assess eff ect of symptoms on occupation, family duties, hobbies and lifestyle expectations.

Tests Plain radiographs show: Loss of joint space, Osteophytes, Subarticular sclerosis and Subchondral cysts. CRP may be slightly elevated.

Management *Core treatments*: Exercise to improve local muscle strength and general aerobic fi tness (irrespective of age, severity or comorbidity). Weight loss if overweight. *Analgesia*: Regular paracetamol ± topical NSAIDS. If ineff ective use codeine or short-term oral NSAID (+PPI). Topical capsaicin (derived from chillies) may help. Intra-articular steroid injections temporarily relieve pain in severe sym ptoms. Intra-articular hyaluronic acid injections (viscosupplementation) are as eff ective as NSAIDS or steroid injection, but are much more expensive. Glucosamine and chondroitin products are not recommended. *Non-pharmacological*: Use a multidisciplinary approach, including physiotherapists and occupational therapists. Try heat or cold packs at the site of pain, walking aids, stretching/manipulation or TENS. *Surgery*: Joint replacement (hips, or knees) is the best way to deal with severe OA that has a substantial impact on quality of life.

Rheumatoid arthritis (RA)

RA is a chronic systemic infl ammatory disease, characterized by a symmetrical, deforming, peripheral polyarthritis. *Epidemiology:* Prevalence is ~1% (in smokers). Peak onset: 5th–6th decade. HLA DR4/DR1 linked (associated with severity).

Presentation *Typically:* symmetrical swollen, painful, and stiff small joints of hands and feet, worse in the morning. This can fl uctuate and larger joints may become involved. *Less common presentations*:

•Sudden onset, widespread arthritis;

•Recurring mono/polyarthritis of various joints (*palindromic RA*);

•Persistent monoarthritis (often knee, shoulder or hip);

•Systemic illness with extra-articular symptoms, eg fa tigue, fever, weight loss, pericarditis and pleurisy, but initially few joint problems;

•Polymyalgic onset—vague limb girdle aches;

•Recurrent soft tissue problems (eg frozen shoulder, carpal tunnel syndrome, de Quervain's tenosynovitis).

Signs *Early* (infl ammation, no joint damage): swollen MCP, PIP, wrist, or MTP joints (often symmetrical). Look for tenosynovitis or bursitis. Later (joint

damage, deformity): ulnar deviation of the fi ngers and dorsal wrist subluxation. Boutonnière and swan-neck deformities of fi ngers or Z-deformity of thumbs occur. Hand extensor tendons may rupture. Foot changes are similar. Larger joints can be involved. Atlanto-axial joint subluxation may threaten the spinal cord (rare).

Extra-articular Nodules—elbows & lungs; lymphadenopathy; vasculitis; fibrosing alveolitis, obliterative bronchiolitis; pleural & pericardial effusion; Raynaud's; carpal tunnel syndrome; peripheral neuropathy; splenomegaly (seen in 5%; only 1% have Felty's syndrome: RA + splenomegaly + neutropenia); episcleritis, scleritis, scleromalacia, keratoconjunctivitis sicca; osteoporosis; amyloidosis.

Investigations Rheumatoid factor (RhF) is positive in ~70%. A high titre is associated with severe disease, erosions and extra-articular disease. Anticyclic citrullinated peptide antibodies (ACPA/anti-CCP) are highly specific (~98%) for RA. There is often anaemia of chronic disease. Inflammation causes platelets, ESR, CRP.

X-rays show soft tissue swelling, juxta-articular osteopenia and joint space. Later there may be bony erosions, subluxation or complete carpal destruction. Ultrasound and MRI can identify synovitis more accurately, and have greater sensitivity in detecting bone erosions than conventional X-rays.

Management Refer early to a rheumatologist (before irreversible destruction).

• Disease activity is measured using the DAS28. 2 Aim to reduce score to <3.

• Early use of DMARDS and biological agents improves long-term outcomes.

• Steroids rapidly reduce symptoms and infl ammation. Avoid starting unless appropriately experienced. They are useful for treating acute exacerbations ('flares'), eg IM depot methylprednisolone 80–120mg. Intra-articular steroids have a rapid but short-term effect. Oral steroids (eg prednisolone 7.5mg/d) may control difficult symptoms, but side-effects preclude routine long-term use.

• NSAIDS are good for symptom relief, but have no effect on disease progression. Paracetamol and weak opiates are rarely eff ective.

• Off er specialist physio- and occupational therapy, eg for aids and splints.

• Surgery may relieve pain, improve function and prevent deformity.

• There is risk of cardiovascular and cerebrovascular disease, as atherosclerosis is accelerated in RA. Manage risk factors. Smoking also symptoms of RA.

Patients want to live as unencumbered by the disease as possible. Depressive symptoms and pain are better predictors of quality of life than disease markers or radiological damage. Assess impact on relationships, work and hobbies. Psychological interventions (eg relaxation, cognitive coping skills) may help. There is little evidence for the long-term efficacy of complementary therapies but don't predjudice patients who may decide to try.

Crystal arthropathies (gout)

Gout typically presents with an acute monoarthropathy with severe joint inflammation. >50% occur at the metatarsophalangeal joint of the big toe (podagra). Other common joints are the ankle, foot, small joints of the hand, wrist, elbow or

knee. It can be polyarticular. It is caused by deposition of monosodium urate crystals in and near joints, precipitated, for example, by trauma, surgery, starvation, infection or diuretics. It is associated with raised plasma urate. In the long term, urate deposits (= tophi, eg in pinna, tendons, joints) and renal disease (stones, interstitial nephritis) may occur. Prevalence: ~1%.

Differential diagnoses Exclude septic arthritis in any acute monoarthropathy. Then consider haemarthrosis, CPPD (below) and palindromic RA.

Causes Hereditary, dietary purines, alcohol excess, diuretics, leukaemia, cytotoxics (tumour lysis). *Associations:* Cardiovascular disease, hypertension, diabetes mellitus and chronic renal failure. Gout is a marker for these, therefore seek out and treat if needed.

Investigations Polarized light microscopy of synovial fl uid shows negatively birefringent urate crystals. Serum urate is usually raised but may be normal. Radiographs show only soft-tissue swelling in the early stages. Later, well-defi ned 'punched out' erosions are seen in juxta-articular bone. There is no sclerotic reaction, and joint spaces are preserved until late.

Treatment of acute gout Use high-dose NSAID or coxib (eg *etoricoxib* 120mg/24h PO). Symptoms should subside in 3–5d. If CI (eg peptic ulcer; heart failure; anticoagulation), *colchicine* (0.5mg/6–12h PO) is effective but slower to work (note new BNF guidelines of max 6mg per course). NB: in renal impairment, NSAIDS and colchicine are problematic. Steroids (oral, IM or intra-articular) may also be used. Rest and elevate the aff ected joint. Ice packs and 'bed cages' can be effective.

Prevention Lose weight. Avoid prolonged fasts, alcohol excess, purine-rich meats and low-dose aspirin (serum urate). *Prophylaxis:* Start if >1 attack in 12 months, tophi or renal stones. The aim is to attacks and prevent damage caused by crystal deposition. Use allopurinol and titrate from 100mg/24h, increasing every 2 weeks until plasma urate < 0.3mmol/L (max 300mg/8h). SE: rash, fever, WCC. Introduction of *allopurinol* may trigger an attack so wait until 3 weeks after an acute episode, and cover with regular NSAID (for up to 6 weeks) or colchicine (0.5mg/12h PO for up to 6 months). Avoid stopping allopurinol in acute attacks once established on treatment. Febuxostat (80mg/24h) is an alternative if allopurinol is CI or not tolerated. It uric acid by inhibiting xanthine oxidase and is more eff ective at reducing serum urate than allopurinol (although the number of acute attacks is the same). Uricosuric drugs urate excretion. They are rarely used in patients who under-excrete uric acid or who are resistant to other treatment (eg sulfinpyrazine).

Spondyloarthritides

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the spine and sacroiliac joints, of unknown aetiology. *Prevalence*: 0.25–1%. Men present earlier: at 16yrs old, and ~2:1 at 30yrs old. ~90% are HLA B27 +ve.

Symptoms and signs: The typical patient is a man < 30 old with gradual onset of low back pain, worse at night, with spinal morning stiff ness relieved by

exercise. Pain radi ates from sacroiliac joints to hips/buttocks, and usually improves towards the end of the day. There is progressive loss of spinal movement (all directions)—hence thoracic expansion. The disease course is variable; a few progress to kyphosis, neck hyperextension, and spino-cranial ankylosis. Other features include enthesitis, especially Achilles tendonitis, plantar fasciitis, at the tibial and ischial tuberosities, and at the iliac crests. Anterior mechanical chest pain due to costochondritis and fatigue may feature. Acute iritis occurs in ~⅓ of patients and may lead to blindness if untreated (but may also have occurred many years before, so enquire directly). AS is also associated with osteoporosis (up to 60%), aortic valve incompetence (<3%) and pulmonary apical fibrosis.

Tests: Diagnosis is clinical, supported by imaging (MRI is most sensitive and better at detecting early disease). Sacroiliitis is the earliest X-ray feature, but may appear late: look for irregularities, erosions, or sclerosis aff ecting the lower half of the sacroiliac joints, especially the iliac side. Vertebral syndesmophytes are characteristic (often T11–L1 initially): bony proliferations due to enthesitis between ligaments and vertebrae. These fuse with the vertebral body above, causing ankylosis. In later stages, calcifi cation of ligaments with ankylosis lead to a 'bamboo spine' appearance. Also: FBC (normocytic anaemia), ESR, CRP, HLA B27+ve (not diagnostic).

Management: Exercise, not rest, for backache, including intense exercise regimens to maintain posture and mobility—ideally with a physiotherapist specializing in AS. NSAIDS (eg ibuprofen or naproxen, if no CI) usually relieve symptoms within 48h, and they may slow radiographic progression. TNF blockers etanercept, adalimumab and golimumab are indicated in severe active AS if NSAIDS fail. Local steroid injections provide temporary relief. Surgery includes hip replacement to improve pain and mobility if the hips are involved, and rarely spinal osteotomy. There is increased risk of osteoporotic spinal fractures (consider bisphosphonates).

Prognosis: There is not always a clear relationship between the activity of arthritis and severity of underlying infl ammation (as for all the spondyloarthritides). Prognosis is worse if ESR >30; onset <16yrs; early hip involvement or poor response to NSAIDs.

Enteric arthropathy

Associations: Inflammatory bowel disease, GI bypass, coeliac and Whipple's disease. Arthropathy often improves with the treatment of bowel symptoms (beware NSAIDs). Use DMARDs for resistant cases.

Psoriatic arthritis (OHCS)

Occurs in 10–40% with psoriasis and can present before skin changes. Patterns are:

•Symmetrical polyarthritis (like RA);

•DIP joints;

•Asymmetrical oligoarthritis;
•Spinal (similar to AS);
•Psoriatic arthritis mutilans (rare, ~3%, severe deformity).
Radiology: Erosive changes, with 'pencil-in-cup' deformity in severe cases. Associated with nail changes in 80%, synovitis (dactylitis), acneiform rashes and palmo-plantar pustulosis. *Management*: NSAIDs, sulfasalazine, methotrexate and ciclosporin. Anti-TNF agents are also eff ective.

Reactive arthritis

A sterile arthritis, typically aff ecting the lower limb ~1–4 weeks after urethritis (*Chlamydia or Ureaplasma* sp.), or dysentery (*Campylobacter, Salmonella, Shigella, or Yersinia* sp.). It may be chronic or relapsing. *Also there may be* iritis, keratoderma blenorrhagica (brown, raised plaques on soles and palms), circinate balanitis (painless penile ulceration secondary to *Chlamydia*), mouth ulcers and enthesitis. *Reiter's syndrome* is a triad of urethritis, arthritis, and conjunctivitis. *Tests*: ESR & CRP. Culture stool if diarrhoea. Infectious serology. Sexual health review. X-ray may show enthesitis with periosteal reaction. *Management*: There is no specifi c cure. Splint aff ected joints acutely; treat with NSAIDs or local steroid injections. Consider sulfasalazine or methotrexate if symptoms >6 months. Treating the original infection may make little diff erence to the arthritis.

Prescribing NSAIDs: dialogue with patients

Around 60% of patients will respond to any NSAID, but there is considerable variation in response and tolerance—if one isn't eff ective, try another. If taken regularly, NSAIDs have both analgesic and anti-infl ammatory eff ect, but the full anti-infl ammatory eff ect may take up to 3 weeks. NSAIDs cause ~1000 deaths/yr in the UK 12 so only use after risk : benefit analysis individualized for each patient, including indication, dose, proposed duration of use, and comorbidity. Follow local recommendations and national guidelines where available.

NSAIDSES The main serious side-eff ects are GI bleeding (gastrointestinal damage may occur without dyspeptic symptoms) and renal impairment. NSAIDs are contraindicated in severe heart failure. SES increase with: prolonged use, age, polypharmacy, history of peptic ulcers and renal impairment (review before and after starting therapy). Avoid giving NSAIDs to patients on aspirin and do not use in active GI ulceration. Ibuprofen has the lowest GI risk.

Inform your patients Many patients prescribed NSAIDs do not need them all the time, so say "Take the lowest possible dose for the shortest possible time". Bleeding is more common in those who know less about their drugs. Explain:

• Drugs are to relieve symptoms: on good days, don't take any. In rheumatoid arthritis, cod liver oil (eg 10g/d) reduces reliance on NSAIDs by 30%.

• Abdominal pain may be a sign of impending GI problems: stop the tablets, and come back for more advice if symptoms continue.

• Report black stools ± faints at once.

• Don’t supplement prescribed NSAIDs with ones bought over the counter (eg ibuprofen): mixing NSAIDs can increase risks 20-fold.

• Smoking and alcohol increase NSAID risk.

Cardiovascular side-eff ects: Consider cardiovascular risk when prescribing any NSAID—all are associated with a small increased risk of MI and stroke (independent of cardiovascular risk factor or duration of use). Specifi cally implicated are celecoxib (any dose), diclofenac (>150mg/24h) and ibuprofen (>1200mg/24h). Naproxen appears to be least harmful.

When should COX-2 selective NSAIDs be tried? Not often—COX-2 selective NSAIDs are associated with a lower risk of serious upper GI SES but are not as safe as we had hoped. Commonly used COX-2 drugs include celecoxib and etoricoxib. Meta-analyses of cardiovascular risk for celecoxib are inconsistent, but appear similar to other conventional NSAIDs (above); for etoricoxib there is increased risk when compared to naproxen or ibuprofen.13 Perhaps use COX-2 selective NSAIDs only when an NSAID is essential and there is past peptic ulceration (but risk is not eliminated, and bleeds that do occur may be very serious) if an ordinary NSAID with PPI (eg omeprazole) is problematic or > 65yrs old (not on aspirin) or needing high-dose NSAID over a long time. If at very high risk of GI bleed, ideally avoid altogether, or combine a COX-2 (eg celecoxib 200mg/12h; avoid if eGFR < 30) with a PPI.

Autoimmune connective tissue diseases

Included under this heading are SLE, systemic sclerosis, primary Sjögren’s syndrome, idiopathic infl ammatory myopathies (myositis), mixed connective tissue disease, relapsing polychondritis, and Behçet’s disease. They overlap with each other, aff ect many organ systems, and often require immunosuppressive therapies.

Osteoporosis

Osteoporosis, the most common disorder of bone and mineral metabolism, affects about 50% of women and 25% of men older than 50 years. The National Institutes of Health Consensus Development Panel on Osteoporosis Prevention defines osteoporosis as a skeletal disorder characterized by compromised bone strength, predisposing a person to an increased risk of fracture. Bone strength has two main components: bone density and bone quality. Bone density reflects the peak adult bone mass and the amount of bone lost in adulthood. Bone quality is determined by bone architecture, bone geometry, bone turnover, mineralization, and damage accumulation (i.e., microfractures).

DEFINITION AND EPIDEMIOLOGY

In the United States, 2 million osteoporotic fractures occur each year. There are almost 300,000 hip fractures each year, which are associated with a mortality rate of more than 20% during the first year. More than 50% of patients with hip fracture are unable to return to their previous ambulatory state, and about 20% of

them are placed in long-term care facilities. When defined by bone mineral densitometry, 48 million Americans have low bone mass, and 9 million have osteoporosis. Although morbidity is less with vertebral fractures, the 5-year mortality rate is similar to that for hip fractures. Only one third of radiologically diagnosed vertebral fractures receive medical attention.

PATHOLOGY AND RISK FACTORS

Peak bone mass is determined primarily by genetic factors. Men have a higher bone mass than women, and African Americans and Hispanics have a higher bone mass than whites. Other factors that contribute to the development of peak bone mass are the use of gonadal steroids, timing of puberty, calcium intake, exercise, and growth hormone. The causes of bone loss in adults are multifactorial. The pattern of bone loss is different in women than than in men, and bone loss is greater in sites rich in trabecular bone (e.g., spine) than cortical bone (e.g., femoral neck). Women lose significantly more trabecular bone than men. Estrogen deficiency during menopause contributes significantly to bone loss in women, and they may lose 1% to 5% of bone mass per year in the first few years after menopause. Women continue to lose bone mass throughout the remainder of their lives, with another acceleration of bone loss occurring after age 75 years. The mechanism of this accelerated loss in old age is not clear.

Multiple causes of secondary bone loss contribute to osteoporosis and fractures. Medications that commonly cause bone loss include glucocorticoids, antiseizure medications, excess thyroid hormone, heparin, androgen deprivation therapy, aromatase inhibitors, and depo-medroxyprogesterone. Endocrine diseases resulting in female or male hypogonadism also lead to bone loss. Hyperparathyroidism, hyperthyroidism, and hypercortisolism commonly cause bone loss, as can vitamin D deficiency. Gastrointestinal problems can contribute to decreased absorption of calcium and vitamin D. Risk factors for falls (e.g., age, poor vision, previous falls, immobility, orthostatic hypotension, cognitive impairment, vitamin D insufficiency, poor balance, gait problems, weak muscles) also contribute to fractures.

CLINICAL PRESENTATION

Unlike many other chronic diseases with multiple signs and symptoms, osteoporosis is considered a silent disease until fractures occur. Whereas 90% of hip fractures occur after a fall, two thirds of vertebral fractures are silent and occur with minimal stress, such as lifting, sneezing, and bending. An acute vertebral fracture may result in significant back pain that decreases gradually over several weeks with analgesics and physical therapy. Patients with significant vertebral osteoporosis may have height loss, kyphosis, and severe cervical lordosis, also known as a dowager’s hump. Prolonged bisphosphonate use (>5 years) may result in an atypical femoral fracture, which may manifest as unilateral or bilateral thigh pain and result in a femoral shaft fracture with no or minimal trauma.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of osteoporosis is made after an acute clinical vertebral or hip fracture or on assessment of bone mineral density.

Radiography

Radiographs can reveal a vertebral compression fracture. However, low bone mass may not be evident on radiographs until 30% of the mass has been lost. When assessing bone mass, radiographs may be read inappropriately as a result of overpenetration or underpenetration of the film. Radiographs therefore are a poor indicator of osteoporosis (with the exception of vertebral fractures), and the diagnosis is instead often based on bone mineral densitometric results.

Bone Mineral Density and Other
Bone Mass Assessments

In 1994, the World Health Organization (WHO) developed a classification system for osteoporosis and low bone mass based on data from white, postmenopausal women. Osteoporosis is defined as a bone mineral density less than or equal to 2.5 standard deviations (SDs) below young adult peak bone mass (T-score ≤ -2.5 SD). Low bone mass (i.e., osteopenia) is defined as a bone mass measurement between 1.0 and 2.5 SDs below adult peak bone mass (T-score between -1.0 and -2.5 SD). Normal bone mineral density is defined as assessments above 1.0 SD below adult peak bone mass (T-score ≥ -1.0 SD).

The standard for assessing bone mineral density is **dual-energy x-ray absorptiometry** (**DEXA**), which has excellent precision and accuracy. Measurements are made at the hip and spine, and in about 30% of cases, discordance is found between these measurements. Classification should be made only if two or more vertebrae are available for analysis because of the high error rate when a single vertebra is assessed. Classification is based on the lowest value (i.e., total spine, total hip, or femoral neck).

In patients with hyperparathyroidism, in which cortical bone loss is often seen, forearm DEXA using the one-third distal radius site should also be assessed. Forearm assessments may be helpful in older patients who often have falsely elevated bone mineral density measurements at the spine as a result of atypical calcifications from degenerative joint disease, sclerosis, or aortic calcifications or in obese patients whose weight exceeds the table limit.

Bone mineral density can be measured by hip or spine quantitative **computed tomography (QCT)**. However, less normative data are available for hip QCT, vertebral precision is inferior to that of DEXA, and radiation doses are significantly higher than those of DEXA. Single-photon absorptiometry of the forearm and peripheral measures, such as heel ultrasound, have also been used to assess bone mass. However, the WHO classification should be used only with the central DEXA measurements.

The National Osteoporosis Foundation (NOF) recommends obtaining a bone mineral density assessment in all women 65 years old or older and postmenopausal women younger than 65 years with a risk factor. The U.S. Preventive Services Task Force (USPSTF) recommends bone density tests in all women age 65 or older and women between 60 and 64 years of age with a risk factor. The NOF recommends obtaining a bone mineral density value for men 70 years old or older; the USPSTF has not recommended screening in men. Databases are available for white, African American, Asian, and Hispanic men and women. These guidelines from the NOF

and USPSTF for screening patients for osteoporosis are relatively similar for postmenopausal women but differ for older men. At the time of their review, the USPSTF did not feel there was ample evidence to determine screening guidelines for men.

The WHO developed a **fracture risk assessment tool (FRAX)** to predict the 10-year risk for hip or any major osteoporotic fracture for women and men between 40 and 90 years of age. The FRAX for the individual patient incorporates femoral neck T-score, age, gender, height, weight, and specific risk factors, including history of adult fracture, parental hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, alcohol (≥3 drinks per day), and secondary osteoporosis. The fracture risk prediction is specific for race and country and should be used for patients not on therapy.

Bone mineral density determined by DEXA usually can be monitored after 2 years of therapy, depending on the site to be assessed and the type of therapy prescribed. For example, trabecular bone, which has greater surface area and is more metabolically active than cortical bone, is more likely to show improvements with stronger-acting antiresorptive agents. Changes in bone mass with potent antiresorptive therapy are more prominent in the spine compared with other areas. Seeing no changes in forearm bone mineral density over time is common despite good precision. Although the heel has a high percentage of trabecular bone, precision is poor, and monitoring should not be done at this site.

All patients with osteoporosis or low bone mass should have a work-up for secondary causes of bone loss. It should include a serum calcium level (corrected for albumin) to rule out hyperparathyroidism or malnutrition; a 25-hydroxyvitamin D level to assess for vitamin D deficiency or insufficiency; an alkaline phosphatase level to assess for Paget's disease, malignancy, cirrhosis, or vitamin D deficiency; liver and renal function tests to assess for abnormalities; a 24-hour urine calcium and creatinine assay to evaluate for hypercalciuria or malabsorption; a test for sprue in patients with anemia, malabsorption, or hypocalciuria; a thyrotropin level to rule out hyperthyroidism; and serum protein electrophoresis to rule out myeloma in older adults with anemia. Measurement of the parathyroid hormone (PTH) level often is needed to interpret the calcium and vitamin D levels. Total testosterone levels are recommended for men.

A more extensive work-up can be done in severe or unusual cases. A bone biopsy is rarely needed. Markers of bone turnover vary considerably in clinical practice, and these tests usually are reserved for research. However, they may be useful for assessing the rate of bone turnover after prolonged bisphosphonate use or a bisphosphonate holiday

PREVENTION

General preventive measures for all patients include adequate calcium and vitamin D intake, exercise, and fall prevention techniques. The recommended daily allowance of calcium for adults, as reviewed by the Institute of Medicine, is 1200 mg. Calcium intake can be accomplished by dietary consumption, supplementation, or the combination of diet plus supplement. The supplements should be pure calcium carbonate or pure calcium citrate, taken in divided doses of about 500 to

600 mg twice daily. Calcium carbonate should be taken with meals for best absorption, whereas calcium citrate may be taken with or without food. Calcium supplements are available as tablets and in chewable and liquid forms. Foods such as orange juice, cereals, breads, and nutrition bars are calcium fortified. There is no benefit to taking more than 1200 mg per day, and excess intake may increase the risk of kidney stones and cardiovascular disease (although data are controversial).

Vitamin D is important for calcium absorption and bone mineralization. Vitamin D has nonskeletal benefits and has been associated with improvement in muscle strength and prevention of falls. Vitamin D comes from two sources: diet and photosynthesis. Because dietary sources of vitamin D are limited (e.g., fortified milk, yogurt) and patients are often advised to avoid sun exposure for prevention of skin cancer and wrinkles, many studies have documented vitamin D deficiency and insufficiency in older adults. Older patients have a reduced ability to synthesize vitamin D in the skin. Low vitamin D levels can lead to secondary hyperparathyroidism.

Vitamin D can be taken in a multivitamin, in a calcium supplement, or in pure form and is available as cholecalciferol (D3) or ergocalciferol (D2). Based on data from noninstitutionalized patients without osteoporosis, the daily dose recommended by the Institute of Medicine is 600 IU per day for adults up to age 70 and 800 units for those older than 70 years to achieve a level of at least 20 ng/dL (50 nmol/L). However, the NOF suggests 800 to 1000 IU per day. Elderly patients, those with malabsorption, and obese patients may need greater amounts of vitamin D. Older patients with severe vitamin D deficiency may be given 50,000 IU of vitamin D once per week for 3 months to bring serum vitamin D into the normal range. Activated vitamin D is rarely needed and should not be given on a regular basis for postmenopausal osteoporosis.

Weight-bearing exercise is important for maintaining skeletal integrity. Study results are controversial concerning different types and durations of exercise by postmenopausal women and men. However, weight-bearing or resistance training exercises usually are suggested and have been shown to improve bone mass or maintain skeletal integrity. In patients with new vertebral fractures, physical therapy is important for improving posture and increasing the strength of back muscles.

Because 90% of hip fractures and a significant number of vertebral fractures occur during a fall, preventive measures are suggested for frail older patients at risk for falling. Fall-proofing the household includes installing grab bars in the bathroom and hand rails on stairways, avoiding loose throw rugs and cords, ensuring good lighting by the bedside, and moving objects within easy reach in the kitchen. Other fall prevention measures include eliminating medications that cause dizziness or postural hypotension (if possible), assessing the need for assistive devices (e.g., canes, walkers), and ensuring appropriate footwear and good vision. The benefits of hip protectors for hip fracture reduction are disappointing and controversial, and compliance with these products is often poor.

TREATMENT AND PROGNOSIS

The NOF developed treatment guidelines that incorporate a 10-year fracture

risk prediction. The NOF suggests treatment for postmenopausal women and men 50 years old or older.

Patients taking glucocorticoids can fracture despite having normal bone density. The American College of Rheumatology suggests that patients starting glucocorticoids who will be treated for 3 months or longer have a bone density test and start antiresorptive therapy if indicated according to their guidelines.

Bisphosphonates

Bisphosphonates are the mainstay of osteoporosis prevention and treatment. They inhibit the cholesterol synthesis pathway in osteoclasts, causing early apoptosis and inhibiting osteoclast migration and attachment. Unlike other agents, bisphosphonates are incorporated into bone, the half-life is long, and the agent may be recycled.

In the United States, the bisphosphonates alendronate, risedronate, ibandronate, and zoledronic acid have been approved for the prevention and treatment of osteoporosis. Alendronate can increase bone mass by about 8% at the spine and 4% at the hip over 3 years. This increase has been associated with an approximately 50% reduction in spine, hip, and forearm fractures. Alendronate is prescribed at 35 mg once weekly for osteoporosis prevention and 70 mg once weekly for the treatment of osteoporosis. Alendronate has been approved for use in men and patients with glucocorticoid-induced osteoporosis.

Risedronate is approved for the prevention and treatment of osteoporosis at a dose of 35 mg per week or 150 mg per month or as a delayed dose after breakfast of 35 mg per week. Largescale, multicenter studies have shown improvements in bone mass of about 6% to 7% at the spine and 3% at the hip over 3 years. These studies revealed a 50% reduction in vertebral fractures, 40% reduction in nonvertebral fractures, and 40% reduction in hip fractures. Risedronate is approved for the treatment of osteoporosis in men and for the prevention and treatment of patients with glucocorticoid-induced osteoporosis.

Oral ibandronate is approved for the prevention and treatment of postmenopausal osteoporosis. After 3 years of treatment, ibandronate increased bone density by 6.5% at the spine and 3.4% at the hip, and it reduced new vertebral fractures by 62%. No reductions in nonvertebral or hip fractures occurred. Ibandronate is approved at an oral dose of 150 mg monthly and for treatment at an intravenous dose of 3 mg every 3 months.

Zoledronic acid is approved for the treatment of postmenopausal osteoporosis, osteoporosis in men, and steroid-induced bone loss. The 3-year pivotal trial demonstrated increases of 6.9% of bone density at the spine and 6.0% at the hip, and the drug reduced spinal fractures by 70%, nonvertebral fractures by 25%, and hip fractures by 41%. Zoledronic acid is given at a dose of 5 mg intravenously once per year for treatment and 5 mg intravenously every 24 months for prevention.

Because oral bisphosphonates are poorly absorbed, they must be taken first thing in the morning on an empty stomach with a full glass of water. Patients must wait 30 minutes (when taking alendronate and risedronate) to 60 minutes (when taking ibandronate) before eating and must not lie down. A delayed-release form of risedronate can be taken after breakfast.

Potential side effects of bisphosphonates include epigastric distress, heartburn, and esophagitis. Intravenous bisphosphonates have been associated with an influenza-like syndrome after infusion. Bisphosphonates can also cause arthralgias and myalgias. They are contraindicated in patients with renal insufficiency (i.e., estimated glomerular filtration rate of 30 to 35 mL/minute). Osteonecrosis of the jaw is a rare adverse event of abnormal bone growth in the jaw, which is more often associated with high-dose intravenous bisphosphonates in patients with cancer and poor oral hygiene. Atypical femoral shaft fractures have been reported rarely after long-term use (>5 years) of bisphosphonates. These fractures may manifest with a prodrome of unilateral or bilateral thigh pain, and fractures may occur with minimal activity. These fractures are rare after osteoporosis treatment but common in cancer patients receiving frequent high doses intravenously.

Calcitonin Calcitonin is a 32-amino-acid peptide produced by the parafollicular cells of the thyroid gland. The pivotal clinical treatment trial did not show significant changes in bone mineral density after 3 years. However, the 200-IU dose of nasal calcitonin was associated with a 50% reduction in vertebral fractures. No reduction in nonvertebral or hip fractures was found. The U.S. Food and Drug Administration (FDA) advisory panel is reviewing an association with cancer.

Denosumab The receptor activator of nuclear factor-κB (RANK) and its ligand (RANKL) are mediators of osteoclast activity. Compared with placebo, denosumab, an antibody to RANKL, produced a relative increase in bone mineral density at the spine of 9.2% and hip of 6.0% over 3 years, and it reduced fractures by 68% at the spine, 40% at the hip, and 20% at nonvertebral sites. Denosumab is approved for postmenopausal women and men with osteoporosis, for men with prostate cancer on androgen deprivation therapy, and for postmenopausal women with breast cancer on aromatase inhibitors. It is given as a subcutaneous 60-mg injection every 6 months.

Estrogen Agonists-Antagonists Estrogen agonists-antagonists were previously called selective estrogen receptor modulators (SERMs) because they have some estrogen-like and anti–estrogen-like benefits. Raloxifene is approved for the prevention and treatment of osteoporosis. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial found that bone mass was increased by 4% at the spine and 2.5% at the femoral neck over 3 years. This increase was associated with a 50% reduction in vertebral fractures. No reduction in nonvertebral or hip fractures was seen. Treatment was associated with improved lipid status, as shown by decreased total and low-density lipoprotein cholesterol.

Raloxifene is not associated with endometrial hyperplasia, and patients should not have bleeding or spotting. They do not have breast tenderness or swelling. Raloxifene reduces the risk for invasive breast cancer in postmenopausal women with osteoporosis and in women at high risk for invasive breast cancer. Patients have the same small risk of deep vein thrombosis or pulmonary embolus that is found with hormone therapy. Raloxifene does not relieve postmenopausal symptoms and may exacerbate hot flashes. Studies have not found a significant impact on cardiovascular disease. Raloxifene can be given with or without food in a

daily oral dose of 60 mg per day.

Hormone Therapy Investigators of the Women's Health Initiative, a large, randomized, placebo-controlled, multicenter trial evaluating hormone therapy, reported a 36% reduction in hip and vertebral fractures after 5.2 years. In addition to improvements in bone mass, benefits include an improved lipid profile, decreased colon cancer incidence, and decreased menopausal symptoms. However, because of the potential risks of hormone therapy (i.e., cardiovascular events, breast cancer, deep vein thrombosis, pulmonary embolus, and gallbladder problems), it should be used only for prevention or management of menopausal symptoms, and other agents should be used for the treatment of osteoporosis.

Parathyroid Hormone Recombinant human PTH (1-34), or teriparatide, is an osteoanabolic agent that increases spinal bone mineral density by 9.7% and hip bone mineral density by 2.6% in 18 months. It is associated with a 65% reduction in vertebral fractures and a 53% reduction in nonvertebral fractures. Teriparatide is taken for up to 2 years as a subcutaneous, 20-µg daily dose for postmenopausal women and men at high risk for fracture. After therapy, patients benefit from antiresorptive therapy to prevent bone loss. Recombinant human PTH (1-84) is approved for use in Europe.

Alternative Therapies

Medical Therapies

Strontium ranelate is an approved agent for the treatment of osteoporosis in Europe, but it is not FDA approved in the United States. The mechanism of action is not fully understood, but strontium is thought to stimulate osteoblast proliferation and inhibit osteoclast formation. Inhibition of the protease cathepsin K appears to prevent bone resorption with no major impact on bone formation. Another promising osteoanabolic therapeutic target is the inhibition of sclerostin, a potent inhibitor of bone formation, with an antibody.

Combination therapy has been examined with two antiresorptive agents or an antiresorptive and osteoanabolic agent together. Overall, studies with combination therapy have suggested minor improvements in bone mass over therapy with single agents. Because studies have not shown greater fracture reduction, this type of combination therapy with two antiresorptive agents or an antiresorptive plus an osteoanabolic usually is not recommended. However, it is recommended to follow osteoanabolic therapy using teriparatide with an antiresorptive therapy such as a bisphosphonate to maintain the gain.

Vertebroplasty and Kyphoplasty

Vertebroplasty involves injection of cement (i.e., polymethylmethacrylate) into a compressed vertebra to prevent the vertebral body from further collapse. Kyphoplasty introduces a balloon into the vertebral body to expand it, followed by cement placement inside the vertebral body. This approach expands the vertebral body and may increase height. Some studies suggest a significant reduction in pain early on, but the long-term pain reduction may be similar to that of placebo. Ongoing studies are needed to determine whether differences in outcomes can be found between vertebroplasty and kyphoplasty. These procedures are recommended only for patients with significant pain from vertebral fractures and are not routinely

performed in asymptomatic patients with vertebral osteoporosis.

Control questions

1. Methods of study of patients with systemic connective tissue diseases:
a) interrogation - complaints, data of anamnesis;
b) examination, palpation, percussion, auscultation;
c) laboratory diagnosis, X-ray examination, biopsy.
2. Etiology, pathogenesis, clinical manifestations, course and diagnostic criteria for rheumatism.
3. Basic directions of pharmacotherapy of rheumatism.
4. Etiology, pathogenesis, clinic and directions of pharmacotherapy of rheumatoid arthritis.
5. Significance of anti-inflammatory drugs, preparations of basic therapy and cytostatic immunosuppressants in the treatment of rheumatoid arthritis.
6. Causes, mechanisms of development, clinical manifestations and diagnostic criteria of systemic lupus erythematosus. Principles of pathogenetic therapy.
7. Etiology, pathogenesis, clinical picture and directions of pharmacotherapy of systemic scleroderma.
8. Causes and mechanisms of development, clinic and the main directions of pharmacotherapy of nodular periarthritis.
9. Write in the recipes and write testimony to the use of the following drugs: sodium diclofenac, nimesulide, meloxicam, ketoprofen, naproxen, sulindac, picroximac, prednisone, dexamethasone, triamcinolone, chloroquine phosphate, hydroxychloroquine, cyclophosphamide, methotrexate, azathioprine, cyclosporine, salazosulfapyridine, salazidine
10. The role of pharmacist in ensuring the effectiveness and prevention of complications of pharmacotherapy of systemic connective tissue diseases.

List of practical works

A. Homework.

1. To know the anatomy and physiology of the bone and joint system and the main regulatory mechanisms of mineral homeotasis.
2. Know the basic principles of diagnosing and identifying diffuse diseases of the connective tissue and joints.
3. To get acquainted with the principles of treatment of diffuse diseases of the connective tissue and joints.
4. To study the strategy of medical therapy for osteochondrosis.

B. Self-employment at the lesson.

1. The cure of the thematic patient in the ward.
2. To study its history of illness (data laboratory-instrumental studies, conclusions

of consultants) and a letter of medical appointments.
3. Write a protocol of independent work of choice for a patient with a drug that corrects connective tissue disease.
4. With a subjective and objective study of the patient to distinguish signs that characterize the disease of the connective tissue.
5. Determine the group of drugs necessary for the patient to correct the detected connective tissue diseases.
6. Select a specific drug, its dose and the mode of administration.

Control the level of knowledge

1. Identify the major systemic connective tissue diseases.

Pathological states	Definition
1. Rheumatism. 2. Rheumatoid arthritis. 3. System red lupus. 4. Systemic scleroderma. 5. Nodular periarthritis.	

1. Fill in the table "Directions of pharmacotherapy of rheumatoid arthritis"

Directions of pharmacotherapy	Pharmacological groups	Medicines.
1. Sanation of chronic foci of infection. 2. Anti-inflammatory therapy 3. Basic therapy (inhibition of immune, laboratory, clinical manifestations of the disease, slowdown of the rate of articular destruction). 4. Immunocorrective therapy. 5. Intra-articular administration of drugs and local therapy.		

2. Fill in the table "Major groups of drugs for the treatment of gout".

Pharmacological groups	Justification of purpose	Drugs, dose, route of administration
1. The use of anesthetics and anti-inflammatory agents in the exacerbation of arthritis 2. The use of drugs that increase the output of uric acid 3. Braking agents synthesis of uric acid		

Solution of situational tasks

1. The department received a patient Yu., 16 years old, with a diagnosis: rheumatic fever, active phase, activity of the I degree, primary rheumatic carditis. Feeling 2 weeks ago after suffering heavy sore throats.

What other research methods should I use? What is the tactic of therapy? Type recipes.

2. In the therapeutic department there is a patient with a diagnosis: rheumatic fever, continuous recurrent course, mitral stenosis, heart failure stage IIA.

What are your recommendations for therapy tactics? Type recipes.

3. Patient I., 37 years old, with rheumatoid arthritis, active articular syndrome, resistant to nonsteroidal anti-inflammatory drugs, were prescribed: methotrexate 2.5 mg 3 times inward, indometacin 0.025 g 1 tablet. 3 times a day, hydrocortisone 125 mg per joint was injected into the cavity of the knee joints once.

Evaluate the tactics of pharmacotherapy. Specify methods for monitoring the efficacy and safety of pharmacotherapy.

4. A patient T., 32 years old, with systemic scleroderma, acute course, III degree of activity, presented a prescription to prednisolone. The pharmacist, dismissed the lack of the necessary drug, released diclofenac sodium. On the third day the patient was admitted to the hospital with adrenal insufficiency.

Give an assessment of the tactician of the pharmacist. Your recommendations in this case.

5. Patient M., 30 years old, complains about pain in the interphalangeal, pharyngeal, pharyngeal, prolapsed, shoulder and lower leg joints, limiting movements in them, in the morning notes stiffness in the joints. Ill 2 months. Deformation and sharp restriction of active motions due to pain in the proximal interphalangeal, knee and lower limb joints. Blood test: erythrocytes - $3,4x10^{12}$ /l, Hb - 96 g / l, count p. - 0.84, white blood cells - $7.7x10^{9}$ /l, ESR - 50 mm / year. Sialic acid - 2.6 mmol/l, CRP - (+++). X-ray findings of the fibrous arteries:

osteoporosis in the epiphyses, narrowing of the articular crack, single usurium of the articular surface.

What disease can be assumed in this patient? What Are the Directions of Pharmacotherapy in a Specific Clinical Situation?

6. A patient, 63 years old, about system scleroderma receives during the year supportive therapy with prednisolone dose of 2 tablets. per day.

What complication do you expect from the use of GK LZ?

7. A patient V., 50 years old, has an overweight of the body. At night, he had a sharp pain and swelling of 1 plyusnefalangovogo joint, increased body temperature (the day before was at the banquet).

Your recommendations on the tactics of the examination and treatment of this patient. Type recipes.

Test tasks

1.The earliest signs of rheumatoid arthritis include:
1. Subfebrile temperature
.2 Morning stiffness
3. General weight loss.
4. Reduction of ESR.
5. Deformation of the joints.

2. Indicate the main clinical manifestation of rheumatic fever:
1. Morning stiffness.
2. Carditis.
3. Weakness.
4. Osteoporosis of bones.
5. Stenocardia attacks.

3. To lab osoprophase indicators in rheumatic fever include the following, except:
1. Leukocytosis.
2. Anemia.
3. Dysproteinemia.
4. Increase ESR.
5. Increase of antibodies against antiretropatokovyh antibodies.

4. Name the group of drugs used in rheumatic fever:
1. Nonsteroidal anti-inflammatory drugs.
2. Nitrates.
3. Nitrofuran preparations.
4. Sulphanilamide agents.
5. Bronchodilators.

5. The main directions of the pharmacotherapy of rheumatic fever are the following, except:
1. Fighting with streptococcal infection.
2. Antianginal therapy.
3. Correction of immunological disorders.
4. Anti-inflammatory therapy.

6. Systemic lupus erythematosus usually occurs in:
1. Old men.
2. Old women.
3. Children.
4. Women of childbearing age.
5. Young men.

7. The development of rheumatoid arthritis has the following meanings:
1. Genetic predisposition.
2. Endogenous intoxication.
3. Exogenous intoxication.
4. Medicines.
5. Increased tone of the sympathoadrenal system.

8. The following therapeutic measures are included in the complex pathogenetic therapy of rheumatoid arthritis, except:
1.Sanation of chronic foci of infection.
2. Anti-inflammatory therapy.
3. Immunodepressive therapy.
4. Antianginal therapy
5.Local therapy of affected joints.

9. For systemic lupus erythematosus is characterized by:
1. Dizziness of joints and extremities.
2. Defeat of the skin and its appendages.
3. Heart damage.
4. Poliorgan defeat: joints, skin, kidneys, serous membranes.
5. Defeat of connective tissue of inflammatory nature.

10. Identify the symptoms that appear the first in systemic scleroderma:
1. Reino syndrome.
2. Lesion of joints.
3. Muscle damage.
4. Change the skin.
5. Heart damage.

11. From which of the mentioned preparations the most appropriate to begin

pathogenetic treatment of systemic lupus erythematosus:
1. Cyclophosphamate.
2. Bicillin.
3. Prednisolone.
4. Diclofenac sodium.
5. Delagil

12. For systemic lupus erythematosus, the following pharmacological groups of the drug are prescribed, except:
1. Immunodepressants.
2. Glucocorticosteroids.
3. Derivatives of 4-amino-hippolyte.
4. Antibacterial.
5. NSAIDs.

13. In the treatment of systemic scleroderma, the leading place is occupied by:
1. Oil refinery.
2. Group B vitamins
3. Immunostimulants.
4. Drugs of nicotinic acid.
5. Corticosteroids

14. With prolonged use of glucocorticoids, the following complications may occur, except:
1. Edema.
2. Stomach ulcer
3. Reduced blood pressure.
4. Osteoporosis.
5. Violation of the sexual function.

15. The main side effect of the refractory drug can be:
1.Gastrotoxic.
2.Gepatotoxic.
3.Nefrotoxic.
4.Cardiotoxic.
5.Ototoxic

16. In the absence of sodium in the pharmacy, diclofenac can be offered:
1. Prodectin.
2. Ibuprofen.
3. Dimedrol.
4. No-sha
5. Cimetidine.

17. Refractory drugs should be taken by:
1. After eating.
2. To eat.
3.In the period between meals.
4. On an empty stomach.
5. Sleep.

18. As antiretroviral therapy of rheumatic fever, use:
1. Ampicillin
2. Amoxicillin
3.Meticillin
4. Oxacillin
5. Bicillin-5

19. Before treatment of rheumatoid arthritis, the following groups of drugs are not included:
1. Antibiotics.
2. Cytostatics.
3. Corticosteroids.
4. Amino-quinoline preparations.
5. Oil refinery.

20. Choose drugs that selectively inhibit cyclooxygenase 2:
1. Indomethacin.
2. Ibuprofen.
3. Diclofenac sodium.
4. Nimesulide.
5. Butadion.

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TOPIC 15. Diseases of blood system: anemia and leukemia: classification, diagnosis, principles of pharmacotherapy.

Actuality of topic.

Anemia associated with iron deficiency in the adult body usually develops as a result of insignificant but frequent and prolonged haemorrhages. Often changes in peripheral blood, not being the central link in pathogenesis, complicate the course of other zaobolevaniyas. Modern pharmacotherapy of erythropoiesis disorders can effectively affect such diseases as hypochromic (normoblastnaya), hyperchromal (megaloblastic), hemolytic and hypoplastic anemia. Leukemia is a malignant neoplasm of the hematopoietic organs, characterized by substitution of the normal bone marrow by blast cells from the clone, which occurs as a result of malignant transformation of the stem-forming hematopoietic cells. The frequency of leukemia in recent years has increased. Modern pharmacotherapy for violations of leukopoiesis can effectively affect such diseases as leukemia.

Purpose of the lesson: The student must learn the etiopathogenetic factors of anemia and leukemia, be able to determine the manifestations of these diseases, explain their causes and mechanism of development, assess the significance of probable complications for the body. Also know the place and role of general blood tests in diagnosing the main diseases of the blood system and have the concept of chemotherapy of malignant diseases of the blood system.

ANEMIAS

General Approach to Anemias

Anemia is present in adults if the hematocrit is below 41% (hemoglobin less than 13.5 g/dL [135 g/L]) in males or below 36% (hemoglobin less than 12 g/dL [120 g/L]) in females. Congenital anemia is suggested by the patient’s personal and family history. The most common cause of anemia is iron deficiency. Poor diet may result in folic acid deficiency and contribute to iron deficiency, but bleeding is the most common cause of iron deficiency in adults. Physical examination demonstrates pallor. Attention to physical signs of primary hematologic diseases (lymphadenopathy; hepatosplenomegaly; or bone tenderness, especially in the sternum or anterior tibia) is important. Mucosal changes such as a smooth tongue suggest megaloblastic anemia.

Anemias are classified according to their pathophysiologic basis, ie, whether related to diminished production (relative or absolute reticulocytopenia) or to increased production due to accelerated loss of red blood cells (reticulocytosis), and according to red blood cell size. A reticulocytosis occurs in one of three pathophysiologic states: acute blood loss, recent replacement of a missing erythropoietic nutrient, or reduced red blood cell survival (ie, hemolysis). A severely microcytic anemia (mean corpuscular volume [MCV] less than 70 fL) is due either to iron deficiency or thalassemia, while a severely macrocytic anemia

(MCV less than 125 fL) is almost always due to either megaloblastic anemia or to cold agglutinins in blood analyzed at room temperature. A bone marrow biopsy is generally needed to complete the evaluation of anemia when the laboratory evaluation fails to reveal an etiology, when there are additional cytopenias present, or when an underlying primary or secondary bone marrow process is suspected.

Classification of anemia by pathophysiology:

Decreased red blood cell production (relative or absolute reticulocytopenia)

- Hemoglobin synthesis lesion: iron deficiency, thalassemia, anemia of chronic disease, hypoerythropoietinemia
- DNA synthesis lesion: megaloblastic anemia, DNA synthesis inhibitor drugs
- Hematopoietic stem cell lesion: aplastic anemia, leukemia
- Bone marrow infiltration: carcinoma, lymphoma, fibrosis, sarcoidosis, Gaucher disease, others
- Immune-mediated inhibition: aplastic anemia, pure red cell aplasia

Increased red blood cell destruction or accelerated red blood cell loss (reticulocytosis)

- Acute blood loss
- Hemolysis (intrinsic)
- Membrane lesion: hereditary spherocytosis, elliptocytosis
- Hemoglobin lesion: sickle cell, unstable hemoglobin
- Glycolysis abnormality: pyruvate kinase deficiency
- Oxidation lesion: glucose-6-phosphate dehydrogenase deficiency
- Hemolysis (extrinsic)
- Immune: warm antibody, cold antibody
- Microangiopathic: thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, mechanical cardiac valve, paravalvular leak
- Infection: Clostridium perfringens, malaria
- Hypersplenism

Classification of anemia by mean red blood cell volume (MCV):

Microcytic

- Iron deficiency
- Thalassemia
- Anemia of chronic disease
- Lead toxicity
- Zinc deficiency

Macrocytic (Megaloblastic)

- Vitamin B12 deficiency
- Folate deficiency
- DNA synthesis inhibitors

Macrocytic (Nonmegaloblastic)

- Myelodysplasia
- Liver disease
- Reticulocytosis
- Hypothyroidism
- Bone marrow failure state (eg, aplastic anemia, marrow infiltrative disorder, etc)
- Copper deficiency

Normocytic

- Kidney disease
- Non-thyroid endocrine gland failure
- Copper deficiency
- Mild form of most acquired microcytic or macrocytic etiologies of anemia

IRON DEFICIENCY ANEMIAS

ESSENTIALS OF DIAGNOSIS

- Iron deficiency is present if serum ferritin is less than 12 ng/mL (27 pmol/L) or less than 30 ng/mL (67 pmol/L) if also anemic.
- Caused by bleeding unless proved otherwise.
- Responds to iron therapy.

General Considerations

Iron deficiency is the most common cause of anemia worldwide. Aside from circulating red blood cells, the major location of iron in the body is the storage pool as ferritin or as hemosiderin in macrophages. The average American diet contains 10–15 mg of iron per day. About 10% of this amount is absorbed in the stomach, duodenum, and upper jejunum under acidic conditions. Dietary iron present as heme is efficiently absorbed (10–20%) but nonheme iron less so (1–5%), largely because of interference by phosphates, tannins, and other food constituents. The major iron transporter from the diet across the intestinal lumen is ferroportin, which also facilitates the transport of iron to apotransferrin in macrophages for delivery to erythroid cells prepared to synthesize hemoglobin. Hepcidin, produced during inflammation, negatively regulates iron transport by promoting the degradation of ferroportin. Small amounts of iron—approximately 1 mg/day—are normally lost through exfoliation of skin and mucosal cells.

With hemorrhage, there is decreased oxygen delivery to the kidneys resulting in stabilization of a hypoxia-inducible factor in the kidneys and increased

erythropoietin generation in the kidneys and liver. The erythropoietin stimulates erythropoiesis, leading to an increased synthesis of erythroferrone. In turn, erythroferrone suppresses hepcidin synthesis leading to ferroportin stability and enhanced iron transport across the gastrointestinal lumen.

Menstrual blood loss plays a major role in iron metabolism. The average monthly menstrual blood loss is approximately 50 mL but may be five times greater in some individuals. To maintain adequate iron stores, women with heavy menstrual losses must absorb 3–4 mg of iron from the diet each day. This strains the upper limit of what may reasonably be absorbed, and women with menorrhagia of this degree will almost always become iron deficient without iron supplementation.

In general, iron metabolism is balanced between absorption of 1 mg/day and loss of 1 mg/day. Pregnancy and lactation upset the iron balance, since requirements increase to 2–5 mg of iron per day. Normal dietary iron cannot supply these requirements, and medicinal iron is needed during pregnancy and lactation. Decreased iron absorption can also cause iron deficiency, such as in people affected by celiac disease, and it commonly occurs after gastric resection or jejunal bypass surgery.

The most important cause of iron deficiency anemia in adults is chronic blood loss, especially menstrual and gastrointestinal blood loss. Iron deficiency demands a search for a source of gastrointestinal bleeding if other sites of blood loss (menorrhagia, other uterine bleeding, and repeated blood donations) are excluded. Prolonged aspirin or nonsteroidal anti-inflammatory drug use may cause it even without a documented structural lesion. Celiac disease (gluten enteropathy), even when asymptomatic, is an occult cause of iron deficiency through poor absorption in the gastrointestinal tract. Zinc deficiency is another cause of poor iron absorption. Chronic hemoglobinuria may lead to iron deficiency, but this is uncommon; traumatic hemolysis due to a prosthetic cardiac valve and other causes of intravascular hemolysis (eg, paroxysmal nocturnal hemoglobinuria) should also be considered. The cause of iron deficiency is not found in up to 5% of cases.

Pure iron deficiency might prove refractory to oral iron replacement. Refractoriness is defined as a hemoglobin increment of less than 1 g/dL (10 g/L) after 4–6 weeks of 100 mg/day of elemental oral iron. The differential diagnosis in these cases includes malabsorption from autoimmune gastritis, Helicobacter pylori gastric infection, celiac disease, and hereditary iron-refractory iron deficiency anemia. Iron-refractory iron deficiency anemia is a rare autosomal recessive disorder due to mutations in the transmembrane serine protease 6 (TMPRSS6) gene, which normally down-regulates hepcidin. In iron-refractory iron deficiency anemia, hepcidin levels are normal to high and ferritin levels are high despite the iron deficiency.

Causes of iron deficiency:

Deficient diet
Decreased absorption
Autoimmune gastritis
Celiac sprue

Helicobacter pylori gastritis
Hereditary iron-refractory iron deficiency anemia
Zinc deficiency
Increased requirements
Pregnancy
Lactation
Blood loss (chronic)
Gastrointestinal
Menstrual
Blood donation
Hemoglobinuria
Iron sequestration
Pulmonary hemosiderosis
Idiopathic

Treatment

The diagnosis of iron deficiency anemia can be made either by the laboratory demonstration of an iron-deficient state or by evaluating the response to a therapeutic trial of iron replacement. Since the anemia itself is rarely life-threatening, the most important part of management is identification of the cause—especially a source of occult blood loss.

A. Oral Iron

Ferrous sulfate, 325 mg three times daily on an empty stomach, which provides 180 mg of iron daily of which up to 10 mg is absorbed, is the preferred therapy. Nausea and constipation limit compliance with ferrous sulfate. Extendedrelease ferrous sulfate with mucoprotease is the best tolerated oral preparation. Compliance is improved by introducing the medicine slowly in gradually escalating doses. Taking ferrous sulfate with food reduces side effects and but also its absorption. An appropriate response is a return of the hematocrit level halfway toward normal within 3 weeks with full return to baseline after 2 months. Iron therapy should continue for 3–6 months after restoration of normal hematologic values to replenish iron stores. Failure of response to iron therapy is usually due to noncompliance, although occasional patients may absorb iron poorly, particularly if the stomach is achlorhydric. Such patients may benefit from concomitant administration of oral ascorbic acid. Other reasons for failure to respond include incorrect diagnosis (anemia of chronic disease, thalassemia), celiac disease, and ongoing gastrointestinal blood loss that exceeds the rate of new erythropoiesis. Treatment of H pylori infection, in appropriate cases, can improve oral iron absorption.

B. Parenteral Iron

The indications are intolerance of or refractoriness to oral iron (including those with iron-refractory iron deficiency anemia), gastrointestinal disease (usually inflammatory bowel disease) precluding the use of oral iron, and continued blood loss that cannot be corrected, such as chronic hemodialysis.

Parenteral iron preparations coat the iron in protective carbohydrate shells.

Historical parenteral iron preparations, such as iron dextran, were problematic due to long infusion times (hours), polyarthralgia, and hypersensitivity reactions, including anaphylaxis. Current preparations are safe and can be infused in less than 5 minutes. Iron oxide coated with polyglucose sorbitol carboxymethyl-ether can be given in doses up to 510 mg by intravenous bolus over 20 seconds, with no test dose required. The iron deficit is calculated by determining the decrement in red cell volume from normal, recognizing there is 1 mg of iron in each milliliter of red blood cells. Total body iron ranges between 2 g and 4 g: approximately 50 mg/kg in men and 35 mg/kg in women. Most (70–95%) of the iron is present in hemoglobin in circulating red blood cells. In men, red blood cell volume is approximately 30 mL/kg; in women, it is about 27 mL/kg. Thus, a 50-kg woman whose hemoglobin is 9 g/dL (75% of normal) has an iron deficit of 0.25 × 27 mL/kg × 50 kg = 337.5 mL of red blood cells (or 337.5 mg of iron). The parenteral iron dose is the iron deficit plus (usually) 1 extra gram to replenish iron stores and anticipate further iron loses, so in this case 1.4 g.

Ferric pyrophosphate citrate (Triferic), approved by the FDA in 2015 to replace the 5–7 mg of iron CKD patients tend to lose to each hemodialysis, is added to the dialysate. It appears to be able to deliver sufficient iron to the marrow to maintain hemoglobin and not increase iron stores; it may obviate the need for intravenous iron in hemodialysis patients.

When to Refer

Patients should be referred to a hematologist if the suspected diagnosis is not confirmed or if they are not responsive to oral iron therapy.

ANEMIA AT CHRONIC DISEASE

ESSENTIALS OF DIAGNOSIS

- Mild or moderate normocytic or microcytic anemia.
- Normal or increased ferritin and normal or reduced transferrin.
- Underlying chronic disease.

General Considerations

Many chronic systemic diseases are associated with mild or moderate anemia. The anemias of chronic disease are characterized according to etiology and pathophysiology. First, the **anemia of inflammation** is associated with chronic inflammatory states (such as inflammatory bowel disease, rheumatoid arthritis, chronic infections, and malignancy) and is mediated through hepcidin (a negative regulator of ferroportin), resulting in reduced iron uptake in the gut and reduced iron transfer from macrophages to erythroid progenitor cells in the bone marrow. This is referred to as iron-restricted erythropoiesis since the patient is iron replete. There is also reduced responsiveness to erythropoietin, the elaboration of hemolysins that shorten red blood cell survival, and the production of inflammatory cytokines that dampen red cell production. The serum iron is low in the anemia of inflammation. Second, the **anemia of organ failure** can occur with kidney disease, hepatic failure, and endocrine gland failure; erythropoietin is reduced and the red

blood cell mass decreases in response to the diminished signal for red blood cell production; the serum iron is normal (except in chronic kidney disease where it is low due to the reduced hepcidin clearance and subsequent enhanced degradation of ferroportin). Third, the **anemia of the elderly** is present in up to 20% of individuals over age 85 years in whom a thorough evaluation for an explanation of anemia is negative. It is a consequence of a relative red blood cell production resistance to erythropoietin, a decrease in erythropoietin production relative to the nephron mass, and a negative erythropoietic influence of low levels of chronic inflammatory cytokines in older adults; the serum iron is normal.

Clinical Findings A.
Symptoms and Signs

The clinical features are those of the causative condition. The diagnosis should be suspected in patients with known chronic diseases. In cases of significant anemia, coexistent iron deficiency or folic acid deficiency should be suspected. Decreased dietary intake of iron or folic acid is common in chronically ill patients, many of whom will also have ongoing gastrointestinal blood losses. Patients undergoing hemodialysis regularly lose both iron and folic acid during dialysis.

B. Laboratory Findings

The hematocrit rarely falls below 60% of baseline (except in kidney failure). The MCV is usually normal or slightly reduced. Red blood cell morphology is usually normal, and the reticulocyte count is mildly decreased or normal. In the anemia of inflammation, serum iron and transferrin values are low, and transferrin saturation may be extremely low, leading to an erroneous diagnosis of iron deficiency. In contrast to iron deficiency, serum ferritin values should be normal or increased. A serum ferritin value less than 30 ng/mL (67 pmol/L) indicates coexistent iron deficiency.

Classic anemia of inflammation has elevated hepcidin levels; however, no clinical test is yet available. In the anemias of organ failure and of the elderly, the iron studies are generally normal. The anemia of the elderly is a diagnosis of exclusion in a patient with anemia who is over age 65 years.

A particular challenge is the diagnosis of iron deficiency in the setting of the anemia of inflammation in which the serum ferritin can be as high as 200 ng/mL (450 pmol/L). The diagnosis is established by a bone marrow biopsy with iron stain. Absent iron staining indicates iron deficiency, whereas iron localized in marrow macrophages indicates pure anemia of inflammation. However, bone marrow biopsies are rarely done for this purpose. Three other tests all support iron deficiency in the setting of inflammation: a reticulocyte hemoglobin concentration of less than 28 pg; a normal hepcidin level; or a soluble serum transferrin receptor (units: mg/L) to log ferritin (units: mcg/L) ratio of 1–8 (a ratio of less than 1 is virtually diagnostic of pure anemia of chronic disease). A functional test is hemoglobin response to oral or parenteral iron in the setting of inflammation when iron deficiency is suspected. A note of caution: certain circumstances of iron-restricted erythropoiesis (such as malignancy) will partially respond to parenteral

iron infusion even when the iron stores are replete due to the immediate distribution of iron to erythropoietic progenitor cells after the infusion.

Treatment

In most cases, no treatment is necessary and the primary management is to address the condition causing the anemia of chronic disease. When the anemia is severe or is adversely affecting the quality of life or functional status, then treatment involves either red blood cell transfusions or parenteral recombinant erythropoietin (epoetin alfa or darbepoetin). The indications for recombinant erythropoietin are hemoglobin less than 10 g/dL and anemia due to rheumatoid arthritis, inflammatory bowel disease, hepatitis C, zidovudine therapy in HIV-infected patients, myelosuppressive chemotherapy of solid malignancy (treated with palliative intent only), or chronic kidney disease (estimated glomerular filtration rate of less than 60 mL/min). The dosing and schedule of recombinant erythropoietin are individualized to maintain the hemoglobin between 10 g/dL (100 g/L) and 12 g/dL (120 g/L). The use of recombinant erythropoietin is associated with an increased risk of venothromboembolism and arterial thrombotic episodes, especially if the hemoglobin rises to greater than 12 g/dL (120 g/L). There is concern that recombinant erythropoietin is associated with reduced survival in patients with malignancy. For patients with end-stage renal disease receiving recombinant erythropoietin who are on hemodialysis, the anemia of chronic kidney disease can be more effectively corrected by adding soluble ferric pyrophosphate to their dialysate than by administering intravenous iron supplementation.

When to Refer

Referral to a hematologist is not necessary.

THE THALASSEMIAS

ESSENTIALS OF DIAGNOSIS

- Microcytosis disproportionate to the degree of anemia.
- Positive family history or lifelong personal history of microcytic anemia.
- Normal or elevated red blood cell count.
- Abnormal red blood cell morphology with microcytes, hypochromia, acanthocytes, and target cells.
- In beta-thalassemia, elevated levels of hemoglobin A2 or F.

General Considerations

The thalassemias are hereditary disorders characterized by reduction in the synthesis of globin chains (alpha or beta). Reduced globin chain synthesis causes reduced hemoglobin synthesis and a hypochromic microcytic anemia because of defective hemoglobinization of red blood cells. Thalassemias can be considered among the hyperproliferative hemolytic anemias, the anemias related to abnormal hemoglobin, and the hypoproliferative anemias, since all of these factors play a role

in pathogenesis. The hallmark laboratory features are small and pale red blood cells (low MCV and mean corpuscular hemoglobin [MCH]), anemia, and a normal to elevated red blood cell count (ie, a large number of small red blood cells are being produced). Although patients often exhibit an elevated reticulocyte count, generally the degree of reticulocyte output is inadequate to meet the degree of red blood cell destruction (hemolysis) and the patients remain anemic. Normal adult hemoglobin is primarily hemoglobin A, which represents approximately 98% of circulating hemoglobin. Hemoglobin A is formed from a tetramer of two alpha chains and two beta chains—and can be designated alpha2beta2. Two copies of the alpha-globin gene are located on each chromosome 16, and there is no substitute for alpha-globin in the formation of adult hemoglobin.

One copy of the beta-globin gene resides on each chromosome 11 adjacent to genes encoding the beta-like globins delta and gamma (the so-called beta-globin gene cluster region). The tetramer of alpha2delta2 forms hemoglobin A2 , which normally comprises 1–3% of adult hemoglobin. The tetramer alpha2gamma2 forms hemoglobin F, which is the major hemoglobin of fetal life but which comprises less than 1% of normal adult hemoglobin.

The thalassemias are described as "**trait**" when there are laboratory features without significant clinical impact, "**intermedia**" when there is an occasional red blood cell transfusion requirement or other moderate clinical impact, and "**major**" when the disorder is life-threatening and the patient is transfusion-dependent. Most patients with thalassemia major die of the consequences of iron overload.

Alpha-thalassemia is due primarily to gene deletions causing reduced alpha-globin chain synthesis. Each alpha-globin gene produces one-quarter of the total alpha-globin quantity, so there is a predictable proportionate decrease in alpha-globin output with each lost alphaglobin gene. Since all adult hemoglobins are alpha containing, alpha-thalassemia produces no change in the proportions of hemoglobins A, A2, and F on hemoglobin electrophoresis. In severe forms of alpha-thalassemia, excess beta chains may form a beta-4 tetramer called hemoglobin H. In the presence of reduced alpha chains, the excess beta chains are unstable and precipitate, leading to damage of red blood cell membranes. This leads to both intramedullary (bone marrow) and peripheral blood hemolysis.

Beta-thalassemias are usually caused by point mutations rather than deletions. These mutations result in premature chain termination or in problems with transcription of RNA and ultimately result in reduced or absent beta-globin chain synthesis. The molecular defects leading to beta-thalassemia are numerous and heterogeneous but run true within families. Defects that result in absent beta-globin chain expression are termed beta0 , whereas those causing reduced but not absent synthesis are termed beta+. In beta+ thalassemia, the degree of reduction of beta-globin synthesis is consistent within families but is quite variable between families. The reduced beta-globin chain synthesis in beta-thalassemia results in a relative increase in the proportions of hemoglobins A2 and F compared to hemoglobin A on hemoglobin electrophoresis, as the beta-like globins (delta and gamma) substitute for the missing beta chains. In the presence of reduced beta chains, the excess alpha chains are unstable and precipitate, leading to damage of

red blood cell membranes. This leads to both intramedullary (bone marrow) and peripheral blood hemolysis. The bone marrow demonstrates erythroid hyperplasia under the stimuli of anemia and ineffective erythropoiesis (intramedullary destruction of the developing erythroid cells). In cases of severe thalassemia, the marked expansion of the erythroid compartment in the bone marrow may cause severe bony deformities, osteopenia, and pathologic fractures.

Clinical Findings

A. Symptoms and Signs

The **alpha-thalassemia** syndromes are seen primarily in persons from southeast Asia and China, and, less commonly, in blacks and persons of Mediterranean origin. Normally, adults have four copies of the alpha-globin chain. When three alpha-globin genes are present, the patient is hematologically normal (silent carrier). When two alpha-globin genes are present, the patient is said to have alpha-thalassemia trait, a form of thalassemia minor. In alpha-thalassemia-1 trait, the alpha gene deletion is heterozygous (alpha –/alpha –) and affects mainly those of Asian descent. In alpha-thalassemia-2 trait, the alpha gene deletion is homozygous (alpha alpha/– –) and affects mainly blacks. These patients are clinically normal and have a normal life expectancy and performance status, with a mild microcytic anemia. When only one alpha globin chain is present (alpha –/– –), the patient has hemoglobin H disease (alpha-thalassemia-3). This is a chronic hemolytic anemia of variable severity (thalassemia minor or intermedia). Physical examination might reveal pallor and splenomegaly. Affected individuals usually do not need transfusions; however, they may be required during transient periods of hemolytic exacerbation caused by infection or other stressors or during periods of erythropoietic shutdown caused by certain viruses (“aplastic crisis”). When all four alpha-globin genes are deleted, no normal hemoglobin is produced and the affected fetus is stillborn (hydrops fetalis). In hydrops fetalis, the only hemoglobin species gamma made is called hemoglobin Bart’s (gamma4).

Beta-thalassemia primarily affects persons of Mediterranean origin (Italian, Greek) and to a lesser extent Asians and blacks. Patients homozygous for beta-thalassemia (beta0 /beta0 or beta+/beta+) have thalassemia major (Cooley anemia). Affected children are normal at birth but after 6 months, when hemoglobin synthesis switches from hemoglobin F to hemoglobin A, severe anemia requiring transfusion develops. Numerous clinical problems ensue, including stunted growth, bony deformities (abnormal facial structure, pathologic fractures), hepatosplenomegaly, jaundice (due to gallstones, hepatitis-related cirrhosis, or both), and thrombophilia. The clinical course is modified significantly by transfusion therapy, but transfusional iron overload (hemosiderosis) results in a clinical picture similar to hemochromatosis, with heart failure, cardiac arrhythmias, cirrhosis, endocrinopathies, and pseudoxanthoma elasticum (calcification and fragmentation of the elastic fibers of the skin, retina, and cardiovascular system), usually after more than 100 units of red blood cells have been transfused. Iron over loading occurs because the human body has no active iron excretory mechanism. Before the application of allogeneic stem cell transplantation and the development

of more effective forms of iron chelation, death from iron overload usually occurred between the ages of 20 and 30 years.

Patients homozygous for a milder form of betathalassemia (beta+/beta+, but allowing a higher rate of beta-globin synthesis) have thalassemia intermedia. These patients have chronic hemolytic anemia but do not require transfusions except under periods of stress or during aplastic crises. They also may develop iron overload because of periodic transfusion. They survive into adult life but with hepatosplenomegaly and bony deformities. Patients heterozygous for beta-thalassemia (beta/beta0 or beta/beta+) have thalassemia minor and a clinically insignificant microcytic anemia. Prenatal diagnosis is available, and genetic counseling should be offered and the opportunity for prenatal diagnosis discussed.

B. Laboratory Findings

1. Alpha-thalassemia trait—These patients have mild anemia, with hematocrits between 28% and 40%. The MCV is strikingly low (60–75 fL) despite the modest anemia, and the red blood count is normal or increased. The peripheral blood smear shows microcytes, hypochromia, occasional target cells, and acanthocytes (cells with irregularly spaced spiked projections). The reticulocyte count and iron parameters are normal. Hemoglobin electrophoresis is normal. Alpha-thalassemia trait is thus usually diagnosed by exclusion. Genetic testing to demonstrate alpha-globin gene deletion is available only in a limited number of laboratories.

2. Hemoglobin H disease—These patients have a more marked anemia, with hematocrits between 22% and 32%. The MCV is remarkably low (60–70 fL) and the peripheral blood smear is markedly abnormal, with hypochromia, microcytosis, target cells, and poikilocytosis. The reticulocyte count is elevated and the red blood cell count is normal or elevated. Hemoglobin electrophoresis will show a fast migrating hemoglobin (hemoglobin H), which comprises 10–40% of the hemoglobin. A peripheral blood smear can be stained with supravital dyes to demonstrate the presence of hemoglobin H.

3. Beta-thalassemia minor—These patients have a modest anemia with hematocrit between 28% and 40%. The MCV ranges from 55 fL to 75 fL, and the red blood cell count is normal or increased. The reticulocyte count is normal or slightly elevated. The peripheral blood smear is mildly abnormal, with hypochromia, microcytosis, and target cells. In contrast to alpha-thalassemia, basophilic stippling is present. Hemoglobin electrophoresis shows an elevation of hemoglobin A2 to 4–8% and occasional elevations of hemoglobin F to 1–5%.

4. Beta-thalassemia intermedia—These patients have a modest anemia with hematocrit between 17% and 33%. The MCV ranges from 55 fL to 75 fL, and the red blood cell count is normal or increased. The reticulocyte count is elevated. The peripheral blood smear is abnormal with hypochromia, microcytosis, basophilic stippling, and target cells. Hemoglobin electrophoresis shows up to 30% hemoglobin A, an elevation of hemoglobin A2 up to 10%, and elevation of hemoglobin F from 6% to 100%. 5. Beta-thalassemia major—These patients have severe anemia, and without transfusion the hematocrit may fall to less than 10%.

The peripheral blood smear is bizarre, showing severe poikilocytosis, hypochromia, microcytosis, target cells, basophilic stippling, and nucleated red blood cells. Little or no hemoglobin A is present. Variable amounts of hemoglobin A2 are seen, and the predominant hemoglobin present is hemoglobin F.

Differential Diagnosis

Mild forms of thalassemia must be differentiated from iron deficiency. Compared to iron deficiency anemia, patients with thalassemia have a lower MCV, a normal or elevated red blood cell count, a more abnormal peripheral blood smear at modest levels of anemia, and usually a reticulocytosis. Iron studies are normal or the transferrin saturation or ferritin (or both) are elevated. Severe forms of thalassemia may be confused with other hemoglobinopathies. The diagnosis of beta-thalassemia is made by the above findings and hemoglobin electrophoresis showing elevated levels of hemoglobins A2 and F (provided the patient is replete in iron), but the diagnosis of alpha-thalassemia is made by exclusion since there is no change in the proportion of the normal adult hemoglobin species. The only other microcytic anemia with a normal or elevated red blood cell count is iron deficiency in a patient with polycythemia vera.

Treatment

Patients with mild thalassemia (alpha-thalassemia trait or beta-thalassemia minor) require no treatment and should be identified so that they will not be subjected to repeated evaluations and treatment for iron deficiency. Patients with hemoglobin H disease should take folic acid supplementation (1 mg/day orally) and avoid medicinal iron and oxidative drugs such as sulfonamides. Patients with severe thalassemia are maintained on a regular transfusion schedule (in part to suppress endogenous erythropoiesis and therefore bone marrow expansion) and receive folic acid supplementation. Splenectomy is performed if hypersplenism causes a marked increase in the transfusion requirement or refractory symptoms. Patients with regular transfusion requirements should be treated with iron chelation (such as oral deferasirox 20–30 mg/kg/day) in order to prevent life-limiting organ damage from iron overload. Allogeneic stem cell transplantation is the treatment of choice for beta-thalassemia major and the only available cure. Children who have not yet experienced iron overload and chronic organ toxicity do well, with long-term survival in more than 80% of cases.

When to Refer

All patients with severe thalassemia should be referred to a hematologist. Any patient with an unexplained microcytic anemia should be referred to help establish a diagnosis. Patients with thalassemia minor or intermedia should be referred for genetic counseling because offspring of thalassemic couples are at risk for inheriting thalassemia major.

VITAMIN B12 DEFICIENCY

ESSENTIALS OF DIAGNOSIS

- Macrocytic anemia.
- Megaloblastic blood smear (macro-ovalocytes and hypersegmented neutrophils).
- Low serum vitamin B12 level.

General Considerations

Vitamin B12 belongs to the family of cobalamins and serves as a cofactor for two important reactions in humans. As methylcobalamin, it is a cofactor for methionine synthetase in the conversion of homocysteine to methionine, and as adenosylcobalamin for the conversion of methylmalonylcoenzyme A (CoA) to succinyl-CoA. These enzymatic steps are critical for annealing Okazaki fragments during DNA synthesis, particularly in erythroid progenitor cells. Vitamin B12 comes from the diet and is present in all foods of animal origin. The daily absorption of vitamin B12 is 5 mcg. The liver contains 2–5 mg of stored vitamin B12. Since daily utilization is 3–5 mcg, the body usually has sufficient stores of vitamin B12 so that it takes more than 3 years for vitamin B12 deficiency to occur if all intake or absorption immediately ceases. Since vitamin B12 is present in foods of animal origin, dietary vitamin B12 deficiency is extremely rare but is seen in vegans—strict vegetarians who avoid all dairy products, meat, and fish. Pernicious anemia is an autoimmune illness whereby autoantibodies destroy gastric parietal cells (that produce intrinsic factor) and cause atrophic gastritis or bind to and neutralize intrinsic factor, or both. Abdominal surgery may lead to vitamin B12 deficiency in several ways. Gastrectomy will eliminate the site of intrinsic factor production; blind loop syndrome will cause competition for vitamin B12 by bacterial overgrowth in the lumen of the intestine; and surgical resection of the ileum will eliminate the site of vitamin B12 absorption. Rare causes of vitamin B12 deficiency include fish tapeworm (Diphyllobothrium latum) infection, in which the parasite uses luminal vitamin B12; pancreatic insufficiency (with failure to inactivate competing cobalamin-binding proteins); and severe Crohn disease, causing sufficient destruction of the ileum to impair vitamin B12 absorption.

Causes of vitamin B12 deficiency:

Dietary deficiency (rare)
Decreased production or neutralization of intrinsic factor
Pernicious anemia (autoimmune)
Gastrectomy
Helicobacter pylori infection
Competition for vitamin B12 in gut
Blind loop syndrome
Fish tapeworm (rare)
Pancreatic insufficiency
Decreased ileal absorption of vitamin B12
Surgical resection

Crohn disease
Transcobalamin II deficiency (rare)

Clinical Findings

A. Symptoms and Signs

Vitamin B12 deficiency causes a moderate to severe anemia of slow onset; patients may have few symptoms relative to the degree of anemia. In advanced cases, the anemia may be severe, with hematocrits as low as 10–15%, and may be accompanied by leukopenia and thrombocytopenia. The deficiency also produces changes in mucosal cells, leading to glossitis, as well as other vague gastrointestinal disturbances such as anorexia and diarrhea. Vitamin B12 deficiency also leads to a complex neurologic syndrome. Peripheral nerves are usually affected first, and patients complain initially of paresthesias. As the posterior columns of the spinal cord become impaired, patients complain of difficulty with balance or proprioception, or both. In more advanced cases, cerebral function may be altered as well, and on occasion dementia and other neuropsychiatric abnormalities may be present. It is critical to recognize that the non-hematologic manifestations of vitamin B12 deficiency can be manifest despite a completely normal complete blood count.

Patients are usually pale and may be mildly icteric or sallow. Typically later in the disease course, neurologic examination may reveal decreased vibration and position sense or memory disturbance (or both).

B. Laboratory Findings

The diagnosis of vitamin B12 deficiency is made by finding a low serum vitamin B12 (cobalamin) level. Whereas the normal vitamin B12 level is greater than 210 pg/mL (155 pmol/L), most patients with overt vitamin B12 deficiency have serum levels less than 170 pg/mL (126 pmol/L), with symptomatic patients usually having levels less than 100 pg/mL (74 pmol/L). The diagnosis of vitamin B12 deficiency in low or low-normal values (level of 170–210 pg/mL [126–155 pmol/L]) is best confirmed by finding an elevated level of serum methylmalonic acid (greater than 1000 nmol/L) or homocysteine. Of note, elevated levels of serum methylmalonic acid can be due to kidney disease.

The anemia of vitamin B12 deficiency is typically moderate to severe with the MCV quite elevated (110–140 fL). However, it is possible to have vitamin B12 deficiency with a normal MCV from coexistent thalassemia or iron deficiency; in other cases, the reason is obscure. Patients with neurologic symptoms and signs that suggest possible vitamin B12 deficiency should be evaluated for that deficiency despite a normal MCV or the absence of anemia. The peripheral blood smear is megaloblastic, defined as red blood cells that appear as macro-ovalocytes, (although other shape changes are usually present) and neutrophils that are hypersegmented (six [or greater]-lobed neutrophils or mean neutrophil lobe counts greater than four).

The reticulocyte count is reduced. Because vitamin B12 deficiency can affect all hematopoietic cell lines, the white blood cell count and the platelet count are reduced in severe cases.

Other laboratory abnormalities include elevated serum lactate dehydrogenase (LD) and a modest increase in indirect bilirubin. These two findings are a reflection of intramedullary destruction of developing abnormal erythroid cells and are similar to those observed in peripheral hemolytic anemias.

Bone marrow morphology is characteristically abnormal. Marked erythroid hyperplasia is present as a response to defective red blood cell production (ineffective erythropoiesis). Megaloblastic changes in the erythroid series include abnormally large cell size and asynchronous maturation of the nucleus and cytoplasm—ie, cytoplasmic maturation continues while impaired DNA synthesis causes retarded nuclear development. In the myeloid series, giant bands and meta-myelocytes are characteristically seen.

Differential Diagnosis

Vitamin B12 deficiency should be differentiated from folic acid deficiency, the other common cause of megaloblastic anemia, in which red blood cell folic acid is low while vitamin B12 levels are normal. The bone marrow findings of vitamin B12 deficiency are sometimes mistaken for a myelodysplastic syndrome or even acute erythrocytic leukemia. The distinction between vitamin B12 deficiency and myelodysplasia is based on the characteristic morphology and the low vitamin B12 and elevated methylmalonic acid levels.

Treatment

Patients with vitamin B12 deficiency have historically been treated with parenteral therapy. Intramuscular or subcutaneous injections of 100 mcg of vitamin B12 are adequate for each dose. Replacement is usually given daily for the first week, weekly for the first month, and then monthly for life. The vitamin deficiency will recur if patients discontinue their therapy. Oral or sublingual methylcobalamin (1 mg/day) may be used instead of parenteral therapy once initial correction of the deficiency has occurred. Oral or sublingual replacement is effective, even in pernicious anemia, since approximately 1% of the dose is absorbed in the intestine via passive diffusion in the absence of active transport. It must be continued indefinitely and serum vitamin B12 levels must be monitored to ensure adequate replacement. For patients with neurologic symptoms caused by vitamin B12 deficiency, long-term parenteral vitamin B12 therapy is prudent. Because many patients are concurrently folic acid deficient from intestinal mucosal atrophy, simultaneous folic acid replacement (1 mg daily) is recommended for the first several months of vitamin B12 replacement.

Patients respond to therapy with an immediate improvement in their sense of well-being. Hypokalemia may complicate the first several days of therapy, particularly if the anemia is severe. A brisk reticulocytosis occurs in 5–7 days, and the hematologic picture normalizes in 2 months.

Central nervous system symptoms and signs are reversible if they are of relatively short duration (less than 6 months) but are likely permanent if of longer duration. Red blood cell transfusions are rarely needed despite the severity of anemia, but when given, diuretics are also recommended to avoid heart failure because this anemia develops slowly and the plasma volume is increased.

When to Refer

Referral to a hematologist is not usually necessary.

FOLIC ACID DEFICIENCY

ESSENTIALS OF DIAGNOSIS

- Macrocytic anemia.
- Megaloblastic blood smear (macro-ovalocytes and hypersegmented neutrophils).
- Reduced folic acid levels in red blood cells or serum.
- Normal serum vitamin B12 level.

General Considerations

Folic acid is the term commonly used for pteroylmonoglutamic acid. Folic acid is present in most fruits and vegetables (especially citrus fruits and green leafy vegetables). Daily dietary requirements are 50–100 mcg. Total body stores of folic acid are approximately 5 mg, enough to supply requirements for 2–3 months.

Alcoholic or anorectic patients, persons who do not eat fresh fruits and vegetables, and those who overcook their food are candidates for folic acid deficiency. Reduced folic acid absorption is rarely seen, since absorption occurs from the entire gastrointestinal tract. However, drugs such as phenytoin, trimethoprim-sulfamethoxazole, or sulfasalazine may interfere with its absorption. Folic acid absorption is poor in some patients with vitamin B12 deficiency due to gastrointestinal mucosal atrophy. Folic acid requirements are increased in pregnancy, hemolytic anemia, and exfoliative skin disease, and in these cases the increased requirements (five to ten times normal) may not be met by a normal diet.

Causes of folic acid deficiency:

Dietary deficiency
Decreased absorption
Tropical sprue
Drugs: phenytoin, sulfasalazine, trimethoprim-sulfamethoxazole
Concurrent vitamin B12 deficiency
Increased requirement
Chronic hemolytic anemia
Pregnancy
Exfoliative skin disease
Excess loss: hemodialysis
Inhibition of reduction to active form Methotrexate

Clinical Findings

A. Symptoms and Signs

The clinical features are similar to those of vitamin B12 deficiency. However, isolated folic acid deficiency does not result in the neurologic abnormalities of vitamin B12 deficiency.

B. Laboratory Findings

Megaloblastic anemia is identical to anemia resulting from vitamin B12 deficiency (see above). A red blood cell folic acid level below 150 ng/mL (340 nmol/L) is diagnostic of folic acid deficiency. The red blood cell folic acid level is preferred over the serum folic acid level because the former reflects body stores over the life span of the red blood cell, while the latter reflects immediate labile serum levels rather than body stores. Usually the serum vitamin B12 level is normal, and it should always be measured when folic acid deficiency is suspected. In some instances, folic acid deficiency is a consequence of the gastrointestinal mucosal megaloblastosis from vitamin B12 deficiency.

Differential Diagnosis

The megaloblastic anemia of folic acid deficiency should be differentiated from vitamin B12 deficiency by the finding of a normal vitamin B12 level and a reduced red blood cell (or serum) folic acid level. Alcoholic patients, who often have nutritional deficiency, may also have anemia of liver disease. Anemia of liver disease causes a macrocytic anemia but does not produce megaloblastic morphologic changes in the peripheral blood; rather, target cells are present. Hypothyroidism is associated with mild macrocytosis and also with pernicious anemia.

Treatment

Folic acid deficiency is treated with daily oral folic acid (1 mg). The response is similar to that seen in the treatment of vitamin B12 deficiency, with rapid improvement and a sense of well-being, reticulocytosis in 5–7 days, and total correction of hematologic abnormalities within 2 months. Large doses of folic acid may produce hematologic responses in cases of vitamin B12 deficiency but permit neurologic damage to progress; hence, obtaining a serum vitamin B12 level in suspected folic acid deficiency is paramount.

When to Refer

Referral to a hematologist is not usually necessary.

HEMOLYTIC ANEMIAS

The hemolytic anemias are a group of disorders in which red blood cell survival is reduced, either episodically or continuously. The bone marrow has the ability to increase erythroid production up to eightfold in response to reduced red cell survival, so anemia will be present only when the ability of the bone marrow to

compensate is outstripped. This will occur when red cell survival is extremely short or when the ability of the bone marrow to compensate is impaired.

Hemolytic disorders are generally classified according to whether the defect is intrinsic to the red cell or due to some external factor.

Classification of hemolytic anemias:

Intrinsic

- Membrane defects: hereditary spherocytosis, hereditary elliptocytosis, paroxysmal nocturnal hemoglobinuria
- Glycolytic defects: pyruvate kinase deficiency, severe hypophosphatemia
- Oxidation vulnerability: glucose-6-phosphate dehydrogenase deficiency, methemoglobinemia
- Hemoglobinopathies: sickle cell syndromes, thalassemia, unstable hemoglobins, methemoglobinemia

Extrinsic

- Immune: autoimmune, lymphoproliferative disease, drug-induced
- Microangiopathic: thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, valve hemolysis, metastatic adenocarcinoma, vasculitis, copper overload
- Infection: Plasmodium, Clostridium, Borrelia
- Hypersplenism
- Burns

Intrinsic defects have been described in all components of the red blood cell, including the membrane, enzyme systems, and hemoglobin; most of these disorders are hereditary. Hemolytic anemias due to external factors are immune and microangiopathic hemolytic anemias and infections of red blood cells.

Certain laboratory features are common to all hemolytic anemias. Haptoglobin, a normal plasma protein that binds and clears free hemoglobin released into plasma, may be depressed in hemolytic disorders. However, the haptoglobin level is influenced by many factors and is not always a reliable indicator of hemolysis, particularly in end-stage liver disease (its site of synthesis). When intravascular hemolysis occurs, transient hemoglobinemia occurs. Hemoglobin is filtered through the glomerulus and is usually reabsorbed by tubular cells. Hemoglobinuria will be present only when the capacity for reabsorption of hemoglobin by renal tubular cells is exceeded. In the absence of hemoglobinuria, evidence for prior intravascular hemolysis is the presence of hemosiderin in shed renal tubular cells (positive urine hemosiderin). With severe intravascular hemolysis, hemoglobinemia and methemalbuminemia may be present. Hemolysis increases the indirect bilirubin, and the total bilirubin may rise to 4 mg/dL (68 mcmol/L). Bilirubin levels higher than this may indicate some degree of hepatic dysfunction. Serum LD levels are strikingly elevated in cases of microangiopathic

hemolysis (thrombotic thrombocytopenic purpura, hemolyticuremic syndrome) and may be elevated in other hemolytic anemias.

APLASTIC ANEMIA

ESSENTIALS OF DIAGNOSIS

- Pancytopenia.
- No abnormal hematopoietic cells seen in blood or bone marrow.
- Hypocellular bone marrow.

General Considerations

Aplastic anemia is a condition of bone marrow failure that arises from suppression of, or injury to, the hematopoietic stem cell. The bone marrow becomes hypoplastic, fails to produce mature blood cells, and pancytopenia develops.

There are a number of causes of aplastic anemia. Direct hematopoietic stem cell injury may be caused by radiation, chemotherapy, toxins, or pharmacologic agents. Systemic lupus erythematosus may rarely cause suppression of the hematopoietic stem cell by an IgG autoantibody directed against the hematopoietic stem cell. However, the most common pathogenesis of aplastic anemia appears to be autoimmune suppression of hematopoiesis by a T-cell-mediated cellular mechanism, so called “idiopathic” aplastic anemia. In some cases of “idiopathic” aplastic anemia, defects in maintenance of the hematopoietic stem cell telomere length (dyskeratosis congenita) or in DNA repair pathways (Fanconi anemia) have been identified and are likely linked to both the initiation of bone marrow failure and the propensity to later progress to myelodysplasia, PNH, or AML. Complex detrimental immune responses to viruses can also cause aplastic anemia.

Causes of aplastic anemia:

- Autoimmune: idiopathic, systemic lupus erythematosus
- Congenital: defects in telomere length maintenance or DNA repair (rare)
- Chemotherapy, radiotherapy
- Toxins: benzene, toluene, insecticides
- Drugs: chloramphenicol, phenylbutazone, gold salts, sulfonamides, phenytoin, carbamazepine, quinacrine, tolbutamide
- Post-viral hepatitis (A, B, C, E, G, non-A through -G)
- Non-hepatitis viruses (EBV, parvovirus, CMV, echovirus 3, others)
- Pregnancy
- Paroxysmal nocturnal hemoglobinuria

Clinical Findings

A. Symptoms and Signs

Patients come to medical attention because of the consequences of bone marrow failure. Anemia leads to symptoms of weakness and fatigue, neutropenia causes vulnerability to bacterial or fungal infections, and thrombocytopenia results

in mucosal and skin bleeding. Physical examination may reveal signs of pallor, purpura, and petechiae. Other abnormalities such as hepatosplenomegaly, lymphadenopathy, or bone tenderness should not be present, and their presence should lead to questioning the diagnosis.

B. Laboratory Findings

The hallmark of aplastic anemia is pancytopenia. However, early in the evolution of aplastic anemia, only one or two cell lines may be reduced.

Anemia may be severe and is always associated with reticulocytopenia. Red blood cell morphology is unremarkable, but there may be mild macrocytosis (increased MCV). Neutrophils and platelets are reduced in number, and no immature or abnormal forms are seen on the blood smear. The bone marrow aspirate and the bone marrow biopsy appear hypocellular, with only scant amounts of morphologically normal hematopoietic progenitors. The bone marrow karyotype should be normal (or germline if normal variant).

Differential Diagnosis Aplastic anemia must be differentiated from other causes of pancytopenia. Hypocellular forms of myelodysplasia or acute leukemia may occasionally be confused with aplastic anemia. These are differentiated by the presence of cellular morphologic abnormalities, increased percentage of blasts, or abnormal karyotype in bone marrow cells. Hairy cell leukemia has been misdiagnosed as aplastic anemia and should be recognized by the presence of splenomegaly and by abnormal lymphoid cells in a hypocellular bone marrow biopsy. Pancytopenia with a normocellular bone marrow may be due to systemic lupus erythematosus, disseminated infection, hypersplenism, nutritional (eg, vitamin B12 or folate) deficiency, or myelodysplasia. Isolated thrombocytopenia may occur early as aplastic anemia develops and may be confused with immune thrombocytopenia.

Treatment

Mild cases of aplastic anemia may be treated with supportive care, including erythropoietic (epoetin or darbepoetin) or myeloid (filgrastim or sargramostim) growth factors, or both. Red blood cell transfusions and platelet transfusions are given as necessary, and antibiotics are used to treat infections.

Severe aplastic anemia is defined by a neutrophil count of less than 500/mcL, platelets less than 20,000/mcL, reticulocytes less than 1%, and bone marrow cellularity less than 20%. The treatment of choice for young adults (under age 40 years) who have an HLA-matched sibling is allogeneic bone marrow transplantation. Children or young adults may also benefit from allogeneic bone marrow transplantation using an unrelated donor. Because of the increased risks associated with unrelated donor allogeneic bone marrow transplantation relative to sibling donors, this treatment is usually reserved for patients who have not responded to immunosuppressive therapy.

For adults over age 40 years or those without HLAmatched donors, the treatment of choice for severe aplastic anemia is immunosuppression with equine antithymocyte globulin (ATG) plus cyclosporine. Equine ATG is given in the

hospital in conjunction with transfusion and antibiotic support. A proven regimen is equine ATG 40 mg/kg/day intravenously for 4 days in combination with cyclosporine, 6 mg/kg orally twice daily. Equine ATG is superior to rabbit ATG, resulting in a higher response rate and better survival. ATG should be used in combination with corticosteroids (prednisone or methylprednisolone 1–2 mg/kg/day orally for 1 week, followed by a taper over 2 weeks) to avoid ATG infusion reactions and serum sickness. Responses usually occur in 1–3 months and are usually only partial, but the blood counts rise high enough to give patients a safe and transfusion-free life. The full benefit of immunosuppression is generally assessed at 4 months post-equine ATG. Cyclosporine is maintained at full dose for 6 months and then stopped in responding patients. Androgens (such as fluoxymesterone 10–20 mg/day orally in divided doses) have been widely used in the past, with a low response rate, and may be considered in mild cases. Androgens appear to partially correct telomere length maintenance defects and increase the production of endogenous erythropoietin. The thrombopoietin mimetic, eltrombopag, may help increase platelets (and also red blood cells and white blood cells) in patients with refractory aplastic anemia.

Course & Prognosis

Patients with severe aplastic anemia have a rapidly fatal illness if left untreated. Allogeneic bone marrow transplant from a HLA-matched sibling donor produces survival rates of over 80% in recipients under 20 years old and of about 65–70% in those 20- to 50-years-old. Respective survival rates drop 10–15% when the donor is HLA-matched but unrelated. Equine ATG-cyclosporine immunosuppressive treatment leads to a response in approximately 70% of patients (including those with hepatitis virus–associated aplastic anemia). Up to one-third of patients will relapse with aplastic anemia after ATG-based therapy. Clonal hematologic disorders, such as PNH, AML, or myelodysplasia, may develop in one-quarter of patients treated with immunosuppressive therapy after 10 years of follow-up. Factors that predict response to ATG-cyclosporine therapy are patient’s age, reticulocyte count, lymphocyte count, and age-adjusted telomere length of leukocytes at the time of diagnosis.

When to Refer

All patients should be referred to a hematologist.

When to Admit

Admission is necessary for treatment of neutropenic infection, the administration of ATG, or allogeneic bone marrow transplantation.

LEUKEMIAS & OTHER MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative disorders are due to acquired clonal abnormalities of the hematopoietic stem cell. Since the stem cell gives rise to myeloid, erythroid, and platelet cells, qualitative and quantitative changes are seen in all these cell lines.

Classically, the myeloproliferative disorders produce characteristic syndromes with well-defined clinical and laboratory features. However, these disorders are grouped together because they may evolve from one into another and because hybrid disorders are commonly seen. All of the myeloproliferative disorders may progress to AML. The Philadelphia chromosome seen in chronic myeloid leukemia (CML) was the first recurrent cytogenetic abnormality to be described in a human malignancy. Since that time, there has been tremendous progress in elucidating the genetic nature of these disorders, with identification of mutations in JAK2, MPL, CALR, CSF3R, and other genes.

Classification of myeloproliferative disorders:

- Myeloproliferative neoplasms
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocytosis
- Chronic myeloid leukemia
- Myelodysplastic syndromes
- Acute myeloid leukemia.

CHRONIC MYELOID LEUKEMIA

ESSENTIALS OF DIAGNOSIS

- Elevated white blood count.
- Markedly left-shifted myeloid series but with a low percentage of promyelocytes and blasts.
- Presence of bcr/abl gene (Philadelphia chromosome).

General Considerations

CML is a myeloproliferative disorder characterized by overproduction of myeloid cells. These myeloid cells continue to differentiate and circulate in increased numbers in the peripheral blood. CML is characterized by a specific chromosomal abnormality and specific molecular abnormality. The Philadelphia chromosome is a reciprocal translocation between the long arms of chromosomes 9 and 22. The portion of 9q that is translocated contains abl, a protooncogene that is the cellular homolog of the Ableson murine leukemia virus. The abl gene is received at a specific site on 22q, the break point cluster (bcr). The fusion gene bcr/abl produces a novel protein that differs from the normal transcript of the abl gene in that it possesses tyrosine kinase activity. This disorder is the first example of tyrosine kinase “addiction” by cancer cells. Early CML (“chronic phase”) does not behave like a malignant disease. Normal bone marrow function is retained, white blood cells differentiate and, despite some qualitative abnormalities, the neutrophils combat infection normally. However, untreated CML is inherently unstable, and without treatment the disease progresses to an accelerated and then acute blast phase, which is morphologically indistinguishable from acute leukemia. Remarkable advances in therapy have changed the natural history of the disease,

and the relentless progression to more advanced stages of disease is at least greatly delayed, if not eliminated.

Clinical Findings

A. Symptoms and Signs

CML is a disorder of middle age (median age at presentation is 55 years). Patients usually complain of fatigue, night sweats, and low-grade fevers related to the hypermetabolic state caused by overproduction of white blood cells. Patients may also complain of abdominal fullness related to splenomegaly. In some cases, an elevated white blood count is discovered incidentally. Rarely, the patient will present with a clinical syndrome related to leukostasis with blurred vision, respiratory distress, or priapism. The white blood count in these cases is usually greater than 1000,000/mcL (100×10^9/L) but less than 500,000/mcL (500×10^9/L). On examination, the spleen is enlarged (often markedly so), and sternal tenderness may be present as a sign of marrow overexpansion. In cases discovered during routine laboratory monitoring, these findings are often absent. Acceleration of the disease is often associated with fever in the absence of infection, bone pain, and splenomegaly.

B. Laboratory Findings

CML is characterized by an elevated white blood count; the median white blood count at diagnosis is 150,000/mcL (150×10^9/L), although in some cases the white blood cell count is only modestly increased. The peripheral blood is characteristic. The myeloid series is left shifted, with mature forms dominating and with cells usually present in proportion to their degree of maturation. Blasts are usually less than 5%. Basophilia and eosinophilia may be present. At presentation, the patient is usually not anemic. Red blood cell morphology is normal, and nucleated red blood cells are rarely seen. The platelet count may be normal or elevated (sometimes to strikingly high levels).

The bone marrow is hypercellular, with left-shifted myelopoiesis. Myeloblasts comprise less than 5% of marrow cells. The hallmark of the disease is that the bcr/abl gene is detected by the polymerase chain reaction (PCR) test in the peripheral blood.

A bone marrow examination is not necessary for diagnosis, although it is useful for prognosis and for detecting other chromosomal abnormalities in addition to the Philadelphia chromosome.

With progression to the accelerated and blast phases, progressive anemia and thrombocytopenia occur, and the percentage of blasts in the blood and bone marrow increases. Blast phase CML is diagnosed when blasts comprise more than 20% of bone marrow cells.

Differential Diagnosis

Early CML must be differentiated from the reactive leukocytosis associated with infection. In such cases, the white blood count is usually less than 50,000/mcL (50×10^9/L), splenomegaly is absent, and the bcr/abl gene is not present. CML must

be distinguished from other myeloproliferative disease. The hematocrit should not be elevated, the red blood cell morphology is normal, and nucleated red blood cells are rare or absent. Definitive diagnosis is made by finding the bcr/abl gene.

Treatment

Treatment is usually not emergent even with white blood counts over 200,000/mcL (200×10^9/L), since the majority of circulating cells are mature myeloid cells that are smaller and more deformable than primitive leukemic blasts. In the rare instances in which symptoms result from extreme hyperleukocytosis (priapism, respiratory distress, visual blurring, altered mental status), emergent leukapheresis is performed in conjunction with myelosuppressive therapy.

In chronic-phase CML, the goal of therapy is normalization of the hematologic abnormalities and suppression of the malignant bcr/abl-expressing clone. The treatment of choice consists of a tyrosine kinase inhibitor (eg, imatinib, nilotinib, dasatinib) targeting the aberrantly active abl kinase. It is expected that a hematologic complete remission, with normalization of blood counts and splenomegaly will occur within 3 months of treatment initiation. Second, a major cytogenetic response should be achieved, ideally within 3 months but certainly within 6 months. A major cytogenetic response is identified when less than 35% of metaphases contain the Philadelphia chromosome. Lastly, a major molecular response is desired within 12 months and is defined as a 3-log reduction of the bcr/abl transcript as measured by quantitative PCR. This roughly corresponds to a bcr/abl ratio (compared to abl) of less than 0.01. Patients who achieve this level of molecular response have an excellent prognosis, with 100% of them remaining progression-free at 8 years. On the other hand, patients have a worse prognosis if these targets are not achieved, cytogenetic or molecular response is subsequently lost, or new mutations or cytogenetic abnormalities develop.

Imatinib mesylate was the first tyrosine kinase inhibitor to be approved and it results in nearly universal (98%) hematologic control of chronic phase disease at a dose of 400 mg/day. The rate of a major molecular response with imatinib in chronic-phase disease is ~30% at 1 year. The second-generation tyrosine kinase inhibitors, nilotinib and dasatinib, have also been approved for use as front-line therapy and have been shown to significantly increase the rate of a major molecular response compared to imatinib (71% for nilotinib at 300–400 mg twice daily by 2 years, 64% for dasatinib at 100 mg/day by 2 years) and result in a lower rate of progression to advanced-stage disease. However, these agents can also salvage 90% of patients who do not respond to treatment with imatinib and may therefore be reserved for use in that setting. A dual bcr/abl tyrosine kinase inhibitor, bosutinib, was approved for patients who are resistant or intolerant to the other tyrosine kinase inhibitors. The complete cytogenetic response rate to bosutinib is 25% but it is not active against the T315I mutation.

Patients taking tyrosine kinase inhibitors should be monitored with a quantitative PCR assay. Those with a consistent increase in bcr/abl transcript or those with a suboptimal molecular response as defined above should undergo abl mutation testing and then be switched to an alternative tyrosine kinase inhibitor.

The T315I mutation in abl is specifically resistant to therapy with imatinib, dasatinib, nilotinib, and bosutinib but appears to be sensitive to the third-generation agent ponatinib. However, ponatinib is associated with a high rate of vascular thrombotic complications. Patients who cannot achieve a good molecular response to any of these agents or who progress following therapy should be considered for treatment with allogeneic stem cell transplantation.

Patients with advanced-stage disease (accelerated phase or myeloid/lymphoid blast crisis) should be treated with a tyrosine kinase inhibitor alone or in combination with myelosuppressive chemotherapy. The doses of tyrosine kinase inhibitors in that setting are usually higher than those appropriate for chronic-phase disease. Since the duration of response to tyrosine kinase inhibitors in this setting is limited, patients who have accelerated or blast phase disease should ultimately be considered for allogeneic stem cell transplantation.

Course & Prognosis

Since the introduction of imatinib therapy in 2001, and with the development of molecular-targeted agents, more than 80% of patients remain alive and without disease progression at 9 years. Patients with good molecular responses to tyrosine kinase inhibitor therapy have an excellent prognosis, with essentially 100% survival at 9 years, and it is likely that some fraction of these patients will be cured. Small studies suggest that some patients with complete molecular responses (undetectable bcr/abl) lasting more than 2 years can stop drug therapy without disease recurrence, but these findings are being confirmed in prospective studies.

When to Refer

All patients with CML should be referred to a hematologist.

When to Admit

Hospitalization is rarely necessary and should be reserved for symptoms of leukostasis at diagnosis or for transformation to acute leukemia.

ACUTE LEUKEMIA

ESSENTIALS OF DIAGNOSIS

- Short duration of symptoms, including fatigue, fever, and bleeding.
- Cytopenias or pancytopenia.
- More than 20% blasts in the bone marrow.
- Blasts in peripheral blood in 90% of patients.

General Considerations

Acute leukemia is a malignancy of the hematopoietic progenitor cell. These cells proliferate in an uncontrolled fashion and replace normal bone marrow elements. Most cases arise with no clear cause. However, radiation and some toxins (benzene) are leukemogenic. In addition, a number of chemotherapeutic agents (especially cyclophosphamide, melphalan, other alkylating agents, and etoposide) may cause leukemia. The leukemias seen after toxin or chemotherapy exposure

often develop from a myelodysplastic prodrome and are often associated with abnormalities in chromosomes 5 and 7. Those related to etoposide may have abnormalities in chromosome 11q23 (MLL locus).

Acute promyelocytic leukemia (APL) is characterized by chromosomal translocation t(15;17), which produces the fusion gene PML-RAR-alpha, which interacts with the retinoic acid receptor to produce a block in differentiation that can be overcome with pharmacologic doses of retinoic acid (see below).

Most of the clinical findings in acute leukemia are due to replacement of normal bone marrow elements by the malignant cells. Less common manifestations result from organ infiltration (skin, gastrointestinal tract, meninges). Acute leukemia is potentially curable with combination chemotherapy.

The lymphoblastic subtype of acute leukemia, ALL, comprises 80% of the acute leukemias of childhood. The peak incidence is between 3 and 7 years of age. It is also seen in adults, causing approximately 20% of adult acute leukemias. The myeloblastic subtype, AML, is primarily an adult disease with a median age at presentation of 60 years and an increasing incidence with advanced age.

Classification of the Leukemias

A. Acute Lymphoblastic Leukemia (ALL)

ALL is most usefully classified by immunologic phenotype as follows: common, early B lineage, and T cell. Hyperdiploidy (with more than 50 chromosomes), especially of chromosomes 4, 10 and 17, and translocation t(12;21) (TEL-AML1), is associated with a better prognosis. Unfavorable cytogenetics are hypodiploidy (less than 44 chromosomes), the Philadelphia chromosome t(9;22), the t(4;11) translocation, which has fusion genes involving the MLL gene at 11q23, and a complex karyotype with more than five chromosomal abnormalities.

B. Acute Myeloid Leukemia (AML)

AML is primarily categorized based on recurrent structural chromosomal and molecular abnormalities. The cytogenetic abnormalities can be identified on traditional karyotyping or metaphase FISH and the molecular abnormalities are identified by either targeted or genome-wide sequencing of tumor DNA. Favorable cytogenetics such as t(8;21) producing a chimeric RUNX1/RUNX1T1 protein and inv(16)(p13;q22) are seen in 15% of cases and are termed the “core-binding factor” leukemias. These patients have a higher chance of achieving both short- and long-term disease control. Unfavorable cytogenetics confer a very poor prognosis. These consist of isolated monosomy 5 or 7, the presence of two or more other monosomies, or three or more separate cytogenetic abnormalities. The majority of cases of AML are of intermediate risk by traditional cytogenetics and have either a normal karyotype or chromosomal abnormalities that do not confer strong prognostic significance. However, there are several recurrent gene mutations with prognostic significance in this subgroup. On the one hand, internal tandem duplication in the gene FLT3 occurs in ~30% of AML and is associated with a very poor prognosis. Other mutations conferring a poor prognosis occur in TET2, MLL-PTD, and ASXL1. On the other hand, a relatively favorable group of patients has been defined that includes mutations of nucleophosmin 1 (NPM1) and lacks the

internal tandem duplication of the FLT3 gene. Other mutations conferring a favorable prognosis occur in IDH1 or IDH2.

C. Acute Promyelocytic Leukemia (APL)

In considering the various types of AML, APL is discussed separately because of its unique biologic features and unique response to non-chemotherapy treatments. APL is characterized by the cytogenetic finding of t(15;17) and the fusion gene PML-RAR-alpha.

D. Acute Leukemia of Ambiguous Lineage

These leukemias consist of blasts that lack differentiation along the lymphoid or myeloid lineage or blasts that express both myeloid and lymphoid lineage-specific antigens (ie, mixed phenotype acute leukemias). This group is considered very high risk and has a poor prognosis.

Clinical Findings

A. Symptoms and Signs

Most patients have been ill only for days or weeks. Bleeding (usually due to thrombocytopenia) occurs in the skin and mucosal surfaces, with gingival bleeding, epistaxis, or menorrhagia. Less commonly, widespread bleeding is seen in patients with disseminated intravascular coagulation (DIC) (in APL and monocytic leukemia). Infection is due to neutropenia, with the risk of infection rising as the neutrophil count falls below 500/mcL (0.5×10^9/L). The most common pathogens are gram-negative bacteria (Escherichia coli, Klebsiella, Pseudomonas) or fungi (Candida, Aspergillus). Common presentations include cellulitis, pneumonia, and perirectal infections; death within a few hours may occur if treatment with appropriate antibiotics is delayed.

Patients may also seek medical attention because of gum hypertrophy and bone and joint pain. The most dramatic presentation is hyperleukocytosis, in which a markedly elevated circulating blast count (total white blood count greater than 100,000/mcL) leads to impaired circulation, presenting as headache, confusion, and dyspnea. Such patients require emergent chemotherapy with adjunctive leukapheresis as mortality approaches 40% in the first 48 hours.

On examination, patients appear pale and have purpura and petechiae; signs of infection may not be present. Stomatitis and gum hypertrophy may be seen in patients with monocytic leukemia, as may rectal fissures. There is variable enlargement of the liver, spleen, and lymph nodes. Bone tenderness may be present, particularly in the sternum, tibia, and femur.

B. Laboratory Findings

The hallmark of acute leukemia is the combination of pancytopenia with circulating blasts. However, blasts may be absent from the peripheral smear in as many as 10% of cases (“aleukemic leukemia”). The bone marrow is usually hypercellular and dominated by blasts. More than 20% marrow blasts are required to make a diagnosis of acute leukemia.

Hyperuricemia may be seen. If DIC is present, the fibrinogen level will be reduced, the prothrombin time prolonged, and fibrin degradation products or fibrin

D-dimers present. Patients with ALL (especially T cell) may have a mediastinal mass visible on chest radiograph. Meningeal leukemia will have blasts present in the spinal fluid, seen in approximately 5% of cases at diagnosis; it is more common in monocytic types of AML and can be seen with ALL.

The Auer rod, an eosinophilic needle-like inclusion in the cytoplasm, is pathognomonic of AML and, if seen, secures the diagnosis. The phenotype of leukemia cells is usually demonstrated by flow cytometry or immunohistochemistry. AML cells usually express myeloid antigens such as CD13 or CD33 and myeloperoxidase. ALL cells of B lineage will express CD19, common to all B cells, and most cases will express CD10, formerly known as the "common ALL antigen." ALL cells of T lineage will usually not express mature T-cell markers, such as CD3, CD4, or CD8, but will express some combination of CD2, CD5, and CD7 and will not express surface immunoglobulin. Almost all ALL cells express terminal deoxynucleotidyl transferase (TdT). The uncommon Burkitt type of ALL has a "lymphoma" phenotype, expressing CD19, CD20, and surface immunoglobulin but not TdT and is best treated with aggressive lymphoma regimens.

Differential Diagnosis

AML must be distinguished from other myeloproliferative disorders, CML, and myelodysplastic syndromes. Acute leukemia may also resemble a left-shifted bone marrow recovering from a previous toxic insult. If the diagnosis is in doubt, a bone marrow study should be repeated in several days to see if maturation has taken place. ALL must be separated from other lymphoproliferative disease such as CLL, lymphomas, and hairy cell leukemia. It may also be confused with the atypical lymphocytosis of mononucleosis and pertussis.

Treatment

Most patients up to age 60 with acute leukemia are treated with the objective of cure. The first step in treatment is to obtain complete remission, defined as normal peripheral blood with resolution of cytopenias, normal bone marrow with no excess blasts, and normal clinical status. The type of initial chemotherapy depends on the subtype of leukemia.

1. AML—Most patients with AML are treated with a combination of an anthracycline (daunorubicin or idarubicin) plus cytarabine, either alone or in combination with other agents. This therapy will produce complete remissions in 80–90% of patients under age 60 years and in 50–60% of older patients. Older patients with AML who are not candidates for traditional chemotherapy may be given 5-azacitidine, decitabine, or clofarabine initially with acceptable outcomes. APL is treated differently from other forms of AML. Induction therapy for APL should include all-trans-retinoic acid (ATRA) with arsenic trioxide with or without chemotherapy. With this approach, 90–95% of patients will achieve complete remission.

Once a patient has entered remission, post-remission therapy should be given with curative intent whenever possible. Options include standard chemotherapy and

stem cell transplantation (either autologous or allogeneic). The optimal treatment strategy depends on the patient's age and clinical status, and the genetic risk factor profile of the leukemia. Patients with a favorable genetic profile can be treated with chemotherapy alone or with autologous transplant with cure rates of 60–80%. Patients who do not enter remission (primary induction failure) or those with high-risk genetics have cure rates of less than 10% with chemotherapy alone and are referred for allogeneic stem cell transplantation. For intermediate-risk patients with AML, cure rates are 35–40% with chemotherapy and 40–60% with allogeneic transplantation. Targeted therapeutics with FLT3 inhibitors are in development and have preliminarily shown activity in patients with FLT3-positive AML. Patients over age 60 have had a poor prognosis, even in first remission, when treated with standard chemotherapy approaches, and only 10–20% become long-term survivors. The use of reduced-intensity allogeneic transplant appears to be improving the outcome for such patients, with initial studies suggesting that up to 40% of selected patients may be cured.

Once leukemia has recurred after initial chemotherapy, the prognosis is poor. For patients in second remission, transplantation offers a 20–30% chance of cure.

2. ALL—Adults with ALL are treated with combination chemotherapy, including daunorubicin, vincristine, prednisone, and asparaginase. This treatment produces complete remissions in 90% of patients. Those patients with Philadelphia chromosome-positive ALL (or bcr-abl positive ALL) should have a tyrosine kinase inhibitor, such as dasatinib, added to their initial chemotherapy. Older patients (over age 60) may be treated with a tyrosine kinase inhibitor–based regimen, and 90% can enter initial remission.

Remission induction therapy for ALL is less myelosuppressive than treatment for AML and does not necessarily produce marrow aplasia. After achieving complete remission, patients receive central nervous system prophylaxis so that meningeal sequestration of leukemic cells does not develop. As with AML, patients may be treated with either additional cycles of chemotherapy or high-dose chemotherapy and stem cell transplantation. Treatment decisions are made based on patient age and disease risk factors. Adults younger than 39 years have uniformly better outcomes when treated under pediatric protocols. Low-risk patients with ALL may be treated with chemotherapy alone with a 70% chance of cure. Intermediate-risk patients have a 30–50% chance of cure with chemotherapy, and high-risk patients are rarely cured with chemotherapy alone. Highrisk patients with adverse cytogenetics or poor responses to chemotherapy are best treated with allogeneic transplantation. Minimal residual disease testing will guide treatment decisions following induction therapy in the future. For patients with relapsed disease, the bispecific antibody blinatumomab has shown remarkable response rates as a bridge to transplantation and was approved for this indication in 2014.

Prognosis

Approximately 70–80% of adults with AML under age 60 years achieve complete remission and ~50% are cured using risk-adapted post-remission therapy. Older adults with AML achieve complete remission in up to 50% of instances. The

cure rates for older patients with AML have been very low (approximately 10–20%) even if they achieve remission and are able to receive post-remission chemotherapy. Reduced-intensity allogeneic transplantation is increasingly being utilized in order to improve on these outcomes. Patients younger than 39 years with ALL have excellent outcomes after undergoing chemotherapy followed by riskadapted intensification and transplantation (cure rates of 60–80%). Patients with adverse cytogenetics, poor response to chemotherapy, or older age have a much lower chance of cure (cure rates of 20–40%).

When to Refer

All patients should be referred to a hematologist.

When to Admit

Most patients with acute leukemia will be admitted for treatment.

CHRONIC LYMPHOCYTIC LEUKEMIA

ESSENTIALS OF DIAGNOSIS

- B-cell lymphocytosis greater than 5000/mcL.
- Coexpression of CD19, CD5 on lymphocytes.

General Considerations

CLL is a clonal malignancy of B lymphocytes. The disease is usually indolent, with slowly progressive accumulation of long-lived small lymphocytes. These cells are immuneincompetent and respond poorly to antigenic stimulation.

CLL is manifested clinically by immunosuppression, bone marrow failure, and organ infiltration with lymphocytes. Immunodeficiency is also related to inadequate antibody production by the abnormal B cells. With advanced disease, CLL may cause damage by direct tissue infiltration.

Information about CLL is evolving rapidly, with new findings in biology and new treatment options, and outcomes are improving significantly.

Clinical Findings

A. Symptoms and Signs

CLL is a disease of older patients, with 90% of cases occurring after age 50 years and a median age at presentation of 70 years. Many patients will be incidentally discovered to have lymphocytosis. Others present with fatigue or lymphadenopathy. On examination, 80% of patients will have lymphadenopathy and 50% will have enlargement of the liver or spleen.

The long-standing Rai classification system remains prognostically useful: stage 0, lymphocytosis only; stage I, lymphocytosis plus lymphadenopathy; stage II, organomegaly (spleen, liver); stage III, anemia; stage IV, thrombocytopenia. These stages can be collapsed into low risk (stages 0–I), intermediate risk (stage II), and high risk (stages III–IV).

CLL usually pursues an indolent course, but some subtypes behave more aggressively; a variant, prolymphocytic leukemia, is more aggressive. The

morphology of the latter is different, characterized by larger and more immature cells. In 5–10% of cases, CLL may be complicated by autoimmune hemolytic anemia or autoimmune thrombocytopenia. In approximately 5% of cases, while the systemic disease remains stable, an isolated lymph node transforms into an aggressive large cell lymphoma (**Richter syndrome**).

B. Laboratory Findings

The hallmark of CLL is isolated lymphocytosis. The white blood count is usually greater than 20,000/mcL (20×10^9/L) and may be markedly elevated to several hundred thousand. Usually 75–98% of the circulating cells are lymphocytes. Lymphocytes appear small and mature, with condensed nuclear chromatin, and are morphologically indistinguishable from normal small lymphocytes, but smaller numbers of larger and activated lymphocytes may be seen. The hematocrit and platelet count are usually normal at presentation. The bone marrow is variably infiltrated with small lymphocytes. The immunophenotype of CLL demonstrates coexpression of the B lymphocyte lineage marker CD19 with the T lymphocyte marker CD5; this finding is commonly observed only in CLL and mantle cell lymphoma. CLL is distinguished from mantle cell lymphoma by the expression of CD23, low expression of surface immunoglobulin and CD20, and the absence of a translocation or overexpression of cyclin D1. Patients whose CLL cells have mutated forms of the immunoglobulin gene (IgVH somatic mutation) have a more indolent form of disease; these cells typically express low levels of the surface antigen CD38 and do not express the zeta-associated protein (ZAP-70). Conversely, patients whose cells have unmutated IgVH genes and high levels of ZAP-70 expression do less well and require treatment sooner. The assessment of genomic changes by fluorescence in-situ hybridization (FISH) provides important prognostic information. The finding of deletion of chromosome 17p (TP53) confers the worst prognosis, while deletion of 11q (ATM) confers an inferior prognosis to the average genotype, and isolated deletion of 13q has a more favorable outcome.

Hypogammaglobulinemia is present in 50% of patients and becomes more common with advanced disease. In some, a small amount of IgM paraprotein is present in the serum.

Differential Diagnosis

Few syndromes can be confused with CLL. Viral infections producing lymphocytosis should be obvious from the presence of fever and other clinical findings; however, fever may occur in CLL from concomitant bacterial infection. Pertussis may cause a particularly high total lymphocyte count. Other lymphoproliferative diseases such as Waldenström macroglobulinemia, hairy cell leukemia, or lymphoma (especially mantle cell) in the leukemic phase are distinguished on the basis of the morphology and immunophenotype of circulating lymphocytes and bone marrow. Monoclonal B-cell lymphocytosis is a disorder characterized by fewer than 5000/mcL B-cells and is considered a precursor to B-CLL.

Treatment

Most cases of early indolent CLL require no specific therapy, and the standard of care for early-stage disease has been observation. Indications for treatment include progressive fatigue, symptomatic lymphadenopathy, anemia, or thrombocytopenia. These patients have either symptomatic and progressive Rai stage II disease or stage III/IV disease. Initial treatment choices for patients younger than age 70 years without significant comorbidities include the combination of fludarabine with cyclophosphamide and rituximab or the combination of bendamustine with rituximab. The latter combination is better tolerated and associated with fewer adverse events but results in a shorter time to progression.

For older patients or young patients with significant comorbidities, chlorambucil, 0.6–1 mg/kg, a well-tolerated agent given orally every 3 weeks for approximately 6 months, has been the standard therapy. The novel monoclonal antibody obinutuzumab, in combination with chlorambucil produces a significant number of responses (75%) including elimination of disease at the molecular level (in 17%) and offers another well-tolerated choice in this patient population. Lastly, the oral agent ibrutinib, an inhibitor of Bruton's tyrosine kinase, a key component in the B-cell receptor signaling pathway, has shown remarkable activity at a dose of 420 mg daily as a first-line agent in older patients, with an overall response rate of 71%, and an estimated progression-free survival rate of 75% at 26 months. The most common nonhematologic adverse events were diarrhea (50%), fatigue (32%), and nausea (18%). Caution should be exercised when this agent is used in conjunction with CYP3A inhibitors or inducers. In addition, there is a potential for serious bleeding when it is used in patients taking warfarin.

For patients with relapsed or refractory disease, both ibrutinib and idelalisib (a PI3 kinase delta inhibitor) demonstrate significant activity, even for patients with high-risk genetics. Both of these agents can be associated with marked lymphocytosis due to release of tumor cells from the lymph nodes into the peripheral blood. This results in a significant early reduction in lymphadenopathy but a potentially misleading, more delayed clearance of peripheral blood and bone marrow. In patients with deletion of chromosome 17p, treatment with ibrutinib can result in a sustained duration of response (85% at 2 years), a breakthrough in this disease. Idelalisib at 150 mg orally twice a day in combination with rituximab has shown similar activity in the relapsed setting across genetic risk groups. Adverse events with idelalisib include fever (29%), fatigue (24%), nausea (24%), and elevations in liver enzymes (35%).

Associated autoimmune hemolytic anemia or immune thrombocytopenia may require treatment with rituximab, prednisone, or splenectomy. Fludarabine should be avoided in patients with autoimmune hemolytic anemia since it may exacerbate it. Rituximab should be used with caution in patients with past HBV infection since HBV reactivation, fulminant hepatitis, and, rarely, death can occur without anti-HBV agent prophylaxis. Patients with recurrent bacterial infections and hypogammaglobulinemia benefit from prophylactic infusions of gamma globulin (0.4 g/kg/month), but this treatment is very expensive and can be justified only when these infections are severe. Patients undergoing therapy with a nucleoside

analogue (fludarabine, pentostatin) should receive anti-infective prophylaxis for Pneumocystis jirovecii pneumonia, herpes viruses, and invasive fungal infections until there is evidence of T-cell recovery.

Allogeneic transplantation offers potentially curative treatment for patients with CLL, but it should be used only in patients whose disease cannot be controlled by standard therapies. Nonmyeloablative allogeneic transplant has produced encouraging results in CLL. Some subtypes of CLL with genomic abnormalities such as chromosome 17p deletions have a sufficiently poor prognosis with standard therapies that early intervention with allogeneic transplant is being studied to assess whether it can improve outcomes.

Prognosis

Therapies have changed the prognosis of CLL. In the past, median survival was approximately 6 years, and only 25% of patients lived more than 10 years. Patients with stage 0 or stage I disease have a median survival of 10–15 years, and these patients may be reassured that they can live a normal life for many years. Patients with stage III or stage IV disease had a median survival of less than 2 years in the past, but with current therapies, 2-year survival is now more than 90% and the long-term outlook appears to be substantially changed. For patients with high-risk and resistant forms of CLL, there is evidence that allogeneic transplantation can overcome risk factors and lead to long-term disease control.

When to Refer

All patients with CLL should be referred to a hematologist.

When to Admit

Hospitalization is rarely needed.

Control questions

1. Structure and physiology of blood: plasma, leukocytes (leukocyte formula), monocytes and lymphocytes.
2. Normal limits of level of leukocytes, red blood cells and hemoglobin in serum of human blood.
3. The leukocytic formula of a healthy person.
4. In what part of the gastrointestinal tract is absorption of iron?
5. What chronic diseases lead to a violation of the processes of absorption of iron in the human body?
6. What kind of pathology of the gastrointestinal tract may develop hypochromic anemia?
7. In which pathology of the gastrointestinal tract is possible development of hyperchromic anemia?
8. Anemia - classification.
9. Acute post-hemorrhagic anemia - etiology, pathogenesis, clinical picture, pharmacotherapy.

10. Iron deficiency anemia: classification, etiology, pathogenesis, clinical picture, pharmacotherapy.
12. Pernicious anemia - etiology, pathogenesis, clinical picture, pharmacotherapy;
13. Folic deficiency anemia, etiology, pathogenesis, clinical picture, pharmacotherapy.
14. Hemolytic anemia: classification, etiology, pathogenesis, clinical picture, pharmacotherapy
15. Basic principles of pharmacotherapy for bleeding.
16. Phytotherapeutic agents and preparations of animal origin used in anemia.
17. Medications that suppress erythropoiesis. Indications for appointment.
18. Characteristics of drugs. Indications and contraindications for appointment. Undesirable effects.
19. Methemoglobinemia - etiology, pathogenesis, clinical picture, pharmacotherapy.
20. Leukemia - classification, characteristic.
21. Pathogenetic factors of leukemia development.
22. Acute leukemia - etiology, pathogenesis, clinical picture, pharmacotherapy, prognosis.
23. Chronic myeloid leukemia - etiology, pathogenesis, clinical picture, pharmacotherapy, prognosis.
24. Formula of blood in myeloid leukemia.
25. Chronic granulocytic leukemia leukemia - etiology, pathogenesis, clinical picture, pharmacotherapy, prognosis.
26. Chronic myeloid leukemia - etiology, pathogenesis, clinical picture, pharmacotherapy, prognosis.
27. Chronic lymphatic leukosis - etiology, pathogenesis, clinical picture, pharmacotherapy.
28. Formula of blood in lymphatic leukemia
29. Pharmacodynamics, pharmacokinetics, pharmacotoxicodynamics of substances that influence leukopoiesis.
30. To write recipes for drugs: sorbifer-durules, totem, methotrexate, vinblastin, vikasol, aminocaproic acid.
31. The role of pharmacist in preventing the development of defective anemia (iron, B12, folio deficiency).
32. The role of pharmacist in improving the quality of life of patients with leukemia.

List of practical works

A. Homework.

1. To study the etiology and pathogenesis of anemia and leukemia.
2. To know the classification and clinic of anemia and leukemia.
2. To study the main directions of treatment of these diseases.
4. To be able to provide first aid to a patient with acute blood loss.

B. Independent practical work at the lesson:

1. The cure of the thematic patient in the ward.

2. To study its history of illness (data laboratory-instrumental studies, conclusions of consultants) and a letter of medical appointments.
3. Pay special attention to blood tests.
4. To distinguish signs in the subjective study of the patient characterizing the violation of iron metabolism or myeloid leukemia.
5. Determine the group of drugs needed by the patient.
6. To distinguish signs at objective research of the patient characterizing a violation of an exchange of iron or myeloid leukemia.
7. To allocate clinical and instrumental criteria for assessing the severity of the disease.
8. To carry out the analysis of laboratory data characterize the disease data.
9. To choose a method of therapy depending on serum hemoglobin level and concomitant pathology.
10. To select a specific patient with the specified pathology, the necessary drugs, to select criteria of therapeutic effectiveness and safety.
11. Appoint a combination therapy.

Control the level of knowledge

1. Fill in the table: "Methods of studying patients with a hematological profile".

Research methods	**The essence of the method**	**Clinical significance**
Questioning Review Palpation Percussion Auscultation		
General clinical examination of blood		
Whey iron		
Sternal puncture		
Ultrasound		

2. Choose the symptoms that are most common in iron deficiency anemia and for pernicious anemia. Answer the table as follows:

Symptoms	**Iron deficiency anemia**	**Pernicious anemia**

1. Shortness of breath 2. Noise in the ears 3. Heartbeat 4. Increase the color index 5. Reducing the amount of leukocytes in the blood 6. Reducing the amount of red blood cells in the blood 7. Reducing the color index 8. Fainting of nails 9. Loss of hair 10. Distortion of taste 11. Red, "varnished" tongue 12. Atrophy of muscles 13. Polyneuritis 14. Pathological forms of erythrocytes in the blood		

Note: the correct answers are marked with a "+" sign

3. Specify the pharmacological groups and standard drugs used to treat major diseases of the blood system.

Disease	**Pharmacological groups**	**Drugs**	**Dose**	**Multiplicity and path introduction**
Iron deficiency anemia Folly deficiency anemia B12-deficiency anemia Aplastic anemia Hemolytic anemia Leukemia				

4. Choose which of the listed etiological factors may be the cause of B12-deficiency and hemolytic anemia:

Etiological factors	**B12-deficiency anemia**	**Hemolytic anemia**

1. Hereditary predisposition 2. Intoxication with heavy metals 3. Resection of the intestine 4. Resection of the stomach 5. Intoxication with drugs 6. Glandular invasion 7. Immunopathology 8. Atrophic gastritis 9. Malaria 10. Genetic defect of erythrocytes		

Note: the correct answers are marked with a "+" sign

5. List the factors that are relevant in the pathogenesis of iron deficiency anemia. Answer the table as follows:

Pathogenetic factors	Answer
1. Reduction of hemoglobin synthesis 2. Reduced synthesis of tissue enzymes 3. Reduction of oxygen transport to tissues 4. Disturbance of membranes of red blood cells 5. Violation of the function of the bone marrow 6. Violation of the development of erythropoietin by the kidneys 7. Hypoxia of tissues 8. Decreased glucocorticoid function of the adrenal glands	

Note: the correct answers are marked with a "+" sign

6. Fill in the table: "Pharmacotherapy for acute leukemia".

Directions of pharmacotherapy	Pharmacological groups	Drugs
1. Immunosuppressive therapy 2. Antibacterial therapy 3. Fighting anemia		

Solution of situational tasks

1. A patient, 42 years old, with a body weight of 67 kg, suffering from severe iron deficiency anemia, takes iron preparations.

After what time from the onset of the reticulocytosis will appear in blood, as a reaction of hematopoiesis to iron preparations?

2. A patient, 67 years old, with a body weight of 86 years, with the diagnosis of hypochromic anemia, continued to take iron preparations. On the background of treatment, it appeared constipation.

Explain the cause and mechanism of their occurrence.

3. The patient, 38 years old, with a weight of 65 kg, entered the therapeutic department with a diagnosis: Adison-Birmer's disease. In the history of stomach ulcer. Two years ago resection of the stomach was performed.

Explain the cause of the disease. Assign a treatment plan indicating the drugs and how to administer them.

4. Releasing from the pharmacy an iron preparation for oral intake - ferrolex, it is necessary to warn the patient that this drug can not be washed with milk and used with it dairy products.

Explain why.

5. A woman, 26 years old, complains about general weakness, increased fragility of nails, loss of hair. Objectively: pulse - 94 beats per minute, AT - 110/70 mm Hg. Art. The skin is pale. Blood analysis: Hb - 90 g / l, er - 3,5 • 1012 / l, CP - 0,7, ESR - 20 mm / h. The level of serum iron is 8.7 μmol / l.

What drugs should appoint this patient? Explain the mechanism of their action.

6. A man, 45, complains of general weakness, dizziness. For 15 years, suffering from ulcerous disease 12 gastric ulcer. Objectively: the temperature is 36.5 ° C, the BM is 20 per min, the pulse is 96 per min, the AT is 115/70 mm Hg. Skin and mucous membranes are pale. In the blood of er - 3.8 • 10^{12} /liter, Hb - 90 g/liter. Gregersen's reaction is weakly positive.

What is the treatment of anemic syndrome in this case?

7. A patient D., 43 years old, was admitted to the hospital with complaints of weakness, dizziness, shortness of breath with insignificant physical activity. Anemia was detected in the blood test (Hb - 60 g/l, col. Count - 1,2). When viewed, the tongue is glossite. In the study of bone marrow punctate, it is a megaloblastic type of hematopoiesis.

What type of anemia can you think of? Suggest methods for follow up and pharmacotherapy for the ill.

8. A patient T., 70 years old, suffered an operation of a large resection of the small intestine on the oncological disease.

What type of anemia can develop in this case? What methods of prevention and treatment can you recommend?

9. Patient K., 54 years old, is examined by a gynecologist in connection with uterine bleeding. Development of what type of anemia can be in this case?

Propose preventive measures and principles of pharmacotherapy.

10. A patient with a disease of the hematopoietic system is prescribed a drug containing iron (ferrolex).

Give testimony to the appointment of this remedy.

11. In a patient, 60 years old, who for 10 years suffered from hemorrhoids, chronic posthemorrhagic anemia developed.

Appointment, which drug is most appropriate in this case?

12. A boy, 12, a year ago, was operated on for a combined mitral heart disease: a mitral valve prosthesis. In order to prevent thromboembolic complications, an indirect anticoagulant - sinkumar - is constantly receiving. The prothrombin index is stable at a level of 50-55%. In connection with the activation of the rheumatic process, the intramuscularly prescribed benzylpenicillin is 1,000,000 OD 8 times a day and sodium diclofenac is injected intravenously to 0.025 g 3 times a day. After 7 days, the child appeared black feces. The prothrombin index declined to 12%.

Explain the cause and mechanism of the development of the complication. Give suggestions on how to change pharmacotherapy to correct the complications that have occurred.

13. In the patient 15 years after the flu, hemorrhagic eruptions on the legs appeared - symmetrical, some at the stage of fading with pigmentation of the skin.

Your previous diagnosis. Associate Therapy.

Test tasks

1. For iron deficiency anemia is characterized by:
1. colonies
2. atrophic gastritis
3. rncertainty about the move
4. "lacquered tongue"
5. presence in the blood of megaloblasts.

2. For the treatment of iron deficiency anemia, the following treatment options are used:
1. iron preparation
2. iron preparation + tsiankobalamin
3. iron preparation + folic acid
4. iron preparation + vitamin B6
5. iron preparation + vitamin A

3. When taking iron products may occur:
1. dyspeptic syndrome
2. violation of teeth growth in children

3. pyelonephritis
4. myocarditis
5. myopia

4. When treating B12 - deficiency anemia, the following treatment option is used:
1. preparation of iron + vitamin B12
2. vitamin B12 + folic acid
3. vitamin B12 + folic acid + iron preparation
4. monotherapy vitamin B12
5. blood transfusion.

5. When chronic blood loss develops:
1. aplastic anemia
2. B12 - deficiency anemia
3. folio-deficiency anemia
4. Hyperchromic anemia
5. All statements are incorrect

6. Name the drug for substitution therapy for iron deficiency anemia:
1. pentoxyl
2. folic acid
3. cyanocobalamin
4. ferrum lek
5. ascorbiinic acid

7. With deficiency in the body of vitamin B12 develops:
1. Hypochromic anemia
2. Hyperchromic anemia
3. Post-hemorrhagic anemia
4. Agranulocytosis
5. Leukemia

8. In the absence of a pharmacy in the pyramid it can be replaced by:
1. Feprazon
2. Ferrolex
3. Fepranon
4. Festal
5. Fenofibrate

9. Iron deficiency anemia is:
1. Hypochromatic.
2. Normochromic.
3. Hyperchromic.

10. Defeat of the nervous system (funicular myelosis) is especially characteristic of:
1. Folly-deficiency anemia
2. Iron deficiency anemia
3.Hhypochromic anemia
4. B12 - deficiency anemia
5. Aplastic anemia.

11. Leukemia is:
1. benign process
2. malignant process
3. autoimmune disease
4. allergic diseases

12. Cytostatics used in treatment:
1. aplastic anemia
2. scarce anemia
3. hyperchromic anemia
4. leukemia
5. hypochromic anemia

13. Before leukemia leads:
1. presence of a deficiency of iron
2. presence of deficiency of vitamin B12
3. presence of deficiency of folic acid
4. presence of chromosomal abnormalities
5. excess vitamin C.

14. What method of treatment of acute leukemia is expedient:
1. Glucocorticoids
2. Antibiotics
3. Polychemotherapy
4. Monochemotherapy
5. Bone marrow transplantation

15. What should be assigned to patients with chronic lymphocytic leukemia in stage 1?
1. Vitamin therapy
2. Polychemotherapy
3. Glucocorticoids
4. Small doses of cytostatics
5. Antibiotics.

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TOPIC 16. Pharmacotherapy of violations of water-electrolyte exchange and acid-base balance.

Actuality of topic.

In a healthy person, the volume and composition of the body's fluids is practically constant. Disorders of the water and electrolyte balance, as a rule, begin with a change of volitional status. The processes of normal human life are possible only with the preservation of homeostasis. Maintenance of the relative dynamic constancy of the internal environment is ensured by regulatory mechanisms, among which one of the leading roles is the acid-base balance. Correction of violations of water-electrolyte balance and acid-base balance is a prerequisite for the successful treatment of patients of any profile. Underestimation of violations of water-electrolyte exchange in a number of independent diseases (diabetes mellitus, myocardial infarction, pulmonary edema, shock), as well as in the uncontrolled use of a number of drugs (diuretics, cardiac glycosides, glucocorticosteroids, antibiotics, etc.). It leads to gross violations homeostasis and may become irreversible. This theme should help to diagnose the presence of water-electrolyte disorders in a timely manner, to evaluate their significance in the pathogenesis of the underlying disease and to make a rational choice of drugs that eliminate detected violations of the water-electrolyte balance, taking into account their maximum efficiency and safety.

Purpose of the lesson: The student should know the types of violations of water-electrolyte exchange: etiology, pathogenesis, clinic, methods of diagnosis and treatment. Have a concept about rehydration therapy. To master the topics of alkalosis and acidosis: classification, etiology, pathogenesis, clinic, diagnostic methods, principles of pharmacotherapy.

ASSESSMENT OF THE PATIENT

The diagnosis and treatment of fluid and electrolyte disorders are based on (1) careful history, (2) physical examination and assessment of total body water and its distribution, (3) serum electrolyte concentrations, (4) urine electrolyte concentrations, and (5) serum osmolality. The pathophysiology of electrolyte disorders is rooted in basic principles of total body water and its distribution across fluid compartments.

A. Body Water and Fluid Distribution

Total body water is different in men than in women, and it decreases with aging. Approximately 50–60% of total body weight is water; two-thirds (40% of body weight) is intracellular, while one-third (20% of body weight) is extracellular. One-fourth of extracellular fluid (5% of body weight) is intravascular. Water may be lost from either or both compartments (intracellular and extracellular). Changes

in total body water content are best evaluated by documenting changes in body weight. Effective circulating volume may be assessed by physical examination (eg, blood pressure, pulse, jugular venous distention). Quantitative measurements of effective circulating volume and intravascular volume may be invasive (ie, central venous pressure or pulmonary wedge pressure) or noninvasive (ie, inferior vena cava diameter and right atrial pressure by echocardiography) but still require careful interpretation.

Total body water (as percentage of body weight) in relation to age and sex:
Age 18–40: Male - 60% Female - 50%
Age 41–60: Male - 60–50% Female - 50–40%
Age Over 60: Male 50% Female - 40%

B. Serum Electrolytes

The cause of electrolyte disorders may be determined by reviewing the history, underlying diseases, and medications.

C. Evaluation of Urine

The urine concentration of an electrolyte indicates renal handling of the electrolyte and whether the kidney is appropriately excreting or retaining the electrolyte. A 24-hour urine collection for daily electrolyte excretion is the gold standard for renal electrolyte handling, but it is slow and onerous. A more convenient method is the fractional excretion of an electrolyte calculated from a spot urine sample. A low fractional excretion indicates renal reabsorption (high avidity or electrolyte retention), while a high fractional excretion indicates renal wasting (low avidity or electrolyte excretion). Thus, the fractional excretion helps the clinician determine whether the kidney's response is appropriate for a specific electrolyte disorder.

D. Serum Osmolality

Solute concentration is measured by osmolality in millimoles per kilogram. Osmolarity is measured in millimoles of solute per liter of solution. At physiologic solute concentrations (normally 285–295 mmol/kg), the two measurements are clinically interchangeable. Tonicity refers to osmolytes that are impermeable to cell membranes. Differences in osmolyte concentration across cell membranes lead to osmosis and fluid shifts, stimulation of thirst, and secretion of antidiuretic hormone (ADH). Substances that easily permeate cell membranes (eg, urea, ethanol) are ineffective osmoles that do not cause fluid shifts across fluid compartments.

Sodium is the major extracellular cation; doubling the serum sodium in the formula for estimated osmolality accounts for counterbalancing anions. A discrepancy between measured and estimated osmolality of greater than 10 mmol/kg suggests an osmolal gap, which is the presence of unmeasured osmoles such as ethanol, methanol, isopropanol, and ethylene glycol.

DISORDERS OF SODIUM CONCENTRATION

HYPONATREMIA

ESSENTIALS OF DIAGNOSIS

- Volume status and serum osmolality are essential to determine etiology.
- Hyponatremia usually reflects excess water retention relative to sodium rather than sodium deficiency.
- The sodium concentration is not a measure of total body sodium.
- Hypotonic fluids commonly cause hyponatremia in hospitalized patients.

General Considerations

Defined as a serum sodium concentration less than 135 mEq/L (135 mmol/L), hyponatremia is the most common electrolyte abnormality in hospitalized patients. The clinician should be wary about hyponatremia since mismanagement can result in neurologic catastrophes from cerebral osmotic demyelination. Indeed, iatrogenic complications from aggressive or inappropriate therapy can be more harmful than hyponatremia itself. A common misconception is that the sodium concentration is a reflection of total body sodium or total body water. In fact, total body water and sodium can be low, normal, or high in hyponatremia since the kidney independently regulates sodium and water homeostasis. Most cases of hyponatremia reflect water imbalance and abnormal water handling, not sodium imbalance, indicating the primary role of ADH in the pathophysiology of hyponatremia. A diagnostic algorithm using serum osmolality and volume status separates the causes of hyponatremia into therapeutically useful categories.

Etiology

A. Isotonic & Hypertonic Hyponatremia

Serum osmolality identifies isotonic and hypertonic hyponatremia, although these cases can often be identified by careful history or previous laboratory tests.

Isotonic hyponatremia is seen with severe hyperlipidemia and hyperproteinemia. Lipids (including chylomicrons, triglycerides, and cholesterol) and proteins (greater than 10 g/dL [100 g/L], eg, paraproteinemias and intravenous immunoglobulin therapy) interfere with the measurement of serum sodium, causing pseudohyponatremia. Serum osmolality is isotonic because lipids and proteins do not affect osmolality measurement. Newer sodium assays using ion-specific electrodes on undiluted serum specimens (ie, the direct assay method) will not result in pseudohyponatremia.

Hypertonic hyponatremia occurs with hyperglycemia and mannitol administration for increased intracranial pressure. Glucose and mannitol osmotically pull intracellular water into the extracellular space. The translocation of water lowers the serum sodium concentration. Translocational hyponatremia is not pseudohyponatremia or an artifact of sodium measurement. The sodium concentration falls 2 mEq/L (or 2 mmol/L) for every 100 mg/dL (or 5.56 mmol/L) rise in glucose when the glucose concentration is between 200 mg/dL and 400 mg/dL (11.1 mmol/L and 22.2 mmol/L). If the glucose concentration is more than

400 mg/dL, the sodium concentration falls 4 mEq/L for every 100 mg/dL rise in glucose. There is some controversy about the correction factor for the serum sodium in the presence of hyperglycemia. Many guidelines recommend a correction factor, whereby the serum sodium concentration decreases by 1.6 mEq/L (or 1.6 mmol/L) for every 100 mg/dL (5.56 mmol/L) rise in plasma glucose above normal, but there is evidence that the decrease may be greater when patients have more severe hyperglycemia (greater than 400 mg/dL or 22.2 mmol/L) or volume depletion, or both. One group has suggested (based on short-term exposure of normal volunteers to markedly elevated glucose levels) that when the serum glucose is more than 200 mg/dL, the serum sodium concentration decreases by at least 2.4 mEq/L (or 2.4 mmol/L).

B. Hypotonic Hyponatremia

Most cases of hyponatremia are hypotonic, highlighting sodium's role as the predominant extracellular osmole. The next step is classifying hypotonic cases by the patient's volume status.

1. Hypovolemic hypotonic hyponatremia—Hypovolemic hyponatremia occurs with renal or extrarenal volume loss and hypotonic fluid replacement. Total body sodium and total body water are decreased. To maintain intravascular volume, the pituitary increases ADH secretion, causing free water retention from hypotonic fluid replacement. The body sacrifices serum osmolality to preserve intravascular volume. In short, losses of water and salt are replaced by water alone. Without ongoing hypotonic fluid intake, the renal or extrarenal volume loss would produce hypovolemic hypernatremia.

Cerebral salt wasting is a distinct and rare subset of hypovolemic hyponatremia seen in patients with intracranial disease (eg, infections, cerebrovascular accidents, tumors, and neurosurgery). Clinical features include refractory hypovolemia and hypotension, often requiring continuous infusion of isotonic or hypertonic saline and ICU monitoring. The exact pathophysiology is unclear but includes renal sodium wasting possibly through B-type natriuretic peptide, ADH release, and decreased aldosterone secretion.

2. Euvolemic hypotonic hyponatremia—Euvolemic hyponatremia has the broadest differential diagnosis. Most causes are mediated directly or indirectly through ADH, including hypothyroidism, adrenal insufficiency, medications, and the syndrome of inappropriate ADH (SIADH). The exceptions are primary polydipsia, beer potomania, and reset osmostat.

A. Hormonal abnormalities—Hypothyroidism and adrenal insufficiency can cause hyponatremia. Exactly how hypothyroidism induces hyponatremia is unclear but may be related to ADH. Adrenal insufficiency may be associated with the hyperkalemia and metabolic acidosis of hypoaldosteronism. Cortisol provides feedback inhibition for ADH release.

B. Thiazide diuretics and other medications— Thiazides induce hyponatremia typically in older female patients within days of initiating therapy.

The mechanism appears to be a combination of mild diuretic-induced volume contraction, ADH effect, and intact urinary concentrating ability resulting in water retention and hyponatremia. Loop diuretics do not cause hyponatremia as frequently because of disrupted medullary concentrating gradient and impaired urine concentration.

Nonsteroidal anti-inflammatory drugs (NSAIDs) increase ADH by inhibiting prostaglandin formation. Prostaglandins and selective serotonin reuptake inhibitors (eg, fluoxetine, paroxetine, and citalopram) can cause hyponatremia, especially in geriatric patients. Enhanced secretion or action of ADH may result from increased serotonergic tone. Angiotensin-converting enzyme (ACE) inhibitors do not block the conversion of angiotensin I to angiotensin II in the brain. Angiotensin II stimulates thirst and ADH secretion. Hyponatremia during amiodarone loading has been reported; it usually improves with dose reduction.

Abuse of 3,4-methylenedioxymethamphetamine (MDMA, also known as Ecstasy) can lead to hyponatremia and severe neurologic symptoms, including seizures, cerebral edema, and brainstem herniation. MDMA and its metabolites increase ADH release from the hypothalamus. Primary polydipsia may contribute to hyponatremia since MDMA users typically increase fluid intake to prevent hyperthermia.

C. Nausea, pain, surgery, and medical procedures—Nausea and pain are potent stimulators of ADH release. Severe hyponatremia can develop after elective surgery in healthy patients, especially premenopausal women. Hypotonic fluids in the setting of elevated ADH levels can produce severe, life-threatening hyponatremia. Medical procedures such as colonoscopy have also been associated with hyponatremia.

D. HIV infection—Hyponatremia is seen in up to 50% of hospitalized HIV-infected patients and 20% of ambulatory HIV-infected patients. The differential diagnosis is broad: medication effect, adrenal insufficiency, hypoaldosteronism, central nervous system or pulmonary disease, SIADH, malignancy, and volume depletion.

E. Exercise-associated hyponatremia—Hyponatremia after exercise, especially endurance events such as triathlons and marathons, may be caused by a combination of excessive hypotonic fluid intake and continued ADH secretion. Reperfusion of the exercise-induced ischemic splanchnic bed causes delayed absorption of excessive quantities of hypotonic fluid ingested during exercise. Sustained elevation of ADH prevents water excretion in this setting. Current guidelines suggest that endurance athletes drink water according to thirst rather than according to specified hourly rates of fluid intake. Specific universal recommendations for fluid replacement rates are not possible given the variability of sweat production, renal water excretion, and environmental conditions. Electrolyte-containing sport drinks do not protect against hyponatremia since they are markedly hypotonic relative to serum.

F. Syndrome of inappropriate antidiuretic hormone secretion—Under normal circumstances, hypovolemia and hyperosmolality stimulate ADH secretion. ADH release is inappropriate without these physiologic cues. Normal regulation of

ADH release occurs from both the central nervous system and the chest via baroreceptors and neural input. The major causes of SIADH are disorders affecting the central nervous system (structural, metabolic, psychiatric, or pharmacologic processes) or the lungs (infectious, mechanical, oncologic). Medications commonly cause SIADH by increasing ADH or its action. Some carcinomas, especially small cell lung carcinoma, can autonomously secrete ADH.

G. Psychogenic polydipsia and beer potomania— Marked free water intake (generally greater than 10 L/day) may produce hyponatremia. Euvolemia is maintained through renal excretion of sodium. Urine sodium is therefore generally elevated (greater than 20 mEq/L), and ADH levels are appropriately suppressed. As the increased free water is excreted, the urine osmolality approaches the minimum of 50 mOsm/kg (or 50 mmol/kg). Polydipsia occurs in psychiatric patients. Psychiatric medications may interfere with water excretion or increase thirst through anticholinergic side effects, further increasing water intake. The hyponatremia of beer potomania occurs in patients who consume large amounts of beer. Free water excretion is decreased because of decreased solute consumption and production; muscle wasting and malnutrition are contributing factors. Without enough solute, these patients have decreased free water excretory capacity even if they maximally dilute the urine.

H. Reset osmostat—Reset osmostat is a rare cause of hyponatremia characterized by appropriate ADH regulation in response to water deprivation and fluid challenges. Patients with reset osmostat regulate serum sodium and serum osmolality around a lower set point, concentrating or diluting urine in response to hyperosmolality and hypoosmolality. The mild hypo-osmolality of pregnancy is a form of reset osmostat.

3. Hypervolemic hypotonic hyponatremia—Hypervolemic hyponatremia occurs in the edematous states of cirrhosis, heart failure, nephrotic syndrome, and advanced kidney disease. In cirrhosis and heart failure, effective circulating volume is decreased due to peripheral vasodilation or decreased cardiac output. Increased reninangiotensin-aldosterone system activity and ADH secretion result in water retention. Note the pathophysiologic similarity to hypovolemic hyponatremia—the body sacrifices osmolality in an attempt to restore effective circulating volume.

The pathophysiology of hyponatremia in nephrotic syndrome is not completely understood, but the primary disturbance may be renal sodium retention, resulting in overfilling of the intravascular space and secondary edema formation as fluid enters the interstitial space. Previously, it was thought that the decreased oncotic pressure of hypoalbuminemia caused fluid shifts from the intravascular space to the interstitial compartment. Intravascular underfilling led to secondary renal sodium retention. However, patients receiving therapy for glomerular disease and nephrotic syndrome often have edema resolution prior to normalization of the serum albumin.

Patients with advanced kidney disease typically have sodium retention and decreased free water excretory capacity, resulting in hypervolemic hyponatremia.

Clinical Findings

A. Symptoms and Signs

Whether hyponatremia is symptomatic depends on its severity and acuity. Chronic disease can be severe (sodium concentration less than 110 mEq/L), yet remarkably asymptomatic because the brain has adapted by decreasing its tonicity over weeks to months. Acute disease that has developed over hours to days can be severely symptomatic with relatively modest hyponatremia. Mild hyponatremia (sodium concentrations of 130–135 mEq/L) is usually asymptomatic.

Mild symptoms of nausea and malaise progress to headache, lethargy, and disorientation as the sodium concentration drops. The most serious symptoms are respiratory arrest, seizure, coma, permanent brain damage, brainstem herniation, and death. Premenopausal women are much more likely than menopausal women to die or suffer permanent brain injury from hyponatremic encephalopathy, suggesting a hormonal role in the pathophysiology.

Evaluation starts with a careful history for new medications, changes in fluid intake (polydipsia, anorexia, intravenous fluid rates and composition), fluid output (nausea and vomiting, diarrhea, ostomy output, polyuria, oliguria, insensible losses). The physical examination should help categorize the patient's volume status into hypovolemia, euvolemia, or hypervolemia.

B. Laboratory Findings

Laboratory assessment should include serum electrolytes, creatinine, and osmolality as well as urine sodium. The etiology of most cases of hyponatremia will be apparent from the history, physical, and basic laboratory tests. Additional tests of thyroid and adrenal function will occasionally be necessary.

SIADH is a clinical diagnosis characterized by (1) hyponatremia; (2) decreased osmolality (less than 280 mOsm/kg [280 mmol/kg]); (3) absence of heart, kidney, or liver disease; (4) normal thyroid and adrenal function; and (5) urine sodium usually over 20 mEq/L. In clinical practice, ADH levels are not measured. Patients with SIADH may have low blood urea nitrogen (BUN) (less than 10 mg/dL [3.6 mmol/L]) and hypouricemia (less than 4 mg/dL [238 mcmol/L]), which are not only dilutional but result from increased urea and uric acid clearances in response to the volume-expanded state. Azotemia may reflect volume contraction, ruling out SIADH, which is seen in euvolemic patients.

Complications

The most serious complication of hyponatremia is iatrogenic cerebral osmotic demyelination from overly rapid sodium correction. Also called central pontine myelinolysis, cerebral osmotic demyelination may occur outside the brainstem. Demyelination may occur days after sodium correction or initial neurologic recovery from hyponatremia. Hypoxic episodes during hyponatremia may contribute to demyelination. The neurologic effects are generally catastrophic and irreversible.

Treatment

Regardless of the etiology of hyponatremia and the patient's volume status, restriction of free water and hypotonic fluid intake is the initial step in hyponatremia management since excessive free water intake will exacerbate hyponatremia. Free water clearance by the kidneys must exceed free water intake for the serum sodium concentration to rise. Free water intake should generally be less than 1–1.5 L/day, although more severe free water restriction may be necessary in patients with minimal free water clearance, and hypertonic saline may be necessary in patients with negative free water clearance.

Hypovolemic patients require adequate fluid resuscitation from isotonic fluids (either normal saline or lactated Ringer solution) to suppress the hypovolemic stimulus for ADH release. Patients with **cerebral salt wasting** may require hypertonic saline to prevent circulatory collapse; some may respond to fludrocortisone. **Hypervolemic** patients may require loop diuretics or dialysis, or both, to correct increased total body water and sodium. **Euvolemic** patients may respond to free water restriction alone.

Pseudohyponatremia from hypertriglyceridemia or hyperproteinemia requires no therapy except confirmation with the clinical laboratory. **Translocational hyponatremia** from glucose or mannitol can be managed with glucose correction or mannitol discontinuation (if possible). No specific therapy is necessary in patients with **reset osmostat** since they successfully regulate their serum sodium with fluid challenges and water deprivation.

Symptomatic and severe hyponatremia generally require hospitalization for careful monitoring of fluid balance and weights, treatment, and frequent sodium checks. Inciting medications should be discontinued if possible.

There is no consensus about the optimal rate of sodium correction in symptomatic hyponatremic patients. Recent guidelines have introduced new recommendations. First, a relatively small increase of 4–6 mEq/L in the serum sodium may be all that is necessary to reverse the neurologic manifestations of symptomatic hyponatremia. Second, acute hyponatremia (eg, exercise-associated hyponatremia) with severe neurologic manifestations can be reversed rapidly with 100 mL of 3% hypertonic saline infused over 10 minutes (repeated twice as necessary). Third, lower correction rates for chronic hyponatremia have been introduced, as low as 4–8 mEq/L per 24 hours in patients at high risk for demyelination. Fourth, chronic hyponatremic patients at high risk for demyelination who are corrected too rapidly are candidates for treatment with a combination of DDAVP and intravenous dextrose 5% to relower the serum sodium.

In severely symptomatic patients, the clinician should calculate the sodium deficit and deliver 3% hypertonic saline.

For patients who cannot adequately restrict free water or have an inadequate response to conservative measures, demeclocycline (300–600 mg orally twice daily) inhibits the effect of ADH on the distal tubule. Onset of action may require 1 week, and urinary concentrating ability may be permanently impaired, resulting in nephrogenic diabetes insipidus (DI) and even hypernatremia. Cirrhosis may increase the nephrotoxicity of demeclocycline.

Vasopressin antagonists may revolutionize the treatment of euvolemic and

hypervolemic hyponatremia, especially in heart failure. Tolvaptan, lixivaptan, and satavaptan are oral selective vasopressin-2 receptor antagonists; conivaptan is an intravenous agent. Tolvaptan and conivaptan are available in the United States, but lixivaptan and satavaptan are not yet approved by the US Food and Drug Administration (FDA).

V2 receptors mediate the diuretic effect of ADH and V2 receptor antagonists are recommended for use in hospital. For hospitalized patients with euvolemic SIADH, tolvaptan is begun as 15 mg orally daily and can be increased to 30 mg daily and 60 mg daily at 24 hour intervals if hyponatremia persists or if the increase in sodium concentration is less than 5 mEq/L over the preceding 24 hours. Conivaptan is given as an intravenous loading dose of 20 mg delivered over 30 minutes, then as 20 mg continuously over 24 hours. Subsequent infusions may be administered every 1–3 days at 20–40 mg/day by continuous infusion. The standard free water restriction for hyponatremic patients should be lifted for patients receiving vasopressin antagonists since the aquaresis can result in excessive sodium correction in a fluid-restricted patient. Frequent monitoring of the serum sodium is necessary.

When to Refer

• Nephrology or endocrinology consultation should be considered in severe, symptomatic, refractory, or complicated cases of hyponatremia.

• Aggressive therapies with hypertonic saline, demeclocycline, vasopressin antagonists, or dialysis mandate specialist consultation.

• Consultation may be necessary with end-stage liver or heart disease.

When to Admit

Hospital admission is necessary for symptomatic patients or those requiring aggressive therapies for close monitoring and frequent laboratory testing.

HYPERNATREMIA

ESSENTIALS OF DIAGNOSIS

- Increased thirst and water intake is the first defense against hypernatremia.
- Urine osmolality helps differentiate renal from nonrenal water loss.

General Considerations

Hypernatremia is defined as a sodium concentration greater than 145 mEq/L. All patients with hypernatremia have hyperosmolality, unlike hyponatremic patients who can have a low, normal, or high serum osmolality. The hypernatremic patient is typically hypovolemic due to free water losses, although hypervolemia is frequently seen, often as an iatrogenic complication in hospitalized patients with impaired access to free water. Rarely, excessive sodium intake may cause hypernatremia. Hypernatremia in primary aldosteronism is mild and usually does not cause symptoms.

An intact thirst mechanism and access to water are the primary defense against hypernatremia. The hypothalamus can sense minimal changes in serum osmolality, triggering the thirst mechanism and increased water intake. Thus, whatever the underlying disorder (eg, dehydration, lactulose or mannitol therapy, central and nephrogenic DI), excess water loss can cause hypernatremia only when adequate water intake is not possible.

Clinical Findings

A. Symptoms and Signs

When the patient is dehydrated, orthostatic hypotension and oliguria are typical findings. Because water shifts from the cells to the intravascular space to protect volume status, these symptoms may be delayed. Lethargy, irritability, and weakness are early signs. Hyperthermia, delirium, seizures, and coma may be seen with severe hypernatremia (ie, sodium greater than 158 mEq/L). Symptoms in the elderly may not be specific; a recent change in consciousness is associated with a poor prognosis. Osmotic cerebral demyelination is an uncommon but reported consequence of severe hypernatremia.

B. Laboratory Findings

1. Urine osmolality greater than 400 mOsm/kg—Renal water-conserving ability is functioning.

A. Nonrenal losses—Hypernatremia will develop if water intake falls behind hypotonic fluid losses from excessive sweating, the respiratory tract, or bowel movements. Lactulose causes an osmotic diarrhea with loss of free water.

B. Renal losses—While severe hyperglycemia can cause translocational hyponatremia, progressive volume depletion from glucosuria can result in hypernatremia. Osmotic diuresis can occur with the use of mannitol or urea.

Treatment

Treatment of hypernatremia includes correcting the cause of the fluid loss, replacing water, and replacing electrolytes (as needed). In response to increases in plasma osmolality, brain cells synthesize solutes called idiogenic osmoles, which cause intracellular fluid shifts. Osmole production begins 4–6 hours after dehydration and takes several days to reach steady state. If hypernatremia is rapidly corrected, the osmotic imbalance may cause cerebral edema and potentially severe neurologic impairment. Fluids should be administered over a 48-hour period, aiming for serum sodium correction of approximately 1 mEq/L/h (1 mmol/L/h). There is no consensus about the optimal rates of sodium correction in hypernatremia.

A. Choice of Type of Fluid for Replacement

1. Hypernatremia with hypovolemia—Hypovolemic patients should receive isotonic 0.9% normal saline to restore euvolemia and to treat hyperosmolality because normal saline (308 mOsm/kg or 308 mmol/kg) is hypoosmolar compared with plasma. After adequate volume resuscitation with normal saline, 0.45% saline

or 5% dextrose (or both) can be used to replace any remaining free water deficit. Milder volume deficits may be treated with 0.45% saline and 5% dextrose.

2. Hypernatremia with euvolemia—Water ingestion or intravenous 5% dextrose will result in the excretion of excess sodium in the urine. If the glomerular filtration rate (GFR) is decreased, diuretics will increase urinary sodium excretion but may impair renal concentrating ability, increasing the quantity of water that needs to be replaced.

3. Hypernatremia with hypervolemia—Treatment includes 5% dextrose solution to reduce hyperosmolality. Loop diuretics may be necessary to promote natriuresis and lower total body sodium. In severe rare cases with kidney disease, hemodialysis may be necessary to correct the excess total body sodium and water.

B. Calculation of Water Deficit

Fluid replacement should include the free water deficit and additional maintenance fluid to replace ongoing and anticipated fluid losses.

1. Acute hypernatremia—In acute dehydration without much solute loss, free water loss is similar to the weight loss. Initially, a 5% dextrose solution may be used. As correction of water deficit progresses, therapy should continue with 0.45% saline with dextrose.

2. Chronic hypernatremia—The water deficit is calculated to restore normal sodium concentration, typically 140 mEq/L. Total body water (TBW) correlates with muscle mass and therefore decreases with advancing age, cachexia, and dehydration and is lower in women than in men. Current TBW equals 40–60% current body weight.

When to Refer

Patients with refractory or unexplained hypernatremia should be referred for subspecialist consultation.

When to Admit

• Patients with symptomatic hypernatremia require hospitalization for evaluation and treatment.

• Significant comorbidities or concomitant acute illnesses, especially if contributing to hypernatremia, may necessitate hospitalization.

VOLUME OVERLOAD

ESSENTIALS OF DIAGNOSIS

- Disorder of excessive sodium retention in the setting of low arterial underfilling (eg, heart failure or cirrhosis).
- Hyponatremia from water retention in edematous states is associated with sodium retention.

The hallmark of a volume overloaded state is sodium retention. Abnormally low arterial filling, such as from heart failure or cirrhosis, activates the

neurohumoral axis, which stimulates the renin-angiotensin-aldosterone system, the sympathetic nervous system, and ADH (vasopressin) release. The result is sodium retention with edema. The stimulus for vasopressin release is nonosmotic. Released in response to baroreceptor activation, vasopressin stimulates renal V2 receptors, resulting in water reabsorption, edema formation, and hyponatremia.

HYPEROSMOLAR DISORDERS & OSMOLAR GAPS

HYPEROSMOLALITY WITH TRANSIENT OR NO SIGNIFICANT SHIFT IN WATER

Urea and alcohol readily cross cell membranes and can produce hyperosmolality. Urea is an ineffective osmole with little effect on osmotic water movement across cell membranes. Alcohol quickly equilibrates between the intracellular and extracellular compartments, adding 22 mOsm/L for every 100 mg/dL (or 21.7 mmol/L) of ethanol. Ethanol ingestion should be considered in any case of stupor or coma with an elevated osmol gap (measured osmolality – calculated osmolality greater than 10 mOsm/kg [10 mmol/kg]). Other toxic alcohols such as methanol and ethylene glycol cause an osmol gap and a metabolic acidosis with an increased anion gap. The combination of an increased anion gap metabolic acidosis and an osmol gap exceeding 10 mOsm/kg (or 10 mmol/kg) is not specific for toxic alcohol ingestion and may occur with alcoholic ketoacidosis or lactic acidosis (see Metabolic Acidosis).

HYPEROSMOLALITY ASSOCIATED WITH SIGNIFICANT SHIFTS IN WATER

Increased concentrations of solutes that do not readily enter cells cause a shift of water from intracellular to extracellular. Hyperosmolality of effective osmoles such as sodium and glucose causes symptoms, primarily neurologic. The severity of symptoms depends on the degree of hyperosmolality and rapidity of development. In acute hyperosmolality, somnolence and confusion can appear when the osmolality exceeds 320–330 mOsm/kg (320–330 mmol/kg); coma, respiratory arrest, and death can result when osmolality exceeds 340–350 mOsm/kg (340–350 mmol/kg).

DISORDERS OF POTASSIUM CONCENTRATION

HYPOKALEMIA

ESSENTIALS OF DIAGNOSIS

- Serum potassium level less than 3.5 mEq/L (3.5 mmol/L)
- Severe hypokalemia may induce dangerous arrhythmias and rhabdomyolysis.
- Transtubular potassium concentration gradient (TTKG) can distinguish

renal from nonrenal loss of potassium.

General Considerations

Hypokalemia can result from insufficient dietary potassium intake, intracellular shifting of potassium from the extracellular space, extrarenal potassium loss, or renal potassium loss. Cellular uptake of potassium is increased by insulin and beta-adrenergic stimulation and blocked by alpha-adrenergic stimulation. Aldosterone is an important regulator of total body potassium, increasing potassium secretion in the distal renal tubule. The most common cause of hypokalemia, especially in developing countries, is gastrointestinal loss from infectious diarrhea. The potassium concentration in intestinal secretion is ten times higher (80 mEq/L) than in gastric secretions. Hypokalemia in the presence of acidosis suggests profound potassium depletion and requires urgent treatment. Selflimited hypokalemia occurs in 50–60% of trauma patients, perhaps related to enhanced release of epinephrine.

Hypokalemia increases the likelihood of digitalis toxicity. In patients with heart disease, hypokalemia induced by beta-2-adrenergic agonists and diuretics may substantially increase the risk of arrhythmias. Numerous genetic mutations affect fluid and electrolyte metabolism, including disorders of potassium metabolism.

Magnesium is an important cofactor for potassium uptake and maintenance of intracellular potassium levels. Loop diuretics (eg, furosemide) cause substantial renal potassium and magnesium losses. Magnesium depletion should be considered in refractory hypokalemia.

Clinical Findings

A. Symptoms and Signs

Muscular weakness, fatigue, and muscle cramps are frequent complaints in mild to moderate hypokalemia. Gastrointestinal smooth muscle involvement may result in constipation or ileus. Flaccid paralysis, hyporeflexia, hypercapnia, tetany, and rhabdomyolysis may be seen with severe hypokalemia (less than 2.5 mEq/L). The presence of hypertension may be a clue to the diagnosis of hypokalemia from aldosterone or mineralocorticoid excess. Renal manifestations include nephrogenic DI and interstitial nephritis.

B. Laboratory Findings

Urinary potassium concentration is low (less than 20 mEq/L) as a result of extrarenal loss (eg, diarrhea, vomiting) and inappropriately high (greater than 40 mEq/L) with renal loss (eg, mineralocorticoid excess, Bartter syndrome, Liddle syndrome). Hypokalemia with a transtubular [K+] gradient (TTKG) more than 4 suggests renal potassium loss with increased distal K+ secretion. In such cases, plasma renin and aldosterone levels are helpful in differential diagnosis. The presence of nonabsorbed anions, such as bicarbonate, increases the TTKG.

C. Electrocardiogram

The electrocardiogram (ECG) shows decreased amplitude and broadening of T

waves, prominent U waves, premature ventricular contractions, and depressed ST segments.

Treatment

Oral potassium supplementation is the safest and easiest treatment for mild to moderate deficiency. Dietary potassium is almost entirely coupled to phosphate—rather than chloride—and is therefore not effective in correcting potassium loss associated with chloride depletion from diuretics or vomiting. In the setting of abnormal kidney function and mild to moderate diuretic dosage, 20 mEq/day of oral potassium is generally sufficient to prevent hypokalemia, but 40–100 mEq/day over a period of days to weeks is needed to treat hypokalemia and fully replete potassium stores.

Intravenous potassium is indicated for patients with severe hypokalemia and for those who cannot take oral supplementation. For severe deficiency, potassium may be given through a peripheral intravenous line in a concentration up to 40 mEq/L and at rates up to 10 mEq/h. Concentrations of up to 20 mEq/h may be given through a central venous catheter. Continuous ECG monitoring is indicated, and the serum potassium level should be checked every 3–6 hours. Avoid glucose-containing fluid to prevent further shifts of potassium into the cells. Magnesium deficiency should be corrected, particularly in refractory hypokalemia.

When to Refer

Patients with unexplained hypokalemia, refractory hyperkalemia, or clinical features suggesting alternative diagnoses (eg, aldosteronism or hypokalemic periodic paralysis) should be referred for endocrinology or nephrology consultation.

When to Admit

Patients with symptomatic or severe hypokalemia, especially with cardiac manifestations, require cardiac monitoring, potassium supplementation, and frequent laboratory testing.

HYPERKALEMIA

ESSENTIALS OF DIAGNOSIS

- Serum potassium level greater than 5.0 mEq/L (5.0 mmol/L).
- Hyperkalemia may develop in patients taking ACE inhibitors, angiotensin-receptor blockers, potassium-sparing diuretics, or their combination, even with no or only mild kidney dysfunction.
- The ECG may show peaked T waves, widened QRS and biphasic QRS–T complexes, or may be normal despite life-threatening hyperkalemia.
- Measurement of plasma potassium level differentiates potassium leak from blood cells in cases of clotting, leukocytosis, and thrombocytosis from truly elevated serum potassium.
- Rule out extracellular potassium shift from the cells in acidosis and

assess renal potassium excretion.

General Considerations

Hyperkalemia usually occurs in patients with advanced kidney disease but can also develop with normal kidney function. Acidosis causes intracellular potassium to shift extracellularly. Serum potassium concentration rises about 0.7 mEq/L for every decrease of 0.1 pH unit during acidosis. Fist clenching during venipuncture may raise the potassium concentration by 1–2 mEq/L by causing acidosis and potassium shift from cells. In the absence of acidosis, serum potassium concentration rises about 1 mEq/L when there is a total body potassium excess of 1–4 mEq/kg. However, the higher the serum potassium concentration, the smaller the excess necessary to raise the potassium levels further.

Mineralocorticoid deficiency from Addison disease or chronic kidney disease (CKD) is another cause of hyperkalemia with decreased renal excretion of potassium. Mineralocorticoid resistance due to genetic disorders, interstitial kidney disease, or urinary tract obstruction also leads to hyperkalemia.

ACE inhibitors or angiotensin-receptor blockers (ARBs), commonly used in patients with heart failure or CKD, may cause hyperkalemia. The concomitant use of spironolactone, eplerenone, or beta-blockers further increases the risk of hyperkalemia. Thiazide or loop diuretics and sodium bicarbonate may minimize hyperkalemia. Persistent mild hyperkalemia in the absence of ACE inhibitor or ARB therapy is usually due to type IV renal tubular acidosis (RTA). Heparin inhibits aldosterone production in the adrenal glands, causing hyperkalemia.

Trimethoprim is structurally similar to amiloride and triamterene, and all three drugs inhibit renal potassium excretion through suppression of sodium channels in the distal nephron.

Cyclosporine and tacrolimus can induce hyperkalemia in organ transplant recipients, especially kidney transplant patients, partly due to suppression of the basolateral Na+–K+-ATPase in principal cells. Hyperkalemia is commonly seen in HIV patients and has been attributed to impaired renal excretion of potassium due to pentamidine or trimethoprim-sulfamethoxazole or to hyporeninemic hypoaldosteronism.

Clinical Findings

Hyperkalemia impairs neuromuscular transmission, causing muscle weakness, flaccid paralysis, and ileus. Electrocardiography is not a sensitive method for detecting hyperkalemia, since nearly half of patients with a serum potassium level greater than 6.5 mEq/L will not manifest ECG changes. ECG changes in hyperkalemia include bradycardia, PR interval prolongation, peaked T waves, QRS widening, and biphasic QRS–T complexes. Conduction disturbances, such as bundle branch block and atrioventricular block, may occur. Ventricular fibrillation and cardiac arrest are terminal events.

Prevention

Inhibitors of the renin-angiotensin-aldosterone axis (ie, ACE inhibitors, ARBs,

and spironolactone) and potassiumsparing diuretics (eplerenone, triamterene) should be used cautiously in patients with heart failure, liver failure, and kidney disease. Laboratory monitoring should be performed within 1 week of drug initiation or dosage increase.

Treatment

The diagnosis should be confirmed by repeat laboratory testing to rule out spurious hyperkalemia, especially in the absence of medications that cause hyperkalemia or in patients without kidney disease or a previous history of hyperkalemia. Plasma potassium concentration can be measured to avoid hyperkalemia due to potassium leakage out of red cells, white cells, and platelets. Kidney dysfunction should be ruled out at the initial assessment.

Treatment consists of withholding exogenous potassium, identifying the cause, reviewing the patient's medications and dietary potassium intake, and correcting the hyperkalemia. Emergent treatment is indicated when cardiac toxicity, muscle paralysis, or severe hyperkalemia (potassium greater than 6.5 mEq/L) is present, even in the absence of ECG changes. Insulin, bicarbonate, and betaagonists shift potassium intracellularly within minutes of administration. Intravenous calcium may be given to antagonize the cell membrane effects of potassium, but its use should be restricted to life-threatening hyperkalemia in patients taking digitalis because hypercalcemia may cause digitalis toxicity. Hemodialysis may be required to remove potassium in patients with acute or chronic kidney injury. Newer agents (patiromer and sodium zirconium cyclosilicate) that bind gastrointestinal potassium have been shown to treat hyperkalemia in outpatients. These drugs have not been approved by the FDA but may offer safer alternatives to sodium polystyrene, which has been associated with colonic necrosis, especially when administered concomitantly with sorbitol and in patients with abnormal bowel function.

When to Refer

• Patients with hyperkalemia from kidney disease and reduced renal potassium excretion should see a nephrologist.

• Transplant patients may need adjustment of their immunosuppression regimen by transplant specialists.

When to Admit

Patients with severe hyperkalemia greater than 6 mEq/L, any degree of hyperkalemia associated with ECG changes, or concomitant illness (eg, tumor lysis, rhabdomyolysis, metabolic acidosis) should be sent to the emergency department for immediate treatment.

DISORDERS OF CALCIUM CONCENTRATION

The normal total plasma (or serum) calcium concentration is 8.5–10.5 mg/dL (or 2.1–2.6 mmol/L). Ionized calcium (normal: 4.6–5.3 mg/dL [or 1.15–1.32

mmol/L]) is physiologically active and necessary for muscle contraction and nerve function. The calcium-sensing receptor, a transmembrane protein that detects the extracellular calcium concentration, has been identified in the parathyroid gland and the kidney. Functional defects in this protein are associated with diseases of abnormal calcium metabolism such as familial hypocalcemia and familial hypocalciuric hypercalcemia.

HYPOCALCEMIA

ESSENTIALS OF DIAGNOSIS

- Often mistaken as a neurologic disorder.
- Check for decreased serum parathyroid hormone (PTH), vitamin D, or magnesium levels.
- If the ionized calcium level is normal despite a low total serum calcium, calcium metabolism is usually normal.

General Considerations

The most common cause of low total serum calcium is hypoalbuminemia. When serum albumin concentration is lower than 4 g/dL (40 g/L), serum Ca2+ concentration is reduced by 0.8–1 mg/dL (0.20–0.25 mmol/L) for every 1 g/dL (10 g/L) of albumin. The most accurate measurement of serum calcium is the ionized calcium concentration. True hypocalcemia (decreased ionized calcium) implies insufficient action of PTH or active vitamin D. The most common cause of hypocalcemia is advanced CKD, in which decreased production of active vitamin D3 (1,25 dihydroxyvitamin D3) and hyperphosphatemia both play a role. Some cases of primary hypoparathyroidism are due to mutations of the calcium-sensing receptor in which inappropriate suppression of PTH release leads to hypocalcemia. Magnesium depletion reduces both PTH release and tissue responsiveness to PTH, causing hypocalcemia. Hypocalcemia in pancreatitis is a marker of severe disease. Elderly hospitalized patients with hypocalcemia and hypophosphatemia, with or without an elevated PTH level, are likely vitamin D deficient.

Clinical Findings

A. Symptoms and Signs

Hypocalcemia increases excitation of nerve and muscle cells, primarily affecting the neuromuscular and cardiovascular systems. Spasm of skeletal muscle causes cramps and tetany. Laryngospasm with stridor can obstruct the airway. Convulsions, perioral and peripheral paresthesias, and abdominal pain can develop. Classic physical findings include Chvostek sign (contraction of the facial muscle in response to tapping the facial nerve) and Trousseau sign (carpal spasm occurring with occlusion of the brachial artery by a blood pressure cuff). QT prolongation predisposes to ventricular arrhythmias. In chronic hypoparathyroidism, cataracts and calcification of basal ganglia may appear.

B. Laboratory Findings

Serum calcium concentration is low (less than 8.5 mg/dL [2.1 mmol/L]). In

true hypocalcemia, the ionized serum calcium concentration is also low (less than 4.6 mg/dL [1.15 mmol/L]). Serum phosphate is usually elevated in hypoparathyroidism or in advanced CKD, whereas it is suppressed in early CKD or vitamin D deficiency. Serum magnesium concentration is commonly low. In respiratory alkalosis, total serum calcium is normal but ionized calcium is low. The ECG shows a prolonged QT interval.

Treatment

A. Severe, Symptomatic Hypocalcemia

In the presence of tetany, arrhythmias, or seizures, intravenous calcium gluconate is indicated. Because of the short duration of action, continuous calcium infusion is usually required. Ten to 15 milligrams of calcium per kilogram body weight, or six to eight 10-mL vials of 10% calcium gluconate (558–744 mg of calcium), is added to 1 L of D5 W and infused over 4–6 hours. By monitoring the serum calcium level frequently (every 4–6 hours), the infusion rate is adjusted to maintain the serum calcium level at 7–8.5 mg/dL.

B. Asymptomatic Hypocalcemia

Oral calcium (1–2 g) and vitamin D preparations, including active vitamin D sterols, are used. Calcium carbonate is well tolerated and less expensive than many other calcium tablets. A check of urinary calcium excretion is recommended after the initiation of therapy because hypercalciuria (urine calcium excretion greater than 300 mg or 7.5 mmol per day) or urine calcium:creatinine ratio greater than 0.3 may impair kidney function in these patients. The low serum calcium associated with hypoalbuminemia does not require replacement therapy. If serum Mg^{2+} is low, therapy must include magnesium replacement, which by itself will usually correct hypocalcemia.

When to Refer

Patients with complicated hypocalcemia from hypoparathyroidism, familial hypocalcemia, or CKD require referral to an endocrinologist or nephrologist.

When to Admit

Patients with tetany, arrhythmias, seizures, or other symptoms of hypocalcemia require immediate evaluation and therapy.

HYPERCALCEMIA

ESSENTIALS OF DIAGNOSIS

- Primary hyperparathyroidism and malignancyassociated hypercalcemia are the most common causes.
- Hypercalciuria usually precedes hypercalcemia.
- Most often, asymptomatic, mild hypercalcemia (≥ 10.5 mg/dL [or 2.6 mmol/L]) is due to primary hyperparathyroidism, whereas the symptomatic, severe hypercalcemia (≥ 14 mg/dL [or 3.5 mmol/L]) is due to hypercalcemia of malignancy.

General Considerations

Primary hyperparathyroidism and malignancy account for 90% of cases. Primary hyperparathyroidism is the most common cause of hypercalcemia (usually mild) in ambulatory patients. Chronic hypercalcemia (over 6 months) or some manifestation such as nephrolithiasis also suggests a benign cause. Tumor production of PTH-related proteins (PTHrP) is the most common paraneoplastic endocrine syndrome, accounting for most cases of hypercalcemia in inpatients. The neoplasm is clinically apparent in nearly all cases when the hypercalcemia is detected, and the prognosis is poor. Granulomatous diseases, such as sarcoidosis and tuberculosis, cause hypercalcemia via overproduction of active vitamin D3 (1,25 dihydroxyvitamin D3).

Milk-alkali syndrome has had a resurgence due to calcium ingestion for prevention of osteoporosis. Heavy calcium carbonate intake causes hypercalcemic acute kidney injury, likely from renal vasoconstriction. The decreased GFR impairs bicarbonate excretion, while hypercalcemia stimulates proton secretion and bicarbonate reabsorption. Metabolic alkalosis decreases calcium excretion, maintaining hypercalcemia.

Hypercalcemia causes nephrogenic DI through activation of calcium-sensing receptors in collecting ducts, which reduces ADH-induced water permeability. Volume depletion further worsens hypercalcemia.

Clinical Findings

A. Symptoms and Signs

The history and physical examination should focus on the duration of hypercalcemia and evidence for a neoplasm. Hypercalcemia may affect gastrointestinal, kidney, and neurologic function. Mild hypercalcemia is often asymptomatic. Symptoms usually occur if the serum calcium is higher than 12 mg/dL (3 mmol/L) and tend to be more severe if hypercalcemia develops acutely. Symptoms include constipation and polyuria, except in hypocalciuric hypercalcemia, in which polyuria is absent. Other symptoms include nausea, vomiting, anorexia, peptic ulcer disease, renal colic, and hematuria from nephrolithiasis. Polyuria from hypercalciuria-induced nephrogenic DI can result in volume depletion and acute kidney injury. Neurologic manifestations range from mild drowsiness to weakness, depression, lethargy, stupor, and coma in severe hypercalcemia. Ventricular ectopy and idioventricular rhythm occur and can be accentuated by digitalis.

B. Laboratory Findings

The ionized calcium exceeds 1.32 mmol/L. A high serum chloride concentration and a low serum phosphate concentration in a ratio greater than 33:1 (or greater than 102 if SI units are utilized) suggests primary hyperparathyroidism where PTH decreases proximal tubular phosphate reabsorption. A low serum chloride concentration with a high serum bicarbonate concentration, along with elevated BUN and creatinine, suggests milk-alkali syndrome. Severe hypercalcemia

(greater than 15 mg/dL [3.75 mmol/L]) generally occurs in malignancy. More than 300 mg (7.5 mmol) per day of urinary calcium excretion suggests hypercalciuria; less than 100 mg (2.5 mmol) per day suggests hypocalciuria. Hypercalciuric patients—such as those with malignancy or those receiving oral active vitamin D therapy—may easily develop hypercalcemia in case of volume depletion. Serum phosphate may or may not be low, depending on the cause. Hypocalciuric hypercalcemia occurs in milk-alkali syndrome, thiazide diuretic use, and familial hypocalciuric hypercalcemia.

The chest radiograph may reveal malignancy or granulomatous disease. The ECG shows a shortened QT interval. Measurements of PTH and PTHrP help distinguish between hyperparathyroidism (elevated PTH) and malignancy-associated hypercalcemia (suppressed PTH, elevated PTHrP).

Treatment

Until the primary cause can be identified and treated, renal excretion of calcium is promoted through aggressive hydration and forced calciuresis. The tendency in hypercalcemia is hypovolemia from nephrogenic DI. In dehydrated patients with normal cardiac and kidney function, 0.45% saline or 0.9% saline can be given rapidly (250–500 mL/h). A metaanalysis questioned the efficacy and safety profile of intravenous furosemide for hypercalcemia. Thiazides can worsen hypercalcemia.

Bisphosphonates are the treatment of choice for hypercalcemia of malignancy. Although they are safe, effective, and normalize calcium in more than 70% of patients, bisphosphonates may require up to 48–72 hours before reaching full therapeutic effect. Calcitonin may be helpful in the short-term until bisphosphonates reach therapeutic levels. In emergency cases, dialysis with low calcium dialysate may be needed. The calcimimetic agent cinacalcet hydrochloride suppresses PTH secretion and decreases serum calcium concentration and holds promise as a treatment option.

Typically, if dialysis patients do not receive proper supplementation of calcium and active vitamin D, hypocalcemia and hyperphosphatemia develop. On the other hand, hypercalcemia can sometimes develop, particularly in the setting of severe secondary hyperparathyroidism, characterized by high PTH levels and subsequent release of calcium from bone. Therapy may include intravenous vitamin D, which further increases the serum calcium concentration. Another type of hypercalcemia occurs when PTH levels are low. Bone turnover is decreased, which results in a low buffering capacity for calcium. When calcium is administered in calcium-containing phosphate binders or dialysate, or when vitamin D is administered, hypercalcemia results. Hypercalcemia in dialysis patients usually occurs in the presence of hyperphosphatemia, and metastatic calcification may occur. Malignancy should be considered as a cause of the hypercalcemia.

When to Refer

• Patients may require referral to an oncologist or endocrinologist depending on the underlying cause of hypercalcemia.

• Patients with granulomatous diseases (eg, tuberculosis and other chronic infections, granulomatosis with polyangiitis [formerly Wegener granulomatosis], sarcoidosis) may require assistance from infectious disease specialists, rheumatologists, or pulmonologists.

When to Admit

• Patients with symptomatic or severe hypercalcemia require immediate treatment.

• Unexplained hypercalcemia with associated conditions, such as acute kidney injury or suspected malignancy, may require urgent treatment and expedited evaluation.

DISORDERS OF PHOSPHORUS CONCENTRATION

Plasma phosphorus is mainly inorganic phosphate and represents a small fraction (less than 0.2%) of total body phosphate. Important determinants of plasma inorganic phosphate are renal excretion, intestinal absorption, and shift between the intracellular and extracellular spaces. The kidney is the most important regulator of the serum phosphate level. PTH decreases reabsorption of phosphate in the proximal tubule while 1,25-dihydroxyvitamin D3 increases reabsorption. Renal proximal tubular reabsorption of phosphate is decreased by volume expansion, corticosteroids, and proximal tubular dysfunction (as in Fanconi syndrome). Fibroblast growth factor 23 (FGF23) is a potent phosphaturic hormone. Intestinal absorption of phosphate is facilitated by active vitamin D. PTH stimulates phosphate release from bone and renal phosphate excretion; primary hyperparathyroidism can lead to hypophosphatemia and depletion of bone phosphate stores. By contrast, growth hormone augments proximal tubular reabsorption of phosphate. Cellular phosphate uptake is stimulated by various factors and conditions, including alkalemia, insulin, epinephrine, feeding, hungry bone syndrome, and accelerated cell proliferation. Phosphorus metabolism and homeostasis are intimately related to calcium metabolism

HYPOPHOSPHATEMIA

ESSENTIALS OF DIAGNOSIS

- Severe hypophosphatemia may cause tissue hypoxia and rhabdomyolysis.
- Renal loss of phosphate can be diagnosed by measuring urinary phosphate excretion and by calculating maximal tubular phosphate reabsorption rate (TmP/GFR).
- PTH and FGF23 are the major factors that decrease TmP/GFR, leading to renal loss of phosphate.

General Considerations

Hypophosphatemia may occur in the presence of normal phosphate stores.

Serious depletion of body phosphate stores may exist with low, normal, or high serum phosphate concentrations. Serum phosphate levels decrease transiently after food intake, thus fasting samples are recommended for accuracy. **Moderate hypophosphatemia** (1.0–2.4 mg/dL [0.32–0.79 mmol/L]) occurs commonly in hospitalized patients and may not reflect decreased phosphate stores.

In **severe hypophosphatemia** (less than 1 mg/dL [0.32 mmol/L]), the affinity of hemoglobin for oxygen increases through a decrease in the erythrocyte 2,3-biphosphoglycerate concentration, impairing tissue oxygenation and cell metabolism and resulting in muscle weakness or even rhabdomyolysis. Severe hypophosphatemia is common and multifactorial in alcoholic patients. In acute alcohol withdrawal, increased plasma insulin and epinephrine along with respiratory alkalosis promote intracellular shift of phosphate. Vomiting, diarrhea, and poor dietary intake contribute to hypophosphatemia. Chronic alcohol use results in a decrease in the renal threshold of phosphate excretion. This renal tubular dysfunction reverses after a month of abstinence. Patients with chronic obstructive pulmonary disease and asthma commonly have hypophosphatemia, attributed to xanthine derivatives causing shifts of phosphate intracellularly and the phosphaturic effects of beta-adrenergic agonists, loop diuretics, xanthine derivatives, and corticosteroids. Refeeding or glucose administration to phosphate-depleted patients may cause fatal hypophosphatemia.

Clinical Findings

A. Symptoms and Signs

Acute, severe hypophosphatemia (less than 1.0 mg/dL [0.32 mmol/L]) can lead to rhabdomyolysis, paresthesias, and encephalopathy (irritability, confusion, dysarthria, seizures, and coma). Respiratory failure or failure to wean from mechanical ventilation may occur as a result of diaphragmatic weakness. Arrhythmias and heart failure are uncommon but serious manifestations. Hematologic manifestations include acute hemolytic anemia from erythrocyte fragility, platelet dysfunction with petechial hemorrhages, and impaired chemotaxis of leukocytes (leading to increased susceptibility to gram-negative sepsis).

Chronic severe depletion may cause anorexia, pain in muscles and bones, and fractures.

B. Laboratory Findings

Urine phosphate excretion is a useful clue in the evaluation of hypophosphatemia. The normal renal response to hypophosphatemia is decreased urinary phosphate excretion to less than 100 mg/day. The fractional excretion of phosphate (FEPO4) should be less than 5%. The main factors regulating FEPO4 are PTH and phosphate intake. Increased PTH or phosphate intake decreases FEPO4 (ie, more phosphate is excreted into the urine).

Measurement of plasma PTH or PTHrP levels may be helpful. The clinical utility of serum FGF levels is undetermined except in uncommon diseases.

Other clinical features may be suggestive of hypophosphatemia, such as hemolytic anemia and rhabdomyolysis. Fanconi syndrome may present with any

combination of uricosuria, aminoaciduria, normoglycemic glucosuria, normal anion gap metabolic acidosis, and phosphaturia. In chronic hypophosphatemia, radiographs and bone biopsies show changes resembling osteomalacia.

Treatment

Hypophosphatemia can be prevented by including phosphate in repletion and maintenance fluids. A rapid decline in calcium levels can occur with parenteral administration of phosphate; oral replacement of phosphate is preferable. Moderate hypophosphatemia (1.0–2.5 mg/dL [or 0.32–0.79 mmol/L]) is usually asymptomatic and does not require treatment. The hypophosphatemia in patients with diabetic ketoacidosis (DKA) will usually correct with normal dietary intake. Chronic hypophosphatemia can be treated with oral phosphate repletion. Mixtures of sodium and potassium phosphate salts may be given to provide 0.5–1 g (16–32 mmol) of phosphate per day. For severe, symptomatic hypophosphatemia (less than 1 mg/dL [0.32 mmol/L]), an infusion should provide 279–310 mg/12 h (or 9–10 mmol/12 h) until the serum phosphorus exceeds 1 mg/dL and the patient can be switched to oral therapy. The infusion rate should be decreased if hypotension occurs. Monitoring of plasma phosphate, calcium, and potassium every 6 hours is necessary because the response to phosphate supplementation is not predictable. Magnesium deficiency often coexists and should be treated.

Contraindications to phosphate replacement include hypoparathyroidism, advanced CKD, tissue damage and necrosis, and hypercalcemia. When an associated hyperglycemia is treated, phosphate accompanies glucose into cells, and hypophosphatemia may ensue.

When to Refer

• Patients with refractory hypophosphatemia with increased urinary phosphate excretion may require evaluation by an endocrinologist (for such conditions as hyperparathyroidism and vitamin D disorders) or a nephrologist (for such conditions as renal tubular defects).

• Patients with decreased gastrointestinal absorption may require referral to a gastroenterologist.

When to Admit

Patients with severe or refractory hypophosphatemia will require intravenous phosphate.

HYPERPHOSPHATEMIA

ESSENTIALS OF DIAGNOSIS

- Advanced CKD is the most common cause.
- Hyperphosphatemia in the presence of hypercalcemia imposes a high risk of metastatic calcification.

General Considerations

Advanced CKD with decreased urinary excretion of phosphate is the most common cause of hyperphosphatemia.

Clinical Findings

A. Symptoms and Signs

The clinical manifestations are those of the underlying disorder or associated condition.

B. Laboratory Findings

In addition to elevated phosphate, blood chemistry abnormalities are those of the underlying disease.

Treatment

Treatment is directed at the underlying cause. Exogenous sources of phosphate, including enteral or parenteral nutrition and medications, should be reduced or eliminated. Dietary phosphate absorption can be reduced by oral phosphate binders, such as calcium carbonate, calcium acetate. Causes of hyperphosphatemia. Massive load of phosphate into the extracellular fluid Exogenous sources Hypervitaminosis D Laxatives or enemas containing phosphate Intravenous phosphate supplement Endogenous sources Rhabdomyolysis (especially if chronic kidney disease coexists) Cell lysis by chemotherapy of malignancy, particularly lymphoproliferative diseases Metabolic acidosis (lactic acidosis, ketoacidosis) Respiratory acidosis (phosphate incorporation into cells is disturbed) Decreased excretion into urine Chronic kidney disease Acute kidney injury Hypoparathyroidism Pseudohypoparathyroidism Acromegaly Pseudohyperphosphatemia Multiple myeloma Hyperbilirubinemia Hypertriglyceridemia Hemolysis in vitro sevelamer carbonate, lanthanum carbonate, and aluminum hydroxide. Sevelamer, lanthanum, and aluminum may be used in patients with hypercalcemia, although aluminum use should be limited to a few days because of the risk of aluminum accumulation and neurotoxicity. In acute kidney injury and advanced CKD, dialysis will reduce serum phosphate.

When to Admit

Patients with acute severe hyperphosphatemia require hospitalization for emergent therapy, possibly including dialysis. Concomitant illnesses, such as acute kidney injury or cell lysis, may necessitate admission.

DISORDERS OF MAGNESIUM CONCENTRATION

Normal plasma magnesium concentration is 1.8–3.0 mg/dL (or 0.75–1.25 mmol/L), with about one-third bound to protein and two-thirds existing as free cation. Magnesium excretion is via the kidney. Magnesium’s physiologic effects on the nervous system resemble those of calcium.

Altered magnesium concentration usually provokes an associated alteration of

Ca2+. Both hypomagnesemia and hypermagnesemia can decrease PTH secretion or action. Severe hypermagnesemia (greater than 5 mg/dL [2.1 mmol/L]) suppresses PTH secretion with consequent hypocalcemia; this disorder is typically seen only in patients receiving magnesium therapy for preeclampsia. Severe hypomagnesemia causes PTH resistance in endorgans and eventually decreased PTH secretion in severe cases.

HYPOMAGNESEMIA

ESSENTIALS OF DIAGNOSIS

- Serum concentration of magnesium may not be decreased even in the presence of magnesium depletion. Check urinary magnesium excretion if renal magnesium wasting is suspected.
- Causes neurologic symptoms and arrhythmias.
- Impairs release of PTH.

General Considerations

Normomagnesemia does not exclude magnesium depletion because only 1% of total body magnesium is in the extracellular fluid (ECF). Hypomagnesemia and hypokalemia share many etiologies, including diuretics, diarrhea, alcoholism, aminoglycosides, and amphotericin. Renal potassium wasting also occurs from hypomagnesemia, and is refractory to potassium replacement until magnesium is repleted. Hypomagnesemia also suppresses PTH release and causes end-organ resistance to PTH and low 1,25-dihydroxyvitamin D3 levels. The resultant hypocalcemia is refractory to calcium replacement until the magnesium is normalized. Molecular mechanisms of magnesium wasting have been revealed in some hereditary disorders. The FDA has issued a warning about hypomagnesemia for patients taking proton pump inhibitors. The presumed mechanism is decreased intestinal magnesium absorption, but it is not clear why this complication develops in only a small fraction of patients taking these medications.

Clinical Findings

A. Symptoms and Signs

Common symptoms are those of hypokalemia and hypocalcemia, with weakness and muscle cramps. Marked neuromuscular and central nervous system hyperirritability may produce tremors, athetoid movements, jerking, nystagmus, Babinski response, confusion, and disorientation. Cardiovascular manifestations include hypertension, tachycardia, and ventricular arrhythmias.

B. Laboratory Findings

Urinary excretion of magnesium exceeding 10–30 mg/day or a fractional excretion greater than 2% indicates renal magnesium wasting. Hypocalcemia and hypokalemia are often present. The ECG shows a prolonged QT interval, due to lengthening of the ST segment. PTH secretion is often suppressed (see Hypocalcemia).

Treatment

Magnesium oxide, 250–500 mg orally once or twice daily, is useful for treating chronic hypomagnesemia. Symptomatic hypomagnesemia requires intravenous magnesium sulfate 1–2 g over 5–60 minutes mixed in either dextrose 5% or 0.9% normal saline. Torsades de pointes in the setting of hypomagnesemia can be treated with 1–2 g of magnesium sulfate in 10 mL of dextrose 5% solution pushed intravenously over 15 minutes. Severe, non–life-threatening deficiency can be treated at a rate to 1–2 g/h over 3–6 hours. Magnesium sulfate may also be given intramuscularly in a dosage of 200–800 mg/day (8–33 mmol/day) in four divided doses. Serum levels must be monitored daily and dosage adjusted to keep the concentration from rising above 3 mg/dL (1.23 mmol/L). Tendon reflexes may be checked for hyporeflexia of hypermagnesemia. K+ and Ca2+ replacement may be required, but patients with hypokalemia and hypocalcemia of hypomagnesemia do not recover without magnesium supplementation.

Patients with normal kidney function can excrete excess magnesium; hypermagnesemia should not develop with replacement dosages. In patients with CKD, magnesium replacement should be done cautiously to avoid hypermagnesemia. Reduced doses (50–75% dose reduction) and more frequent monitoring (at least twice daily) are indicated.

HYPERMAGNESEMIA

ESSENTIALS OF DIAGNOSIS

Often associated with advanced CKD and chronic intake of magnesium-containing drugs.

General Considerations

Hypermagnesemia is almost always the result of advanced CKD and impaired magnesium excretion. Antacids and laxatives are underrecognized sources of magnesium. Pregnant patients may have severe hypermagnesemia from intravenous magnesium for preeclampsia and eclampsia. Magnesium replacement should be done cautiously in patients with CKD; dose reductions up to 75% may be necessary to avoid hypermagnesemia.

Clinical Findings

A. Symptoms and Signs

Muscle weakness, decreased deep tendon reflexes, mental obtundation, and confusion are characteristic manifestations. Weakness, flaccid paralysis, ileus, urinary retention, and hypotension are noted. Serious findings include respiratory muscle paralysis and cardiac arrest.

B. Laboratory Findings

Serum Mg2+ is elevated. In the common setting of CKD, BUN, creatinine, potassium, phosphate, and uric acid may all be elevated. Serum Ca2+ is often low. The ECG shows increased PR interval, broadened QRS complexes, and peaked T

waves, probably related to associated hyperkalemia.

Treatment

Exogenous sources of magnesium should be discontinued. Calcium antagonizes Mg2+ and may be given intravenously as calcium chloride, 500 mg or more at a rate of 100 mg (4.1 mmol) per minute. Hemodialysis or peritoneal dialysis may be necessary to remove magnesium, particularly with severe kidney disease.

Long-term use of magnesium hydroxide and magnesium sulfate should be avoided in patients with advanced stages of CKD.

ACID–BASE DISORDERS

Assessment of a patient's acid–base status requires measurement of arterial pH, Pco2, and plasma bicarbonate (HCO3−). Blood gas analyzers directly measure pH and Pco2. The HCO3− value is calculated from the Henderson– Hasselbalch equation.

The total venous CO2 measurement is a more direct determination of HCO3−. Because of the dissociation characteristics of carbonic acid (H2 CO3) at body pH, dissolved CO2 is almost exclusively in the form of HCO3−, and for clinical purposes the total carbon dioxide content is equivalent (±3 mEq/L) to the HCO3− concentration.

Venous blood gases can provide useful information for acid–base assessment since the arteriovenous differences in pH and Pco2 are small and relatively constant. Venous blood pH is usually 0.03–0.04 units lower than arterial blood pH, and venous blood Pco2 is 7 or 8 mm Hg higher than arterial blood Pco2. Calculated HCO3− concentration in venous blood is at most 2 mEq/L higher than arterial blood HCO3−. Arterial and venous blood gases will not be equivalent during a cardiopulmonary arrest; arterial samples should be obtained for the most accurate measurements of pH and Pco2.

TYPES OF ACID–BASE DISORDERS

There are ***two types*** of acid–base disorders: ***acidosis*** and ***alkalosis***. These disorders can be either ***metabolic*** (***decreased or increased HCO3−***) or ***respiratory*** (***decreased or increased Pco2***). Primary respiratory disorders affect blood acidity by changes in PCO2, and primary metabolic disorders are disturbances in HCO3− concentration. A primary disturbance is usually accompanied by a compensatory response, but the compensation does not fully correct the pH disturbance of the primary disorder. If the pH is < 7.40, the primary process is acidosis, either respiratory (Pco2 greater than 40 mm Hg) or metabolic (HCO3− less than 24 mEq/L). If the pH is > 7.40, the primary process is alkalosis, either respiratory (Pco2 less than 40 mm Hg) or metabolic (HCO3− greater than 24 mEq/L). One respiratory or metabolic disorder with its appropriate compensatory response is a

simple acid-base disorder.

MIXED ACID–BASE DISORDERS

Two or three simultaneous disorders can be present in a mixed acid-base disorder, but there can never be two primary respiratory disorders. Uncovering a mixed acid-base disorder is clinically important, but requires a methodical approach to acid-base analysis (see Step-by-Step Analysis of Acid-Base Status). Once the primary disturbance has been determined, the clinician should assess whether the compensatory response is appropriate. An inadequate or an exaggerated response indicates the presence of another primary acid-base disturbance.

The anion gap should always be calculated for two reasons. First, it is possible to have an abnormal anion gap even if the sodium, chloride, and bicarbonate concentrations are normal. Second, an anion gap larger than 20 mEq/L suggests a primary metabolic acid-base disturbance regardless of the pH or serum bicarbonate level because a markedly abnormal anion gap is never a compensatory response to a respiratory disorder. In patients with an increased anion gap metabolic acidosis, clinicians should calculate the corrected bicarbonate. In increased anion gap acidoses, there should be a mole for mole decrease in $HCO3^-$ as the anion gap increases. A corrected $HCO3^-$ value higher or lower than normal (24 mEq/L) indicates the concomitant presence of metabolic alkalosis or normal anion gap metabolic acidosis, respectively.

STEP-BY-STEP ANALYSIS OF ACID-BASE STATUS

Step 1: Determine the primary (or main) disorder—whether it is metabolic or respiratory—from blood pH, $HCO3^-$, and Pco2 values.

Step 2: Determine the presence of mixed acid-base disorders by calculating the range of compensatory responses.

Step 3: Calculate the anion gap.

Step 4: Calculate the corrected $HCO3^-$ concentration if the anion gap is increased (see above).

Step 5: Examine the patient to determine whether the clinical signs are compatible with the acid-base analysis.

METABOLIC ACIDOSIS

ESSENTIALS OF DIAGNOSIS

- Decreased $HCO3^-$ with acidemia.
- Classified into increased anion gap acidosis and normal anion gap acidosis.
- Lactic acidosis, ketoacidosis, and toxins produce metabolic acidoses with the largest anion gaps.
- Normal anion gap acidosis is mainly caused by gastrointestinal $HCO3^-$ loss or RTA. Urinary anion gap may help distinguish between these

causes.

General Considerations

The hallmark of metabolic acidosis is decreased HCO3–. Metabolic acidoses are classified by the anion gap, usually normal or increased. The anion gap is the difference between readily measured anions and cations.

Major unmeasured cations are calcium (2 mEq/L), magnesium (2 mEq/L), gamma-globulins, and potassium (4 mEq/L). Major unmeasured anions are albumin (2 mEq/L per g/dL), phosphate (2 mEq/L), sulfate (1 mEq/L), lactate (1–2 mEq/L), and other organic anions (3–4 mEq/L). Traditionally, the normal anion gap has been 12±4 mEq/L. With current auto-analyzers, the reference range may be lower (6±1 mEq/L), primarily from an increase in Cl– values. Despite its usefulness, the anion gap can be misleading. Non–acid-base disorders may cause errors in anion gap interpretation; these disorders including hypoalbuminemia, hypernatremia, or hyponatremia; antibiotics (eg, carbenicillin is an unmeasured anion; polymyxin is an unmeasured cation) may also cause errors in anion gap interpretation. Although not usually associated with metabolic acidosis, a decreased anion gap can occur because of a reduction in unmeasured anions or an increase in unmeasured cations. In hypoalbuminemia, a 2 mEq/L decrease in anion gap will occur for every 1 g/dL decline in serum albumin.

INCREASED ANION GAP ACIDOSIS
(Increased Unmeasured Anions)

Normochloremic metabolic acidosis generally results from addition of organic acids such as lactate, acetoacetate, betahydroxybutyrate, and exogenous toxins. Other anions such as isocitrate, alpha-ketoglutarate, malate and d-lactate, may contribute to the anion gap of lactic acidosis, DKA, and acidosis of unknown etiology. Uremia causes an increased anion gap metabolic acidosis from unexcreted organic acids and anions.

A. Lactic Acidosis

Lactic acid is formed from pyruvate in anaerobic glycolysis, typically in tissues with high rates of glycolysis, such as gut (responsible for over 50% of lactate production), skeletal muscle, brain, skin, and erythrocytes. Normally, lactate levels remain low (1 mEq/L) because of metabolism of lactate principally by the liver through gluconeogenesis or oxidation via the Krebs cycle. The kidneys metabolize about 30% of lactate.

In lactic acidosis, lactate levels are at least 4–5 mEq/L but commonly 10–30 mEq/L. There are two basic types of lactic acidosis.

Type A (hypoxic) lactic acidosis is more common, resulting from decreased tissue perfusion; cardiogenic, septic, or hemorrhagic shock; and carbon monoxide or cyanide poisoning. These conditions increase peripheral lactic acid production and decrease hepatic metabolism of lactate as liver perfusion declines.

Type B lactic acidosis may be due to metabolic causes (eg, diabetes,

ketoacidosis, liver disease, kidney disease, infection, leukemia, or lymphoma) or toxins (eg, ethanol, methanol, salicylates, isoniazid, or metformin). Propylene glycol can cause lactic acidosis from decreased liver metabolism; it is used as a vehicle for intravenous drugs, such as nitroglycerin, etomidate, and diazepam. Parenteral nutrition without thiamine causes severe refractory lactic acidosis from deranged pyruvate metabolism. Patients with short bowel syndrome may develop d-lactic acidosis with encephalopathy due to carbohydrate malabsorption and subsequent fermentation by colonic bacteria.

Nucleoside analog reverse transcriptase inhibitors can cause type B lactic acidosis due to mitochondrial toxicity.

Idiopathic lactic acidosis, usually in debilitated patients, has an extremely high mortality rate.

B. Diabetic Ketoacidosis (DKA)

DKA is characterized by hyperglycemia and metabolic acidosis with an increased anion gap.

The anion gap should be calculated from the measured serum electrolytes; correction of the serum sodium for the dilutional effect of hyperglycemia will exaggerate the anion gap. Diabetics with ketoacidosis may have lactic acidosis from tissue hypoperfusion and increased anaerobic metabolism. During the recovery phase of DKA, a hyperchloremic non-anion gap acidosis can develop because saline resuscitation results in chloride retention, restoration of GFR, and ketoaciduria. Ketone salts (NaB) are formed as bicarbonate is consumed:

$$HB + NaHCO3 \rightarrow NaB + H2\ CO3$$

The kidney reabsorbs ketone anions poorly but can compensate for the loss of anions by increasing the reabsorption of Cl^-.

Patients with DKA and normal kidney function may have marked ketonuria and severe metabolic acidosis but only a mildly increased anion gap. Thus, the size of the anion gap correlates poorly with the severity of the DKA; the urinary loss of Na^+ or K^+ salts of beta-hydroxybutyrate will lower the anion gap without altering the H^+ excretion or the severity of the acidosis. Urine dipsticks for ketones test primarily for acetoacetate and, to a lesser degree, acetone but not the predominant ketoacid, beta-hydroxybutyrate. Dipstick tests for ketones may become more positive even as the patient improves due to the metabolism of beta-hydroxybutyrate. Thus, the patient's clinical status and pH are better markers of improvement than the anion gap or ketone levels.

C. Alcoholic Ketoacidosis

Chronically malnourished patients who consume large quantities of alcohol daily may develop alcoholic ketoacidosis. Most of these patients have mixed acid–base disorders (10% have a triple acid–base disorder). Although decreased $HCO3^-$ is usual, 50% of the patients may have normal or alkalemic pH. Three types of metabolic acidosis are seen in alcoholic ketoacidosis: (1) Ketoacidosis is due to betahydroxybutyrate and acetoacetate excess. (2) Lactic acidosis: Alcohol metabolism increases the NADH: NAD ratio, causing increased production and

decreased utilization of lactate. Accompanying thiamine deficiency, which inhibits pyruvate carboxylase, further enhances lactic acid production in many cases. Moderate to severe elevations of lactate (greater than 6 mmol/L) are seen with concomitant disorders such as sepsis, pancreatitis, or hypoglycemia. (3) Hyperchloremic acidosis from bicarbonate loss in the urine is associated with ketonuria (see above). Metabolic alkalosis occurs from volume contraction and vomiting. Respiratory alkalosis results from alcohol withdrawal, pain, or associated disorders such as sepsis or liver disease. Half of the patients have hypoglycemia or hyperglycemia. When serum glucose levels are greater than 250 mg/dL (13.88 mmol/L), the distinction from DKA is difficult. The absence of a diabetic history and normoglycemia after initial therapy support the diagnosis of alcoholic ketoacidosis.

D. Toxins

Multiple toxins and drugs increase the anion gap by increasing endogenous acid production. Common examples include methanol (metabolized to formic acid), ethylene glycol (glycolic and oxalic acid), and salicylates (salicylic acid and lactic acid). The latter can cause a mixed disorder of metabolic acidosis with respiratory alkalosis. In toluene poisoning, the metabolite hippurate is rapidly excreted by the kidney and may present as a normal anion gap acidosis. Isopropanol, which is metabolized to acetone, increases the osmolar gap, but not the anion gap.

E. Uremic Acidosis

As the GFR drops below 15–30 mL/min, the kidneys are increasingly unable to excrete H^+ and organic acids, such as phosphate and sulfate, resulting in an increased anion gap acidosis. Hyperchloremic normal anion gap acidosis develops in earlier stages of CKD.

NORMAL ANION GAP ACIDOSIS

The two major causes are gastrointestinal HCO_3^- loss and defects in renal acidification (renal tubular acidosis). The urinary anion gap can differentiate between these causes.

A. Gastrointestinal HCO_3^- Loss

The gastrointestinal tract secretes bicarbonate at multiple sites. Small bowel and pancreatic secretions contain large amounts of HCO_3^-; massive diarrhea or pancreatic drainage can result in HCO_3^- loss. Hyperchloremia occurs because the ileum and colon secrete HCO_3^- in exchange for Cl^- by countertransport. The resultant volume contraction causes increased Cl^- retention by the kidney in the setting of decreased HCO_3^-. Patients with ureterosigmoidostomies can develop hyperchloremic metabolic acidosis because the colon secretes HCO_3^- in the urine in exchange for Cl^-.

B. Renal Tubular Acidosis (RTA)

Hyperchloremic acidosis with a normal anion gap and normal (or near normal) GFR, and in the absence of diarrhea, defines RTA. The defect is either inability to excrete H+ (inadequate generation of new HCO3–) or inappropriate reabsorption of HCO3–. Three major types can be differentiated by the clinical setting, urinary pH, urinary anion gap (see below), and serum K+ level. The pathophysiologic mechanisms of RTA have been elucidated by identifying the responsible molecules and gene mutations.

1. Classic distal RTA (type I)—This disorder is characterized by selective deficiency in H+ secretion in alpha intercalated cells in the collecting tubule. Despite acidosis, urinary pH cannot be acidified and is above 5.5, which retards the binding of H+ to phosphate ($H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$) and inhibits titratable acid excretion. Furthermore, urinary excretion of $NH_4^+Cl^-$ is decreased, and the urinary anion gap is positive (see below). Enhanced K+ excretion occurs probably because there is less competition from H+ in the distal nephron transport system. Furthermore, hyperaldosteronism occurs in response to renal salt wasting, which will increase potassium excretion. Nephrocalcinosis and nephrolithiasis are often seen in patients with distal RTA since chronic acidosis decreases tubular calcium reabsorption. Hypercalciuria, alkaline urine, and lowered level of urinary citrate cause calcium phosphate stones and nephrocalcinosis.

Distal RTA develops as a consequence of paraproteinemias, autoimmune disease, and drugs and toxins such as amphotericin.

2. Proximal RTA (type II)—Proximal RTA is due to a selective defect in the proximal tubule's ability to reabsorb filtered HCO_3^-. Carbonic anhydrase inhibitors (acetazolamide) can cause proximal RTA. About 90% of filtered HCO_3^- is absorbed by the proximal tubule. A proximal defect in HCO_3^- reabsorption will overwhelm the distal tubule's limited capacity to reabsorb HCO_3^-, resulting in bicarbonaturia and metabolic acidosis. Distal delivery of HCO_3^- declines as the plasma HCO_3^- level decreases. When the plasma HCO_3^- level drops to 15–18 mEq/L, the distal nephron can reabsorb the diminished filtered load of HCO_3^-. Bicarbonaturia resolves, and the urinary pH can be acidic. Thiazide-induced volume contraction can be used to enhance proximal HCO_3^- reabsorption, leading to the decrease in distal HCO_3^- delivery and improvement of bicarbonaturia and renal acidification. The increased delivery of HCO_3^- to the distal nephron increases K+ secretion, and hypokalemia results if a patient is loaded with excess HCO_3^- and K+ is not adequately supplemented. Proximal RTA can exist with other proximal reabsorption defects, such as Fanconi syndrome, resulting in glucosuria, aminoaciduria, phosphaturia, and uricosuria. Causes include multiple myeloma and nephrotoxic drugs.

3. Hyporeninemic hypoaldosteronemic RTA (type IV)— Type IV is the most common RTA in clinical practice. The defect is aldosterone deficiency or antagonism, which impairs distal nephron Na+ reabsorption and K+ and H+

excretion. Renal salt wasting and hyperkalemia are frequently present. Common causes are diabetic nephropathy, tubulointerstitial renal diseases, hypertensive nephrosclerosis, and AIDS. In patients with these disorders, drugs, such as ACE inhibitors, spironolactone, and NSAIDs, can exacerbate the hyperkalemia.

C. Dilutional Acidosis

Rapid dilution of plasma volume by 0.9% NaCl may cause hyperchloremic acidosis.

D. Recovery from DKA

See Increased Anion Gap Acidosis (Increased Unmeasured Anions).

E. Posthypocapnia

In prolonged respiratory alkalosis, HCO_3^- decreases and Cl^- increases from decreased renal $NH_4^+ + Cl^-$ excretion. If the respiratory alkalosis is corrected quickly, HCO_3^- will remain low until the kidneys can generate new HCO_3^-, which generally takes several days. In the meantime, the increased P_{CO_2} with low HCO_3^- causes metabolic acidosis.

F. Hyperalimentation

Hyperalimentation fluids may contain amino acid solutions that acidify when metabolized, such as arginine hydrochloride and lysine hydrochloride.

Assessment of Hyperchloremic Metabolic Acidosis by Urinary Anion Gap

Increased renal $NH_4^+ + Cl^-$ excretion to enhance H^+ removal is the normal physiologic response to metabolic acidosis. The daily urinary excretion of NH_4Cl can be increased from 30 mEq to 200 mEq in response to acidosis.

The urinary anion gap ($Na^+ + K^+ - Cl^-$) reflects the ability of the kidney to excrete NH_4Cl. The urinary anion gap differentiates between gastrointestinal and renal causes of hyperchloremic acidosis. If the cause is gastrointestinal HCO_3^- loss (diarrhea), renal acidification remains normal and NH_4Cl excretion increases, and the urinary anion gap is negative. If the cause is distal RTA, the urinary anion gap is positive, since the basic lesion in the disorder is the inability of the kidney to excrete H^+ as NH_4Cl. In proximal (type II) RTA, the kidney has defective HCO_3^- reabsorption, leading to increased HCO_3^- excretion rather than decreased NH_4Cl excretion; the urinary anion gap is often negative.

Urinary pH may not readily differentiate between the two causes. Despite acidosis, if volume depletion from diarrhea causes inadequate Na^+ delivery to the distal nephron and therefore decreased exchange with H^+, urinary pH may not be lower than 5.3. In the presence of this relatively high urinary pH, however, H^+ excretion continues due to buffering of NH_3 to NH_4^+, since the pK of this reaction is as high as 9.1. Potassium depletion, which can accompany diarrhea (and surreptitious laxative abuse), may also impair renal acidification. Thus, when volume depletion is present, the urinary anion gap is a better measure of ability to acidify the urine than urinary pH.

Clinical Findings

A. Symptoms and Signs

Symptoms of metabolic acidosis are mainly those of the underlying disorder. Compensatory hyperventilation is an important clinical sign and may be misinterpreted as a primary respiratory disorder; Kussmaul breathing (deep, regular, sighing respirations) may be seen with severe metabolic acidosis.

B. Laboratory Findings

Blood pH, serum HCO_3^-, and P_{CO_2} are decreased. Anion gap may be normal (hyperchloremic) or increased (normochloremic). Hyperkalemia may be seen.

Treatment

A. Increased Anion Gap Acidosis

Treatment is aimed at the underlying disorder, such as insulin and fluid therapy for diabetes and appropriate volume resuscitation to restore tissue perfusion. The metabolism of lactate will produce HCO_3^- and increase pH. Supplemental HCO_3^- is indicated for treatment of hyperkalemia and some forms of normal anion gap acidosis but has been controversial for treatment of increased anion gap metabolic acidosis with respect to efficacy and safety. Large amounts of HCO_3^- may have deleterious effects, including hypernatremia, hyperosmolality, volume overload, and worsening of intracellular acidosis. In addition, alkali administration stimulates phosphofructokinase activity, thus exacerbating lactic acidosis via enhanced lactate production. Ketogenesis is also augmented by alkali therapy. In salicylate intoxication, alkali therapy must be started to decrease central nervous system damage unless blood pH is already alkalinized by respiratory alkalosis, since an increased pH converts salicylate to more impermeable salicylic acid. In alcoholic ketoacidosis, thiamine should be given with glucose to avoid Wernicke encephalopathy. The bicarbonate deficit can be calculated as follows:

$$HCO_3^- \text{ deficit} = 0.5 \times \text{body weight in kg} \times (24 - HCO_3)$$

Half of the calculated deficit should be administered within the first 3–4 hours to avoid overcorrection and volume overload. In methanol intoxication, inhibition of alcohol dehydrogenase by fomepizole is now standard care. Ethanol had previously been used as a competitive substrate for alcohol dehydrogenase, which metabolizes to formaldehyde.

B. Normal Anion Gap Acidosis

Treatment of RTA is mainly achieved by administration of alkali (either as bicarbonate or citrate) to correct metabolic abnormalities and prevent nephrocalcinosis and CKD.

Large amounts of oral alkali (10–15 mEq/kg/day) may be required to treat proximal RTA because most of the alkali is excreted into the urine, which exacerbates hypokalemia. Thus, a mixture of sodium and potassium salts is

preferred. Thiazides may reduce the amount of alkali required, but hypokalemia may develop. Treatment of type 1 distal RTA requires less alkali (1–3 mEq/kg/day) than proximal RTA. Potassium supplementation may be necessary.

For type IV RTA, dietary potassium restriction may be necessary and potassium-retaining drugs should be withdrawn. Fludrocortisone may be effective in cases with hypoaldosteronism, but should be used with care, preferably in combination with loop diuretics. In some cases, oral alkali supplementation (1–3 mEq/kg/day) may be required.

When to Refer

Most clinicians will refer patients with renal tubular acidoses to a nephrologist for evaluation and possible alkali therapy.

When to Admit

Patients will require emergency department evaluation or hospital admission depending on the severity of the acidosis and underlying conditions.

METABOLIC ALKALOSIS

ESSENTIALS OF DIAGNOSIS

- High HCO3 – with alkalemia.
- Evaluate effective circulating volume by physical examination.
- Check urinary chloride concentration to differentiate saline-responsive alkalosis from salineunresponsive alkalosis.

Classification

Metabolic alkalosis is characterized by high HCO3−. Abnormalities that generate HCO3– are called “initiation factors,” whereas abnormalities that promote renal conservation of HCO3– are called “maintenance factors.” Thus, metabolic alkalosis may remain even after the initiation factors have resolved.

The causes of metabolic alkalosis are classified into two groups based on “saline responsiveness” using the urine Cl– as a marker for volume status. Salineresponsive metabolic alkalosis is a sign of extracellular volume contraction, and saline-unresponsive alkalosis implies excessive total body bicarbonate with either euvolemia or hypervolemia. The compensatory increase in Pco2 rarely exceeds 55 mm Hg; higher Pco2 values imply a superimposed primary respiratory acidosis.

A. Saline-Responsive Metabolic Alkalosis

Much more common than saline-unresponsive alkalosis, saline-responsive alkalosis is characterized by normotensive extracellular volume contraction and hypokalemia. Hypotension and orthostasis may be seen. In vomiting or nasogastric suction, loss of acid (HCl) initiates the alkalosis, but volume contraction from Cl− loss maintains the alkalosis because the kidney avidly reabsorbs Na+ to restore the ECF. Increased sodium reabsorption necessitates increased HCO3− reabsorption

proximally, and the urinary pH remains acidic despite alkalemia (paradoxical aciduria). Renal Cl– reabsorption is high, and urine Cl– is low (less than 10–20 mEq/L). In alkalosis, bicarbonaturia may force Na+ excretion as the accompanying cation even if volume depletion is present. Therefore, urine Cl− is preferred to urine Na+ as a measure of extracellular volume. Diuretics may limit the utility of urine chloride by increasing urine chloride and sodium excretion, even in the setting of volume contraction.

Metabolic alkalosis is generally associated with hypokalemia due to the direct effect of alkalosis on renal potassium excretion and secondary hyperaldosteronism from volume depletion. Hypokalemia exacerbates the metabolic alkalosis by increasing bicarbonate reabsorption in the proximal tubule and hydrogen ion secretion in the distal tubule. Administration of KCl will correct the disorder.

1. Contraction alkalosis—Diuretics decrease extracellular volume from urinary loss of NaCl and water. The plasma HCO_3^- concentration increases because the extracellular fluid volume contracts around a stable total body bicarbonate. Contraction alkalosis is the opposite of dilutional acidosis.

2. Posthypercapnia alkalosis—In chronic respiratory acidosis, the kidney decreases bicarbonate excretion, increasing plasma HCO_3^- concentration. Hypercapnia directly affects the proximal tubule to decrease NaCl reabsorption, which can cause extracellular volume depletion. If P_{CO_2} is rapidly corrected, metabolic alkalosis will exist until the kidney excretes the retained bicarbonate. Many patients with chronic respiratory acidosis receive diuretics, which further exacerbates the metabolic alkalosis.

B. Saline-Unresponsive Alkalosis

1. Hyperaldosteronism—Primary hyperaldosteronism causes extracellular volume expansion and hypertension by increasing distal sodium reabsorption. Aldosterone increases H+ and K+ excretion, producing metabolic alkalosis and hypokalemia. In an attempt to decrease extracellular volume, high levels of NaCl are excreted resulting in a high urine Cl− (greater than 20 mEq/L). Therapy with NaCl will only increase volume expansion and hypertension and will not treat the underlying problem of mineralocorticoid excess.

2. Alkali administration with decreased GFR—The normal kidney has a substantial capacity for bicarbonate excretion, protecting against metabolic alkalosis even with large HCO_3^- intake. However, urinary excretion of bicarbonate is inadequate in CKD. If large amounts of HCO_3^- are consumed, as with intensive antacid therapy, metabolic alkalosis will occur. Lactate, citrate, and gluconate can also cause metabolic alkalosis because they are metabolized to bicarbonate. In milk-alkali syndrome, sustained heavy ingestion of absorbable antacids and milk causes hypercalcemic kidney injury and metabolic alkalosis. Volume contraction from renal hypercalcemic effects exacerbates the alkalosis.

Clinical Findings

A. Symptoms and Signs

There are no characteristic symptoms or signs. Orthostatic hypotension may be

encountered. Concomitant hypokalemia may cause weakness and hyporeflexia. Tetany and neuromuscular irritability occur rarely.

B. Laboratory Findings

The arterial blood pH and bicarbonate are elevated. With respiratory compensation, the arterial Pco2 is increased. Serum potassium and chloride are decreased. There may be an increased anion gap. The urine chloride can differentiate between saline-responsive (less than 25 mEq/L) and unresponsive (greater than 40 mEq/L) causes.

Treatment

Mild alkalosis is generally well tolerated. Severe or symptomatic alkalosis (pH > 7.60) requires urgent treatment.

A. Saline-Responsive Metabolic Alkalosis

Therapy for saline-responsive metabolic alkalosis is correction of the extracellular volume deficit with isotonic saline. Diuretics should be discontinued. H2 -blockers or proton pump inhibitors may be helpful in patients with alkalosis from nasogastric suctioning. If pulmonary or cardiovascular disease prohibits adequate resuscitation, acetazolamide will increase renal bicarbonate excretion. Hypokalemia may develop because bicarbonate excretion may induce kaliuresis. Severe cases, especially those with reduced kidney function, may require dialysis with low-bicarbonate **dialysate.**

B. Saline-Unresponsive Metabolic Alkalosis

Therapy for saline-unresponsive metabolic alkalosis includes surgical removal of a mineralocorticoid-producing tumor and blockage of aldosterone effect with an ACE inhibitor or with spironolactone. Metabolic alkalosis in primary aldosteronism can be treated only with potassium repletion.

RESPIRATORY ACIDOSIS (HYPERCAPNIA)

Respiratory acidosis results from hypoventilation and subsequent hypercapnia. Pulmonary and extrapulmonary disorders can cause hypoventilation.

Acute respiratory failure is associated with severe acidosis and only a small increase in the plasma bicarbonate. After 6–12 hours, the primary increase in Pco2 evokes a renal compensation to excrete more acid and to generate more HCO3–; complete metabolic compensation by the kidney takes several days.

Chronic respiratory acidosis is generally seen in patients with underlying lung disease, such as chronic obstructive pulmonary disease. Renal excretion of acid as NH4Cl results in hypochloremia. When chronic respiratory acidosis is corrected suddenly, posthypercapnic metabolic alkalosis ensues until the kidneys excrete the excess bicarbonate over 2–3 days.

Clinical Findings

A. Symptoms and Signs

With acute onset, somnolence, confusion, mental status changes, asterixis, and myoclonus may develop. Severe hypercapnia increases cerebral blood flow, cerebrospinal fluid pressure, and intracranial pressure; papilledema and pseudotumor cerebri may be seen.

B. Laboratory Findings

Arterial pH is low and Pco2 is increased. Serum HCO_3^- is elevated but does not fully correct the pH. If the disorder is chronic, hypochloremia is seen.

Treatment

If opioid overdose is a possible diagnosis or there is no other obvious cause for hypoventilation, the clinician should consider a diagnostic and therapeutic trial of intravenous naloxone. In all forms of respiratory acidosis, treatment is directed at the underlying disorder to improve ventilation.

RESPIRATORY ALKALOSIS (HYPOCAPNIA)

Respiratory alkalosis occurs when hyperventilation reduces the Pco2, increasing serum pH. The most common cause of respiratory alkalosis is hyperventilation syndrome, but bacterial septicemia and cirrhosis are other common causes. In pregnancy, progesterone stimulates the respiratory center, producing an average Pco2 of 30 mm Hg and respiratory alkalosis. Symptoms of acute respiratory alkalosis are related to decreased cerebral blood flow induced by the disorder. Determination of appropriate metabolic compensation may reveal an associated metabolic disorder (see Mixed Acid–Base Disorders).

As in respiratory acidosis, the metabolic compensation is greater if the respiratory alkalosis is chronic. Although serum HCO_3^- is frequently less than 15 mEq/L in metabolic acidosis, such a low level in respiratory alkalosis is unusual and may represent a concomitant primary metabolic acidosis.

Clinical Findings

A. Symptoms and Signs

In acute cases (hyperventilation), there is light-headedness, anxiety, perioral numbness, and paresthesias. Tetany occurs from a low ionized calcium, since severe alkalosis increases calcium binding to albumin.

B. Laboratory Findings

Arterial blood pH is elevated, and Pco2 is low. Serum bicarbonate is decreased in chronic respiratory alkalosis.

Treatment

Treatment is directed toward the underlying cause. In acute hyperventilation syndrome from anxiety, the traditional treatment of breathing into a paper bag should be discouraged because it does not correct Pco2 and may decrease Po2.

Reassurance may be sufficient for the anxious patient, but sedation may be necessary if the process persists. Hyperventilation is usually self-limited since muscle weakness caused by the respiratory alkalemia will suppress ventilation. Rapid correction of chronic respiratory alkalosis may result in metabolic acidosis as Pco2 is increased with a previous compensatory decrease in HCO3−. The severity of hypocapnia in critically ill patients has been associated with adverse outcomes.

FLUID MANAGEMEN

Daily parenteral maintenance fluids and electrolytes for an average adult would include at least 2 L of water in the form of 0.45% saline with 20 mEq/L of potassium chloride. Patients with hypoglycemia, starvation ketosis, or ketoacidosis being treated with insulin may require 5% dextrosecontaining solutions.

Weight loss or gain is the best indication of water balance. Insensible water loss should be considered in febrile patients. Water loss increases by 100–150 mL/day for each degree of body temperature over 37°C.

In patients requiring maintenance and possibly replacement of fluid and electrolytes by parenteral infusion, the total daily ration should be administered continuously over 24 hours to ensure optimal utilization.

If intravenous fluids are the only source of water, electrolytes, and calories for longer than a week, parenteral nutrition containing amino acids, lipids, trace metals, and vitamins may be indicated.

For parenteral alimentation, 620 mg (20 mmol) of phosphorus is required for every 1000 nonprotein kcal to maintain phosphate balance and to ensure anabolic function. For prolonged parenteral fluid maintenance, a daily ration is 620–1240 mg (20–40 mmol) of phosphorus.

The ideal resuscitation fluid composition and dose are not established; and there is little evidence that one type of fluid (crystalloid, colloid, or semisynthetic colloid) is superior or safer than another. Excessive fluid resuscitation and maintenance are complications in hospitalized patients, especially those with critical illness or acute kidney injury, and have been associated with worsened outcomes such as prolonged mechanical ventilation, dependence on dialysis, and longer hospitalization with increased mortality.

Control questions

1. List the diseases and syndromes that are accompanied by the most severe violations of water-electrolyte balance in the body.
2. Determine the pathophysiological and pathochemical mechanisms of these violations.
3. The biological role of Mg, Ca, Na and K in the body.
4. Specify the clinical and laboratory-instrumental criteria that characterize the violation of the water-electrolyte balance.
5. List the main groups of drugs used for the correction of extracellular and

intracellular dehydration, extracellular and intracellular hyperhydration, hypo and hypernatremia, hypo and hypercalemia, hypo and hypercalcemia, hypo and hypermagnemia, hypo-and hyperchloremia.
6. What determines the osmolarity of the blood plasma, in which states it is broken?
7. Explain the significance of the leading pharmacokinetic parameters in the individual choice of drugs that normalize the water-electrolyte balance.
8. What concomitant diseases can complicate the conducted pharmacotherapy of the disturbed water-electrolyte balance?
9. Application, which drugs can lead to severe violations of water-electrolyte balance in the body. Suggest a scheme for the prevention of such violations.
10. Pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of drugs used for major violations of water-electrolyte metabolism.
11. Leading pathogenetic mechanisms at major violations of water-electrolyte metabolism, which is the subject of medicinal effect.
12. Undesirable effects of drugs used to normalize the disturbed water-electrolyte balance.
13. Principles of combining these drugs.
14. Criteria for the effectiveness and safety of the proposed drugs.
15. Pharmacodynamics, pharmacokinetics, pharmacotoxicodynamics of medicine , used for correction of various violations of acid-alkaline equilibrium.
16. Drugs used for correction of acidosis.
17. Drugs used for correction of alkalosis.

List of practical works

A. Homework.

1. To know at what diseases there is a possibility of violation of water-electrolyte exchange.
2. To know clinical and laboratory-instrumental criteria, characterizing violation of water-electrolyte exchange.
3. To study the main directions of correction of violations of water-electrolyte exchange.
4. To specify and explain possible combinations of drugs used in violation of water-electrolyte equilibrium (WEE), as well as the possibility of their interchange.

B. Self-employment at the lesson.

1. The cure of the thematic patient in the ward.
2. To study its history of illness (data laboratory-instrumental studies, conclusions of consultants) and a letter of medical appointments.
3. To write a protocol of independent work of choice for the patient of the patient, correcting violations of the WEE.
4. With a subjective and objective study of the patient to distinguish signs that characterize the violation of WEE.
5. Determine the group of LS necessary for the patient to correct the violations

detected WEE.
6. Select a specific drug, its dose and the mode of administration.
7. To substantiate the urgent medical help directed on normalization of the violated water-electrolyte balance at:
- Hyperglycemic (hyperosmolar) coma;
- Hyperglycemic (ketoacidic) coma;
- Infectious-toxic shock;
- Acute posthemorrhagic hypovolemia;
- Threatening lung edema, brain;
--excasios of pregnancy;
- Burn disease.

Control the level of knowledge

1. Identify the main violation acid-alkaline equilibrium.

Pathological states	Definition
1. Metabolic acidosis 2. Respiratory acidosis 3. Mixed respiratory and non-respiratory acidosis 4. Metabolic alkalosis 5. Respiratory alkalosis	

2. Fill out the table "Basic directions of pharmacotherapy of alkalosis".

Pharmacological groups	Drugs	Way of administration, dose
1. Acid solutions 2. Amino acids 3. Chlorides 4. Diuretics		

3. Fill in the table "Basic directions of pharmacotherapy of acidosis".

Directions of pharmacotherapy	Drugs	Way of administration, dose
1. Means of metabolic therapy 2. Antihypoxants 3. Improvement of microcirculation means 4. Symptomatic means		

4. Fill in the table "Pharmacotherapy of the main violations of water-electrolyte exchange".

Directions of pharmacotherapy	Pharmacological groups	Drugs
1. Solutions of crystalloids 2. Colloidal Plasma Substitutes: - high molecular weight - medium-molecular - low molecular weight		

5. Explain the mechanisms of water-electrolyte disturbances in patients with prolonged administration of glucocorticosteroids.

Plan an early detection and prevention plan. What other groups of drugs can cause such violations of homeostasis

Solution of situational tasks

1. A boy, 5 years old, after eating a lot of fatty foods, felt bad. There was nausea, vomiting, headache. Urine reaction is sharply acidic; Exhaust air with smell of acetone.

What is the drug that you prefer to relieve ketoacidosis in a child. Justify your choice.

2. A patient, 42 years of age, 67 kg of body weight, suffering from a severe form of insulin-dependent diabetes mellitus, on the background of chronic alcoholism, entered the endocrinology department in a coma state. The

deterioration has come after alcoholic excess. Skin is pale, dry and hot. BH - 40 per 1 minute. Breathing deep, noisy; Heart rate - 110 for 1 min, heart tone muffled. The abdomen is bloated, the peristalsis is sluggish. Blood sugar level 32 mmol / l. Acetone in urine (++++).

Explain the likely genesis of the coma, compile a plan for follow-up and emergency care for the patient.

3. The patient, 38 years old, with a weight of 65 kg, was admitted to the therapeutic department in connection with the exacerbation of chronic cholecystitis-pancreatitis. The patient is suffering from pains in the epigastrium, repeated vomiting with bile, sharp weakness, dizziness. Objectively: pale, cold, sticky sweat. Breathing is frequent, superficial. BP - 100/50 mm Hg. st .. heart rate - 92 for 1 min. The abdomen is painful in the upper half, symptoms of peritoneal irritation are absent, peristalsis is preserved. Another doctor prescribed treatment with cholinolytics, anesthetics, non-narcotic analgesics (all drugs are administered parenterally), in addition, 200 ml of 4% solution of sodium bicarbonate is injected intravenously. Contrary to the hopes of the doctor after the events, the patient's condition deteriorated. Increased nausea, vomiting, weakness, dizziness, BP - 90/50 mm Hg. st., heart rate 106 for 1 min.

Explain the cause of deterioration. What did the doctor do not take into account? Assign correction for existing violations of the CRL, indicating the drugs and how to enter them.

4. A child, aged 10, suffers from profuse diarrhea for several days. Developed a sharp muscular weakness, loss of appetite, vomiting, decreased blood pressure, arrhythmia, tachycardia.

What are the causes of these pathological changes? Plan a correction plan for them.

5. The patient, 65 years old, indicates an increase in general weakness, shortness of breath, edema of the extremities and facial that appeared 3 weeks after surgery for a strangulated hernia with resection of the intestine. Objectively: pulse 90 for 1 min, rhythmic, satisfactory filling. BP - 110/80 mm Hg. Art. Heart tones are rhythmic, sonorous. In the lungs, moist rales are heard in the lower parts. On the shins and trunk - edema.

How to explain changes in the patient, what are they related to? How to prove your assumption? What corrective therapy should be given to the patient?

6. A patient, 42 years old, with a body weight of 74 kg, was taken to the department by an ambulance car without consciousness. Breathing deep, noisy. The smell of acetone from the mouth. Skin is pale, dry. Turgor skin is lowered. The muscles are relaxed. BP - 90/45 mm Hg Body temperature is normal. The level of glucose in the blood is 22.2 mmol / l. BE (-10), plasma osmolarity of 320 mmoles.

Your diagnosis? What types of homeostasis disorders need to be corrected? Plan of treatment.

7. The patient, 32 years old, transfused incompatible blood. After 2 hours, oliguria developed, which was replaced by anuria. In the patient consciousness is preserved, it is inhibited. BP - 130/75 mmHg Tones of the heart are muffled, at the apex systolic noise. ECG - reduction of the voltage of the tooth R in the left chest compartments, extension of the atrial-ventricular and intraventricular conduction, high, sharpened teeth T.

What types of homeostasis violations did you encounter? Your tactic of correction of homeostasis disorder in a patient.

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TOPIC 17. Diabetes mellitus: classification, diagnosis, principles of pharmacotherapy.

Actuality of theme.

Among the endocrine pathology, diabetes is ranked first in prevalence (more than 50% of all endocrine diseases). Every 10-15 years in all countries of the world the number of patients is doubled. At present, more than 60 million people are suffering from diabetes in the globe. An estimated 25.8 million people (8.3%) in the United States have diabetes mellitus, of which approximately 1 million have type 1 diabetes and most of the rest have type 2 diabetes. Diabetes mellitus has become the main cause of blindness, a significant factor in the growth of the number of cardiovascular diseases. Among the causes of death, diabetes ranks third after cardiovascular and oncological diseases. Patients with diabetes often go to the intensive care unit with complications of varying degrees of severity, from mild hyperglycemia to severe ketoacidosis. Approximately 80% of episodes of diabetic ketoacidosis develops repeatedly. Diabetics with experience account for almost 75% of all cases of diabetic ketoacidosis, 50% of which are provoked by concomitant diseases such as infections or myocardial infarction. Only 20-25% of diabetic ketoacidosis is the result of a lack of insulin. Hypoglycaemic conditions, most commonly seen as a complication of diabetes mellitus.

Purpose of the lesson: Student should know diabetes mellitus type 1 and 2: etiology, pathogenesis, clinical manifestations, diagnostic methods, differentiated choice of pharmacotherapy. Diabetic coma: concept, classification. Hyperglycemic coma: pathogenesis, principles of treatment. Hypoglycemic coma: pathogenesis, treatment principles, and requirements for drugs used to treat diabetes.

DIABETES MELLITUS

ESSENTIALS OF DIAGNOSIS

Type 1 diabetes:

- Polyuria, polydipsia, and weight loss associated with random plasma glucose of 200 mg/dL (11.1 mmol/L) or more.
- Plasma glucose of 126 mg/dL (7.0 mmol/L) or more after an overnight fast, documented on more than one occasion.
- Ketonemia, ketonuria, or both.
- Islet autoantibodies are frequently present.

Type 2 diabetes:

- Many patients are over 40 years of age and obese.
- Polyuria and polydipsia. Ketonuria and weight loss generally are uncommon at time of diagnosis. Candidal vaginitis in women may be an initial manifestation. Many patients have few or no symptoms.

- Plasma glucose of 126 mg/dL or more after an overnight fast on more than one occasion. Two hours after 75 g oral glucose, diagnostic values are 200 mg/dL (11.1 mmol) or more.
- HbA1c 6.5% or more.
- Hypertension, dyslipidemia, and atherosclerosis are often associated.

Classification & Pathogenesis

Diabetes mellitus is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin secretion or to a combination of insulin resistance and inadequate insulin secretion to compensate for the resistance.

<u>Other specific types of diabetes mellitus</u>

- Genetic defects of pancreatic B cell function:

- MODY 1 (HNF-4alpha); rare
- MODY 2 (glucokinase); less rare
- MODY 3 (HNF-1alpha); accounts for two-thirds of all MODY
- MODY 4 (PDX1); very rare
- MODY 5 (HNF-1beta); very rare
- MODY 6 (neuroD1); very rare Mitochondrial DNA

- Genetic defects in insulin action:

- Type A insulin resistance
- Leprechaunism
- Rabson-Mendenhall syndrome
- Lipoatrophic diabetes

- Diseases of the exocrine pancreas
- Endocrinopathies
- Drug- or chemical-induced diabetes
- Other genetic syndromes (Down, Klinefelter, Turner, others) sometimes associated with diabetes

A. Type 1 Diabetes Mellitus

This form of diabetes is due to pancreatic islet B cell destruction predominantly by an autoimmune process in over 95% of cases (type 1A) and idiopathic in less than 5% (type 1B). The rate of pancreatic B cell destruction is quite variable, being rapid in some individuals and slow in others. Type 1 diabetes is usually associated with ketosis in its untreated state. It occurs at any age but most commonly arises in children and young adults with a peak incidence before school age and again at around puberty. It is a catabolic disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, and the pancreatic B cells fail to respond to all insulinogenic stimuli. Exogenous insulin is therefore required to reverse the catabolic state, prevent ketosis, reduce the hyperglucagonemia, and

reduce blood glucose.

1. Immune-mediated type 1 diabetes mellitus (type 1A)—Approximately one-third of the disease susceptibility is due to genes and two-thirds to environmental factors. Genes that are related to the HLA locus contribute about 40% of the genetic risk. About 95% of patients with type 1 diabetes possess either HLA-DR3 or HLA-DR4, compared with 45–50% of white controls. HLA-DQ genes are even more specific markers of type 1 susceptibility, since a particular variety (HLA-DQB1*0302) is found in the DR4 patients with type 1, while a "protective" gene (HLADQB1*0602) is often present in the DR4 controls. The other important gene that contributes to about 10% of the genetic risk is found at the 5′ polymorphic region of the insulin gene. Mutations in genes associated with T cell tolerance can also cause autoimmune diabetes. The autoimmune regulatory gene (AIRE) product regulates the expression of several proteins in the thymus causing the deletion of self-reactive T cells. Type 1 diabetes mellitus as well as other autoimmune disorders (autoimmune polyglandular syndrome 1) develop in 20% of individuals with homozygote mutations in AIRE. FOXP3, an X chromosome gene, encodes a transcription factor required for the formation of regulatory T cells. Most patients with type 1 diabetes mellitus have circulating antibodies to islet cells (ICA), glutamic acid decarboxylase 65 (GAD65), insulin (IAA), tyrosine phosphatase IA2 (ICA-512), and zinc transporter 8 (ZnT8) at the time the diagnosis is made. These antibodies facilitate screening for an autoimmune cause of diabetes, particularly screening siblings of affected children, as well as adults with atypical features of type 2 diabetes mellitus. Screening with GAD65, ICA-512, IAA, and ZnT8 autoantibodies may identify about 98% of people who have an autoimmune basis for their beta cell loss. Antibody levels decline with increasing duration of disease. Also, low levels of anti-insulin antibodies develop in almost all patients once they are treated with insulin.

Family members of diabetic probands are at increased lifetime risk for developing type 1 diabetes mellitus. A child whose mother has type 1 diabetes has a 3% risk of developing the disease and a 6% risk if the child's father has it. The risk in siblings is related to the number of HLA haplotypes that the sibling shares with the diabetic proband. If one haplotype is shared, the risk is 6% and if two haplotypes are shared, the risk increases to 12–25%. The highest risk is for identical twins, where the concordance rate is 25–50%.

Some patients with a milder expression of type 1 diabetes mellitus initially retain enough B cell function to avoid ketosis, but as their B cell mass diminishes later in life, dependence on insulin therapy develops. Islet cell antibody surveys among northern Europeans indicate that up to 15% of "type 2" diabetic patients may actually have this mild form of type 1 diabetes (latent autoimmune diabetes of adulthood; LADA). Evidence for environmental factors playing a role in the development of type 1 diabetes include the observation that the disease is more common in Scandinavian countries and becomes progressively less frequent in countries nearer and nearer to the equator. Also, the risk for type 1 diabetes increases when individuals who normally have a low risk emigrate to the Northern Hemisphere. For example, Pakistani children born and raised in Bradford, England

have a higher risk for developing type 1 diabetes compared with children who lived in Pakistan all their lives.

Which environmental factor is responsible for the increased risk is not known. There have been a number of different hypotheses including infections with certain viruses (mumps, rubella, Coxsackie B4) and consumption of cow's milk. Also, in developed countries, childhood infections have become less frequent and so perhaps the immune system becomes dysregulated with development of autoimmunity and conditions such as asthma and diabetes. This theory is referred to as the hygiene hypothesis. Part of the difficulty in determining the causative environmental factor is that autoimmune injury is initiated many years before the clinical presentation of diabetes.

2. Idiopathic type 1 diabetes mellitus (type 1B)—Approximately 5% of subjects have no evidence of pancreatic B cell autoimmunity to explain their insulinopenia and ketoacidosis. This subgroup has been classified as "idiopathic type 1 diabetes" and designated as "type 1B." Although only a minority of patients with type 1 diabetes fall into this group, most of these individuals are of Asian or African origin. About 4% of the West Africans with ketosis-prone diabetes are homozygous for a mutation in PAX-4 (Arg133Trp)—a transcription factor that is essential for the development of pancreatic islets.

B. Type 2 Diabetes Mellitus

This represents a heterogeneous group of conditions that used to occur predominantly in adults, but it is now more frequently encountered in children and adolescents. Circulating endogenous insulin is sufficient to prevent ketoacidosis but is inadequate to prevent hyperglycemia in the face of increased needs owing to tissue insensitivity (insulin resistance).

Genetic and environmental factors combine to cause both the insulin resistance and the beta cell loss. Most epidemiologic data indicate strong genetic influences, since in monozygotic twins over 40 years of age, concordance develops in over 70% of cases within a year whenever type 2 diabetes develops in one twin. Genome-wide association studies have made considerable progress in identifying the at-risk genes. So far, more than 30 genetic loci have been associated with an increased risk of type 2 diabetes. A significant number of the identified loci appear to code for proteins that have a role in beta cell function or development. One of the genetic loci with the largest risk effect is TCF7L2. This gene codes for a transcription factor involved in the WNT signaling pathway that is required for normal pancreatic development.

Early in the disease process, hyperplasia of pancreatic B cells occurs and probably accounts for the fasting hyperinsulinism and exaggerated insulin and proinsulin responses to glucose and other stimuli. With time, chronic deposition of amyloid in the islets may combine with inherited genetic defects progressively to impair B cell function.

Obesity is the most important environmental factor causing insulin resistance. The degree and prevalence of obesity varies among different racial groups with type 2 diabetes. While obesity is apparent in no more than 30% of

Chinese and Japanese patients with type 2, it is found in 60–70% of North Americans, Europeans, or Africans with type 2 and approaches 100% of patients with type 2 among Pima Indians or Pacific Islanders from Nauru or Samoa.

Visceral obesity, due to accumulation of fat in the omental and mesenteric regions, correlates with insulin resistance; subcutaneous abdominal fat seems to have less of an association with insulin insensitivity. There are many patients with type 2 diabetes who, while not overtly obese, have increased visceral fat; they are termed the "metabolically obese." Exercise may affect the deposition of visceral fat as suggested by CT scans of Japanese wrestlers, whose extreme obesity is predominantly subcutaneous. Their daily vigorous exercise program prevents accumulation of visceral fat, and they have normal serum lipids and euglycemia despite daily intakes of 5000–7000 kcal and development of massive subcutaneous obesity.

C. Other Specific Types of Diabetes Mellitus

1. Maturity-onset diabetes of the young (MODY)—This subgroup is a relatively rare monogenic disorder characterized by non–insulin-dependent diabetes with autosomal dominant inheritance and an age at onset of 25 years or younger. Patients are nonobese, and their hyperglycemia is due to impaired glucose-induced secretion of insulin. Six types of MODY have been described. Except for MODY 2, in which a glucokinase gene is defective, all other types involve mutations of a nuclear transcription factor that regulates islet gene expression.

2. Diabetes due to mutant insulins—This is a very rare subtype of nonobese type 2 diabetes, with no more than ten families having been described. Since affected individuals were heterozygous and possessed one normal insulin gene, diabetes was mild, did not appear until middle age, and showed autosomal dominant genetic transmission. There is generally no evidence of clinical insulin resistance, and these patients respond well to standard therapy.

3. Diabetes due to mutant insulin receptors—Defects in one of their insulin receptor genes have been found in more than 40 people with diabetes, and most have extreme insulin resistance associated with acanthosis nigricans. In very rare instances when both insulin receptor genes are abnormal, newborns present with a leprechaun-like phenotype and seldom live through infancy.

4. Diabetes mellitus associated with a mutation of mitochondrial DNA—Since sperm do not contain mitochondria, only the mother transmits mitochondrial genes to her offspring. Diabetes due to mutations of mitochondrial DNA occurs in less than 2% of patients with diabetes. The most common cause is the A3243G mutation in the gene coding for the tRNA (Leu, UUR). Diabetes usually develops in these patients in their late 30s, and characteristically, they also have hearing loss (maternally inherited diabetes and deafness [MIDD]).

5. Wolfram syndrome—Wolfram syndrome is an autosomal recessive neurodegenerative disorder first evident in childhood. It consists of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, hence the acronym DIDMOAD. It is due to mutations in a gene named WFS1, which encodes a 100.3 KDa transmembrane protein localized in the endoplasmic reticulum. Cranial

diabetes insipidus and sensorineural deafness develop during the second decade in 60–75% of patients. Ureterohydronephrosis, neurogenic bladder, cerebellar ataxia, peripheral neuropathy, and psychiatric illness develop later in many patients.

6. Autosomal recessive syndromes—Homozygous mutations in a number of pancreatic transcription factors, NEUROG3, PTF1A, RFX6, and GLI-similar 3 (GLIS3), cause neonatal or childhood diabetes. Homozygous PTF1A mutations result in absent pancreas and cerebellar atrophy; NEUROG3 mutations cause severe malabsorption and diabetes before puberty. Homozygous mutations in RFX6 cause the Mitchell-Riley syndrome characterized by absence of all islet cell types apart from pancreatic polypeptide cells, hypoplasia of the pancreas and gallbladder, and intestinal atresia. GLIS3 gene plays a role in transcription of insulin gene, and homozygous mutations cause neonatal diabetes and congenital hypothyroidism. The gene EIF2AK3 encodes PKR-like ER kinase (PERK), which controls one of the pathways of the unfolded protein response. Absence of PERK leads to inadequate response to ER stress and accelerated beta cell apoptosis. Patients with mutation in this gene have neonatal diabetes, epiphyseal dysplasia, developmental delay, and hepatic and renal dysfunction (Wolcott-Rallison syndrome).

7. Diabetes mellitus secondary to other causes—Endocrine tumors secreting growth hormone, glucocorticoids, catecholamines, glucagon, or somatostatin can cause glucose intolerance. In the first four of these situations, peripheral responsiveness to insulin is impaired. With excess of glucocorticoids, catecholamines, or glucagon, increased hepatic output of glucose is a contributory factor; in the case of catecholamines, decreased insulin release is an additional factor in producing carbohydrate intolerance, and with somatostatin, inhibition of insulin secretion is the major factor. Diabetes mainly occurs in individuals with underlying defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved.

High-titer anti-insulin receptor antibodies that inhibit insulin binding causes a clinical syndrome characterized by severe insulin resistance, glucose intolerance or diabetes mellitus, and acanthosis nigricans. These patients usually have other autoimmune disorders. There are reports of spontaneous remission or remission with cytotoxic therapy.

Many medications are associated with carbohydrate intolerance or frank diabetes. The medications act by decreasing insulin secretion or by increasing insulin resistance or both. Cyclosporine and tacrolimus impair insulin secretion; sirolimus principally increases insulin resistance. These agents contribute to the development of new-onset diabetes after transplantation. Corticosteroids increase insulin resistance but may also have an effect on beta cell function; in a case control study and a large population cohort study, oral corticosteroids doubled the risk for development of diabetes. Thiazide diuretics and beta-blockers modestly increase the risk for diabetes. Treating the hypokalemia due to thiazides may reverse the hyperglycemia. Atypical antipsychotics, particularly olanzapine and clozapine, have been associated with increased risk of glucose intolerance. These medications cause weight gain and insulin resistance but may also impair beta cell function; an increase in rates of diabetic ketoacidosis has been reported.

Chronic pancreatitis or subtotal pancreatectomy reduces the number of functioning B cells and can result in a metabolic derangement very similar to that of genetic type 1 diabetes except that a concomitant reduction in pancreatic A cells may reduce glucagon secretion so that relatively lower doses of insulin replacement are needed.

Insulin Resistance Syndrome (Syndrome X; Metabolic Syndrome)

Twenty-five percent of the general nonobese, nondiabetic population has insulin resistance of a magnitude similar to that seen in type 2 diabetes. These insulin-resistant nondiabetic individuals are at much higher risk for developing type 2 diabetes than insulin-sensitive persons. In addition to diabetes, these individuals have increased risk for elevated plasma triglycerides, lower high-density lipoproteins (HDLs), and higher blood pressure—a cluster of abnormalities termed **syndrome X or metabolic syndrome**. These associations have been expanded to include small, dense, low-density lipoprotein (LDL), hyperuricemia, abdominal obesity, prothrombotic state with increased levels of plasminogen activator inhibitor type 1 (PAI-1), and proinflammatory state. These clusters of abnormalities significantly increase the risk of atherosclerotic disease. It has been postulated that hyperinsulinemia and insulin resistance play a direct role in these metabolic abnormalities, but supportive evidence is inconclusive. Although hyperinsulinism and hypertension often coexist in whites, that is not the case in blacks or Pima Indians. Moreover, patients with hyperinsulinism due to insulinoma are not hypertensive, and there is no fall in blood pressure after surgical removal of the insulinoma restores normal insulin levels. The main value of grouping these disorders as a syndrome, however, is to remind clinicians that the therapeutic goals are not only to correct hyperglycemia but also to manage the elevated blood pressure and dyslipidemia that result in increased cerebrovascular and cardiac morbidity and mortality in these patients.

Clinical Findings

A. Symptoms and Signs

1. Type 1 diabetes—A characteristic symptom complex of hyperosmolality and hyperketonemia from the accumulation of circulating glucose and fatty acids typically presents in patients with type 1 diabetes who have an absolute deficiency of insulin. Increased urination and thirst are consequences of osmotic diuresis secondary to sustained hyperglycemia. The diuresis results in a loss of glucose as well as free water and electrolytes in the urine. Blurred vision often develops as the lenses are exposed to hyperosmolar fluids.

Weight loss despite normal or increased appetite is a common feature of type 1 when it develops subacutely. The weight loss is initially due to depletion of water, glycogen, and triglycerides; thereafter, reduced muscle mass occurs as amino acids are diverted to form glucose and ketone bodies.

Lowered plasma volume produces symptoms of postural hypotension. Total body potassium loss and the general catabolism of muscle protein contribute to the weakness.

Paresthesias may be present at the time of diagnosis, particularly when the onset is subacute. They reflect a temporary dysfunction of peripheral sensory nerves, which clears as insulin replacement restores glycemic levels closer to normal, suggesting neurotoxicity from sustained hyperglycemia.

When absolute insulin deficiency is of acute onset, the above symptoms develop abruptly. Ketoacidosis exacerbates the dehydration and hyperosmolality by producing anorexia and nausea and vomiting, interfering with oral fluid replacement.

The patient's level of consciousness can vary depending on the degree of hyperosmolality. When insulin deficiency develops relatively slowly and sufficient water intake is maintained, patients remain relatively alert and physical findings may be minimal. When vomiting occurs in response to worsening ketoacidosis, dehydration progresses and compensatory mechanisms become inadequate to keep serum osmolality below 320–330 mOsm/L. Under these circumstances, stupor or even coma may occur. The fruity breath odor of acetone further suggests the diagnosis of diabetic ketoacidosis.

Hypotension in the recumbent position is a serious prognostic sign. Loss of subcutaneous fat and muscle wasting are features of more slowly developing insulin deficiency. In occasional patients with slow, insidious onset of insulin deficiency, subcutaneous fat may be considerably depleted.

2. Type 2 diabetes—While increased urination and thirst may be presenting symptoms in some patients with type 2 diabetes, many other patients have an insidious onset of hyperglycemia and are asymptomatic initially. This is particularly true in obese patients, whose diabetes may be detected only after glycosuria or hyperglycemia is noted during routine laboratory studies. Occasionally, when the disease has been occult for some time, patients with type 2 diabetes may have evidence of neuropathic or cardiovascular complications at the time of presentation. Chronic skin infections are common. Generalized pruritus and symptoms of vaginitis are frequently the initial complaints of women. Diabetes should be suspected in women with chronic candidal vulvovaginitis as well as in those who have delivered babies larger than 9 lb (4.1 kg) or have had polyhydramnios, preeclampsia, or unexplained fetal losses. Balanoposthitis (inflammation of the foreskin and glans in uncircumcised males) may occur.

Many patients with type 2 diabetes are overweight or obese. Even those who are not significantly obese often have characteristic localization of fat deposits on the upper segment of the body (particularly the abdomen, chest, neck, and face) and relatively less fat on the appendages, which may be quite muscular. This centripetal fat distribution is characterized by a high waist circumference; a waist circumference larger than 40 inches (102 cm) in men and 35 inches (88 cm) in women is associated with an increased risk of diabetes. Some patients may have acanthosis nigricans, which is associated with significant insulin resistance; the skin in the axilla, groin, and back of neck is hyperpigmented and hyperkeratotic. Mild hypertension is often present in obese patients with diabetes. Eruptive xanthomas on the flexor surface of the limbs and on the buttocks and lipemia retinalis due to

hyperchylomicronemia can occur in patients with uncontrolled type 2 diabetes who also have a familial form of hypertriglyceridemia.

Hyperglycemic hyperosmolar coma can also be present; in these cases, patients are profoundly dehydrated, hypotensive, lethargic or comatose but without Kussmaul respirations.

B. Laboratory Findings

1. Urine glucose—A specific and convenient method to detect glucosuria is the paper strip impregnated with glucose oxidase and a chromogen system (Clinistix, Diastix), which is sensitive to as little as 100 mg/dL (5.5 mmol) glucose in urine. Diastix can be directly applied to the urinary stream, and differing color responses of the indicator strip reflect glucose concentration.

A normal renal threshold for glucose as well as reliable bladder emptying is essential for interpretation.

Nondiabetic glycosuria (renal glycosuria) is a benign asymptomatic condition wherein glucose appears in the urine despite a normal amount of glucose in the blood, either basally or during a glucose tolerance test. Its cause may vary from mutations in the SGLT2 gene coding for sodium-glucose transporter 2 (familial renal glycosuria) to one associated with dysfunction of the proximal renal tubule (Fanconi syndrome, chronic kidney disease), or it may merely be a consequence of the increased load of glucose presented to the tubules by the elevated glomerular filtration rate (GFR) during pregnancy. As many as 50% of pregnant women normally have demonstrable sugar in the urine, especially during the third and fourth months. This sugar is practically always glucose except during the late weeks of pregnancy, when lactose may be present.

2. Urine and blood ketones—Qualitative detection of ketone bodies can be accomplished by nitroprusside tests (Acetest or Ketostix). Although these tests do not detect beta-hydroxybutyric acid, which lacks a ketone group, the semiquantitative estimation of ketonuria thus obtained is nonetheless usually adequate for clinical purposes. Many laboratories measure beta-hydroxybutyric acid, and there are meters available (Precision Xtra; Nova Max Plus) for patient use that measures beta-hydroxybutyric acid levels in capillary glucose samples. Beta-hydroxybutyrate levels greater than 0.6 mmol/L require evaluation. Patients with levels greater than 3.0 mmol/L, equivalent to very large urinary ketones, require hospitalization.

3. Plasma or serum glucose—The glucose concentration is 10–15% higher in plasma or serum than in whole blood because structural components of blood cells are absent. A plasma glucose level of 126 mg/dL (7 mmol/L) or higher on more than one occasion after at least 8 hours of fasting is diagnostic of diabetes mellitus. Criteria for the diagnosis of diabetes. Normal Glucose Tolerance Impaired Glucose Tolerance Diabetes Mellitus2 Fasting plasma glucose mg/dL (mmol/L) < 100 (5.6) 100–125 (5.6–6.9) ≥ 126 (7.0) Two hours after glucose load1 mg/dL (mmol/L) < 140 (7.8) ≥ 140–199 (7.8–11.0) ≥ 200 (11.1) HbA1c (%) < 5.7 5.7–6.4 ≥ 6.5 1 Give

75 g of glucose dissolved in 300 mL of water after an overnight fast in persons who have been receiving at least 150–200 g of carbohydrate daily for 3 days before the test. 2 A fasting plasma glucose ≥ 126 mg/dL (7.0 mmol) or HbA1c of ≥ 6.5% is diagnostic of diabetes if confirmed by repeat testing. glucose levels of 100–125 mg/dL (5.6–6.9 mmol/L) are associated with increased risk of diabetes (impaired fasting glucose tolerance).

4. Oral glucose tolerance test—If the fasting plasma glucose level is less than 126 mg/dL (7 mmol/L) when diabetes is nonetheless suspected, then a standardized oral glucose tolerance test may be done. In order to optimize insulin secretion and effectiveness, especially when patients have been on a low-carbohydrate diet, a minimum of 150–200 g of carbohydrate per day should be included in the diet for 3 days preceding the test. The patient should eat nothing after midnight prior to the test day. On the morning of the test, adults are then given 75 g of glucose in 300 mL of water; children are given 1.75 g of glucose per kilogram of ideal body weight. The glucose load is consumed within 5 minutes. The test should be performed in the morning because there is some diurnal variation in oral glucose tolerance, and patients should not smoke or be active during the test.

Blood samples for plasma glucose are obtained at 0 and 120 minutes after ingestion of glucose. An oral glucose tolerance test is normal if the fasting venous plasma glucose value is less than 100 mg/dL (5.6 mmol/L) and the 2-hour value falls below 140 mg/dL (7.8 mmol/L). A fasting value of 126 mg/dL (7 mmol/L) or higher or a 2-hour value of greater than 200 mg/dL (11.1 mmol/L) is diagnostic of diabetes mellitus. Patients with 2-hour value of 140–199 mg/dL (7.8–11.1 mmol/L) have impaired glucose tolerance. False-positive results may occur in patients who are malnourished, bedridden, or afflicted with an infection or severe emotional stress.

5. Glycated hemoglobin (hemoglobin A1) measurements—Hemoglobin becomes glycated by ketoamine reactions between glucose and other sugars and the free amino groups on the alpha and beta chains. Only glycation of the N-terminal valine of the beta chain imparts sufficient negative charge to the hemoglobin molecule to allow separation by charge dependent techniques. These charge separated hemoglobins are collectively referred to as hemoglobin A1 (HbA1). The major form of HbA1 is hemoglobin A1c (HbA1c) where glucose is the carbohydrate. HbA1c comprises 4–6% of total hemoglobin A1. The hemoglobin A1c fraction is abnormally elevated in diabetic persons with chronic hyperglycemia. Office-based immunoassays using capillary blood give a result in about 9 minutes and this allows for nearly immediate feedback to the patients regarding their glycemic control.

Since glycohemoglobins circulate within red blood cells whose life span lasts up to 120 days, they generally reflect the state of glycemia over the preceding 8–12 weeks, thereby providing an improved method of assessing diabetic control. The HbA1c value, however, is weighted to more recent glucose levels (previous month) and this explains why significant changes in HbA1c are observed with short-term (1

month) changes in mean plasma glucose levels. Measurements should be made in patients with either type of diabetes mellitus at 3- to 4-month intervals. In patients monitoring their own blood glucose levels, HbA1c values provide a valuable check on the accuracy of monitoring. In patients who do not monitor their own blood glucose levels, HbA1c values are essential for adjusting therapy. There is a linear relationship between the HbA1c and the average glucose levels in the previous 3 months. In a study using a combination of intermittent seven-point capillary blood glucose profiles (preprandial, postprandial, and bedtime) and intermittent continuous glucose monitoring data, the change in glucose values was 28.7 mg/dL for every 1% change in HbA1c. Substantial individual variability exists, however, between HbA1c and mean glucose concentration. For HbA1c values between 6.9% and 7.1%, the glucose levels ranged from 125 mg/dL to 205 mg/dL (6.9–11.4 mmol/L; 95% CIs). For HbA1c of 6%, the mean glucose levels ranged from 100 mg/dL to 152 mg/dL (5.5–8.5 mmol/L); and for 8% they ranged from 147 mg/dL to 217 mg/dL (8.1–12.1 mmol/L). For this reason, caution should be exercised in estimating average glucose levels from measured HbA1c.

The accuracy of HbA1c values can be affected by hemoglobin variants or traits; the effect depends on the specific hemoglobin variant or derivative and the specific assay used. In patients with high levels of hemoglobin F, immunoassays give falsely low values of HbA1c. The National Glycohemoglobin Standardization Program website (www.ngsp.org) has information on the impact of frequently encountered hemoglobin variants and traits on the results obtained with the commonly used HbA1c assays.

Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (eg, recovery from acute blood loss, hemolytic anemia) will falsely lower HbA1c irrespective of the assay method used. Intravenous iron and erythropoietin therapy for treatment of anemia in chronic kidney disease also falsely lower HbA1c levels. Alternative methods such as fructosamine should be considered for these patients. Vitamins C and E are reported to falsely lower test results possibly by inhibiting glycation of hemoglobin.

The ADA has endorsed using the HbA1c as a diagnostic test for type 1 and type 2 diabetes. A cutoff value of 6.5% was chosen because the risk for retinopathy increases substantially above this value. The advantages of using the HbA1c to diagnose diabetes is that there is no need to fast; it has lower intraindividual variability than the fasting glucose test and the oral glucose tolerance test; and it provides an estimate of glucose control for the preceding 2–3 months. People with HbA1c levels of 5.7–6.4% should be considered at high risk for developing diabetes (prediabetes). The diagnosis should be confirmed with a repeat HbA1c test, unless the patient is symptomatic with plasma glucose levels greater than 200 mg/dL (11.1 mmol/L). This test is not appropriate to use in populations with high prevalence of hemoglobinopathies or in conditions with increased red cell turnover.

6. Serum fructosamine—Serum fructosamine is formed by nonenzymatic glycosylation of serum proteins (predominantly albumin). Since serum albumin has a much shorter half-life than hemoglobin, serum fructosamine generally reflects the

state of glycemic control for only the preceding 1–2 weeks. Reductions in serum albumin (eg, nephrotic state, protein-losing enteropathy, or hepatic disease) will lower the serum fructosamine value. When abnormal hemoglobins or hemolytic states affect the interpretation of glycohemoglobin or when a narrower time frame is required, such as for ascertaining glycemic control at the time of conception in a diabetic woman who has recently become pregnant, serum fructosamine assays offer some advantage. Normal values vary in relation to the serum albumin concentration and are 200–285 mcmol/L when the serum albumin level is 5 g/dL. HbA1c values and serum fructosamine are highly correlated. Serum fructosamine levels of 300, 367, and 430 mcmol/L approximate to HbA1c values of 7%, 8%, and 9%, respectively. Substantial individual variability exists, though, when estimating the likely HbA1c value from the fructosamine measurement.

7. Self-monitoring of blood glucose—Capillary blood glucose measurements performed by patients themselves, as outpatients, are extremely useful. In type 1 patients in whom "tight" metabolic control is attempted, they are indispensable. There are several paper strip (glucose oxidase, glucose dehydrogenase, or hexokinase) methods for measuring glucose on capillary blood samples. A reflectance photometer or an amperometric system is then used to measure the reaction that takes place on the reagent strip. A large number of blood glucose meters are now available. All are accurate, but they vary with regard to speed, convenience, size of blood samples required, reporting capability, and cost. Popular models include those manufactured by LifeScan (One Touch), Bayer Corporation (Breeze, Contour), Roche Diagnostics (Accu-Chek), Sanofi Aventis (iBGStar), and Abbott Laboratories (Precision, FreeStyle). These blood glucose meters are relatively inexpensive. Test strips remain a major expense. Each glucose meter also comes with a lancet device and disposable 26- to 33-gauge lancets. Most meters can store from 100 to 1000 glucose values in their memories and have capabilities to download the values into a computer spreadsheet for review by the patients and their health care team. iBGStar is a glucose meter that connects directly to the iPhone. The accuracy of data obtained by home glucose monitoring does require education of the patient in sampling and measuring procedures as well as in properly calibrating the instruments.

The clinician should be aware of the limitations of the self-monitoring glucose systems. The strips have limited lifespans and improper storage (high temperature; open vial) can affect their function. Patients should also be advised not to use expired strips. Some of the older meters require input of a code for each batch of strips and failure to enter the code can result in misleading results. The newer meters no longer require this step. Increases or decreases in hematocrit can decrease or increase the measured glucose values. The mechanism underlying this effect is not known but presumably it is due to the impact of red cells on the diffusion of plasma into the reagent layer. Meters and the test strips are calibrated over the glucose concentrations ranging from 60 mg/dL (3.3 mmol/L) to 160 mg/dL (8.9 mmol/L) and the accuracy is not as good for higher and lower glucose levels. When the glucose is less than 60 mg/dL (3.3 mmol/L), the difference between the meter

and the laboratory value may be as much as 20%. Glucose oxidase–based amperometric systems underestimate glucose levels in the presence of high oxygen tension. This may be important in the critically ill who are receiving supplemental oxygen; under these circumstances, a glucose dehydrogenase–based system may be preferable. Glucosedehydrogenase pyrroloquinoline quinone (GDH-PQQ) systems may report falsely high glucose levels in patients who are receiving parenteral products containing nonglucose sugars such as maltose, galactose, or xylose or their metabolites. Some meters have been approved for measuring glucose in blood samples obtained at alternative sites such as the forearm and thigh. There is, however, a 5- to 20-minute lag in the glucose response on the arm with respect to the glucose response on the finger. Forearm blood glucose measurements could therefore result in a delay in detection of rapidly developing hypoglycemia. Impaired circulation to the fingers (for example, in patients with Raynaud disease) will artificially lower finger-stick glucose measurements (pseudohypoglycemia).

8. Continuous glucose monitoring systems—A number of continuous glucose monitoring systems are available for clinical use. The systems manufactured by Medtronic Minimed, DexCom systems, and Abbott Diagnostics (outside the United States), involve inserting a subcutaneous sensor (rather like an insulin pump cannula) that measures glucose concentrations in the interstitial fluid for 3–7 days. The data are transmitted to a separate pager-like device with a screen. The MiniMed system also has the option to wirelessly transmit the data to the screen of their insulin pump. The systems allow the patient to set “alerts” for low and high glucose values and rate of change of glucose levels. Patients still have to calibrate the devices with periodic fingerstick glucose levels, and since there are concerns regarding reliability, it is still necessary to confirm the displayed glucose level with a fingerstick glucose before making interventions such as injecting extra insulin or eating extra carbohydrates. A 6-month randomized controlled study of type 1 patients showed that adults (25 years and older) using these systems had improved glycemic control without an increase in the incidence of hypoglycemia. A randomized controlled study of continuous glucose monitoring during pregnancy showed improved glycemic control in the third trimester, lower birth weight, and reduced risk of macrosomia. The individual glucose values are not that critical—what matters is the direction and the rate at which the glucose is changing, allowing the user to take corrective action. The wearer also gains insight into the way particular foods and activities affect their glucose levels. The other main benefit is the low glucose alert warning. The MiniMed insulin pump can be programmed to automatically suspend insulin delivery for up to 2 hours when the glucose levels on its continuous glucose monitoring device falls to a preset level and the patient does not respond to the alert. This insulin suspension feature has been shown to reduce the amount of time patients are in the hypoglycemic range at night. Many of these systems are covered by insurance.

There is great interest in using the data obtained from these continuous glucose monitoring systems to automatically deliver insulin by continuous subcutaneous insulin infusion pump. Algorithms have been devised to link continuous glucose

monitoring to insulin delivery and preliminary clinical studies appear promising.

9. Lipoprotein abnormalities in diabetes—Circulating lipoproteins are just as dependent on insulin as is the plasma glucose. In type 1 diabetes, moderately deficient control of hyperglycemia is associated with only a slight elevation of LDL cholesterol and serum triglycerides and little if any change in HDL cholesterol. Once the hyperglycemia is corrected, lipoprotein levels are generally normal. However, in patients with type 2 diabetes, a distinct "diabetic dyslipidemia" is characteristic of the insulin resistance syndrome. Its features are a high serum triglyceride level (300–400 mg/dL [3.4–4.5 mmol/L]), a low HDL cholesterol (less than 30 mg/dL [0.8 mmol/L]), and a qualitative change in LDL particles, producing a smaller dense particle whose membrane carries supranormal amounts of free cholesterol. These smaller dense LDL particles are more susceptible to oxidation, which renders them more atherogenic. Since a low HDL cholesterol is a major feature predisposing to macrovascular disease, the term "dyslipidemia" has preempted the term "hyperlipidemia," which mainly denoted the elevated triglycerides. Measures designed to correct the obesity and hyperglycemia, such as exercise, diet, and hypoglycemic therapy, are the treatment of choice for diabetic dyslipidemia, and in occasional patients in whom normal weight was achieved, all features of the lipoprotein abnormalities cleared. Since primary disorders of lipid metabolism may coexist with diabetes, persistence of lipid abnormalities after restoration of normal weight and blood glucose should prompt a diagnostic workup and possible pharmacotherapy of the lipid disorder.

Clinical Trials in Diabetes

Findings of the Diabetes Complications and Control Trial (DCCT) and of the United Kingdom Prospective Diabetes Study (UKPDS), have confirmed the beneficial effects of improved glycemic control in both type 1 and type 2 diabetes.

The Diabetes Control and Complications Trial, a long-term therapeutic study involving 1441 patients with type 1 diabetes mellitus, reported that "near" normalization of blood glucose resulted in a delay in the onset and a major slowing of the progression of established microvascular and neuropathic complications of diabetes during a follow-up period of up to 10 years. Multiple insulin injections (66%) or insulin pumps (34%) were used in the intensively treated group, who were trained to modify their therapy in response to frequent glucose monitoring. The conventionally treated groups used no more than two insulin injections, and clinical well-being was the goal with no attempt to modify management based on HbA1c determinations or the glucose results. In half of the patients, a mean hemoglobin A1c of 7.2% (normal: less than 6%) and a mean blood glucose of 155 mg/dL (8.6 mmol/L) were achieved using intensive therapy, while in the conventionally treated group HbA1c averaged 8.9% with an average blood glucose of 225 mg/dL (12.5 mmol/L). Over the study period, which averaged 7 years, there was an approximately 60% reduction in risk between the two groups in regard to diabetic retinopathy, nephropathy, and neuropathy. The intensively treated group also had a nonsignificant reduction in the risk of macrovascular disease of 41% (95% CI, –10

to 68). Intensively treated patients had a threefold greater risk of serious hypoglycemia as well as a greater tendency toward weight gain. However, there were no deaths definitely attributable to hypoglycemia in any persons in the DCCT study, and no evidence of posthypoglycemic cognitive damage was detected. Subjects participating in the DCCT study were subsequently enrolled in a follow-up observational study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Even though the between-group differences in mean HbA1c narrowed over 4 years, the group assigned to intensive therapy had a lower risk of retinopathy at 4 years, microalbuminuria at 7 to 8 years, and impaired GFR (less than 60 mL/min/1.73 m2) at 22 years of continued study follow-up. Moreover, by the end of the 11-year follow-up period, the intensive therapy group had significantly reduced their risk of any cardiovascular disease events by 42% (95% CI, 9% to 23%; P = 0.02). Thus, it seems that the benefits of good glucose control persist even if control deteriorates at a later date. The general consensus of the ADA is that intensive insulin therapy associated with comprehensive selfmanagement training should become standard therapy in patients with type 1 diabetes mellitus after the age of puberty. Exceptions include those with advanced chronic kidney disease and the elderly, since in these groups the detrimental risks of hypoglycemia outweigh the benefits of tight glycemic control.

The Diabetes Prevention Program was aimed at discovering whether treatment with either diet and exercise or metformin could prevent the onset of type 2 diabetes in people with impaired glucose tolerance; 3234 overweight men and women aged 25–85 years with impaired glucose tolerance participated in the study. Intervention with a low-fat diet and 150 minutes of moderate exercise (equivalent to a brisk walk) per week reduced the risk of progression to type 2 diabetes by 71% compared with a matched control group. Participants taking 850 mg of metformin twice a day reduced their risk of developing type 2 diabetes by 31%, but this intervention was relatively ineffective in those who were either less obese or in the older age group.

With the demonstration that intervention can be successful in preventing progression to diabetes in these subjects, a recommendation has been made to change the terminology from the less comprehensible “impaired glucose tolerance” to “prediabetes.” The latter is a term that the public can better understand and thus respond to by implementing healthier diet and exercise habits.

Treatment Regimens

A. Diet

A well-balanced, nutritious diet remains a fundamental element of therapy. The ADA recommends about 45–65% of total daily calories in the form of carbohydrates; 25–35% in the form of fat (of which less than 7% are from saturated fat), and 10–35% in the form of protein. In patients with type 2 diabetes, limiting the carbohydrate intake and substituting some of the calories with monounsaturated fats, such as olive oil, rapeseed (canola) oil, or the oils in nuts and avocados, can lower triglycerides and increase HDL cholesterol. In addition, in those patients with

obesity and type 2 diabetes, weight reduction by caloric restriction is an important goal of the diet. Patients with type 1 diabetes or type 2 diabetes who take insulin should be taught “carbohydrate counting,” so they can administer their insulin bolus for each meal based on its carbohydrate content. In obese individuals with diabetes, an additional goal is weight reduction by caloric restriction.

The current recommendations for both types of diabetes continue to limit cholesterol to 300 mg daily, and individuals with LDL cholesterol more than 100 mg/dL (2.6 mmol/L) should limit dietary cholesterol to 200 mg daily. High protein intake may cause progression of kidney disease in patients with diabetic nephropathy; for these individuals, a reduction in protein intake to 0.8 kg/day (or about 10% of total calories daily) is recommended.

1. Dietary fiber—Plant components such as cellulose, gum, and pectin are indigestible by humans and are termed dietary “fiber.” Insoluble fibers such as cellulose or hemicellulose, as found in bran, tend to increase intestinal transit and may have beneficial effects on colonic function. In contrast, soluble fibers such as gums and pectins, as found in beans, oatmeal, or apple skin, tend to retard nutrient absorption rates so that glucose absorption is slower and hyperglycemia may be slightly diminished. Although its recommendations do not include insoluble fiber supplements such as added bran, the ADA recommends food such as oatmeal, cereals, and beans with relatively high soluble fiber content as staple components of the diet in diabetics. High soluble fiber content in the diet may also have a favorable effect on blood cholesterol levels

2. Glycemic index—The glycemic index of a carbohydrate containing food is determined by comparing the glucose excursions after consuming 50 g of test food with glucose excursions after consuming 50 g of reference food (white bread). Eating low glycemic index foods results in lower glucose levels after meals. Low glycemic index foods have values of 55 or less and include many fruits, vegetables, grainy breads, pasta, and legumes. High glycemic index foods have values of 70 or greater and include baked potato, white bread, and white rice. Glycemic index is lowered by presence of fats and protein when food is consumed in a mixed meal. Even though it may not be possible to accurately predict the glycemic index of a particular food in the context of a meal, it is reasonable to choose foods with low glycemic index.

3. Artificial and other sweeteners—Aspartame (Nutra Sweet) consists of two major amino acids, aspartic acid and phenylalanine, which combine to produce a sweetener that is 180 times as sweet as sucrose. A major limitation is that it is not heat stable, so it cannot be used in cooking. Saccharin (Sweet ‘N Low), sucralose (Splenda), acesulfame potassium (Sweet One), and rebiana (Truvia) are other “artificial” sweeteners that can be used in cooking and baking. Aspartame, saccharin, sucralose, acesulfame, and rebiana **do not raise blood glucose levels**.

Fructose represents a “natural” sugar substance that is a highly effective sweetener, induces only slight increases in plasma glucose levels, and does not

require insulin for its metabolism. However, because of potential adverse effects of large amounts of fructose on raising serum cholesterol, triglycerides, and LDL cholesterol, it does not have any advantage as a sweetening agent in the diabetic diet. This does not preclude, however, ingestion of fructose-containing fruits and vegetables or fructose-sweetened foods in moderation.

Sugar alcohols, also known as polyols or polyalcohol, are commonly used as sweeteners and bulking agents. They occur naturally in a variety of fruits and vegetables but are also commercially made from sucrose, glucose, and starch. Examples are sorbitol, xylitol, mannitol, lactitol, isomalt, maltitol, and hydrogenated starch hydrolysates (HSH). They are not as easily absorbed as sugar, so they do not raise blood glucose levels as much. Therefore, sugar alcohols are often used in food products that are labeled as "sugar free," such as chewing gum, lozenges, hard candy, and sugar-free ice cream. However, if consumed in large quantities, they will raise blood glucose and can cause bloating and diarrhea.

B. Medications for Treating Hyperglycemia

1. Medications that primarily stimulate insulin secretion by binding to the sulfonylurea receptor on the beta cell—

A. Sulfonylureas—The primary mechanism of action of the sulfonylureas is to stimulate insulin release from pancreatic B cells. Specific receptors on the surface of pancreatic B cells bind sulfonylureas in the rank order of their insulinotropic potency (glyburide with the greatest affinity and tolbutamide with the least affinity). It has been shown that activation of these receptors closes potassium channels, resulting in depolarization of the B cell. This depolarized state permits calcium to enter the cell and actively promote insulin release. Sulfonylureas are used in patients with type 2 but not type 1 diabetes, since these medications require functioning pancreatic B cells to produce their effect on blood glucose.

***(1) First-generation sulfonylureas (tolbutamide, tolazamide, acetohexamide, chlorpropamide)*—Tolbutamide** is rapidly oxidized in the liver to inactive metabolites, and its approximate duration of effect is relatively short (6–10 hours). Tolbutamide is probably best administered in divided doses (eg, 500 mg before each meal and at bedtime); however, some patients require only one or two tablets daily with a maximum dose of 3000 mg/day. Because of its short duration of action, which is independent of kidney function, tolbutamide is relatively safe to use in renal impairment.

Tolazamide, acetohexamide, and chlorpropamide are rarely used. Chlorpropamide has a prolonged biologic effect, and severe hypoglycemia can occur especially in the elderly as their renal clearance declines with aging. Its other side effects include alcohol-induced flushing and hyponatremia due to its effect on vasopressin secretion and action.

(2) Second-generation sulfonylureas (glyburide, glipizide, gliclazide, glimepiride)—Glyburide, glipizide, gliclazide, and glimepiride are 100–200 times more potent than tolbutamide. These medications should be used with caution in patients with cardiovascular disease or in elderly patients, in whom prolonged hypoglycemia would be especially dangerous.

The usual starting dose of **glyburide** is 2.5 mg/day, and the average maintenance dose is 5–10 mg/day given as a single morning dose; maintenance doses higher than 20 mg/day are not recommended. Some reports suggest that 10 mg is a maximum daily therapeutic dose, with 15–20 mg having no additional benefit in poor responders and doses over 20 mg actually worsening hyperglycemia. Elderly patients are at particular risk for hypoglycemia even with relatively small daily doses.

The recommended starting dose of **glipizide** is 5 mg/ day, with up to 15 mg/day given as a single daily dose before breakfast. When higher daily doses are required, they should be divided and given before meals. The maximum dose recommended by the manufacturer is 40 mg/d, although doses above 10–15 mg probably provide little additional benefit in poor responders and may even be less effective than smaller doses. For maximum effect in reducing postprandial hyperglycemia, glipizide should be ingested 30 minutes before meals, since rapid absorption is delayed when the medication is taken with food.

Gliclazide (not available in the United States) is another intermediate duration sulfonylurea with a duration of action of about 12 hours. The recommended starting dose is 40–80 mg/day with a maximum dose of 320 mg. Doses of 160 mg and above are given as divided doses before breakfast and dinner.

Glimepiride has a long duration of effect with a halflife of 5 hours allowing once or twice daily dosing. Glimepiride achieves blood glucose lowering with the lowest dose of any sulfonylurea compound. A single daily dose of 1 mg/day has been shown to be effective, and the maximal recommended dose is 8 mg. It is completely metabolized by the liver to relatively inactive metabolic products.

B. Meglitinide analogs—Repaglinide is structurally similar to glyburide but lacks the sulfonic acid-urea moiety. It acts by binding to the sulfonylurea receptor and closing the adenosine triphosphate (ATP)-sensitive potassium channel. The medication therefore causes a brief but rapid pulse of insulin. The starting dose is 0.5 mg three times a day 15 minutes before each meal. The dose can be titrated to a maximum daily dose of 16 mg. Like the sulfonylureas, repaglinide can be used in combination with metformin.

Mitiglinide is a benzylsuccinic acid derivative that binds to the sulfonylurea receptor and is similar to repaglinide in its clinical effects. It has been approved for use in Japan.

C. D-Phenylalanine derivative—Nateglinide stimulates insulin secretion by binding to the sulfonylurea receptor and closing the ATP-sensitive potassium channel. This compound is rapidly absorbed from the intestine, reaching peak plasma levels within 1 hour. It is metabolized in the liver and has a plasma half-life of about 1.5 hours. Like repaglinide, it causes a brief rapid pulse of insulin, and when given before a meal it reduces the postprandial rise in blood glucose. For most patients, the recommended starting and maintenance dose is 120 mg three times a day before meals. Use 60 mg in patients who have mild elevations in HbA1c. Like the other insulin secretagogues, its main side effects are hypoglycemia

and weight gain.

2. Medications that primarily lower glucose levels by their actions on the liver, muscle, and adipose tissue—

A. Metformin—Metformin (1,1-dimethylbiguanide hydrochloride) is used, either alone or in conjunction with other oral agents or insulin, in the treatment of patients with type 2 diabetes. Metformin's therapeutic effects primarily derive from the increasing hepatic adenosine monophosphate-activated protein kinase activity, which reduces hepatic gluconeogenesis and lipogenesis.

Metformin has a half-life of 1.5–3 hours, is not bound to plasma proteins or metabolized, being excreted unchanged by the kidneys.

Metformin is the first-line therapy for patients with type 2 diabetes. The current recommendation is to start this medication at diagnosis. A side benefit of metformin therapy is its tendency to improve both fasting and postprandial hyperglycemia and hypertriglyceridemia in obese patients with diabetes without the weight gain associated with insulin or sulfonylurea therapy. Metformin is ineffective in patients with type 1 diabetes. Patients with chronic kidney disease should not be given this medication because failure to excrete it would produce high blood and tissue levels of metformin that could stimulate lactic acid overproduction.

The maximum dosage of metformin is 2.55 g, although little benefit is seen above a total dose of 2000 mg. It is important to begin with a low dose and increase the dosage very gradually in divided doses—taken with meals—to reduce minor gastrointestinal upsets. A common schedule would be one 500 mg tablet three times a day with meals or one 850 mg or 1000 mg tablet twice daily at breakfast and dinner. Up to 2000 mg of the extended-release preparation can be given once a day. Lower doses should be used in patients with eGFRs between 30 and 45 mL/min per 1.73 m2 .

B. Thiazolidinediones—Two medications of this class, rosiglitazone and pioglitazone, are available for clinical use. These medications sensitize peripheral tissues to insulin. They bind a nuclear receptor called peroxisome proliferatoractivated receptor gamma (PPAR-gamma) and affect the expression of a number of genes. Like the biguanides, this class of medications does not cause hypoglycemia.

Two medications of this class, rosiglitazone and pioglitazone, are available for clinical use. Both are effective as monotherapy and in combination with sulfonylureas or metformin or insulin, lowering HbA1c by 1% to 2%. When used in combination with insulin, they can result in a 30–50% reduction in insulin dosage, and some patients can come off insulin completely. The dosage of rosiglitazone is 4–8 mg daily and of pioglitazone, 15–45 mg daily, and the medications do not have to be taken with food.

The combination of a thiazolidinedione and metformin has the advantage of not causing hypoglycemia. Patients inadequately managed on sulfonylureas can do well on a combination of sulfonylurea and rosiglitazone or pioglitazone.

3. Medications that affect absorption of glucose— Alpha-glucosidase inhibitors competitively inhibit the alphaglucosidase enzymes in the gut that digest dietary starch and sucrose. Two of these medications—acarbose and miglitol— are available for clinical use in the United States. Voglibose, another alpha-glucosidase inhibitor is available in Japan, Korea, and India. Acarbose and miglitol are potent inhibitors of glucoamylase, alpha-amylase, and sucrase but have less effect on isomaltase and hardly any on trehalase and lactase. Acarbose binds 1000 times more avidly to the intestinal disaccharidases than do products of carbohydrate digestion or sucrose. Both medications delay the absorption of carbohydrate and lower postprandial glycemic excursion.

A. Acarbose—The recommended starting dose of acarbose is 50 mg twice daily, gradually increasing to 100 mg three times daily. For maximal benefit on postprandial hyperglycemia, acarbose should be given with the first mouthful of food ingested.

B. Miglitol—Miglitol is similar to acarbose in terms of its clinical effects. It is indicated for use in diet- or sulfonylureatreated patients with type 2 diabetes. Therapy is initiated at the lowest effective dosage of 25 mg three times a day. The usual maintenance dose is 50 mg three times a day, although some patients may benefit from increasing the dose to 100 mg three times a day.

4. Incretins— *Exenatide* is a GLP-1 receptor agonist isolated from the saliva of the Gila Monster (a venomous lizard) that is more resistant to DPP-4 action and cleared by the kidney. Its half-life is 2.4 hours, and its glucose lowering effect is about 6 hours. Exenatide is dispensed as two fixed-dose pens (5 mcg and 10 mcg). It is injected 60 minutes before breakfast and before dinner. Patients with type 2 diabetes should be prescribed the 5 mcg pen for the first month and, if tolerated, the dose can then be increased to 10 mcg twice a day.

Liraglutide The dosing is initiated at 0.6 mg daily, increased after 1 week to 1.2 mg daily. Some patients may benefit from increasing the dose to 1.8 mg. In clinical trials lasting 26 and 52 weeks, adding liraglutide to the therapeutic regimen (metformin, sulfonylurea, thiazolidinedione) of patients with type 2 diabetes further lowered the HbA1c value. Depending on the dose and design of the study, the HbA1c decline was in the range of 0.6% to 1.5%. The patients had sustained weight loss of 1–6 pounds. Liraglutide at a dose of 3 mg daily has been approved for weight loss.

Albiglutide is a human GLP-1 dimer fused to human albumin. The halflife of albiglutide is about 5 days and a steady state is reached after 4–5 weeks of once weekly administration. The usual dose is 30 mg weekly by subcutaneous injection. The dose can be increased to 50 mg weekly if necessary. The pen contains a lyophilized powder that is reconstituted just prior to administration. Albiglutide monotherapy and combination therapy lowers HbA1c by about 0.8%. Weight loss is much less than with exenatide and liraglutide.

Dulaglutide The usual dose is 0.75 mg weekly by subcutaneous injection. The maximum recommended dose is 1.5 mg weekly.

B. DPP-4 inhibitors— An alternate approach to the use of GLP-1 receptor agonists is to inhibit the enzyme DPP-4 and prolong the action of endogenously released GLP-1 and GIP. Four oral DPP-4 inhibitors, sitagliptin, saxagliptin, linagliptin, and alogliptin, are available in the United States for the treatment of type 2 diabetes. An additional DPP-4 inhibitor, vildagliptin, is available in Europe.

Sitagliptin The usual dose of sitagliptin is 100 mg once daily, but the dose is reduced to 50 mg daily if the calculated creatinine clearance is 30–50 mL/min and to 25 mg for clearances less than 30 mL/min.

Vildagliptin The dose is 50 mg once or twice daily.

5. Sodium-glucose co-transporter 2 inhibitors— —Glucose is freely filtered by the renal glomeruli and is reabsorbed in the proximal tubules by the action of sodium-glucose co-transporters (SGLT). Sodium-glucose co-transporter 2 (SGLT2) accounts for about 90% of glucose reabsorption and its inhibition causes glycosuria in people with diabetes, lowering plasma glucose levels. The SGLT2 inhibitors *canagliflozin, dapagliflozin, and empagliflozin* are approved for clinical use in the United States.

Canagliflozin It also results in modest weight loss of 2–5 kg. The usual dose is 100 mg daily but up to 300 mg daily can be used in patients with normal kidney function.

Empagliflozin The usual dosage is 10 mg daily but a higher dose of 25 mg daily can be used.

6. Others—*Pramlintide* is a synthetic analog of islet amyloid polypeptide (IAPP or amylin). In patients with type 1 diabetes, the initial dose of pramlintide is 15 mcg before each meal and titrated up by 15 mcg increments to a maintenance dose of 30 mcg or 60 mcg before each meal. In patients with type 2 diabetes, the starting dose is 60 mcg premeals increased to 120 mcg in 3 to 7 days if no significant nausea occurs.

Bromocriptine, a dopamine 2 receptor agonist, has been shown to modestly lower HbA1c by 0.1–0.5% when compared to baseline and 0.4–0.5% compared to placebo. The tablet dose is 0.8 mg and the daily dose is 2 (1.6 g) to 6 (4.8 mg) tablets as tolerated. Common side effects are nausea, vomiting, dizziness, and headache.

7. Medication combinations—Several medication combinations are available in different dose sizes, including glyburide and metformin (Glucovance); glipizide and metformin (Metaglip); repaglinide and metformin (PrandiMet); rosiglitazone and metformin (Avandamet); pioglitazone and metformin (ACTOplusMet); rosiglitazone and glimepiride (Avandaryl); pioglitazone and glimepiride (Duetact); sitagliptin and metformin (Janumet); saxagliptin and metformin XR (Kombiglyze XR); linagliptin and metformin (Jentadueto); alogliptin and metformin (Kazano); alogliptin and pioglitazone (Oseni); dapagliflozin and metformin (Xigduo); and canagliflozin and metformin (Invokamet). These medication combinations,

however, limit the clinician's ability to optimally adjust dosage of the individual medications and for that reason are not recommended.

C. Insulin

Insulin is indicated for type 1 diabetes as well as for type 2 diabetic patients with insulinopenia whose hyperglycemia does not respond to diet therapy either alone or combined with other hypoglycemic medications.

Insulin preparations

Rapidly acting human insulin analogs

- Insulin lispro (Humalog, Lilly)
- Insulin aspart (Novolog, Novo Nordisk)
- Insulin glulisine (Apidra, Sanofi Aventis)

Short-acting regular insulin

- Regular insulin (Lilly, Novo Nordisk)
- Technosphere inhaled regular insulin (Afrezza)

Intermediate-acting insulins

- NPH insulin (Lilly, Novo Nordisk)

NPH - neutral protamine Hagedorn

Premixed insulins

- 70% NPH/30% regular (70/30 insulin—Lilly, Novo Nordisk)
- 70% NPL/25% insulin lispro (Humalog Mix 75/25—Lilly)
- 50% NPL/50% insulin lispro (Humalog Mix 50/50—Lilly)
- 70% insulin aspart protamine/30% insulin aspart (Novolog Mix 70/30—Novo Nordisk)

Long-acting human insulin analogs

- Insulin glargine (Lantus, Sanofi Aventis)
- Insulin detemir (Levemir, Novo Nordisk)

Methods of insulin administration—

A. Insulin syringes and needles—Plastic disposable syringes are available in 1 mL, 0.5 mL, and 0.3 mL sizes. The "low-dose" 0.3 mL syringes have become increasingly popular, because many patients with diabetes do not take more than 30 units of insulin in a single injection except in rare instances of extreme insulin resistance. Two lengths of needles are available: short (8 mm) and long (12.7 mm). Long needles are preferable in obese patients to reduce variability of insulin absorption. Ultrafine needles as small as 31 gauge reduce the pain of injections. "Disposable" syringes may be reused until blunting of the needle occurs (usually after three to five injections). Sterility adequate to avoid infection with reuse

appears to be maintained by recapping syringes between uses. Cleansing the needle with alcohol may not be desirable since it can dissolve the silicone coating and can increase the pain of skin puncturing.

Any part of the body covered by loose skin can be used, such as the abdomen, thighs, upper arms, flanks, and upper buttocks. Preparation with alcohol is no longer required prior to injection as long as the skin is clean. Rotation of sites continues to be recommended to avoid delayed absorption when fibrosis or lipohypertrophy occurs from repeated use of a single site. However, considerable variability of absorption rates from different sites, particularly with exercise, may contribute to the instability of glycemic control in certain type 1 patients if injection sites are rotated too frequently in different areas of the body. Consequently, it is best to limit injection sites to a single region of the body and rotate sites within that region. The abdomen is recommended for subcutaneous injections, since regular insulin has been shown to absorb more rapidly from there than from other subcutaneous sites. The effect of anatomic regions appears to be much less pronounced with the analog insulins.

B. Insulin pen injector devices—Insulin pens eliminate the need for carrying insulin vials and syringes. Cartridges of insulin lispro and insulin aspart are available for reusable pens (Eli Lilly, Novo Nordisk, and Owen Mumford). Disposable prefilled pens are also available for insulin lispro, insulin aspart, insulin glulisine, insulin detemir, insulin glargine, NPH, 70% NPH/30% regular, 75% NPL/25% insulin lispro, 50% NPL/50% insulin lispro, and 70% insulin aspart protamine/30% insulin aspart. Thirtyone gauge needles (5, 6, and 8 mm long) for these pens make injections almost painless.

C. Insulin pumps—In the United States, Medtronic MiniMed, Animas, Insulet, Roche, and Tandem make battery operated continuous subcutaneous insulin infusion (CSII) pumps. These pumps are small (about the size of a pager) and very easy to program. They offer many features, including the ability to set a number of different basal rates throughout the 24 hours and to adjust the time over which bolus doses are given. They also are able to detect pressure build-up if the catheter is kinked. The catheter connecting the insulin reservoir to the subcutaneous cannula can be disconnected, allowing the patient to remove the pump temporarily (eg, for bathing). Ominpod (Insulet Corporation) is an insulin infusion system in which the insulin reservoir and infusion set are integrated into one unit (pod), so there is no catheter (electronic patch pump). The pod, placed on the skin, delivers subcutaneous basal and bolus insulin based on wirelessly transmitted instructions from a personal digital assistant. The great advantage of continuous subcutaneous insulin infusion (CSII) is that it allows for establishment of a basal profile tailored to the patient. The patient therefore is able to eat with less regard to timing because the basal insulin infusion should maintain constant blood glucose between meals. Also the ability to adjust the basal insulin infusion makes it easier for the patient to manage glycemic excursions that occur with exercise. The pumps also have software that can assist the patient to calculate boluses based on glucose reading

and carbohydrates to be consumed. They keep track of the time elapsed since last insulin bolus and the patient is reminded of this when he or she attempts to give additional correction bolus before the effect of the previous bolus has worn off ("insulin on board" feature). This feature reduces the risk of overcorrecting and subsequent hypoglycemia.

CSII therapy is appropriate for patients with type 1 diabetes who are motivated, mechanically inclined, educated about diabetes (diet, insulin action, treatment of hypoglycemia and hyperglycemia), and willing to monitor their blood glucose four to six times a day. Known complications of CSII include ketoacidosis, which can occur when insulin delivery is interrupted, and skin infections. Another disadvantage is its cost and the time demanded of the clinician and staff in initiating therapy.

V-go (Valeritas) is a mechanical patch pump designed specifically for people with type 2 diabetes who employ a basal/bolus insulin regimen. The device is preset to deliver one of three fixed and flat basal rates (20, 30, or 40 units) for 24 hours (at which point it must be replaced) and there is a button that delivers two units per press to help cover meals.

D. Inhaled insulin—The dry-powder formulation of recombinant human regular insulin that is delivered by inhalation (technosphere insulin, Afrezza) is approved for use in adults with diabetes. Pharmacokinetic studies show that technosphere insulin is rapidly absorbed with peak insulin levels reached in 12–15 minutes and declining to baseline in 3 hours. Pharmacodynamic studies show that median time to maximum effect with inhaled insulin is approximately 1 hour and declines to baseline by about 3 hours. In contrast, the median time to maximum effect with subcutaneous insulin lispro is about 2 hours and declines to baseline by 4 hours. In clinical trials, technosphere insulin combined with basal insulin was as effective in glucose lowering as rapid-acting insulin analogs combined with basal insulin. It is formulated as a single use cartridge delivering 4 or 8 units immediately before the meal. The manufacturer provides a dose conversion table; patients injecting up to 4 units of rapid-acting insulin analog should use the 4 unit cartridge. Those injecting 5 to 8 units should use the 8-unit cartridge. If the dose is 9–12 units of rapid-acting insulin pre-meal then one 4-unitcartridge and one 8-unit cartridge should be used. The inhaler is about the size of a referee's whistle.

The most common adverse reaction of the inhaled insulin was a cough affecting about 27% of patients. A small decrease in pulmonary function (forced expiratory volume in 1 second [FEV1]) was seen in the first 3 months of use, which persisted over 2 years of follow-up. Inhaled insulin is contraindicated in smokers and patients with chronic lung disease, such as asthma and chronic obstructive pulmonary disease. Spirometry should be performed to identify potential lung disease prior to initiating therapy. During the clinical trials, there were two cases of lung cancer in patients who were taking inhaled insulin and none in the comparator-treated patients. All the patients in whom lung cancer developed had a history of prior cigarette smoking. There were also two cases of squamous cell carcinoma of the lung in nonsmokers exposed to inhaled insulin; these cases occurred after

completion of the clinical trials. Cases of lung cancer were also reported in cigarette smokers using a previously available inhaled insulin preparation (Exubera). The incidence rate in the Exubera treated group was 0.13 per 1000 patient years and 0.03 per 1000 patient years in the comparator-treated group

D. Transplantation

Pancreas transplantation at the time of kidney transplantation is becoming more widely accepted. Patients undergoing simultaneous pancreas and kidney transplantation have an 83% chance of pancreatic graft survival at 1 year and 69% at 5 years. Solitary pancreatic transplantation in the absence of a need for kidney transplantation is considered only in those rare patients who do not respond to all other insulin therapeutic approaches and who have frequent severe hypoglycemia or who have life-threatening complications related to their lack of metabolic control. Pancreas transplant alone graft survival is 78% at 1 year and 54% at 5 years.

People with type 1 diabetes can become insulin independent after receiving an islet cell transplant. The islets are isolated from donor pancreas. They are then infused into the portal vein using a percutaneous transhepatic approach, and they lodge in the liver releasing insulin in response to physiologic stimuli. Long-term immunosuppression is necessary to prevent allograft rejection and to suppress the autoimmune process that led to the disease in the first place. Insulin independence for more than 5 years has been demonstrated in patients who got anti-CD3 antibody or anti-thymocyte globulin induction immunosuppression and calcineurin inhibitors, mTor inhibitors, and mycophenolate mofetil as maintenance immunosuppression. Islet cell transplant trials with different kinds and combinations of immunosuppressive agents are currently underway. One major limitation is the need for more than one islet infusion to achieve insulin independence. This is because of significant loss of islets during isolation and the period prior to engraftment. Widespread application of islet transplantation will depend on improving insulin independence rates with one infusion and also demonstrating that the long-term outcomes are as good as those of pancreas transplant alone.

Steps in the Management of the Diabetic Patient

A. Diagnostic Examination

An attempt should be made to characterize the diabetes as type 1 or type 2, based on the clinical features present and on whether or not ketonuria accompanies the glycosuria. Features that suggest end-organ insulin insensitivity to insulin, such as visceral obesity, acanthosis nigricans, or both, must be identified. The family history should document not only the incidence of diabetes in other members of the family but also the age at onset, association with obesity, the need for insulin, and whether there were complications. For the occasional patient, measurement of GAD65, IAA, ICA 512, and zinc transporter 8 antibodies can help distinguish between type 1 and type 2 diabetes. Many patients with newly diagnosed type 1 diabetes still have significant endogenous insulin production, and C peptide levels do not reliably distinguish between type 1 and type 2 diabetes. Other factors that

increase cardiac risk, such as smoking history, presence of hypertension or hyperlipidemia, or oral contraceptive pill use, should be recorded.

Laboratory diagnosis of diabetes should document fasting plasma glucose levels above 126 mg/dL (7 mmol/L) or postprandial values consistently above 200 mg/dL (11.1 mmol/L) or HbA1c of at least 6.5% and whether ketonuria accompanies the glycosuria. An HbA1c measurement is also useful for assessing the effectiveness of future therapy. Baseline values include fasting plasma triglycerides, total cholesterol and HDL-cholesterol, electrocardiography, kidney function studies, peripheral pulses, and neurologic, podiatric, and ophthalmologic examinations to help guide future assessments.

B. Patient Education (Self-Management Training)

Since diabetes is a lifelong disorder, education of the patient and the family is probably the most important obligation of the clinician who provides initial care. The best persons to manage a disease that is affected so markedly by daily fluctuations in environmental stress, exercise, diet, and infections are the patients themselves and their families. The “teaching curriculum” should include explanations by the clinician or nurse of the nature of diabetes and its potential acute and chronic hazards and how they can be recognized early and prevented or treated. Selfmonitoring of blood glucose should be emphasized, especially in insulin-requiring diabetic patients, and instructions must be given on proper testing and recording of data.

Patients taking insulin should have an understanding of the actions of basal and bolus insulins. They should be taught to determine whether the basal dose is appropriate and how to adjust the rapidly acting insulin dose for thecarbohydrate content of a meal. Patients and their families and friends should be taught to recognize signs and symptoms of hypoglycemia and how to treat low glucose reactions. Strenuous exercise can precipitate hypoglycemia, and patients must therefore be taught to reduce their insulin dosage in anticipation of strenuous activity or to take supplemental carbohydrate. Injection of insulin into a site farthest away from the muscles most involved in the exercise may help ameliorate exercise-induced hypoglycemia, since insulin injected in the proximity of exercising muscle may be more rapidly mobilized. Exercise training also increases the effectiveness of insulin and insulin doses should be adjusted accordingly. Infections can cause insulin resistance, and patients should be instructed on how to manage the hyperglycemia with supplemental rapidly acting insulin.

The targets for blood glucose control should be elevated appropriately in elderly patients since they have the greatest risk if subjected to hypoglycemia and the least long-term benefit from more rigid glycemic control. Advice on personal hygiene, including detailed instructions on foot and dental care, should be provided. All infections (especially pyogenic ones) provoke the release of high levels of insulin antagonists, such as catecholamines or glucagon, and thus bring about a marked increase in insulin requirements. Patients who are taking oral agents may decompensate and temporarily require insulin. Patients should be told about community agencies, such as Diabetes Association chapters, that can serve as a

continuing source of instruction.

Finally, vigorous efforts should be made to persuade patients with newly diagnosed diabetes who smoke to give up the habit, since large vessel peripheral vascular disease and debilitating retinopathy are less common in nonsmoking diabetic patients.

C. Therapy

Treatment must be individualized on the basis of the type of diabetes and specific needs of each patient. However, certain general principles of management can be outlined for hyperglycemic states of different types.

1. Type 1 diabetes—Traditional once- or twice-daily insulin regimens are usually ineffective in type 1 patients without residual endogenous insulin. In these patients, information and counseling based on the findings of the DCCT should be provided about the advantages of taking multiple injections of insulin in conjunction with self-blood glucose monitoring. If near-normalization of blood glucose is attempted, at least four measurements of capillary blood glucose and three or four insulin injections are necessary.

A combination of rapidly acting insulin analogs and long-acting insulin analogs allows for more physiologic insulin replacement. The rapidly acting insulin analogs have been advocated as a safer and much more convenient alternative to regular human insulin for preprandial use. However, because of their relatively short duration (no more than 3–4 hours), the rapidly acting insulin analogs need to be combined with longer-acting insulins to provide basal coverage and avoid hyperglycemia prior to the next meal. In addition to carbohydrate content of the meal, theeffect of simultaneous fat ingestion must also be considered a factor in determining the rapidly acting insulin analog dosage required to control the glycemic increment during and just after the meal. With low-carbohydrate content and high-fat intake, there is an increased risk of hypoglycemia from insulin lispro within 2 hours after the meal.

Insulin glargine is usually given once in the evening to provide 24-hour coverage. This insulin cannot be mixed with any of the other insulins and must be given as a separate injection. There are occasional patients in whom insulin glargine does not seem to last for 24 hours, and in such cases it needs to be given twice a day. As shown, insulin detemir may also need to be given twice a day to get adequate 24-hour basal coverage. Alternatively, small doses of NPH (~3–4 units) can be given with each meal to provide daytime basal coverage with a larger dose at night. Unlike the long-acting insulin analogs, NPH can be mixed in the same syringe as the insulin lispro, insulin aspart, and insulin glulisine.

Continuous subcutaneous insulin infusion (CSII) by portable battery-operated “open loop” devices currently provides the most flexible approach, allowing the setting of different basal rates throughout the 24 hours and permitting patients to delay or skip meals and vary meal size and composition. The dosage is usually based on providing 50% of the estimated insulin dose as basal and the remainder as intermittent boluses prior to meals. For example, a 70-kg man requiring 35 units of

insulin per day may require a basal rate of 0.7 units per hour throughout the 24 hours with the exception of 3 am to 8 am, when 0.8 units per hour might be appropriate (given the "dawn phenomenon"—reduced tissuesensitivity to insulin between 5 am and 8 am). The meal bolus would depend on the carbohydrate content of the meal and the premeal blood glucose value. **One unit per 15 g of carbohydrate plus 1 unit for 50 mg/dL (2.8 mmol/L) of blood glucose above a target value (eg, 120 mg/dL [6.7 mmol/L]) is a common starting point.** Further adjustments to basal and bolus dosages would depend on the results of blood glucose monitoring. The majority of patients use the rapidly acting insulin analogs in the pumps. One of the more difficult therapeutic problems in managing patients with type 1 diabetes is determining the proper adjustment of insulin dose when the prebreakfast blood glucose level is high. Occasionally, the prebreakfast hyperglycemia is due to the Somogyi effect, in which nocturnal hypoglycemia leads to a surge of counterregulatory hormones to produce high blood glucose levels by 7 am. However, a more common cause for prebreakfast hyperglycemia is the waning of circulating insulin levels by the morning. Also, the dawn phenomenon is present in as many as 75% of type 1 patients and can aggravate the hyperglycemia.

The diagnosis of the cause of prebreakfast hyperglycemia can be facilitated by self-monitoring of blood glucose at 3 am in addition to the usual bedtime and 7 am measurements. This is required for only a few nights, and when a particular pattern emerges from monitoring blood glucose levels overnight, appropriate therapeutic measures can be taken. The Somogyi effect can be treated by eliminating the dose of intermediate insulin at dinnertime and giving it at a lower dosage at bedtime or by supplying more food at bedtime. When a waning insulin level is the cause, then either increasing the evening dose or shifting it from dinnertime to bedtime (or both) can be effective. A bedtime dose either of insulin glargine or insulin detemir provides more sustained overnight insulin levels than human NPH and may be effective in managing refractory prebreakfast hyperglycemia. If this fails, insulin pump therapy may be required.

2. Type 2 diabetes—Therapeutic recommendations are based on the relative contributions of beta cell insufficiency and insulin insensitivity in individual patients. The possibility that the individual patient has a specific etiologic cause for their diabetes should always be considered, especially when the patient does not have a family history of type 2 diabetes or does not have any evidence of central obesity or insulin resistance. Such patients should be evaluated for other types of diabetes such as LADA or MODY. Patients with LADA should be prescribed insulin when the disease is diagnosed and treated like patients with type 1 diabetes. It is also important to note that many patients with type 2 diabetes mellitus have a progressive loss of beta cell function and will require additional therapeutic interventions with time.

A. Weight reduction—One of the primary modes of therapy in the obese patient with type 2 diabetes is weight reduction. Normalization of glycemia can be achieved by weight loss and improvement in tissue sensitivity to insulin. A

combination of caloric restriction, increased exercise, and behavior modification is required if a weight reduction program is to be successful. Understanding the risks associated with the diagnosis of diabetes may motivate the patient to lose weight.

For selected patients, medical or surgical options for weight loss should be considered. Orlistat, phentermine/ topiramate, lorcaserin, naltrexone/extended-release bupropion, and high-dose liraglutide (3 mg daily) are weight loss medications approved for use in combination with diet and exercise.

Bariatric surgery (Roux-en-Y, gastric banding, gastric sleeve, biliopancreatic diversion/duodenal switch) typically results in substantial weight loss and improvement in glucose levels. A meta-analysis examining the impact of bariatric surgery on patients with diabetes and BMI of 40 kg/m2 or greater noted that 82% of patients had resolution of clinical and laboratory manifestations of diabetes in the first 2 years after surgery and 62% remained free of diabetes more than 2 years after surgery. The improvement was most marked in the procedure that caused the greatest weight loss (biliopancreatic diversion/duodenal switch). There was, however, a high attrition of patients available for follow-up, and there was little information about different ethnic types. Weight regain does occur after bariatric surgery, and it can be expected that 20–25% of the lost weight will be regained over 10 years. The impact of this weight gain on diabetes recurrence depends principally on the degree of beta cell dysfunction.

Nonobese patients with type 2 diabetes frequently have increased visceral adiposity—the so-called metabolically obese normal weight patient. There is less emphasis on weight loss, but exercise remains an important aspect of treatment.

B. Glucose lowering agents—The current recommendation is to start **metformin** therapy at diagnosis and notwait to see whether the patient can achieve target glycemic control with weight management and exercise.

The medication, however, cannot be used in patients with end-stage renal disease, and sometimes gastrointestinal side effects develop at even the lowest doses and persist over time. Under these circumstances the choice of the initial agent depends on a number of factors, including comorbid conditions, adverse reactions to the medications, ability of the patient to monitor for hypoglycemia, medication cost, and patient and clinician preferences. **Sulfonylureas** have been available for many years and their use in combination with metformin is well established. They do, however, have the propensity of causing hypoglycemia and weight gain. **Pioglitazone** improves peripheral insulin resistance and lowers glucose without causing hypoglycemia. Troublesome adverse reactions include weight gain, fluid retention and heart failure, increased fracture risk in women, and possible increased risk of bladder cancer. Pioglitazone is contraindicated in patients with active liver disease and in patients with liver enzymes are 2.5 times or more the upper limit of normal. The **alpha-glucosidase inhibitors (acarbose, miglitol)** have modest glucose lowering effects and have gastrointestinal side effects. The **GLP-1 receptor agonists (eg, exenatide or liraglutide)** have a lower risk of hypoglycemia than the sulfonylureas and they promote weight loss; however, they need to be given by injection. These agents cause nausea, may cause pancreatitis,

and are contraindicated in patients with gastroparesis. The **DPP-4 inhibitors (eg, sitagliptin)** also have a low risk of hypoglycemia, and they do not cause nausea or vomiting. They can also be used in patients with kidney impairment. There are, however, reports of serious allergic reactions, including anaphylaxis, angioedema, and Stevens-Johnson syndrome. There is also concern that they may, like the GLP-1 receptor agonists, cause pancreatitis. The SGLT2 inhibitors (eg, canagliflozin) lower fasting and postprandial glucose levels. They also have a low risk of hypoglycemia, promote weight loss, and lower blood pressure levels. They increase the risk for mycotic genital infections and urinary tract infections, however. They can cause volume depletion and are less effective in patients with kidney disease.

When diabetes is not well controlled with initial therapy (usually metformin), then a second agent should be added. In patients who experience hyperglycemia after a carbohydrate-rich meal (such as dinner), a short-acting secretagogue (repaglinide or nateglinide) before meals may suffice to get the glucose levels into the target range. Patients with severe insulin resistance may be candidates for pioglitazone. Patients who are very concerned about weight gain may benefit from a trial of GLP-1 receptor agonist or DPP-4 inhibitor or SGLT2 inhibitor. If two agents are inadequate, then a third agent is added, although data regarding efficacy of such combined therapy are limited.

When the combination of oral agents (and injectable GLP-1 receptor agonists) fail to achieve euglycemia in patients with type 2 diabetes, then insulin treatment shouldbe instituted. Various insulin regimens may be effective. One proposed regimen is to continue the oral combination therapy and then simply add a bedtime dose of NPH or long-acting insulin analog (insulin glargine or insulin detemir) to reduce excessive nocturnal hepatic glucose output and improve fasting glucose levels. If the patient does not achieve target glucose levels during the day, then daytime insulin treatment can be initiated. A convenient insulin regimen under these circumstances is a split dose of 70/30 NPH/regular mixture (or Humalog Mix 75/25 or NovoLogMix 70/30) before breakfast and before dinner. If this regimen fails to achieve satisfactory glycemic goals or is associated with unacceptable frequency of hypoglycemic episodes, then a more intensive regimen of multiple insulin injections can be instituted as in patients with type 1 diabetes. Metformin principally reduces hepatic glucose output, and it is reasonable to continue with this medication when insulin therapy is instituted. Pioglitazone, which improves peripheral insulin sensitivity, can be used together with insulin but this combination is associated with more weight gain and peripheral edema. The sulfonylureas also continue to be of benefit. There is limited information on the benefits of continuing the GLP1-receptor agonists or the DPP-4 inhibitors or the SGLT2 inhibitors once insulin therapy is initiated. Weight-reducing interventions should continue even after initiation of insulin therapy and may allow for simplification of the therapeutic regimen in the future.

D. Acceptable Levels of Glycemic Control

A reasonable aim of therapy is to approach normal glycemic excursions without provoking severe or frequent hypoglycemia. **Criteria for “acceptable”**

control includes the following: (1) blood glucose levels of 90–130 mg/dL (5–7.2 mmol/L) before meals and after an overnight fast, (2) levels no higher than 180 mg/dL (10 mmol/L) 1 hour after meals and 150 mg/dL (8.3 mmol/L) 2 hours after meals, and (3) HbA1c levels less than 7% for nonpregnant adults. Less stringent HbA1c goals may be appropriate in children, those with a history of severe hypoglycemia, limited life expectancy, and advanced microvascular and macrovascular disease. In the elderly frail patient, an HbA1c target of approximately 8% (preprandial blood glucose levels in the range of the 150–159 mg/dL) may be reasonable although formal evidence is lacking. **The UKPDS study demonstrated that blood pressure control was as significant or more significant than glycemic control in patients with type 2 diabetes regarding the prevention of microvascular as well as macrovascular complications.**

Complications of Insulin Therapy

Hypoglycemia

Hypoglycemic reactions are the most common complications that occur in patients with diabetes who are treated with insulin. The signs and symptoms of hypoglycemia may be divided into those resulting from stimulation of the autonomic nervous system and those from neuroglycopenia (insufficient glucose for normal central nervous system function). When the blood glucose falls to around 54 mg/dL (3 mmol/L), the patient starts to experience both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger) nervous system symptoms. If these autonomic symptoms are ignored and the glucose levels fall further (to around 50 mg/dL [2.8 mmol/L]), then neuroglycopenic symptoms appear, including irritability, confusion, blurred vision, tiredness, headache, and difficulty speaking. A further decline in glucose can then lead to loss of consciousness or even a seizure. With repeated episodes of hypoglycemia, there is adaptation, and autonomic symptoms do not occur until the blood glucose levels are much lower and so the first symptoms are often due to neuroglycopenia. This condition is referred to as “hypoglycemic unawareness.” It has been shown that hypoglycemic unawareness can be reversed by keeping glucose levels high for a period of several weeks. Except for sweating, most of the sympathetic symptoms of hypoglycemia are blunted in patients receiving beta-blocking agents for angina pectoris or hypertension. Though not absolutely contraindicated, these medications must be used with caution in patients with diabetes who require insulin, and beta-1-selective blocking agents are preferred.

Hypoglycemia can occur in patient taking sulfonylureas, repaglinide, and nateglinide, particularly if the patient is elderly, has kidney or liver disease, or is taking certain other medications that alter metabolism of the sulfonylureas (eg, phenylbutazone, sulfonamides, or warfarin). It occurs more frequently with the use of long-acting sulfonylureas than when shorter-acting agents are used. Otherwise, hypoglycemia in insulin-treated patients with diabetes occurs as a consequence of three factors: behavioral issues, impaired counterregulatory systems, and complications of diabetes.

Behavioral issues include injecting too much insulin for the amount of carbohydrates ingested. Drinking alcohol in excess, especially on an empty stomach, can also cause hypoglycemia. In patients with type 1 diabetes, hypoglycemia can occur during or even several hours after exercise, and so glucose levels need to be monitored and food and insulin adjusted. Some patients do not like their glucose levels to be high, and they treat every high glucose level aggressively. These individuals who "stack" their insulin—that is, give another dose of insulin before the first injection has had its full action—can develop hypoglycemia.

Counterregulatory issues resulting in hypoglycemia include impaired glucagon response, sympatho-adrenal responses, and cortisol deficiency. Patients with diabetes of greater than 5 years, duration lose their glucagon response to hypoglycemia. As a result, they are at a significant disadvantage in protecting themselves against falling glucose levels. Once the glucagon response is lost, their sympatho-adrenalresponses take on added importance. Unfortunately, aging, autonomic neuropathy, or hypoglycemic unawareness due to repeated low glucose levels further blunts the sympathoadrenal responses. Occasionally, Addison disease develops in persons with type 1 diabetes mellitus; when this happens, insulin requirements fall significantly, and unless insulin dose is reduced, recurrent hypoglycemia will develop.

Complications of diabetes that increase the risk for hypoglycemia include autonomic neuropathy, gastroparesis, and end-stage chronic kidney disease. The sympathetic nervous system is an important system alerting the individual that the glucose level is falling by causing symptoms of tachycardia, palpitations, sweating, and tremulousness. Failure of the sympatho-adrenal responses increases the risk of hypoglycemia. In addition, in patients with gastroparesis, if insulin is given before a meal, the peak of insulin action may occur before the food is absorbed causing the glucose levels to fall. Finally, in end-stage chronic kidney disease, hypoglycemia can occur presumably because of decreased insulin clearance as well as loss of renal contribution to gluconeogenesis in the postabsorptive state

To prevent and treat insulin-induced hypoglycemia, the diabetic patient should carry glucose tablets or juice at all times. For most episodes, ingestion of 15 grams of carbohydrate is sufficient to reverse the hypoglycemia. The patient should be instructed to check the blood glucose in 15 minutes and treat again if the glucose level is still low. A parenteral glucagon emergency kit (1 mg) should be provided to every patient with diabetes who is receiving insulin therapy. Family or friends should be instructed how to inject it subcutaneously or intramuscularly into the buttock, arm, or thigh in the event that the patient is unconscious or refuses food. The medication can occasionally cause vomiting, and the unconscious patient should be turned on his or her side to protect the airway. The glucagon mobilizes glycogen from the liver, raising the blood glucose by about 36 mg/dL (2 mmol/L) in about 15 minutes. After the patient recovers consciousness, additional oral carbohydrate should be given. People with diabetes receiving hypoglycemic medication therapy should also wear an identification MedicAlert bracelet or

necklace or carry a card in his or her wallet (1-800-ID-ALERT, www .medicalert.org).

Medical personnel treating severe hypoglycemia can give 50 mL of 50% glucose solution by rapid intravenous infusion. If intravenous access is not available, 1 mg of glucagon can be injected intramuscularly.

THE HYPOGLYCEMIC STATES

Spontaneous hypoglycemia in adults is of two principal types: fasting and postprandial. Symptoms begin at plasma glucose levels in the range of 60 mg/dL (3.3 mmol/L) and impairment of brain function at approximately 50 mg/dL (2.8 mmol/L). Fasting hypoglycemia is often subacute or chronic and usually presents with neuroglycopenia as its principal manifestation; postprandial hypoglycemia is relatively acute and is often heralded by symptoms of neurogenic autonomic discharge (sweating, palpitations, anxiety, tremulousness).

Common causes of hypoglycemia in adults

Fasting hypoglycemia

- Pancreatic B cell tumor
- Surreptitious administration of insulin or sulfonylureas
- Extrapancreatic tumors

Postprandial hypoglycemia

- Alimentary
- Noninsulinoma pancreatogenous hypoglycemia syndrome
- Functional
- Occult diabetes mellitus

Alcohol-related hypoglycemia

Immunopathologic hypoglycemia

- Idiopathic anti-insulin antibodies (which release their bound insulin)
- Antibodies to insulin receptors (which act as agonists)

Drug-induced hypoglycemia

POSTPRANDIAL HYPOGLYCEMIA

1. Hypoglycemia Following Gastric Surgery

Hypoglycemia sometimes develops in patients who have undergone gastric surgery (eg, gastrectomy, vagotomy, pyloroplasty, gastrojejunostomy, Nissan fundoplication, Bilroth II procedure and Roux-en-Y), especially when they consume foods containing high levels of carbohydrates. This late dumping syndrome occurs about 1–3 hours after a meal and is a result of rapid delivery of high concentration of carbohydrates in the proximal small bowel and rapid absorption of glucose. The hyperinsulinemic response to the high carbohydrate load causes hypoglycemia. The symptoms include lightheadedness, sweating, confusion

and even loss of consciousness after eating a high carbohydrate meal. It is likely that gastrointestinal hormones such as GLP-1 play a role in the hyperinsulinemic response. It has been reported that treatment with exendin 9-39, a GLP-1 receptor agonist can prevent post gastric bypass hypoglycemia. The incidence of secondary dumping syndrome declined with the advent of medical therapy for peptic ulcer disease. There has been resurgence of cases, however, with the popularity of Roux-en-Y gastric bypass surgery for the treatment of morbid obesity. Patients typically complain of symptoms that are more severe after consumption of large amounts of readily absorbable carbohydrates. In terms of documenting hypoglycemia, it is reasonable to request the patient to consume a meal that leads to symptoms during everyday life. An oral glucose tolerance test is not recommended because many normal persons have false-positive test results. There have been case reports of insulinoma and noninsulinoma pancreatogenous hypoglycemia syndrome in patients with hypoglycemia post Roux-en-Y surgery. It is unclear how often this occurs. A careful history may identify patients who have a history of hypoglycemia with exercise or meals, and these individuals may require a formal 72-hour fast to rule out an insulinoma.

Treatment for secondary dumping includes dietary modification, but this may be difficult to sustain. Patients can try more frequent meals with smaller portions of less rapidly digested carbohydrates. Alpha-glucosidase therapy may be a useful adjunct to a low carbohydrate diet. Octreotide 50 mcg administered subcutaneously two or three times a day 30 minutes prior to each meal has been reported to improve symptoms due to late dumping syndrome. Various surgical procedures to delay gastric emptying have been reported to improve symptoms but long-term efficacy studies are lacking.

2. Noninsulinoma Pancreatogenous Hypoglycemia Syndrome (Islet Cell Hyperplasia)

In a very small number of patients with organic hyperinsulinism, islet cell hyperplasia is present rather than an adenoma. This condition is referred to as noninsulinoma pancreatogenous hypoglycemia syndrome. These patients typically have documented hyperinsulinemic hypoglycemia after meals but not with fasting up to 72 hours. The patients have a positive response to calcium-stimulated angiography. A gradient-guided partial pancreatectomy leads to clinical remission, and the pathology of the pancreas shows evidence of islet cell hyperplasia and nesidioblastosis. These patients do not have mutations in the pancreatic islet beta-cell ATP-sensitive potassium channel inward rectifier (Kir 6.2) and the sulfonylurea receptor-1 (SUR1) genes, which have been reported in children with familial hyperinsulinemic hypoglycemia.

3. Functional Alimentary Hypoglycemia

Patients have symptoms suggestive of increased sympathetic activity, including anxiety, weakness, tremor, sweating or palpitations after meals. Physical examination and laboratory tests are normal. It is not recommended that patients with symptoms suggestive of increased sympathetic activity undergo either a

prolonged oral glucose tolerance test or a mixed meal test. Instead, the patients should be given home blood glucose monitors (with memories) and instructed to monitor fingerstick glucose levels at the time of symptoms. Only patients who have symptoms when their fingerstick blood glucose is low (less than 50 mg/dL) and who have resolution of symptoms when the glucose is raised by eating rapidly released carbohydrate need additional evaluation. Patients who do not have evidence for low glucose levels at time of symptoms are generally reassured by their findings. Counseling and support should be the mainstays in therapy, with dietary manipulation only an adjunct.

4. Occult Diabetes

This condition is characterized by a delay in early insulin release from pancreatic B cells, resulting in initial exaggeration of hyperglycemia during a glucose tolerance test. In response to this hyperglycemia, an exaggerated insulin release produces a late hypoglycemia 4–5 hours after ingestion of glucose. These patients are often obese and frequently have a family history of diabetes mellitus.

Patients with this type of postprandial hypoglycemia often respond to reduced intake of refined sugars with multiple, spaced, small feedings high in dietary fiber. In the obese, treatment is directed at weight reduction to achieve ideal weight. These patients should be considered to have prediabetes or early diabetes (type 1 or 2) and advised to have periodic medical evaluations.

5. Autoimmune Hypoglycemia

Patients with autoimmune hypoglycemia have early postprandial hyperglycemia followed by hypoglycemia 3–4 hours later. The hypoglycemia is attributed to a dissociation of insulin-antibody immune complexes, releasing free insulin.

The disorder is associated with methimazole treatment for Graves disease, although it can also occur in patients treated with various other sulfhydryl-containing medications (captopril, penicillamine) as well as other drugs such as hydralazine, isoniazid, and procainamide. In addition, it has been reported in patients with autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and polymyositis as well as in multiple myeloma and other plasma cell dyscrasias where paraproteins or antibodies cross-react with insulin. There is also an association with the HLA class II alleles (DRB1* 0406, DQA1* 0301, and DQB1* 0302). These alleles are 10 to 20 times more common in Japanese and Korean populations, which explains why the disorder has been reported mostly in Japanese patients.

High titers of insulin autoantibodies, usually IgG class, can be detected. Insulin, proinsulin, and C-peptide levels may be elevated, but the results may be erroneous because of the interference of the insulin antibodies with the immunoassays for these peptides.

In most cases, the hypoglycemia is transient and usually resolves spontaneously within 3–6 months of diagnosis, particularly when the offending medications are stopped. The most consistent therapeutic benefit in management of

this syndrome has been achieved by dietary treatment with small, frequent low-carbohydrate meals. Prednisone (30–60 mg orally daily) has been used to lower the titer of insulin antibodies.

MEDICATION-INDUCED HYPOGLYCEMIA

A number of medications apart from the sulfonylureas can occasionally cause hypoglycemia. Common offenders include the fluoroquinolones such as gatifloxacin and levofloxacin, pentamidine, quinine, ACE inhibitors, salicylates and beta-adrenergic blocking agents. The fluoroquinolones, particularly gatifloxacin, have been associated with both hypoglycemia and hyperglycemia. It is thought that the drug acts on the ATP sensitive potassium channels in the beta cell. Hypoglycemia is an early event, and hyperglycemia occurs several days into therapy. Intravenous pentamidine is cytotoxic to beta cells and causes acute hyperinsulinemia and hypoglycemia followed by insulinopenia and hyperglycemia. Fasting patients taking noncardioselective beta-blockers can have an exaggerated hypoglycemic response to starvation. The beta-blockade inhibits fatty acids and gluconeogenesis substrate release and reduces plasma glucagon response. Therapy with ACE inhibitors increases the risk of hypoglycemia in patients who are taking insulin or sulfonylureas presumably because these drugs increase sensitivity to circulating insulin by increasing blood flow to the muscle.

Ethanol-associated hypoglycemia may be due to hepatic depletion of NADH and altered NADH:NAD ratio. This in turn limits conversion of lactate to pyruvate, the main substrate for hepatic gluconeogenesis. With prolonged starvation, glycogen reserves become depleted within 18–24 hours and hepatic glucose output becomes totally dependent on gluconeogenesis. Under these circumstances, a bloodconcentration of ethanol as low as 45 mg/dL (9.8 mmol/L) can induce profound hypoglycemia by blocking gluconeogenesis. Neuroglycopenia in a patient whose breath smells of alcohol may be mistaken for alcoholic stupor. Prevention consists of adequate food intake during ethanol ingestion. Therapy consists of glucose administration to replenish glycogen stores until gluconeogenesis resumes.

When sugar-containing soft drinks are used as mixers to dilute alcohol in beverages (gin and tonic, rum and cola), there seems to be a greater insulin release than when the soft drink alone is ingested and a tendency for more of a late hypoglycemic overswing to occur 3–4 hours later. Prevention would consist of avoiding sugar mixers while ingesting alcohol and ensuring supplementary food intake to provide sustained absorption.

DIABETIC COMA

Coma may be due to a variety of causes not directly related to diabetes. Certain causes directly related to diabetes require differentiation: (1) Hypoglycemic coma resulting from excessive doses of insulin or oral hypoglycemic agents. (2) Hyperglycemic coma associated with either severe insulin deficiency (diabetic ketoacidosis) or mild to moderate insulin deficiency (hyperglycemic hyperosmolar

state). (3) Lactic acidosis associated with diabetes, particularly in patients with diabetes stricken with severe infections or with cardiovascular collapse.

DIABETIC KETOACIDOSIS

ESSENTIALS OF DIAGNOSIS

- Hyperglycemia greater than 250 mg/dL (13.9 mmol/L).
- Acidosis with blood pH < 7.3.
- Serum bicarbonate less than 15 mEq/L.
- Serum positive for ketones.

General Considerations

Diabetic ketoacidosis may be the initial manifestation of type 1 diabetes or may result from increased insulin requirements in type 1 diabetes patients during the course of infection, trauma, myocardial infarction, or surgery. It is a life-threatening medical emergency with a mortality rate just under 5% in individuals under 40 years of age, but with a more serious prognosis in the elderly, who have mortality rates over 20%. The National Data Group reports an annual incidence of five to eight episodes of diabetic ketoacidosis per 1000 diabetic persons. Ketoacidosis may develop in patients with type 2 diabetes when severe stress such as sepsis or trauma is present. Diabetic ketoacidosis has been found to be one of the more common serious complications of insulin pump therapy, occurring in approximately 1 per 80 patient-months of treatment. Many patients who monitor capillary blood glucose regularly ignore urine ketone measurements, which would signal the possibility of insulin leakage or pump failure before serious illness develops. Poor compliance, either for psychological reasons or because of inadequate education, is one of the most common causes of diabetic ketoacidosis, particularly when episodes are recurrent.

Clinical Findings

A. Symptoms and Signs

The appearance of diabetic ketoacidosis is usually preceded by a day or more of polyuria and polydipsia associated with marked fatigue, nausea, and vomiting. If untreated, mental stupor ensues that can progress to coma. Drowsiness is fairly common, but frank coma only occurs in about 10% of patients. On physical examination, evidence of dehydration in a stuporous patient with rapid deep breathing and a “fruity” breath odor of acetone would strongly suggest the diagnosis. Hypotension with tachycardia indicates profound fluid and electrolyte depletion, and mild hypothermia is usually present. Abdominal pain and even tenderness may be present in the absence of abdominal disease. Conversely, cholecystitis or pancreatitis may occur with minimal symptoms and signs.

B. Laboratory Findings

Typically, the patient with moderately severe diabetic ketoacidosis has a plasma glucose of 350–900 mg/dL (19.4–50 mmol/L), serum ketones at a dilution of 1:8 or greater, hyperkalemia (serum potassium level of 5–8 mEq/L), slight

hyponatremia (serum sodium of approximately 130 mEq/L), hyperphosphatemia (serum phosphate level of 6–7 mg/dL [1.9–2.3 mmol/L]), and elevated blood urea nitrogen and serum creatinine levels. Acidosis may be severe (pH ranging from 6.9 to 7.2 and serum bicarbonate ranging from 5 mEq/L to 15 mEq/L); Pco2 is low (15–20 mm Hg) related to hyperventilation. Fluid depletion is marked, typically about 100 mL/kg.

The difference between venous and arterial pH is 0.02 to 0.15 pH units and venous and arterial bicarbonate is 1.88 mEq/L. These small differences will not affect either the diagnosis or the management of diabetic ketoacidosis, and there is no need to collect arterial blood for measuring the acid-base status.

The hyperkalemia occurs despite total body potassium depletion because of the shift of potassium from the intracellular to extracellular spaces that occurs in systemic acidosis. The average total body potassium deficit resulting from osmotic diuresis, acidosis, and gastrointestinal losses is about 3–5 mEq/kg. Similarly, despite the elevated serum phosphate, total body phosphate is generally depleted. Serum sodium is generally reduced due to loss of sodium ions (7–10 mEq/kg) by polyuria and vomiting and because severe hyperglycemia shifts intracellular water into the interstitial compartment. There is some controversy about the correction factor for the serum sodium in the presence of hyperglycemia. Many guidelines recommend a correction factor, whereby the serum sodium concentration decreases by 1.6 mEq/L for every 100 mg/dL (5.56 mmol/L) rise in plasma glucose above normal, but there is evidence that the decrease may be greater when patients have more severe hyperglycemia (greater than 400 mg/dL or 22.2 mmol/L) and/or volume depletion. One group has suggested (based on short-term exposure of normal volunteers to markedly elevated glucose levels) that, when the serum glucose is greater than 200 mg/dL (11.1 mmol/L), the serum sodium concentration decreases by at least 2.4 mEq/L. Serum osmolality can be directly measured by standard tests of freezing point depression or can be estimated by calculating the molarity of sodium, chloride, and glucose in the serum.

Central nervous system depression or coma occurs when the effective serum osmolality exceeds 320–330 mOsm/L. Coma in a diabetic patient with a lower osmolality should prompt a search for cause of coma other than hyperosmolality.

Ketoacidemia represents the effect of insulin lack at multiple enzyme loci. Insulin lack associated with elevated levels of growth hormone, catecholamines, and glucagon contributes to increases in lipolysis from adipose tissue and in hepatic ketogenesis. In addition, reduced ketolysis by insulin-deficient peripheral tissues contributes to the ketoacidemia. The only true “keto” acid present is acetoacetic acid which, along with its by-product acetone, is measured by nitroprusside reagents (Acetest and Ketostix). The sensitivity for acetone, however, is poor, requiring over 10 mmol/L, which is seldom reached in the plasma of ketoacidotic patients—although this detectable concentration is readily achieved in urine. Thus, in the plasma of ketotic patients, only acetoacetate is measured by these reagents. The more prevalent beta-hydroxybutyric acid has no ketone group and is therefore not detected by conventional nitroprusside tests. This takes on special importance in the presence of circulatory collapse during diabetic ketoacidosis, wherein an

increase in lactic acid can shift the redox state to increase beta-hydroxybutyric acid at the expense of the readily detectable acetoacetic acid. Bedside diagnostic reagents are then unreliable, suggesting no ketonemia in cases where beta-hydroxybutyric acid is a major factor in producing the acidosis. Combined glucose and ketone meter (Precision Xtra, Nova Max Plus) that measure blood beta-hydroxybutyrate concentration on capillary blood are now available. Many clinical laboratories also offer direct blood beta-hydroxybutyrate measurement.

Nonspecific elevations of serum amylase and lipase occurs in about 16–25% of cases of diabetic ketoacidosis, and an imaging study may be necessary if the diagnosis of acute pancreatitis is being seriously considered. Leukocytosis as high as 25,000/mcL with a left shift may occur with or without associated infection. The presence of an elevated or even a normal temperature would suggest the presence of an infection, since patients with diabetic ketoacidosis are generally hypothermic if uninfected.

Treatment

Patients with mild diabetic ketoacidosis are alert and have pH levels between 7.25 and 7.30 and beta-hydroxybutyrate levels of 3–4 mmol/L; those with moderate ketoacidosis are either alert or little drowsy and have pH levels between 7.0 and 7.24 and beta-hydroxybutyrate levels of 4–8 mmol/L; and those with severe ketoacidosis are stuporose and have a pH < 7.0 and beta-hydroxybutyrate levels of greater than 8 mmol/L. Those with mild ketoacidosis can be treated in the emergency department, but those with moderate or severe ketoacidosis require admission to the ICU or stepdown unit. Therapeutic goals are to restore plasma volume and tissue perfusion, reduce blood glucose and osmolality toward normal, correct acidosis, replenish electrolyte losses, and identify and treat precipitating factors. Gastric intubation is recommended in the comatose patient to prevent vomiting and aspiration that may occur as a result of gastric atony, a common complication of diabetic ketoacidosis. An indwelling catheter may also be necessary. In patients with preexisting heart or kidney failure or those in severe cardiovascular collapse, a central venous pressure catheter should be inserted to evaluate the degree of hypovolemia and to monitor subsequent fluid administration.

A comprehensive flow sheet that includes vital signs, serial laboratory data, and therapeutic interventions (eg, fluids, insulin) should be meticulously maintained by the clinician responsible for the patient’s care. Plasma glucose should be recorded hourly and electrolytes and pH at least every 2–3 hours during the initial treatment period. Bedside glucose meters should be used to titrate the insulin therapy. The patient should not receive sedatives or opioids in order to avoid masking signs and symptoms of impeding cerebral edema.

A. Fluid Replacement

In most patients, the fluid deficit is 4–5 L. Initially, 0.9% saline solution is the solution of choice to help reexpand the contracted vascular volume and should be started in the emergency department as soon as the diagnosis is established. The saline should be infused rapidly to provide 1 L/h over the first 1–2 hours. After the

first 2 L of fluid have been given, the intravenous infusion should be at the rate of 300–400 mL/h. Use 0.9% (“normal”) saline unless the serum sodium is greater than 150 mEq/L, when 0.45% (“half normal”) saline solution should be used. The volume status should be very carefully monitored. Failure to give enough volume replacement (at least 3–4 L in 8 hours) to restore normal perfusion is one of the most serious therapeutic short-comings adversely influencing satisfactory recovery. Excessive fluid replacement (more than 5 L in 8 hours) may contribute to acute respiratory distress syndrome or cerebral edema. When blood glucose falls to approximately 250 mg/dL (13.9 mmol/L), the fluids should be changed to a 5% glucose-containing solution to maintain serum glucose in the range of 250–300 mg/dL (13.9–16.7 mmol/L). This will prevent the development of hypoglycemia and will also reduce the likelihood of cerebral edema, which could result from too rapid decline of blood glucose.A comprehensive flow sheet that includes vital signs, serial laboratory data, and therapeutic interventions (eg, fluids, insulin) should be meticulously maintained by the clinician responsible for the patient’s care. Plasma glucose should be recorded hourly and electrolytes and pH at least every 2–3 hours during the initial treatment period. Bedside glucose meters should be used to titrate the insulin therapy. The patient should not receive sedatives or opioids in order to avoid masking signs and symptoms of impeding cerebral edema.

B. Insulin Replacement

Immediately after initiation of fluid replacement, regular insulin should be given intravenously in a loading dose of 0.1 unit/kg as a bolus to prime the tissue insulin receptors. Following the initial bolus, intravenous doses of insulin as low as 0.1 unit/kg/h are continuously infused or given hourly as an intramuscular injection; this is sufficient to replace the insulin deficit in most patients. A prospective randomized study showed that a bolus dose is not required if patients are given hourly insulin infusion at 0.14 unit/kg. Replacement of insulin deficiency helps correct the acidosis by reducing the flux of fatty acids to the liver, reducing ketone production by the liver, and also improving removal of ketones from the blood. Insulin treatment reduces the hyperosmolality by reducing the hyperglycemia. It accomplishes this by increasing removal of glucose through peripheral utilization as well as by decreasing production of glucose by the liver. This latter effect is accomplished by direct inhibition of gluconeogenesis and glycogenolysis as well as by lowered amino acid flux from muscle to liver and reduced hyperglucagonemia.

The insulin dose should be “piggy-backed” into the fluid line so the rate of fluid replacement can be changed without altering the insulin delivery rate. If the plasma glucose level fails to fall at least 10% in the first hour, a repeat loading dose (0.1 or 0.14 unit/kg) is recommended. Rarely, a patient with immune insulin resistance is encountered, and this requires doubling the insulin dose every 2–4 hours if hyperglycemia does not improve after the first two doses of insulin. The insulin dose should be adjusted to lower the glucose concentration by about 50–70 mg/dL (2.8–3.9 mmol/L). Patients who are normally take insulin glargine or insulin detemir can be given their usual maintenance doses during initial treatment of their diabetic ketoacidosis. The continuation of their subcutaneous basal insulins means

that lower doses of intravenous insulin will be needed, and there will be a smoother transition from intravenous insulin infusion to the subcutaneous regimen.

C. Potassium

Total body potassium loss from polyuria and vomiting may be as high as 200 mEq. However, because of shifts of potassium from cells into the extracellular space as a consequence of acidosis, serum potassium is usually normal to slightly elevated prior to institution of treatment. As the acidosis is corrected, potassium flows back into the cells, and hypokalemia can develop if potassium replacement is not instituted. If the patient is not uremic and has an adequate urinary output, potassium chloride in doses of 10–30 mEq/h should be infused during the second and third hours after beginning therapy as soon as the acidosis starts to resolve. Replacement should be started sooner if the initial serum potassium is inappropriately normal or low and should be delayed if serum potassium fails to respond to initial therapy and remains above 5 mEq/L, as in cases of chronic kidney disease. Occasionally, a patient may present with a serum potassium level less than 3.5 mEq/L, in which case insulin therapy should be delayed until the potassium level is corrected to greater than 3.5 mEq/L. An ECG can be of help in monitoring the patient's potassium status: High peaked T waves are a sign of hyperkalemia, and flattened T waves with U waves are a sign of hypokalemia. Foods high in potassium content should be prescribed when the patient has recovered sufficiently to take food orally. Tomato juice has 14 mEq of potassium per 240 mL, and a medium-sized banana provides about 10 mEq.

D. Sodium Bicarbonate

The use of sodium bicarbonate in management of diabetic ketoacidosis has been questioned since clinical benefit was not demonstrated in one prospective randomized trial and because of the following potentially harmful consequences: (1) development of hypokalemia from rapid shift of potassium into cells if the acidosis is overcorrected; (2) tissue anoxia from reduced dissociation of oxygen from hemoglobin when acidosis is rapidly reversed (leftward shift of the oxygen dissociation curve); and (3) cerebral acidosis resulting from lowering of cerebrospinal fluid pH. It must be emphasized, however, that these considerations are less important when very severe acidosis exists. Therefore, it is recommended that bicarbonate be administered to diabetic patients in ketoacidosis if the arterial blood pH is 7.0 or less, with careful monitoring to prevent overcorrection. One or two ampules of sodium bicarbonate (one ampule contains 44 mEq/50 mL) should be added to 1 L of 0.45% saline. (**Note**: Addition of sodium bicarbonate to 0.9% saline would produce a markedly hypertonic solution that could aggravate the hyperosmolar state already present.) This should be administered rapidly (over the first hour). It can be repeated until the arterial pH reaches 7.1, but *it should not be given if the pH is 7.1 or greater* since additional bicarbonate would increase the risk of rebound metabolic alkalosis as ketones are metabolized. Alkalosis shifts potassium from serum into cells, which could precipitate a fatal cardiac arrhythmia.

E. Phosphate

Phosphate replacement is seldom required in treating diabetic ketoacidosis. However, if severe hypophosphatemia of less than 1 mg/dL (0.32 mmol/L) develops during insulin therapy, a small amount of phosphate can be replaced per hour as the potassium salt. However, three randomized studies in which phosphate was replaced in patients with diabetic ketoacidosis did not show any apparent clinical benefit from phosphate administration. Moreover, attempts to use potassium phosphate as the sole means of replacing potassium have led to a number of reported cases of severe hypocalcemia with tetany. To minimize the risk of inducing tetany from too-rapid replacement of phosphate, the average deficit of 40–50 mmol of phosphate should be replaced intravenously at a rate *no greater than 3–4 mmol/h* in a 60–70-kg person. A stock solution (Abbott) provides a mixture of 1.12 g KH2 PO4 and 1.18 g K2 HPO4 in a 5-mL single-dose vial (this equals 22 mmol of potassium and 15 mmol of phosphate). One-half of this vial (2.5 mL) should be added to 1 L of either 0.45% saline or 5% dextrose in water. Two liters of this solution, infused at a rate of 400 mL/h, will correct the phosphate deficit at the optimal rate of 3 mmol/h while providing 4.4 mEq of potassium per hour. (Additional potassium should be administered as potassium chloride to provide a total of 10–30 mEq of potassium per hour, as noted above.) If the serum phosphate remains below 2.5 mg/dL (0.8 mmol/L) after this infusion, a repeat 5-hour infusion can be given.

F. Hyperchloremic Acidosis

During Therapy Because of the considerable loss of keto acids in the urine during the initial phase of therapy, substrate for subsequent regeneration of bicarbonate is lost and correction of the total bicarbonate deficit is hampered. A portion of the bicarbonate deficit is replaced with chloride ions infused in large amounts as saline to correct the dehydration. In most patients, as the ketoacidosis clears during insulin replacement, a hyperchloremic, low-bicarbonate pattern emerges with a normal anion gap. This is a relatively benigncondition that reverses itself over the subsequent 12–24 hours once intravenous saline is no longer being administered. Using a balanced electrolyte solution similar to serum in chloride concentration and pH during resuscitation instead of normal saline has been reported to prevent the hyperchloremic acidosis.

G. Treatment of Associated Infection

Antibiotics are prescribed as indicated. Cholecystitis and pyelonephritis may be particularly severe in these patients.

H. Transition to Subcutaneous Insulin Regimen

Once the diabetic ketoacidosis is controlled and the patient is awake and able to eat, subcutaneous insulin therapy can be initiated. The patient with type 1 diabetes may have persistent significant tissue insulin resistance and may require a total daily insulin dose of approximately 0.6 units/kg. The amount of insulin required in the previous 8 hours can also be helpful in estimating the initial insulin

doses. Half the total daily dose can be given as a long-acting basal insulin and the other half as short-acting insulin premeals. The patient should receive subcutaneous basal insulin and rapid-acting insulin analog with the first meal and the insulin infusion discontinued an hour later. The overlap of the subcutaneous insulin action and insulin infusion is necessary to prevent relapse of the diabetic ketoacidosis. The increased insulin resistance is only present for a few days, and it is important to reduce both the basal and bolus insulins to avoid hypoglycemia. A patient with new-onset type 1 diabetes usually still has significant beta cell function and may not need any basal insulin and only very low doses of rapid-acting insulin before meals after recovery from the ketoacidosis. Patients with type 2 diabetes and diabetes ketoacidosis due to severe illness may initially require insulin therapy but can often transition back to oral agents during outpatient follow-up.

Prognosis

Low-dose insulin infusion and fluid and electrolyte replacement combined with careful monitoring of patients' clinical and laboratory responses to therapy have dramatically reduced the mortality rates of diabetic ketoacidosis to less than 5%. However, this complication remains a significant risk in the aged who have mortality rates greater than 20% and in patients in profound coma in whom treatment has been delayed. Acute myocardial infarction and infarction of the bowel following prolonged hypotension worsen the outlook. A serious prognostic sign is end-stage chronic kidney disease, and prior kidney dysfunction worsens the prognosis considerably because the kidney plays a key role in compensating for massive pH and electrolyte abnormalities. Symptomatic cerebral edema occurs primarily in the pediatric population. Risk factors for its development include severe baseline acidosis, rapid correction of hyperglycemia, and excess volume administration in the first 4 hours. Onset of headache or deterioration in mental status during treatment should lead to consideration of this complication. Intravenous mannitol at a dosage of 1–2 g/kg given over 15 minutes is the mainstay of treatment. Excess crystalloid infusion can precipitate pulmonary edema. Acute respiratory distress syndrome is a rare complication of treatment of diabetic ketoacidosis.

After recovery and stabilization, patients should be instructed on how to recognize the early symptoms and signs of ketoacidosis. Urine ketones or capillary blood beta-hydroxybutyrate should be measured in patients with signs of infection or in insulin pump-treated patients when capillary blood glucose remains unexpectedly and persistently high. When heavy ketonuria and glycosuria persist on several successive examinations, supplemental rapid acting insulin should be administered and liquid foods such as lightly salted tomato juice and broth should be ingested to replenish fluids and electrolytes. The patient should be instructed to contact the clinician if ketonuria persists, and especially if there is vomiting and inability to keep down fluids. Recurrent episodes of severe ketoacidosis often indicate poor compliance with the insulin regimen, and these patients will require intensive counseling.

HYPERGLYCEMIC HYPEROSMOLAR STATE

ESSENTIALS OF DIAGNOSIS

- Hyperglycemia greater than 600 mg/dL (33.3 mmol/L).
- Serum osmolality greater than 310 mOsm/kg.
- No acidosis; blood pH > 7.3.
- Serum bicarbonate greater than 15 mEq/L.
- Normal anion gap (less than 14 mEq/L).

General Considerations

This second most common form of hyperglycemic coma is characterized by severe hyperglycemia in the absence of significant ketosis, with hyperosmolality and dehydration. It occurs in patients with mild or occult diabetes, and most patients are typically middle-aged to elderly. Accurate figures are not available as to its true incidence, but from data on hospital discharges it is rarer than diabetic ketoacidosis even in older age groups. Underlying chronic kidney disease or heart failure is common, and the presence of either worsens the prognosis. A precipitating event such as infection, myocardial infarction, stroke, or recent operation is often present. Certain medications such as phenytoin, diazoxide, corticosteroids, and diuretics have been implicated in its pathogenesis, as have procedures associated with glucose loading such as peritoneal dialysis.

Pathogenesis

A partial or relative insulin deficiency may initiate the syndrome by reducing glucose utilization of muscle, fat, and liver while inducing hyperglucagonemia and increasinghepatic glucose output. With massive glycosuria, obligatory water loss ensues. If a patient is unable to maintain adequate fluid intake because of an associated acute or chronic illness or has suffered excessive fluid loss, marked dehydration results. As the plasma volume contracts, kidney function becomes impaired, limiting the urinary glucose losses and exacerbating the hyperglycemia. Severe hyperosmolality develops that causes mental confusion and finally coma. It is not clear why ketosis is virtually absent under these conditions of insulin insufficiency, although reduced levels of growth hormone may be a factor, along with portal vein insulin concentrations sufficient to restrain ketogenesis.

Clinical Findings

A. Symptoms and Signs

Onset may be insidious over a period of days or weeks, with weakness, polyuria, and polydipsia. The lack of features of ketoacidosis may retard recognition of the syndrome and delay therapy until dehydration becomes more profound than in ketoacidosis. Reduced intake of fluid is not an uncommon historical feature, due to either inappropriate lack of thirst, nausea, or inaccessibility of fluids to elderly, bedridden patients. Lethargy and confusion develop as serum osmolality exceeds 310 mOsm/kg, and convulsions and coma can occur if osmolality exceeds 320–330 mOsm/kg. Physical examination confirms the presence

of profound dehydration in a lethargic or comatose patient without Kussmaul respirations.

B. Laboratory Findings

Severe hyperglycemia is present, with blood glucose values ranging from 800 mg/dL to 2400 mg/dL (44.4 mmol/L to 133.2 mmol/L) (Table 27–11). In mild cases, where dehydration is less severe, dilutional hyponatremia as well as urinary sodium losses may reduce serum sodium to 120–125 mEq/L, which protects to some extent against extreme hyperosmolality. However, as dehydration progresses, serum sodium can exceed 140 mEq/L, producing serum osmolality readings of 330–440 mOsm/kg. Ketosis and acidosis are usually absent or mild. Prerenal azotemia is the rule, with serum urea nitrogen elevations over 100 mg/dL (35.7 mmol/L) being typical.

Treatment

A. Fluid Replacement

Fluid replacement is of paramount importance in treating nonketotic hyperglycemic coma. The onset of hyperosmolarity is more insidious in elderly people without ketosis than in younger individuals with high serum ketone levels, which provide earlier indicators of severe illness (vomiting, rapid deep breathing, acetone odor, etc). Consequently, diagnosis and treatment are often delayed until fluid deficit has reached levels of 6–10 L.

If hypovolemia is present as evidenced by hypotension and oliguria, fluid therapy should be initiated with 0.9% saline. In all other cases, 0.45% saline appears to be preferable as the initial replacement solution because the body fluids of these patients are markedly hyperosmolar. As much as 4–6 L of fluid may be required in the first 8–10 hours. Careful monitoring of the patient is required for proper sodium and water replacement. Once blood glucose reaches 250 mg/dL (13.9 mmol/L), fluid replacement should include 5% dextrose in either water, 0.45% saline solution, or 0.9% saline solution. The rate of dextrose infusion should be adjusted to maintain glycemic levels of 250–300 mg/dL (13.9–16.7 mmol/L) in order to reduce the risk of cerebral edema. An important end point of fluid therapy is to restore urinary output to 50 mL/h or more.

B. Insulin

Less insulin may be required to reduce the hyperglycemia in nonketotic patients as compared to those with diabetic ketoacidotic coma. In fact, fluid replacement alone can reduce hyperglycemia considerably by correcting the hypovolemia, which then increases both glomerular filtration and renal excretion of glucose. An initial insulin dose of 0.1 unit/kg is followed by an insulin infusion of 0.1 unit/kg/h (or just an infusion of 0.14 unit/kg/h without a bolus), which is titrated to lower blood glucose levels by 50–70 mg/dL per hour (2.8–3.9 mmol/L/h). Once the patient has stabilized and the blood glucose falls to around 250 mg/dL (13.9 mmol/L), insulin can be given subcutaneously

C. Potassium

With the absence of acidosis, there may be no initial hyperkalemia unless associated end-stage chronic kidney disease is present. This results in less severe total potassium depletion than in diabetic ketoacidosis, and less potassium replacement is therefore needed. However, because initial serum potassium is usually not elevated and because it declines rapidly as a result of insulin's effect on driving potassium intracellularly, it has been recommended that potassium replacement be initiated earlier than in ketotic patients, assuming that no chronic kidney disease or oliguria is present. Potassium chloride (10 mEq/L) can be added to the initial bottle of fluids administered if the patient's serum potassium is not elevated.

D. Phosphate

If severe hypophosphatemia (serum phosphate less than 1 mg/dL [0.32 mmol/L]) develops during insulin therapy, phosphate replacement can be given as described for ketoacidotic patients (at 3 mmol/h).

Prognosis

The severe dehydration and low output state may predispose the patient to complications such as myocardial infarction, stroke, pulmonary embolism, mesenteric vein thrombosis, and disseminated intravascular coagulation. Fluid replacement remains the primary approach to the prevention of these complications. Low-dose heparin prophylaxis is reasonable but benefits of routine anticoagulation remain doubtful. Rhabdomyolysis is a recognized complication and should be looked for and treated.

The overall mortality rate of hyperglycemic hyperosmolar state coma is more than ten times that of diabetic ketoacidosis, chiefly because of its higher incidence in older patients, who may have compromised cardiovascular systems or associated major illnesses and whose dehydration is often excessive because of delays in recognition and treatment. (When patients are matched for age, the prognoses of these two hyperglycemic emergencies are reasonably comparable.) When prompt therapy is instituted, the mortality rate can be reduced from nearly 50% to that related to the severity of coexistent disorders.

After the patient is stabilized, the appropriate form of long-term management of the diabetes must be determined. Insulin treatment should be continued for a few weeks but patients usually recover sufficient endogenous insulin secretion to make a trial of diet or diet plus oral agents worthwhile. When the episode occurs in a patient who has known diabetes, then education of the patient and caregivers should be instituted. They should be taught how to recognize situations (nausea and vomiting, infection) that predispose to recurrence of the hyperglycemic, hyperosmolar state, as well as detailed information on how to prevent the escalating dehydration that culminates in hyperosmolar coma (small sips of sugar-free liquids, increase in usual hypoglycemic therapy, or early contact with the clinician).

LACTIC ACIDOSIS

ESSENTIALS OF DIAGNOSIS

- Severe acidosis with hyperventilation.
- Blood pH below 7.30.
- Serum bicarbonate less than 15 mEq/L.
- Anion gap greater than 15 mEq/L.
- Absent serum ketones.
- Serum lactate greater than 5 mmol/L.

General Considerations

Lactic acidosis is characterized by accumulation of excess lactic acid in the blood. Normally, the principal sources of this acid are the erythrocytes (which lack enzymes for aerobic oxidation), skeletal muscle, skin, and brain. Conversion of lactic acid to glucose and its oxidation principally by the liver but also by the kidneys represent the chief pathways for its removal. Overproduction of lactic acid (tissue hypoxia), deficient removal (hepatic failure), or both (circulatory collapse) can cause accumulation. Lactic acidosis is not uncommon in any severely ill patient suffering from cardiac decompensation, respiratory or hepatic failure, septicemia, or infarction of bowel or extremities. Lactic acidosis in patients with diabetes mellitus is uncommon but 1 In collecting samples, it is essential to rapidly chill and separate the blood in order to remove red cells, whose continued glycolysis at room temperature is a common source of error in reports of high plasma lactate. Frozen plasma remains stable for subsequent assay. occasionally occurs in metformin-treated patients (see above) and it still must be considered in the acidotic diabetic patient, especially if the individual is seriously ill. Most cases of metformin-associated lactic acidosis occur in patients in whom there were contraindications to the use of metformin, in particular kidney failure.

Clinical Findings

A. Symptoms and Signs

The main clinical feature of lactic acidosis is marked hyperventilation. When lactic acidosis is secondary to tissue hypoxia or vascular collapse, the clinical presentation is variable, being that of the prevailing catastrophic illness. However, in the idiopathic, or spontaneous, variety, the onset is rapid (usually over a few hours), blood pressure is normal, peripheral circulation is good, and there is no cyanosis.

B. Laboratory Findings

Plasma bicarbonate and blood pH are quite low, indicating the presence of severe metabolic acidosis. Ketones are usually absent from plasma and urine or at least not prominent. The first clue may be a high anion gap (serum sodium minus the sum of chloride and bicarbonate anions [in mEq/L] should be no greater than 15). A higher value indicates the existence of an abnormal compartment of anions. If this cannot be clinically explained by an excess of keto acids (diabetes),

inorganic acids (uremia), or anions from medication overdosage (salicylates, methyl alcohol, ethylene glycol), then lactic acidosis is probably the correct diagnosis. In the absence of azotemia, hyperphosphatemia may be a clue to the presence of lactic acidosis for reasons that are not clear. The diagnosis is confirmed by demonstrating, in a sample of blood that is promptly chilled and separated, a plasma lactic acid concentration of 5 mmol/L or higher (values as high as 30 mmol/L have been reported). Normal plasma values average 1 mmol/L, with a normal lactate/pyruvate ratio of 10:1. This ratio is greatly exceeded in lactic acidosis.

Treatment

Aggressive treatment of the precipitating cause of lactic acidosis is the main component of therapy, such as ensuring adequate oxygenation and vascular perfusion of tissues. Empiric antibiotic coverage for sepsis should be given after culture samples are obtained in any patient in whom the cause of the lactic acidosis is not apparent.

Alkalinization with intravenous sodium bicarbonate to keep the pH above 7.2 has been recommended by some in the emergency treatment of lactic acidosis; as much as 2000 mEq in 24 hours has been used. However, there is no evidence that the mortality rate is favorably affected byadministering bicarbonate, and its use remains controversial. Hemodialysis may be useful in cases where large sodium loads are poorly tolerated and in cases associated with metformin toxicity.

Prognosis

The mortality rate of spontaneous lactic acidosis is high. The prognosis in most cases is that of the primary disorder that produced the lactic acidosis.

Control questions

1. Etiology and features of the pathogenesis of diabetes mellitus.
2. Clinical picture of diabetes mellitus.
3. Classification of diabetes and other categories of disorders of glucose tolerance.
4. Types of diabetic coma, their symptomatology.
5. Pharmacotherapy of diabetes, taking into account the type of diabetes mellitus, complications and concomitant pathology, as well as assistance with hypoglycaemic and hyperglycemic coma.
6. To know the pharmacokinetics, pharmacodynamics, pharmacotoxicodinamics of LS, reducing the blood sugar content when:
a) insulin-dependent (Type II) diabetes mellitus:
b) insulin-dependent (type I) diabetes mellitus - (insulin preparations).
7. Pharmacological effects of insulin. Indications, principles of appointment and calculation of doses, complications of insulin therapy.
8. Prophylaxis, treatment of hypoglycemic coma.
9. Classification of diabetic com.
10. Pharmacotherapy of hyperosmolar coma.
11. Pharmacotherapy of ketoacidosis coma.

12. Pharmacotherapy of hypoglycemic coma.
13. To write in the recipes and write the testimony to the use of the following drugs: insulin preparations: short-acting - Hodomard P, actropid NN, pharmaceutical salmon H; Medium duration - Hodomard B, Protaphan NM, Pharmacoline NPH; long-acting - Ultrastard NN, MK sulinsulin ultra-long; glibenclamide, glycididone, glipizide, diabetic, metformin.

List of practical works

A. Homework.

1. To know the etiology and peculiarities of the pathogenesis of diabetes mellitus.
2. Know the basic principles of diagnosing and identifying various types of diabetes.
3. To familiarize with principles of treatment of a diabetes.
4. To be able to provide urgent help with hyper- and hypoglycemic coma.

B. Independent practical work at the lesson.

1. The cure of the thematic patient in the ward.
2. To distinguish in patients complaints signs of diabetes, determine its type.
3. With an objective and laboratory-instrumental study, specify the degree of gravity, the state of compensation.
4. Write a diagnosis (main, concomitant diseases and their complications).
5. Determine the groups of drugs necessary for the patient.
6. On the basis of theoretical data and own observations, make a choice of a sugar lowering drug for a specific patient.

Control the level of knowledge

1. Choose which of these etiological factors may cause diabetes mellitus type I and type II. Answer the tables as follows:

Etiological factors	Diabetes mellitus Type I	Diabetes mellitus Type II
1. The presence of certain antigens of the HLA system 2. Viral infections 3. Adiposity 4. Autoimmunity stroke 5. Accompanied diseases structural changes in the pancreas 6.Head 7.Resistance to overeating carbohydrates 8. High level of contrnsular		

Hormones		

Note: Make sure the correct answers are marked with a "+" sign.

2. Which of the following complaints are typical of diabetes?
Emphasize the right answers.

1.Polyphage
2.Tachycardia
3. Bradycardia
4.Exophthalm
5.Itchy skin
6.Polyartralgii
7.Decrease in body weight
8.Poliuria
9.Polidopsia
10.Furunkuloz

3. Fill in the table "Principles of pharmacotherapy for diabetic coma".

Hyperglycemic coma	**Groups of for treatment, purpose of purpose mechanism of action**	**Hypoglycemic coma**	**Groups of for treatment, purpose of purpose mechanism of action**
1. Ketoacidotic Coma		1. Hypoglycemic coma	
2. Hyperosmolar Coma			

4. Which of the following features is typical for hypoglycemic, and which - for a hyperglycemic coma? Answer the tables as follows:

Clinical signs	**Hyperglycemic coma**	**Hypoglycemic coma**
1. Musculoskeletal function, absence of tendon reflexes 2. Reliable muscles, trembling of the		

limbs, convulsions 3. Increased appetite, feeling of hunger 4. Absence of appetite, often nausea, vomiting 5. Skin moisture 6. Dry skin 7.Apple of acetone from the mouth		

Note: Make sure the correct answers are marked with a "+" sign.

5. "Main directions of pharmacotherapy of diabetes mellitus".

Pathological states	**Pharmacotherapeutic group**	**Drugs**
Diabetes mellitus Type I		
Diabetes mellitus Type II		

Solution of situational tasks

1. In a patient who is in a state of a diabetic coma, in the course of resuscitation measures, pathological brain symptoms appeared: facial expressions, sailing of one cheek, symptom of Babynsky. Reanimation was carried out in high-dose mode. Within 4 hours, blood glucose levels decreased from 28 mmol/l to 11 mmol/l.

What can be caused by the appearance of pathological symptoms in the patient in this case?

2. The patient presented a recipe for insulin. The agent dismissed the necessary drug. The patient, who was motivated by the fact that during the day he did not inject insulin and feels ill, made an injection of insulin in the pharmacy with the help of a pharmacist. After some time the patient was pale, sweaty droplets appeared on his face, he complained of a sharp headache, then he lost consciousness.

What could have been the cause of this urgent situation? What is the precautionary tactic?

Test tasks

1. What cells of the pancreas produce insulin?
1. Endothelium of the vessels and capillaries of the pancreas.
2. The cells of the outflow ducts.
3. Acinar cells of the pancreas.
4. Langerhans Island Beta Cages.
5. Alger cells of Langerhans islands.

2. How to withdraw a patient with a hypoglycemic coma?
1. Conduct an intravenous 40% solution of glucose 40-80 ml
2. Inject insulin 20-80 Units intramuscularly or intravenously.
3. Inject isotonic solution of calcium chloride.
4. Inject prednisone 40 ml intramuscularly
5. Enter intravenous carboxylase 50-100 ml.

3. To the type II diabetes mellitus, the following are included, except:
1. Obesity.
2. Heredity is burdened.
3. Violation of immunity.
4. Chronic hepatitis.
5. Chronic pancreatitis.

4. The following drugs can cause hyperglycemia and provoke diabetes mellitus, except:
1. Glucocorticoids.
2. Oral contraceptives.
3. Enzyme preparations
4. Diuretics.
5. Thyroid hormones.

5. Name the main diagnostic criterion for diabetes:
1. Glucosuria.
2. Hyperglycemia.
3. Tachycardia.
4. Hypercholesterolemia.
5. Exophthalmos.

6. What is the mechanism of hypoglycemic insulin action?
1. Promotes penetration of glucose into cells, its utilization.
2. Strengthens anaerobic glycolysis
3. Prevents absorption of glucose in the small intestine.
4. Reduces glykoneogenesis.
5. Strengthens the isolation of endogenous insulin cells of the pancreas.

7. Anti-diabetic preparations of sulfanilicure derivatives include:
1. Sulphalen.
2. Glibenclamide.
3. Metformin.
4. Buformin.
5. Mercazolyl.

8. To note the antidiabetic preparation, the mechanism of hypoglycemic action which is associated with stimulation of beta-cells of the pancreas:
1. Chlorpropamide.
2. Metformin.
3. Buformin.
4. Suspension of zinc insulin.
5. Lithoronin.

9. Indications for treatment with biguanids are:
1. Renal insufficiency.
2. Hepatic insufficiency.
3. Insulin-dependent diabetes mellitus.
4. Insulin-dependent diabetes mellitus.
5. Ketoacidosis.

Indications for the administration of insulin are as follows:
1. Pregnancy in patients with diabetes mellitus.
2. Ketoacidosis.
3. Operative intervention in patients with diabetes mellitus.
4. Insulin-dependent diabetes mellitus.
5. Infectious diseases.

11. Which of the following causes leads to the development of a gipoglycemic coma?
1. Insufficient energy value of the daily ration.
2. The use of large doses of diuretics.
3. Dehydration due to diarrhea.
4. Administration of an insufficient dose of insulin or a sudden termination of its administration.
5. Administration of an overdose of insulin.

12. Hypoglycemia in combination with oral hypoglycemic agents may cause:
1. Penicillin.
2. Captopril.
3. Sulfanilamides antibacterial.
4. Nifedipine.
5. Alopurinol.

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TOPIC 18. Basic principles of pharmacotherapy for infectious diseases. Complications of antimicrobial therapy, their prophylaxis and treatment.

Actuality of topic. The formation of ideas about infectious diseases is in the distant past, but scientifically substantiated facts that allow formulating scientific discipline were obtained only at the turn of the XIX-XX centuries. This time is often called the "golden age of bacteriology", since in the very short historical period (just a few decades) discoveries have been made that formed the theoretical basis for all further research until the middle of the 20th century.

Despite the advances in clinical medicine, the problem of infectious diseases continues to be quite complicated in all countries of the world without exception. Almost throughout the 20th century, clinical medicine was mainly engaged in the study of infectious diseases, which occur in typical, clinically manifested forms. At the present stage, new aspects of problems have been identified, one of which is the establishment of the role of infectious agents in the development of chronic inflammatory diseases in humans, which means that the proportion of infectious diseases in the overall structure of human pathology can reach 60-70%.

Purpose of the lesson: The student should know the general principles of antimicrobial therapy; an algorithm for selecting a specific patient for an antibacterial drug. Have a concept about etiology and pathogenesis of infectious diseases, general complications of antimicrobial therapy, methods of detection, prevention and treatment.

Etiology and pathogenesis of infectious diseases

Bacteria are a common cause of disease, but have beneficial as well as harmful effects. For example, the gastrointestinal bacterial flora of the healthy human assists in preventing colonization by pathogens.

Both systemic and localized infections can cause fever. Tuberculosis and endocarditis are the most common systemic infections, but mycoses, viral diseases (particularly infection with Epstein-Barr virus and CMV), toxoplasmosis, brucellosis, Q fever, cat-scratch disease, salmonellosis, malaria, and many other less common infections have been implicated. Primary infection with HIV or opportunistic infections associated with AIDS— particularly mycobacterial infections—can also present as fever. The most common form of localized infection causing fever is an occult abscess. Liver, spleen, kidney, brain, and bone abscesses may be difficult to detect. A collection of pus may form in the peritoneal cavity or in the subdiaphragmatic, subhepatic, paracolic, or other areas. Cholangitis, osteomyelitis, urinary tract infection, dental abscess, or paranasal sinusitis may cause prolonged fever.

Immunocompromised patients have defects in their natural defense mechanisms resulting in an increased risk for infection. In addition, infection is often severe, rapidly progressive, and life threatening. Organisms that are not usually problematic in the immunocompetent person may be important pathogens in the compromised patient (eg, Staphylococcus epidermidis, Corynebacterium jeikeium, Propionibacterium acnes, Bacillus species). Therefore, culture results must be interpreted with caution, and isolates should not be disregarded as merely contaminants. Although the type of immunodeficiency is associated with specific infectious disease syndromes, any pathogen can cause infection in any immunosuppressed patient at any time. Thus, a systematic evaluation is required to identify a specific organism.

Defects in humoral immunity are often congenital, although hypogammaglobulinemia can occur in multiple myeloma, chronic lymphocytic leukemia, and in patients who have undergone splenectomy. Patients with ineffective humoral immunity lack opsonizing antibodies and are at particular risk for infection with encapsulated organisms, such as Haemophilus influenzae, Neisseria meningitides, and Streptococcus pneumoniae. Although rituximab is normally thought of as being linked to impaired cellular immunity, it has been associated with the development of Pneumocystis jirovecii infection as well as with hepatitis B reactivation.

A large group of patients who are not specifically immunodeficient are at increased risk for infection due to debilitating injury (eg, burns or severe trauma), invasive procedures (eg, chronic central intravenous catheters, Foley catheters, dialysis catheters), central nervous system dysfunction (which predisposes patients to aspiration pneumonia and decubitus ulcers), obstructing lesions (eg, pneumonia due to an obstructed bronchus, pyelonephritis due to nephrolithiasis, cholangitis secondary to cholelithiasis), and use of broad-spectrum antibiotics. Patients with diabetes mellitus have alterations in cellular immunity, resulting in mucormycosis, emphysematous pyelonephritis, and foot infections.

There is great interest in preventing infection with prophylactic antimicrobial regimens but no uniformity of opinion about optimal drugs or dosage regimens. Hand washing is the simplest and most effective means of decreasing hospital-associated infections, especially in the compromised patient. Invasive devices such as central and peripheral lines and Foley catheters are potential sources of infection. Some centers use laminar airflow isolation or high-efficiency particulate air (HEPA) filtering in hematopoietic cell transplant patients. Rates of infection and episodes of febrile neutropenia, but not mortality, are decreased if colony-stimulating factors are used during chemotherapy or during stem-cell transplantation.

Health care–associated infections are acquired during the course of receiving health care treatment for other conditions. Hospital-associated infections are a subset of health care–associated infections defined as those not present or incubating at the time of hospital admission and developing 48 hours or more after admission. Most health care–associated infections are preventable. Hand washing is

the most effective means of preventing health care–associated infections and should be done routinely even when gloves are worn.

In the United States, approximately 5% of patients acquire a health care–associated infection, resulting in prolongation of the hospital stay, increase in cost of care, significant morbidity, and a 5% mortality rate. The most common infections are urinary tract infections, usually associated with Foley catheters or urologic procedures; bloodstream infections, most commonly from indwelling catheters but also from secondary sites, such as surgical wounds, abscesses, pneumonia, the genitourinary tract, and the gastrointestinal tract; pneumonia in intubated patients or those with altered levels of consciousness; surgical wound infections; MRSA infections; and Clostridium difficile colitis. Some general principles are helpful in preventing, diagnosing, and treating health care–associated infections:

1. Many infections are a direct result of the use of invasive devices for monitoring or therapy, such as intravenous catheters, Foley catheters, shunts, surgical drains, catheters placed by interventional radiology for drainage, nasogastric tubes, and orotracheal or nasotracheal tubes for ventilatory support. Early removal of such devices reduces the possibility of infection.

2. Patients in whom health care–associated infections develop are often critically ill, have been hospitalized for extended periods, and have received several courses of broad-spectrum antibiotic therapy. As a result, health care–associated infections are often due to multidrug resistant pathogens and are different from those encountered in community-acquired infections. For example, S aureus and S epidermidis (a frequent cause of prosthetic device infection) are often resistant to nafcillin and cephalosporins and require vancomycin for therapy; Enterococcus faecium resistant to ampicillin and vancomycin; gram-negative infections caused by Pseudomonas, Citrobacter, Enterobacter, Acinetobacter, and Stenotrophomonas may be resistant to most antibacterials. When choosing antibiotics to treat the seriously ill patient with a health care–associated infection, antimicrobial history and the “local ecology” must be considered. In the most seriously ill patients, broadspectrum coverage with vancomycin and a carbapenem with or without an aminoglycoside is recommended. Once a pathogen is isolated and susceptibilities are known, the most narrow spectrum, least toxic, most cost-effective drug should be used.

Cat and human bites have higher rates of infection than dog bites. Hand bites are particularly concerning for the possibility of closed-space infection. Antibiotic prophylaxis indicated for noninfected bites of the hand and hospitalization required for infected hand bites. All infected wounds need to be cultured to direct therapy.

About 1000 dog bite injuries require emergency department attention each day in the United States, most often in urban areas. Dog bites occur most commonly in the summer months. Biting animals are usually known by their victims, and most biting incidents are provoked (ie, bites occur while playing with the animal or after surprising the animal while eating or waking it abruptly from sleep). Failure to elicit a history of provocation is important, because an unprovoked attack raises the possibility of rabies. Human bites are usually inflicted

by children while playing or fighting; in adults, bites are associated with alcohol use and closed-fist injuries that occur during fights. The animal inflicting the bite, the location of the bite, and the type of injury inflicted are all important determinants of whether they become infected. Cat bites are more likely to become infected than human bites—between 30% and 50% of all cat bites become infected. Infections following human bites are variable. Bites inflicted by children rarely become infected because they are superficial, and bites by adults become infected in 15–30% of cases, with a particularly high rate of infection in closed-fist injuries. Dog bites, for unclear reasons, become infected only 5% of the time. Bites of the head, face, and neck are less likely to become infected than bites on the extremities. "Through and through" bites (eg, involving the mucosa and the skin) have an infection rate similar to closed-fist injuries. Puncture wounds become infected more frequently than lacerations, probably because the latter are easier to irrigate and debride.

The bacteriology of bite infections is polymicrobial. Following dog and cat bites, over 50% of infections are caused by aerobes and anaerobes and 36% are due to aerobes alone. Pure anaerobic infections are rare. Pasteurella species are the single most common isolate (75% of infections caused by cat bites and 50% of infections caused by dog bites). Other common aerobic isolates include streptococci, staphylococci, Moraxella, and Neisseria; the most common anaerobes are Fusobacterium, Bacteroides, Porphyromonas, and Prevotella. The median number of isolates following human bites is four (three aerobes and one anaerobe). Like dog and cat bites, infections caused by most human bites are a mixture of aerobes and anaerobes (54%) or are due to aerobes alone (44%). Streptococci and S aureus are the most common aerobes. Eikenella corrodens (found in up to 30% of patients), Prevotella, and Fusobacterium are the most common anaerobes. Although the organisms noted are the most common, innumerable others have been isolated—including Capnocytophaga (dog and cat), Pseudomonas, and Haemophilus—emphasizing the point that all infected bites should be cultured to define the microbiology. HIV can be transmitted from bites (either from biting or receiving a bite from an HIV-infected patient) but has rarely been reported.

Vigorous cleansing and irrigation of the wound as well as debridement of necrotic material are the most important factors in decreasing the incidence of infections. Radiographs should be obtained to look for fractures and the presence of foreign bodies. Careful examination to assess the extent of the injury (tendon laceration, joint space penetration) is critical to appropriate care. If wounds require closure for cosmetic or mechanical reasons, suturing can be done. However, one should never suture an infected wound, and wounds of the hand should generally not be sutured since a closed-space infection of the hand can result in loss of function.

Prophylaxis is indicated in high-risk bites and in high-risk patients. Cat bites in any location and hand bites by any animal, including humans, should receive prophylaxis. Individuals with certain comorbidities (diabetes, liver disease) are at increased risk for severe complications and should receive prophylaxis even for low-risk bites, as should patients without functional spleens who are at increased

risk for overwhelming sepsis (primarily with Capnocytophaga species). Amoxicillin-clavulanate (Augmentin) 500 mg orally three times daily for 5–7 days is the regimen of choice. For patients with serious allergy to penicillin, a combination of clindamycin 300 mg orally three times daily together with one of the following is recommended for 5–7 days: doxycycline 100 mg orally twice daily, or double-strength TMP-SMZ orally twice daily, or a fluoroquinolone (ciprofloxacin 500 mg orally twice daily or levofloxacin 500–750 mg orally once daily). Moxifloxacin, a fluoroquinolone with good aerobic and anaerobic activity, may be suitable as monotherapy at 400 mg orally once daily for 5–7 days. Agents such as dicloxacillin, cephalexin, erythromycin, and clindamycin should not be used alone because they lack activity against Pasteurella species. Doxycycline and TMP-SMZ have poor activity against anaerobes and should only be used in combination with clindamycin. Because the risk of HIV transmission is so low following a bite, routine postexposure prophylaxis is not recommended. Each case should be evaluated individually and consideration for prophylaxis should be given to those who present within 72 hours of the incident, the source is known to be HIV infected, and the exposure is high risk.

All sexually transmitted diseases (STDs) have subclinical or latent periods, and patients may be asymptomatic. Simultaneous infection with several organisms is common. All patients who seek STD testing should be screened for syphilis and HIV. Partner notification and treatment are important to prevent further transmission and reinfection in the index case.

The most common STDs are gonorrhea, syphilis, human papillomavirus (HPV)–associated condyloma acuminatum, chlamydial genital infections, herpesvirus genital infections, trichomonas vaginitis, chancroid, granuloma inguinale, scabies, louse infestation, and bacterial vaginosis (among women who have sex with women). However, shigellosis; hepatitis A, B, and C; amebiasis; giardiasis; cryptosporidiosis; salmonellosis; and campylobacteriosis may also be transmitted by sexual (oral-anal) contact, especially in men who have sex with men. Both homosexual and heterosexual contact are risk factors for the transmission of HIV. All STDs have subclinical or latent phases that play an important role in long-term persistence of the infection or in its transmission from infected (but largely asymptomatic) persons to other contacts. Simultaneous infection by several different agents is common. Infections typically present in one of several ways, each of which has a defined differential diagnosis, which should prompt appropriate diagnostic tests.

All persons who seek STD testing should undergo routine screening for HIV infection, using rapid HIV-testing (if patients may not follow up for results obtained by standard methods) or nucleic acid amplification followed by confirmatory serology (if primary HIV infection may be a possibility) as indicated. Patients in whom STDs have been diagnosed and treated (in particular, chlamydia or gonorrhea) are at a high risk for reinfection and should be encouraged to be rescreened for STDs at 3 months following the initial STD diagnosis. Asymptomatic patients often request STD screening at the time of initiating a new sexual relationship. Routine HIV testing and hepatitis B serology testing should be

offered to all such patients. In sexually active women who have not been recently screened, cervical Papanicolaou testing and nucleic acid amplification testing of a urine specimen for gonorrhea and chlamydia are recommended. Among men who have sex with men, additional screening is recommended for syphilis; hepatitis A; urethral, pharyngeal, and rectal gonorrhea; as well as urethral and rectal chlamydia. Nucleic acid amplification testing is FDA-approved for testing urine for gonorrhea or chlamydia. However, the use of nucleic acid amplification testing of secretions in the rectum and pharynx has not been validated in many laboratories. There are no recommendations to screen heterosexual men for urethral chlamydia but this could be considered in STD clinics, adolescent clinics, or correctional facilities. The periodicity of screening thereafter depends on sexual risk, but most screening should be offered at least annually to sexually active adults (particularly to those 25-years-old and under). If not immune, hepatitis B vaccination is recommended for all sexually active adults, and hepatitis A vaccination in men who have sex with men. Persons between the ages of 9 and 26 may be offered vaccination against HPV. The risk of developing an STD following a sexual assault is difficult to accurately ascertain given high rates of baseline infections and poor follow-up. Victims of assault have a high baseline rate of infection (N gonorrhoeae, 6%; C trachomatis, 10%; T vaginalis, 15%; and bacterial vaginosis, 34%), and the risk of acquiring infection as a result of the assault is significant but is often lower than the preexisting rate (N gonorrhoeae, 6–12%; C trachomatis, 4–17%; T vaginalis, 12%; syphilis, 0.5–3%; and bacterial vaginosis, 19%). Victims should be evaluated within 24 hours after the assault, and nucleic acid amplification tests for N gonorrhoeae and C trachomatis should be performed. Vaginal secretions are obtained for Trichomonas wet mount and culture, or point-of-care testing. If a discharge is present, if there is itching, or if secretions are malodorous, a wet mount should be examined for Candida and bacterial vaginosis. In addition, a blood sample should be obtained for immediate serologic testing for syphilis, hepatitis B, and HIV. Follow-up examination for STDs should be repeated within 1–2 weeks, since concentrations of infecting organisms may not have been sufficient to produce a positive test at the time of initial examination. If prophylactic treatment was given (may include postexposure hepatitis B vaccination without hepatitis B immune globulin; treatment for chlamydial, gonorrheal, or trichomonal infection; and emergency contraception), tests should be repeated only if the victim has symptoms. If prophylaxis was not administered, the individual should be seen in 1 week so that any positive tests can be treated. Follow-up serologic testing for syphilis and HIV infection should be performed in 6, 12, and 24 weeks if the initial tests are negative. The usefulness of presumptive therapy is controversial, some feeling that all patients should receive it and others that it should be limited to those in whom follow-up cannot be ensured or to patients who request it.

Although seroconversion to HIV has been reported following sexual assault when this was the only known risk, this risk is believed to be low. The likelihood of HIV transmission from vaginal or anal receptive intercourse when the source is known to be HIV positive is 1 per 1000 and 5 per 1000, respectively. Although prophylactic antiretroviral therapy has not been studied in this setting, the

Department of Health and Human Services recommends the prompt institution of postexposure prophylaxis with highly active antiretroviral therapy if the person seeks care within 72 hours of the assault, the source is known to be HIV positive, and the exposure presents a substantial risk of transmission. In addition to screening asymptomatic patients with STDs, other strategies for preventing further transmission include evaluating sex partners and administering preexposure vaccination of preventable STDs to individuals at risk; other strategies include the consistent use of male and female condoms and male circumcision. Adult male circumcision has been shown to decrease the transmission of HIV by 50%, and of herpes simplex virus and HPV by 30% in heterosexual couples in sub-Saharan Africa. For each patient, there are one or more sexual contacts who require diagnosis and treatment. Prompt treatment of contacts by giving antibiotics to the index case to distribute to all sexual contacts (patient-delivered therapy) is an important strategy for preventing further transmission and to prevent reinfection in the index case. Note that vaginal spermicides and condoms containing nonoxynol-9 provide no additional protection against STDs. Early initiation of antiretroviral therapy in HIVinfected individuals can prevent HIV acquisition in an uninfected sex partner. Also, preexposure prophylaxis with a once-daily pill containing tenofovir plus emtricitabine has been shown to be effective in preventing HIV infection among high-risk men who have sex with men.

The widespread use of antibacterial drugs has led to the appearance of multiresistant bacteria which are now a significant cause of morbidity and mortality in the UK. Consequently, antibacterial therapy should not be used indiscriminately.

A distinction is conventionally drawn between bactericidal drugs that kill bacteria and bacteriostatic drugs that prevent their reproduction, elimination depending on host defence.

Classification of antibacterial agents into bactericidal and bacteriostatic

Bactericidal:

- Penicillins
- Cephalosporins
- Aminoglycosides
- Co-trimoxazole
-

Bacteriostatic:

- Erythromycin
- Tetracyclines
- Chloramphenicol
- Sulphonamides
- Trimethoprim

This difference is relative, as bacteriostatic drugs are often bactericidal at high concentrations and in the presence of host defence mechanisms. In clinical

practice, the distinction is seldom important unless the body's defence mechanisms are depressed. Antibacterial drugs can be further classified into five main groups according to their mechanism of action.

Inhibition of cell wall synthesis:

- Penicillins
- Cephalosporins
- Monobactams
- Vancomycin

Inhibition of DNA gyrase: Quinolones

Inhibition of RNA polymerase: Rifampicin

Inhibition of protein synthesis:

- Aminoglycosides
- Tetracyclines
- Erythromycin
- Chloramphenicol

Inhibition of folic acid metabolism:

- Trimethoprim
- Sulphonamides

The choice of antibacterial drug, together with its dose and route of administration, depend on the infection (in particular the responsible pathogen(s), but also anatomical site and severity), absorption characteristics of the drug, and patient factors (in particular age, weight, renal function). In addition, the dose may be guided by plasma concentration measurements of drugs with a narrow therapeutic index (e.g. aminoglycosides). The duration of therapy depends on the nature of the infection and response to treatment.

The *British National Formulary* provides a good guide to initial treatments for common bacterial infections. In view of regional variations in patterns of bacterial resistance, these may be modified according to local guidelines.

Close liaison with the local microbiology laboratory provides information on local prevalence of organisms and sensitivities.

The minimum inhibitory concentration (MIC) is often quoted by laboratories and in promotional literature. It is the minimal concentration of a particular agent below which bacterial growth is not prevented. Although the MIC provides useful information for comparing the susceptibility of organisms to antibacterial drugs, it is an in vitro test in a homogenous culture system, whilst in vivo the concentration at the site of infection may be considerably lower than the plasma concentration which one might predict to be bactericidal (e.g. drug penetration and concentration in an abscess cavity are very low).

General algorithm for the treatment of bacterial infections

1). Diagnosis of bacterial infection confirmed

– clinical symptoms/signs plus

– positive microbiology

Yes

Is bacterial sensitivity profile available?

Yes

Treat with appropriate antibiotic

Consider other measures (e.g. drainage of abscess) Consider length of antibiotic treatment according to appropriate guidelines

Are signs, symptoms and markers of infection (e.g. CRP, ESR, temperature, white cell count) improving?

Yes

Complete course of treatment.

2). Diagnosis of bacterial infection confirmed

– clinical symptoms/signs plus
– positive microbiology

Yes

Is bacterial sensitivity profile available?

No

Treat with most appropriate antibiotic according to predominant causative organism(s) and sensitivities (including local sensitivity patterns)

Consider other measures (e.g. drainage of abscess) Consider length of antibiotic treatment according to appropriate guidelines

Are signs, symptoms and markers of infection (e.g. CRP, ESR, temperature, white cell count) improving?

No

Consider – alternative (or additional) diagnosis – poor penetrance of antibiotic to site of infection – possible change in antibiotic therapy.

3). Diagnosis of bacterial infection confirmed

– clinical symptoms/signs plus
– positive microbiology

No

Is bacterial infection likely?

No - No antibiotic treatment

If Yes - Treat with most appropriate antibiotic according to predominant causative organism(s) and sensitivities (including local sensitivity patterns)

further as in 1) and 2).

Laboratory Tests

In addition to routine laboratory studies, blood cultures should always be obtained, preferably when the patient has not taken antibiotics for several days, and should be held by the laboratory for 2 weeks to detect slow-growing organisms. Cultures on special media are requested if Legionella, Bartonella, or nutritionally deficient streptococci are possible pathogens. “Screening tests” with immunologic

or microbiologic serologies (“febrile agglutinins”) are of low yield and should not be done. If the history or physical examination suggests a specific diagnosis, specific serologic tests with an associated fourfold rise or fall in titer may be useful. Because infection is the most common cause of fever, other body fluids are usually cultured, ie, urine, sputum, stool, cerebrospinal fluid, and morning gastric aspirates (if one suspects tuberculosis). Direct examination of blood smears may establish a diagnosis of malaria or relapsing fever (Borrelia).

Biopsy

Invasive procedures are often required for diagnosis. Any abnormal finding should be aggressively evaluated: Headache calls for lumbar puncture to rule out meningitis; skin rash should be biopsied for cutaneous manifestations of collagen vascular disease or infection; and enlarged lymph nodes should be aspirated or biopsied for neoplasm and sent for culture. Bone marrow aspiration with biopsy is a relatively low-yield procedure (15–25%; except in HIV-positive patients, in whom mycobacterial infection is a common cause of fever), but the risk is low and the procedure should be done if other less invasive tests have not yielded a diagnosis, particularly in persons with hematologic abnormalities. Liver biopsy will yield a specific diagnosis in 10–15% of patients with fever and should be considered in any patient with abnormal liver function tests even if the liver is normal in size. CT scanning and MRI have decreased the need for exploratory laparotomy; however, surgical visualization and biopsies should be considered when there is continued deterioration or lack of diagnosis.

Special diagnostic procedures should also be considered. The cause of pulmonary infiltrates can be easily determined with simple techniques in some situations—eg, induced sputum yields a diagnosis of Pneumocystis pneumonia in 50–80% of AIDS patients with this infection. In other situations, more invasive procedures may be required (bronchoalveolar lavage, transbronchial biopsy, open lung biopsy). Next generation DNA-sequencing analysis is being evaluated as an option for diagnosis of infectious diseases in immunocompromised persons.

BACTERIAL RESISTANCE

The resistance of bacterial populations to antimicrobial agents is constantly changing and can become a serious clinical problem, rendering previously useful drugs inactive. Overuse of antibiotics will lead to a future where infectious disease has the same impact as in in the pre-antibiotic era. The dates on tombstones in Victorian cemeteries should be required reading for over-enthusiastic prescribers and medical students! (Whole families of infants died in infancy, followed by their mother from puerperal sepsis.) Although most multiresistant bacteria have developed in hospitalized patients, the majority of antimicrobial prescribing in the UK takes place in primary care. Current guidelines therefore emphasize the following points:

1. no prescribing of antibiotics for coughs and colds or viral sore throats;

2. limit prescribing for uncomplicated cystitis to three days for otherwise fit women; and

3. limit prescribing of antibiotics over the telephone to exceptional cases.

Antimicrobial resistance is particularly common in intensive care units and transplant units, where the use of antimicrobial agents is frequent and the patients may be immunocompromised. The evolution of drug resistance involves:

1. selection of naturally resistant strains (which have arisen by spontaneous mutation) that exist within the bacterial population by elimination of the sensitive strain by therapy. Thus the incidence of drug resistance is related to the prescription of that drug. The hospital environment with intensive and widespread use of broad-spectrum antibacterials is particularly likely to promote the selection of resistant organisms;

2. transfer of resistance between organisms can occur by transfer of naked DNA (transformation), by conjugation with direct cell-to-cell transfer of extrachromosomal DNA (plasmids), or by passage of the information by bacteriophage (transduction). In this way, transfer of genetic information concerning drug resistance (frequently to a group of several antibiotics simultaneously) may occur between species.

Mechanisms of drug resistance can be broadly divided into three groups:

1. inactivation of the antimicrobial agent either by disruption of its chemical structure (e.g. penicillinase) or by addition of a modifying group that inactivates the drug (e.g. chloramphenicol, inactivated by acetylation);

2. restriction of entry of the drug into the bacterium by altered permeability or efflux pump (e.g. sulphonamides, tetracycline);

3. modification of the bacterial target – this may take the form of an enzyme with reduced affinity for an inhibitor, or an altered organelle with reduced drug-binding properties (e.g. erythromycin and bacterial ribosomes).

DRUG COMBINATIONS

Most infections can be treated with a single agent. However, there are situations in which more than one antibacterial drug is prescribed concurrently:

• to achieve broad antimicrobial activity in critically ill patients with an undefined infection (e.g. aminoglycoside plus a penicillin to treat septicaemia);

• to treat mixed bacterial infections (e.g. following perforation of the bowel) in cases where no single agent would affect all of the bacteria present;

• to prevent the emergence of resistance (e.g. in treating tuberculosis);

• to achieve an additive or synergistic effect (e.g. use of co-trimoxazole in the treatment of Pneumocystis carinii pneumonia).

PROPHYLACTIC USE OF ANTIBACTERIAL DRUGS

On a few occasions it is appropriate to use antibacterial drugs prophylactically. Wherever possible a suitably specific narrowspectrum drug should be used.

ANTIBIOTIC PROPHYLAXIS OF INFECTIVE ENDOCARDITIS

An important recent change is that fewer patients are deemed to require antibiotic prophylaxis against infective endocarditis; it should be restricted to patients who have previously had endocarditis, cardiac valve replacement surgery (mechanical or biological prosthetic valves), or surgically constructed systemic or pulmonary shunts or conduits. In such patients, all dental procedures involving dento-gingival manipulation will require antibiotic prophylaxis, as will certain genito-urinary, gastrointestinal, respiratory or obstetric/gynaecological procedures. Intravenous antibiotics are no longer recommended unless the patient cannot take oral antibiotics. For dental procedures, in addition to prophylactic antibiotics, the use of chlorhexidine 0.2% mouthwash five minutes before the procedure may be a useful supplementary measure.

PROPHYLACTIC PREOPERATIVE ANTIBIOTICS GENERAL PRINCIPLES

1. Prophylaxis should be restricted to cases where the procedure commonly leads to infection, or where infection, although rare, would have devastating results.

2. The antimicrobial agent should preferably be bactericidal and directed against the likely pathogen.

3. The aim is to provide high plasma and tissue concentrations of an appropriate drug at the time of bacterial contamination. Intramuscular injections can usually be given with the premedication or intravenous injections at the time of induction. Drug administration should seldom exceed 48 hours. Many problems in this area arise because of failure to discontinue ‘prophylactic’ antibiotics, a mistake that is easily made by a busy junior house-surgeon who does not want to take responsibility for changing a prescription for a patient who is apparently doing well post-operatively. Local hospital drug and therapeutics committees can help considerably by instituting sensible guidelines on the duration of prophylactic antibiotics.

4. If continued administration is necessary, change to oral therapy post-operatively wherever possible. The British National Formulary provides a good summary of the use of antibacterial drugs preoperatively, which may be varied according to local guidelines based on regional patterns of bacterial susceptibility/resistance.

RECENTLY INTRODUCED ANTIBACTERIAL AGENTS

Increasing antibiotic resistance (especially meticillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci) is a matter of deep concern. Although the spread of multi-resistant organisms can be minimized by judicious use of antibiotics and the instigation of tight infection-

control measures, there is a continuing need for the development of well-tolerated, easily administered, broad-spectrum antibiotics. Lists some recently introduced antibiotics which fulfil these criteria, together with their main features. At present, their use is restricted and should be administered under close microbiological supervision.

New antibacterial agents

Linezolid

Antibiotic class - ***Oxazolidinone***

Mechanism of action - inhibits formation of the 70S ribosomal initiation complex, preventing bacterial protein synthesis; primarily bacteriostatic action.

Spectrum of activity: Gram-positive bacteria and a few Gram-negative anaerobic bacteria; active against staphylococci, pneumococococci and enterococci, including those resistant to penicillin and vancomycin.

Moxifloxacin

Antibiotic class - ***Fluoroquinolone with an 8-methoxyquinolone structure***

Mechanism of action - inhibits topoisomerase II and IV with bactericidal activity.

Spectrum of activity: Gram-positives, including staphylococci, enterococci, Streptococcus pneumoniae including penicillin-resistant strains; atypicals, including Legionella and Mycoplasma pneumoniae; Gram-negatives, including Haemophilus influenzae, Moraxella catarrhalis, coliforms, Neisseria gonorrhoeae; low activity against Pseudomonas and some enterobacteriaceae; active against Mycobacterium tuberculosis, including multiresistant strains; inhibits 90 % of anaerobic bacteria including clostridia, Bacteroides, Fusobacterium, Porphyromonas.

Telithromycin

Antibiotic class - ***Ketolide; a semisynthetic member of the macrolide-lincosamide streptogramin B family of antibiotics***

Mechanism of action - inhibits bacterial protein synthesis by direct binding to the 50S subunit of bacterial ribosomes, preventing translation and ribosome assembly.

Spectrum of activity: Gram-positives, including Streptococcus pneumoniae (including erythromycin resistant strains), Streptococcus pyogenes MRSA; some Gram-negative bacteria, including Haemophilus influenzae, Moraxella catarrhalis; atypicals, including Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella; not active against erythromycin resistant strains of MRSA.

Ertapenem

Antibiotic class - ***Carbapenem***

Mechanism of action - attaches to penicillin-binding proteins, inhibiting bacterial cell wall synthesis; bactericidal activity.

Spectrum of activity: Most enteric bacteria, including those producing beta-lactamase; Gram-negative respiratory pathogens, including Moraxella catarrhalis and Haemophilus influenzae; Gram-positive bacteria, including Streptococcus pneumoniae (including those resistant to penicillin) and MRSA; also effective against many anaerobes, including Bacteroides Prevotella and Porphyromonas; limited activity against Pseudomonas aeruginosa Acinetobacter; Enterococcus, Lactobacillus, MRSA.

Key points

• If practicable, take specimens for microbiological analyses before starting antibacterial therapy.
• Consider the severity of the illness.
• Consider the likely pathogen(s).
• Consider patient factors, particularly allergies and potential drug interactions.
• Select the most appropriate route of administration.
• Monitor the response and alter the therapy and route of administration as appropriate.
• Some drugs require routine plasma concentration monitoring (e.g. aminoglycosides, vancomycin).
• For most bacterial infections other than those involving bone, joint or heart valve tissue, five to seven days of treatment are sufficient.

Beta-Lactams

Amoxicillin

Adverse Reactions. Adverse effects are similar to those of ampicillin, although diarrhea and rashes are much less frequent with amoxicillin.

Amoxicillin + **potassium clavulanate** (**Augmentin**)

Adverse Reactions. Adverse effects of this preparation include those of amoxicillin; however, diarrhea is more frequent with the combination and depends on the dosage of clavulanate. The 12-hr formulations reduce the frequency of diarrhea. Nausea and diarrhea is less frequent when this preparation is administered with food.

Ampicillin

Adverse Reactions. Nausea and diarrhea occur frequently with oral therapy. Other reactions include frequent skin rash (more frequent in patients receiving allopurinol and very frequent in patients with Epstein-Barr virus infection [mononucleosis]). Most of these eruptions probably are not hypersensitivity reactions but immunologically mediated. They are generally dose related (higher frequency at higher dosages), are macular rather than urticarial, and disappear with continued administration of the drug.

Antistaphylococcal penicillin (methicillin, nafcillin, oxacillin, cloxacillin, and dicloxacillin)

Adverse Reactions. Interstitial nephritis is frequent with methicillin but occurs only rarely with the other drugs. Hepatic damage occurs rarely with oxacillin. Nafcillin has a propensity for local irritation at the IV infusion site and causes neutropenia more frequently than other antistaphylococcal penicillins.

Monobactams

Aztreonam

Adverse Reactions. Adverse effects of aztreonam are minimal. Crossallergenicity between aztreonam and other beta-lactams is low, and aztreonam has been used safely in penicillin- or cephalosporin-allergic patients.

Cephalosporins

Adverse Reactions. Most cephalosporins are generally well tolerated, although a few agents have unique adverse reactions. Hypersensitivity reactions can occur in approximately 10% of patients known to be allergic to penicillin; do not administer these agents to patients with histories of an immediate reaction to penicillin. Nausea and diarrhea occur with all agents; however, diarrhea is more common with ceftriaxone and cefoperazone because of high biliary excretion. Colitis caused by Clostridium difficile has been reported with all the cephalosporins but might be more common with ceftriaxone and cefoperazone. Nephrotoxicity is rare, particularly when used without other nephrotoxic agents. All agents with an N-methylthiotetrazole (NMTT) moiety in the 3 positions of the cephem nucleus (cefoperazone, cefamandole, cefotetan, and cefmetazole) can produce a disulfiram-like reaction in some patients with ingestion of alcohol-containing beverages. In addition, these agents might be associated to varying degrees with bleeding secondary to hypoprothrombinemia, which is corrected or prevented by vitamin K administration. Although controversial, the mechanism of this reaction appears to involve inhibition of enzymatic reactions requiring vitamin K in the activation of prothrombin precursors by NMTT. However, other factors (eg, malnutrition, liver disease) might be more important risk factors for bleeding than the NMTT-containing cephalosporins. Thus, cautious use (and perhaps even avoidance) of agents with the NMTT side chain is recommended in patients with poor oral intake and critical illness. Administration of vitamin K and monitoring of the prothrombin time are indicated with these agents, particularly when therapy is prolonged. Positive direct Coombs' tests occur frequently but hemolysis is rare. Ceftriaxone has been associated with biliary pseudolithiasis (sludging), which can be asymptomatic or resemble acute cholecystitis. This adverse effect occurs most often with dosages of ≥2 g/day, especially in patients receiving prolonged therapy or those with impaired gallbladder emptying. The mechanism is ceftriaxone-calcium complex formation, and it is usually reversible with drug discontinuation. Neonates given ceftriaxone can develop kernicterus caused by displacement of bilirubin from

plasma protein binding sites; its use in this population is best avoided. Development of resistance during treatment of infections caused by Enterobacter sp., Serratia spp., and P. aeruginosa has occurred with all these agents.

Precautions. Penicillin allergy. Use agents with NMTT side chain with caution in patients with underlying bleeding diathesis, poor oral intake, or critical illness. Use with caution in renal impairment and in those on oral anticoagulants (especially NMTT-containing drugs). Avoid use of ceftriaxone in neonates, particularly premature infants.

Drug Interactions. Avoid concomitant ingestion of alcohol or alcohol-containing products with agents containing the NMTT side chain. Probenecid reduces renal clearance and increases serum levels of most agents, except.

Parameters to Monitor. Monitor prothrombin time 2–3 times/week with agents having an NMTT side chain, particularly when using large dosages; monitor bleeding time with high dosages of agents having an NMTT side chain. Obtain antimicrobial susceptibility tests for development of resistance in patients relapsing during therapy. Monitor renal function tests initially and periodically during highdose regimens or when the drug is used concurrently with nephrotoxic agents. Monitor for diarrhea, particularly with ceftriaxone and cefoperazone; test stool specimen for C. difficile toxin if diarrhea persists or is associated with fever or abdominal pain.

Carbapenems

Imipenem

Adverse Reactions. Nausea and vomiting occur in 1–2% of patients, sometimes associated with hypotension or diaphoresis, particularly with high doses and rapid infusion. Rashes occur occasionally, and cross-allergenicity with penicillins has been documented. Convulsions have occurred, primarily in the elderly, in those with underlying CNS disease, with overdosage in patients with renal failure, or with other predisposing factors.

Precautions. Use with caution in elderly patients or those with a history of seizures or who are otherwise predisposed. Adjust dosage carefully in renal impairment. Imipenem can cause immediate hypersensitivity reactions in patients with a history of anaphylaxis to penicillin.

Drug Interactions. Concomitant administration with probenecid produces higher and prolonged serum concentrations of imipenem and cilastatin. Imipenem has been shown in vitro to antagonize the activity of other -lactams (eg, acylureidopenicillins, most cephalosporins) presumably via -lactamase induction; although the clinical relevance is unclear, avoid co-administration. Co-administration of imipenem/cilastatin with ganciclovir has been associated with generalized seizures in a few patients; the mechanism of this interaction is unknown.

Parameters to Monitor. Obtain renal function tests periodically.

Notes. Used alone, emergence of resistance during treatment of Pseudomonas aeruginosa infections occurs frequently; however, cross-resistance to

other classes (eg, aminoglycosides, cephalosporins) does not occur. Addition of an aminoglycoside might prevent development of resistance, but in vitro synergism occurs only infrequently.

Vials may be reconstituted into a suspension using 10 mL of the infusion solution and then diluted further by transferring the suspension into the infusion container; alternatively, the powder in the 120-mL vials can be diluted initially with 100 mL of solution. The initial dilution must be shaken well to ensure suspension/solution. Do not inject the suspension. The resulting solution ranges from colorless to yellow. Reconstituted solutions are stable in dextrose-containing solutions for 4 hr at room temperature and 24 hr under refrigeration, and in normal saline for 10 hr at room temperature and 48 hr under refrigeration. With IM administration use 2 mL of lidocaine 1% injection to reconstitute a 500 mg vial and give the suspension by deep IM injection into a large muscle mass (eg, gluteal muscle).

Meropenem

Adverse Reactions. Adverse effects are similar to imipenem; the most common are injection-site reactions, rash, nausea, vomiting, and diarrhea. Animal studies suggest that meropenem has a lower epileptogenic potential, which has been supported by a low frequency of seizures in clinical trials, including studies in patients with meningitis.

Precautions. Use with caution in patients with hypersensitivity to penicillins because meropenem can cause immediate hypersensitivity reactions in patients allergic to penicillins. Adjust dosage in renal impairment.

Drug Interactions. Probenecid can reduce renal clearance of meropenem and increase its half-life by 38% and AUC by 56%; avoid the combination.

Parameters to Monitor. Obtain renal function tests periodically.

Notes. Meropenem is more active than imipenem against enteric Gram-negative bacilli; the two have equivalent activity against Pseudomonas aeruginosa and Bacteroides fragilis, and meropenem is slightly less active than imipenem against Gram-positive organisms.

Aminoglycoside

Adverse Reactions. Aminoglycoside-induced nephrotoxicity is usually mild and reversible; progression to severe renal disease and dependence on dialysis is rare. Nephrotoxicity is manifested by elevations in Crs, BUN, and aminoglycoside concentrations and appearance of renal tubular casts, enzymes, and 2-microglobulin and occurs in 5–30% of patients, depending on the criteria used and the population risk factors present.

Duration of therapy, prior aminoglycoside therapy, advanced age, pre-existing renal disease, liver disease, volume depletion, and female sex have been identified as risk factors for nephrotoxicity.

Concomitant use of nephrotoxic drugs also increases the risk of nephrotoxicity. Elevated trough levels are not a risk factor but often a result of

nephrotoxicity. There is no evidence that there are clinically important differences in nephrotoxicity between gentamicin, tobramycin, netilmicin, and amikacin. Depletion of magnesium and other minerals caused by increased renal excretion occurs. Occasional, but often permanent, vestibular toxicity is reported, usually in association with streptomycin. Subclinical vestibular disturbances can be detected in 40% or more of patients receiving aminoglycosides. Early cochlear damage can be detected only by sequential audiometric examination because hearing loss in conversational frequencies is a sign of advanced auditory impairment. Furthermore, early auditory damage is not as apparent in the elderly or others with pre-existing high-tone deficits. Risk factors for ototoxicity are duration of therapy, bacteremia, hypovolemia, peak temperature, and liver disease. Elevated serum concentrations apparently are not associated with increased ototoxicity risk, and there are no apparent clinically important differences between gentamicin, tobramycin, netilmicin, and amikacin. Oral aminoglycosides, primarily neomycin, have been associated with a sprue-like malabsorption syndrome. Neuromuscular blockade with respiratory failure is rare, except in predisposed patients.

Precautions. Pregnancy; pre-existing renal impairment; vestibular or cochlear impairment; myasthenia gravis; hypocalcemia; postoperative or other conditions that depress neuromuscular transmission.

Drug Interactions. Concurrent or sequential use of other nephro- or ototoxic agents can increase the risk of aminoglycoside toxicities. Concurrent use of aminoglycosides with neuromuscular blocking agents can potentiate neuromuscular blockade and cause respiratory paralysis. The action of oral anticoagulants can be potentiated by oral neomycin, presumably via reduced absorption or synthesis of vitamin K. Ticarcillin and acylampicillins can degrade aminoglycosides in vitro, resulting in artificially low levels; the extent of degradation is dependent on time, temperature, and -lactam concentration. Degradation can occur in vivo in patients with renal insufficiency. Amikacin is the aminoglycoside least susceptible to -lactam inactivation.

Parameters to Monitor. Renal function tests before and q 2–3 days during therapy. Audiometry and electronystagmography may be performed in patients able to cooperate. Monitor aminoglycoside serum concentrations carefully, especially in the elderly, those with renal impairment, hemodynamically unstable patients, and those requiring high peak serum concentrations or prolonged (>10 days) therapy. In adults receiving conventional therapy, monitor serum levels after steady state is achieved. With once-daily therapy targeting high peaks and undetectable troughs, obtain levels after the first dose. Obtain follow-up levels if renal function changes. In neonates or other patients with rapidly changing renal function, obtain serum drug concentrations initially and q 2–3 days until stable. However, with once- or twice-daily dosage and in pediatric patients, trough serum levels are often undetectable and other sampling strategies are necessary.

Notes. Of the available aminoglycosides, gentamicin, tobramycin, netilmicin, and amikacin are the most clinically useful. Streptomycin use is largely restricted to the treatment of enterococcal endocarditis (in combination with ampicillin), tuberculosis, brucellosis, plague, and tularemia; it is currently available

only for compassionate use from the manufacturer. Amikacin is often used as part of a combination regimen for treatment of Mycobacterium avium complex infection. Neomycin is much more toxic than the other aminoglycosides when given parenterally; it is restricted to oral use for gut sterilization and topical use for minor infections. Resistance among Gram-negative organisms, especially P. aeruginosa, has virtually eliminated the systemic use of kanamycin. Tobramycin is roughly equivalent to gentamicin therapeutically, although it is about 2–4 times more active against P. aeruginosa than is gentamicin, is often active against gentamicinresistant P. aeruginosa, and might be preferred because of a superior peak-to-MIC ratio. Resistance of Gram-negative bacilli is lowest with amikacin; amikacin use does not appear to result in increased resistance to the drug.

Antifungal drugs

Amphotericin B

Adverse Reactions. Frequent adverse effects include infusion-related reactions, nephrotoxicity, normochromic normocytic anemia and phlebitis. Infusion reactions ordinarily include rigors, chills, and fever. Less common infusion-related reactions include nausea, tachycardia, tachypnea, hypotension, hypertension, bradycardia, myalgia, and arthralgia. Symptoms generally occur during or within 60–90 min after completion of the infusion. Symptoms decrease with ancillary medications and repeated administration. Meperidine 25–50 mg IV reduces the duration and intensity of rigors and chilling. Acetaminophen 325–650 mg PO reduces hyperpyrexia, and is often administered as premedication. Diphenhydramine 25–50 mg PO or IV is often included as a premedication. Hydrocortisone, which reduces fever, chills, and nausea, is reserved for patients with infusion reactions refractory to other ancillary medications. Case reports describe the use of dantrolene for refractory rigors and chills. Although premedication with ibuprofen reduces the rigors and chills, most patients receiving amphotericin B are at risk for adverse effects from the nephrotoxic and antiplatelet effects of NSAIDs. The prevalence of infusion reactions is greater with conventional amphotericin B or amphotericin B cholesteryl sulfate than with amphotericin B lipid complex or liposomal amphotericin. Rapid infusion (<60 min) of amphotericin B can cause hyperkalemia and cardiovascular collapse in anephric or hyperkalemic patients. Amphotericin B cholesteryl sulfate, amphotericin B lipid complex, and liposomal amphotericin are each less nephrotoxic than conventional amphotericin B. However, the lipid-based formulations are not devoid of nephrotoxicity. Nephrotoxicity is generally reversible. Permanent renal impairment can occur, particularly in patients receiving conventional amphotericin B at doses over 1 mg/kg/day or have pre-existing renal impairment, prolonged therapy, sodium depletion, or concurrent nephrotoxic drugs. Signs of nephrotoxicity are increased BUN and Crs, hypomagnesemia, hypokalemia, and renal tubular acidosis. Nephrotoxicity can be reduced with infusion of 0.9% NaCl 250–1000 mL over 30–45 min immediately before amphotericin B. The saline infusion may be repeated immediately after amphotericin B administration. The patient’s body size and

cardiovascular status must be considered when selecting the volume and rate of 0.9% NaCl infusion. Normochromic normocytic anemia, which is secondary to amphotericin B–induced nephrotoxicity, is mild and transient and rarely requires intervention. Phlebitis is secondary to chronic peripheral administration of conventional amphotericin B. Some advocate adding heparin 1 IU/mL to minimize phlebitis.

Rare adverse effects reported with amphotericin B are anorexia, emesis, diarrhea, cramping epigastric pain, premature ventricular contraction, bradycardia, dilated cardiomyopathy, hypertension, diffuse alveolar hemorrhage, rhabdomyolysis, and parkinsonian syndrome.

Intrathecal administration of amphotericin B causes headache, nausea, vomiting, abdominal pain, urinary retention, tinnitus, visual changes, ventriculitis, paresthesias, numbness, mono- or paraparesis, arachnoiditis, focal neurologic defects, and chemical or bacterial meningitis. Life-threatening brain puncture and hemorrhage can occur with intracisternal injection.

Precautions. Pregnancy. Impaired renal function. Avoid rapid infusions (<4 hr) in patients with Clcr< 20 mL/min, hyperkalemia, or reduced ability to excrete potassium.18 Separate from neutrophil infusions by at least 6 hr. Complete infusion at least 2 hr before platelet transfusions.

Drug Interactions. Additive nephrotoxicity can occur with cyclosporine, tacrolimus, aminoglycosides, loop diuretics, or other nephrotoxic agents. Corticosteroids can enhance potassium loss.

Parameters to Monitor. Monitor infusion-related adverse effects with first 3 doses, then as indicated by severity of reactions. Monitor serum Crs, BUN, magnesium, potassium before therapy, and at least twice weekly during therapy. Monitor patients at great risk for renal dysfunction daily. Monitor Hb at least weekly. Monitor microbiologic, radiographic, and clinical signs of fungal infection. Ancillary use of hydrocortisone, acetaminophen, or aspirin might mask fevers.

Notes. To ensure even lipid complex distribution, invert admixtures of amphotericin B lipid complex several times immediately before starting the infusion and q 2 hr thereafter. Because amphotericin B has a propensity to precipitate, avoid admixture or Y-site administration of all amphotericin B formulations with IV fluids (except dextrose solution), other intravenous drugs, or blood products. Avoid admixture of conventional amphotericin B with lipid emulsion. Physical incompatibility of this admixture evolves >10 particles and phase separation.

Acronyms for the various amphotericin B formulations are as follows: conventional amphotericin B, DAmB; amphotericin B cholesteryl sulfate, ABCD; amphotericin B lipid complex, ABLC; liposomal amphotericin B, L-AmB. Amphotericin B cholesteryl sulfate is also known as amphotericin B colloidal dispersion and Amphocil.

Clotrimazole

Adverse Reactions. Nausea, vomiting, bad taste, and mildly abnormal liver function tests have occurred with oral troche. Vulvovaginal burning, itching, and

irritation have been reported with vaginal products. Skin rash occurs occasionally with vaginal or topical use.

Fluconazole

Adverse Reactions. Occasional nausea, vomiting, diarrhea, abdominal pain, or elevations of liver transaminases occur. Severe hepatitis or exfoliative skin reactions occur rarely.

Precautions. Observe patients who develop rash for worsening of the lesions and discontinue the drug if necessary.

Drug Interactions. Rifampin induces the metabolism of fluconazole and can lead to clinical failure. Fluconazole inhibits metabolism of phenytoin, warfarin, and, to a minor extent, cyclosporine. Low dosages have been shown to increase the serum levels of tolbutamide, glipizide, glyburide, and possibly other sulfonylureas. This could lead to a greater hypoglycemic effect, and dosage reduction might be necessary.

Parameters to Monitor. Liver function tests weekly initially, then monthly. Monitor renal function tests weekly if abnormal at outset of therapy. Monitor patients with elevated transaminases more carefully for hepatitis.

Notes. Combination therapy with fluconazole and flucytosine for treatment of cryptococcal meningitis appears to be superior to single-agent therapy; further studies of this combination and of fluconazole plus amphotericin B are needed. Fluconazole-resistant Candida albicans has been clinically demonstrated; increased use of prophylactic fluconazole increases the likelihood of the emergence of resistant strains such as Candida krusei.

Ketoconazole

Adverse Reactions. Generally well tolerated, with the most frequent side effects being nausea, vomiting, pruritus, and abdominal discomfort. Hepatotoxicity, including massive hepatic necrosis, occurs occasionally, but mild elevations of transaminases occur frequently. Gynecomastia occurs, probably caused by ketoconazole-induced suppression of testosterone synthesis. Ketoconazole also blocks cortisol production; however, clinically apparent hypoadrenalism occurs rarely. Irritation, pruritus, and stinging can occur with topical use.

Contraindications. Co-administration with astemizole or cisapride.

Precautions. Pregnancy; lactation.

Drug Interactions. Ketoconazole inhibits human CYP3A4 and inhibits metabolism of certain drugs such as cyclosporine, methylprednisolone, and warfarin. Warfarin dosage reduction may be necessary during concurrent use. H2-receptor antagonists, antacids, and probably proton-pump inhibitors (eg, omeprazole, lansoprazole) might reduce ketoconazole oral absorption.

Parameters to Monitor. Monitor liver function tests before starting therapy and often during therapy. Closely monitor prothrombin time in patients on concurrent warfarin and cyclosporine levels in patients taking this drug.

Notes. Achlorhydric patients may be given the drug with glutamic acid hydrochloride or 0.1 N HCl (using a drinking straw) to increase absorption. An acidic drink (eg, a cola) also may be used to increase ketoconazole absorption by about 65% in achlorhydria.

Antimycobacterial Drugs

Ethambutol

Adverse Reactions. Adverse reactions are rare with the recommended dosage of 15–25 mg/kg/day. Optic neuritis (manifested as blurred vision, color blindness, and restricted visual fields) occurs rarely with dosages of 15 mg/kg/day and is usually reversible with prompt drug discontinuation. Hyperuricemia can occur because of impairment of uric acid excretion.

Isoniazid

Adverse Reactions. Pyridoxine-responsive peripheral neuropathy can occur, especially in alcoholics, diabetics, patients with renal failure, malnourished patients, and slow acetylators, and with dosages >5 mg/kg/day.66 Subclinical hepatitis is frequent (10–20%) and characterized by usually asymptomatic elevations of AST and ALT, which can return to normal despite continued therapy; it might be more frequent with combined INH–rifampin therapy. Clinical hepatitis is rare in those < 20 yr, but is strikingly related to age (rising to 2–3% in 50–65 yr-old patients). Rare cases of massive liver atrophy resulting in death usually appear in association with alcoholism or pre-existing liver disease; most severe cases occur within the first 6 months. With acute overdosage (usually 6–10 g), INH can produce severe CNS toxicity including coma and seizures as well as hypotension, acidosis, and occasionally death.

Contraindications. Acute or chronic liver disease; previous INH-associated hepatitis.

Precautions. Pregnancy; lactation. Use with caution in daily users of alcohol, elderly patients, and those with a slow acetylator phenotype.

Drug Interactions. INH can inhibit the metabolism of carbamazepine and phenytoin, increasing the risk of toxicity, particularly of phenytoin in slow acetylators. Mental changes can result from effects of INH and disulfiram on metabolism of adrenergic neurotransmitters; avoid the use of disulfiram in patients who must take INH. Aluminum-containing antacids can interfere with INH absorption. Rifampin can increase the metabolism of INH to hepatotoxic metabolites.

Parameters to Monitor. Question for prodromal signs of hepatitis (eg, fever, malaise) and signs of peripheral neuropathy (eg, burning, tingling, numbness) monthly during therapy. Baseline and monthly AST and ALT are recommended only in high-risk groups (those >35 yr, daily alcohol users, and those with a history of liver dysfunction), although they are not predictive of clinical hepatitis.

Notes. It is generally recommended that all patients receive INH for treatment of latent tuberculosis infection who have had positive reactions to

intermediatestrength purified protein derivative (PPD, 5 tuberculin units) and who (1) are household contacts of patients with active tuberculosis; (2) converted their PPD to positive within the past 12–24 months; (3) have radiologic evidence of inactive tuberculosis or a history of inadequately treated active tuberculosis; (4) are foreignborn persons (and their families) from high-prevalence areas who have entered the United States within the past 2 years; (5) are persons with known or suspected HIV infection; (6) are persons with medical or iatrogenic conditions that increase the risk of tuberculosis—silicosis, gastrectomy, jejunoileal bypass, weight of 10% or more below ideal, chronic renal failure, diabetes mellitus, corticosteroid or other immunosuppressive therapy, hematopoietic malignancy, other malignancy, and other conditions in which immunosuppression results from the disease or its treatment. Most sources suggest that the use of INH prophylaxis in patients >35 yr should be further restricted because of the increased risk of fatal hepatotoxicity, although this is controversial.

To prevent peripheral neuropathy, give pyridoxine in a dosage of 50 mg/day to adults receiving large dosages of INH (10 mg/kg/day or more) and those who are predisposed to peripheral neuritis (eg, diabetics, HIV-infected, alcoholics). Pyridoxine IV in a dosage equal to the estimated amount of INH ingested is recommended for acute INH overdose.

Add ethambutol or streptomycin to the initial treatment regimen until drug susceptibility studies are available, or unless there is little possibility of drug resis tance (ie, there is< 4% primary resistance to INH in the patient's community, and the patient has had no previous treatment with antituberculosis medications, is not from a country with a high prevalence of drug resistance, and has no known exposure to a drug-resistant case).

Pyrazinamide

Adverse Reactions. Frequent hyperuricemia, probably caused by prevention of uric acid excretion by one of the metabolites, and occasional dose-dependent hepatotoxicity occur. As many as 1–5% of patients taking regimens including isoniazid, rifampin, and pyrazinamide develop laboratory evidence of hepatic damage.

Rifampin

Adverse Reactions. Adverse reactions are more frequent and severe with intermittent, high-dose administration. GI symptoms are frequent. Acute, reversible renal failure, characterized as tubular damage with interstitial nephritis, sometimes appearing with concomitant hepatic failure has been reported rarely, especially in association with intermittent administration. Asymptomatic elevation of liver enzymes occurs frequently, whereas clinical hepatitis is rare but more common with pre-existing liver disease or alcoholism; the effect of isoniazid coadministration on the frequency of hepatitis is unclear.67 Competition with bile for biliary excretion can produce jaundice, especially with pre-existing liver disease. Intermittent therapy is also associated with thrombocytopenia and a flu-like syndrome (ie, fever, joint pain, muscle cramps).

Contraindications. Hypersensitivity to any rifamycin derivative.

Precautions. Pregnancy; lactation. Use with caution in daily users of alcohol, those with pre-existing liver disease, and those with a history of drug-associated hepatic damage (especially from antituberculars).

Drug Interactions. Rifampin accelerates the metabolism of many drugs such as oral contraceptives, corticosteroids, cyclosporine, enalapril, HIV protease inhibitors, propranolol, methadone, metoprolol, mexiletine, phenytoin, quinidine, theophylline, tolbutamide, oral verapamil, warfarin, and zidovudine because of potent inducing effects on CYP3A. The dosage of these drugs may need to be increased during concurrent use. Rifampin can increase the metabolism of isoniazid to hepatotoxic metabolites.

Parameters to Monitor. Question for prodromal signs of hepatitis (eg, fever, malaise). Baseline and monthly AST and ALT have been recommended, especially for patients with factors predisposing to hepatotoxicity (eg, alcoholism, preexisting liver disease), although they are not predictive of clinical hepatitis in the absence of symptoms.

Notes. Rifampin is a useful drug for tuberculosis but should be used only in combination regimens because of rapid emergence of resistant mutants of Mycobacterium tuberculosis when it is used alone. The recent emergence of multiple drug resistance among strains of M. tuberculosis in patients with AIDS includes highlevel rifampin resistance. The routine use of rifampin in methicillin-resistant Staphylococcus aureus (MRSA) endocarditis is not recommended except after failure of conventional therapy and possibly with renal, myocardial, splenic, or cerebral abscess. If rifampin is added to vancomycin for treatment of MRSA, add a third drug (eg, gentamicin) to reduce the likelihood of resistance development. In nonendocarditis infections caused by MRSA, do not use rifampin unless there is inadequate response to vancomycin alone.

Antiparasitic Drugs

Albendazole

Adverse Reactions. Occasionally, diarrhea, abdominal pain, and migration of roundworms through the mouth and nose occur. Rarely, leukopenia, alopecia, or increased transaminases occur.

Precautions. Pregnancy; liver dysfunction.

Drug Interactions. Concurrent dexamethasone increases serum levels by 50%.

Parameters to Monitor. Monitor hepatic transaminases and WBC count during prolonged therapy.

Praziquantel

Adverse Reactions. Side effects are usually mild. Dizziness, headache, and malaise occur frequently after large doses. Occasionally, abdominal discomfort, fever, sweating, and eosinophilia occur. Drowsiness or fatigue might occur because of a structural similarity to benzodiazepines. Pruritus and rash occur rarely. In

patients treated for cysticercosis, an inflammatory response, presumably caused by dead and dying organisms, occurs that is manifested by headache, seizures, and increased intracranial pressure.

Contraindications. Ocular cysticercosis.

Precautions. Pregnancy; liver disease; avoid breastfeeding for 72 hr after the last dose.

Drug Interactions. Drugs that induce CYP3A3/4 (eg, dexamethasone, carbamazepine, phenobarbital, phenytoin) can increase clearance, decrease bioavailability, and cause treatment failure; drugs that inhibit CYP3A3/4 (eg, cimetidine, ketoconazole, erythromycin) decrease clearance, increase serum levels, and lengthen half-life.

Parameters to Monitor. Observe for CNS toxicity when treating cysticercosis.

Notes. Concomitant corticosteroid therapy is recommended for patients treated for neurocysticercosis.

Pyrantel

Adverse Reactions. Occasional nausea, vomiting, headaches, dizziness, rash, and transient AST elevations.

Contraindications. Liver disease.

Precautions. Avoid during pregnancy.

Drug Interactions. Piperazine and pyrantel might be mutually antagonistic in ascariasis.

Notes. Except for pinworms, for which it is virtually 100% effective, and monilaformis, pyrantel is an alternative to other drugs.

Antiviral Drugs

Acyclovir

Adverse Reactions. (Acyclovir) nephrotoxicity, thought to be caused by precipitation of acyclovir crystals in the nephron, occurs in about 10% of patients if the drug is given by bolus (<10 min) injection. Phlebitis at injection site occurs frequently with IV infusion because of the high pH (9–11) of the product. Other reported side effects are CNS toxicity (eg, headache, lethargy, tremulousness, delirium, seizures), nausea, vomiting, and skin rash. CNS toxicity occurs primarily in patients with underlying neurologic disease or end-stage renal disease, or with cancer chemotherapy and irradiation to the CNS, and might not be primarily caused by the drug. Topical application to herpes lesions can be painful. (Valacyclovir) adverse reactions appear comparable to acyclovir. Nausea, vomiting, diarrhea, abdominal pain, and headache have been reported frequently with valacyclovir use. Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome has been reported in patients with advanced HIV disease and in bone marrow and renal transplant patients. This phenomenon has not been reported in immunocompetent patients.

Contraindications. (Valacyclovir) allergy to the drug or to acyclovir.

Precautions. Use caution in renal impairment, dehydration, or pre-existing neurologic disorders. Valacyclovir not indicated in immunocompromised patients.

Drug Interactions. Zidovudine and acyclovir can result in drowsiness and lethargy. Probenecid can increase oral bioavailability and half-life of acyclovir.

Parameters to Monitor. Monitor renal function and injection site for signs of phlebitis daily. Carefully monitor patients with underlying neurologic diseases for evidence of neurotoxicity.

Notes. Acyclovir-resistant strains of virus that are deficient in thymidine kinase have been isolated from patients after treatment. Although thought to be less virulent than sensitive strains, HSV strains resistant to acyclovir have been described in AIDS patients.

Lamivudine

Adverse Reactions. The most frequently reported adverse effects have been headache, fatigue, nausea, insomnia, neuropathy, and musculoskeletal pain.

Zidovudine

Adverse Reactions. Severe anemia and granulocytopenia occur frequently and might necessitate blood transfusions; epoetin might help alleviate anemia in patients with low serum erythropoietin levels. Other frequent adverse reactions associated with zidovudine in placebo-controlled trials include abdominal discomfort, nausea, vomiting, insomnia, myalgias, and headaches. Adverse reactions that occasionally occur with long-term use (>12 weeks) are myopathy and nail pigmentation.

Contraindications. Life-threatening allergy to the drug or its components.

Precautions. Pregnancy; lactation. Use with caution in liver disease or hepatomegaly, especially in obese women.

Drug Interactions. Several drugs decrease the glucuronidation of zidovudine, including atovaquone, methadone, probenecid, valproic acid, and possibly fluconazole; rifampin increases zidovudine glucuronidation; however, the clinical importance of these interactions is not established. Initial studies showed that prolonged administration of acetaminophen was associated with increased hematologic toxicity from zidovudine, but further study does not support this finding.

Parameters to Monitor. Hemoglobin, hematocrit, MCV, and WBC for hematologic toxicity. Monitor clinical signs, symptoms, and laboratory markers for progression of HIV disease to help decide regimen changes in antiretroviral therapy. Baseline CD4 and HIV-1 RNA polymerase chain reaction viral load tests are useful to measure clinical benefit of therapy. Repeat tests after 1 month and q 3–4 months thereafter have been suggested to monitor benefit of antiretroviral therapy.

Notes. Viral resistance to zidovudine has occurred in vitro with isolates recovered from patients and is associated with prolonged zidovudine use and more advanced disease; correlation between viral resistance in vitro and progression of disease has not been established. Studies with lamivudine (3TC) suggest that the

combination can delay or prevent HIV-1 viral resistance to zidovudine. Aztec (Verex) is an SR dosage form in late-stage testing.

Antiretroviral therapy

The use of protease inhibitors and/or nonnucleoside reverse transcriptase inhibitors in combination with nucleoside reverse transcriptase inhibitors has dramatically changed the treatment of HIV infection. Regimens containing a protease inhibitor or nonnucleoside reverse transcriptase inhibitor have enhanced the ability to inhibit replication of HIV, affecting immunologic and viral markers, delaying progression of disease, and improving survival. Many formidable hurdles stand in the way of effective treatment, including patient adherence to dosage regimens, adverse effects, and drug–drug interactions. These hurdles interfere with quality of life and control of the viral burden and also contribute to the emergence of resistance. It is essential for health care providers and patients to appreciate the complexity of antiretroviral medication regimens to achieve harmony between goals of antiretroviral therapy and optimal patient care. General principals of treatment that guide contemporary treatment decisions are outlined below:

- Viral load monitoring is essential to guide decision making.
- Attaining and maintaining an undetectable HIV RNA in blood (which can indirectly reflect lymph concentrations) is the goal of therapy.
- Introduce effective antiretroviral therapy before extensive immune system damage has occurred.
- Three-drug combination therapy, is the regimen most likely to achieve the goal of an undetectable HIV RNA level and provide a durable response.
- Compliance with the treatment regimen is critical to success and must be considered in initiating and choosing regimens.
- Change most or all drugs in a failing regimen simultaneously; use antiretroviral drug resistance testing to guide new antiretroviral regimen decisions.

Oseltamivir phosphate (Tamiflu)

Adverse Reactions. Nausea and vomiting are the most frequent adverse events, occurring in about 10% of patients. Bronchitis, insomnia, and vertigo occur occasionally.

Drug Interactions. Oseltamivir is not a substrate and does not affect cytochrome P450 isoenzymes. There are no known drug interactions.

Parameters to Monitor. Progression of influenza symptoms.

Notes. There are no data to support the safety or efficacy in patients who begin oseltamivir after 48 hr of influenza symptom onset. Patients should continue to receive an annual influenza vaccination according to guidelines on immunization practices.

Zanamivir

Adverse Reactions. Nasal and throat discomfort, cough, headache have occurred in 2–3% of patients. This prevalence is similar to placebo and might be

related to inhalation of the lactose vehicle. Bronchospasm has occurred occasionally in patients with asthma or COPD.

Precautions. Use with extreme caution in patients with underlying airway diseases such as asthma or COPD because of the potential for causing bronchospasm. Instruct patients who use inhaled bronchodilators concurrently with zanamivir to use their bronchodilators before inhaling zanamivir.

Drug Interactions. Zanamivir is not a substrate and does not affect cytochrome P450 isoenzymes. There are no known clinically relevant drug interactions.

Parameters to Monitor. Inhalation technique, progression of influenza symptoms.

Notes. There are no data to support the safety or efficacy in patients who begin zanamivir treatment after 48 hr of influenza symptom onset. Patients should continue to receive an annual influenza vaccination.

Case history

While on holiday in Spain, a 66-year-old man develops a cough, fever and breathlessness at rest. He is told that his chest x-ray confirms that he has pneumonia. He is started on a seven-day course of oral antibiotics by a local physician and stays in his hotel for the remainder of his ten-day holiday. When he returns home, he is reviewed by his own GP who notices that he looks pale and sallow and is still breathless on exertion, but his chest examination no longer reveals any signs of pneumonia. A full blood count reveals a haemoglobin level of 6.7 g/dL (previously normal), normal white blood count and platelets, and a reticulocyte count of 4.1%.

Question

What other tests should you do and what antibiotics would be most likely to cause this clinical scenario?

Answer

The patient received a course of antibiotics for pneumonia and then developed what appears to be a haemolytic anaemia. This could be further confirmed by raised unconjugated bilirubin levels and low haptoglobin levels, and observation of target cells and poikilocytosis on the blood film. Mycoplasma pneumonia should be excluded by performing Mycoplasma titres, as this can itself be complicated by a haemolytic anaemia.

However, considering the drugs as the potential cause, it is important to define the patient's glucose-6-phosphate dehydrogenase status, and if he was deficient then to consider such agents as co-trimoxazole (containing sulfamethoxazole, a sulphonamide), the fluoroquinolones (e.g. ciprofloxacin or nitrofurantoin) or chloramphenicol, which can cause haemolytic anaemia in susceptible individuals. Note that chloramphenicol is more commonly prescribed in certain countries on the European mainland. Aplastic anaemia (not the picture in this patient) is a major concern with the use of systemic chloramphenicol. If the patient's glucose-6-phosphate dehydrogenase status is normal, then rarely the β-

lactams (penicillins or early (first- and second-) generation cephalosporins) or (less likely) rifampicin may cause an autoimmune haemolytic anaemia due to the production of antibodies to the antibiotic which binds to the red blood cells. This could be further confirmed by performing a direct Coombs' test in which the patient's serum in the presence of red cells and the drug would cause red cell lysis. Management involves stopping the drug, giving folic acid and monitoring recovery of the haemoglobin. It should be noted in the patient's record that certain antibiotics led him to have a haemolytic anaemia.

Case history

A 70-year-old man with a history of chronic obstructive pulmonary disease visits his GP in December during a local flu epidemic. He complains of worsening shortness of breath, productive cough, fever and malaise. On examination, his sputum is viscous and green, his respiratory rate is 20 breaths per minute at rest but, in addition to wheezes, bronchial breathing is audible over the right lower lobe. The GP prescribes amoxicillin which has been effective in previous exacerbations of chronic obstructive pulmonary disease in this patient. Twenty-four hours later, the patient is brought to the local Accident and Emergency Department confused, cyanosed and with a respiratory rate of 30 breaths per minute. His chest x-ray is consistent with lobar pneumonia.

Question

In addition to controlled oxygen and bronchodilators, which three antibacterial drugs would you prescribe and why?

Answer

This patient is seriously ill with community-acquired lobar pneumonia. The previously abnormal chest, the concurrent flu epidemic and the rapid deterioration suggest Staphylococcus, but Streptococcus pneumoniae and Legionella are also possible pathogens. The following antibacterial drugs should be prescribed:

• Flucloxacillin – active against Staphylococcus and Gram-positive organisms;

• Cefuroxime – broad spectrum and active against Staphylococcus;

• Erythromycin – active against Legionella and Mycoplasma, and also some Staphylococcus and other Gram-positive bacteria.

Case history

A 20-year-old man presented to his GP during a flu epidemic complaining of a throbbing headache which was present when he woke up that morning. He had been studying hard and was anxious about his exams. Physical examination was normal and he was sent home with paracetamol and vitamins. He presented to casualty 12 hours later with a worsening headache. Examination revealed a temperature of 39°C, blood pressure of 110/60 mmHg, neck stiffness and a purpuric rash on his arms and legs which did not blanch when pressure was applied.

Question

Which antibacterial drugs would you use and why?

Answer

This young man has meningococcal meningitis and requires benzylpenicillin i.v. immediately.

REMEMBER: Treatment of bacterial meningitis must never be delayed.

Control questions

1. Infection and infectious process, the concept of pathogenicity, virulence, toxigenicity.
2. Classification of infectious diseases.
3. Immunological criterion for infectious diseases - immunity, mechanisms of protection against infectious agents
4. Chemotherapeutic agents. used for the treatment of infectious diseases.
5. Pharmacotherapy of infectious diseases.
6. Causes of resistance of bacteria to drugs.
7. Complications of pharmacotherapy of infectious diseases.
8. Specific immunotherapy.
9. Intestinal infections:

• amebiasis - etiology, pathogenesis, clinical picture, pharmacotherapy.
• Escherichia coli - etiology, pathogenesis, clinical picture, pharmacotherapy.
• food poisoning - etiology, pathogenesis, clinical picture, pharmacotherapy.
• Cholera - etiology, pathogenesis, clinical picture, pharmacotherapy.

10. Airborne infections:

• herpes - etiology, pathogenesis, clinical picture, pharmacotherapy.
• diphtheria - etiology, pathogenesis, clinical picture, pharmacotherapy.
• measles - etiology, pathogenesis, clinical picture, pharmacotherapy.

11. Blood transmissive infections:

• hemorrhagic fever - etiology, pathogenesis, clinical picture, pharmacotherapy.
• malaria - etiology, pathogenesis, clinical picture, pharmacotherapy.

12. Zoonotic diseases:

• Raza - etiology, pathogenesis, clinical picture, pharmacotherapy.
• toxoplasmosis - etiology, pathogenesis, clinical picture, pharmacotherapy.
• FMD - etiology, pathogenesis, clinical picture, pharmacotherapy.

13. Infections transmitted through damage to the skin:

• Tetanus - etiology, pathogenesis, clinical picture, pharmacotherapy.

14. Natural pox - etiology, pathogenesis, clinical picture, pharmacotherapy.
15. Poliomyelitis - etiology, pathogenesis, clinical picture, pharmacotherapy.
16. Epidemic typhoid fever - etiology, pathogenesis, clinical picture, pharmacotherapy.
17. Endemic (flea) typhoid fever - etiology, pathogenesis, clinical picture, pharmacotherapy.
18. Marseilles fever - etiology, pathogenesis, clinical picture,

pharmacotherapy.

19. Plague - etiology, pathogenesis, clinical picture, pharmacotherapy.

20. Siberian ulcer - etiology, pathogenesis, clinical picture, pharmacotherapy.

21. Leptospirosis - etiology, pathogenesis, clinical picture, pharmacotherapy.

22. Recipes should be prescribed: metronidazole, emetine, tetracycline, doxycycline (vibramycin), plakvenlyl, primaxin (primaquin), chloroquine (hingamine), ciprofloxacin, levomicetin, ampiox, benzatin (bicillin-1, extensilin, reparin), meslocillin (baypen), azithromycin, clarithromycin, mececamycin (macropen), gentamicin, amikacin.

List of practical works

A. Homework.

1. To know the classification of infectious diseases.
2. Know the basic principles of diagnosing and identifying various types of infectious diseases.
3. To familiarize with the principles of treatment of these diseases.

B. Independent practical work at the lesson.

1. The curation of the thematic patient in the ward.
2. To distinguish in the complaints of sick signs of infectious diseases, to determine to what type it belongs.
3. With an objective and laboratory-instrumental study, specify the degree of severity of the infectious paroxysm.
4. Write a diagnosis (main, concomitant diseases and their complications).
5. Determine the groups of LS necessary for the patient.
6. On the basis of theoretical data and own observations, choose a drug for a specific patient.

Control the level of knowledge

1. Fill in the table: "Directions of pharmacotherapy of major viral diseases".

Infections	Exciter, transmission path	Directions pharmacotherapy
Flu Paragrip Adenovirus Measles Varicella Rubella		

2. Fill in the table: "Directions of pharmacotherapy of major bacterial diseases".

Infections	Exciter, transmission path	Directions pharmacotherapy
Dietary Toxic Infections Dysentery Salmonella Giardiasis Toxoplasmosis		

3. Fill in the table: "Directions of pharmacotherapy for highly dangerous bacterial diseases".

Infections	Exciter, transmission path	Directions pharmacotherapy
Plague Cholera Meningococcal infection Typhoid Tetanus Siberian ulcer		

Solution of situational tasks

1. In the admission department of the infectious disease hospital three patients were admitted for 6 hours with suspected food poisoning. Patients are concerned about thirst, diarrhea (up to 10-12 times a day), which began several hours ago. The diarrhea was initially fecal, then liquid watery, by type of rice broth. One patient had a vomiting fountain without nausea and pain in the epigastrium. From anamnesis of the disease - all three were eating fish caught from standing water 2 - 3 days ago. At examination of patients, attention is drawn to their difficult condition, dryness of the skin, tongue, adynamia, inflamed stomach.

What can a previous diagnosis be? Directions of pharmacotherapy.

2. In the admissions department of the infectious disease hospital, a patient with complaints of nausea, vomiting of food eaten, abdominal pain, dizziness, weakness, body temperature up to 380C, diarrhea. The survey found that the patient 4-5 hours ago ate cakes with meat bought from a merchant on the beach.

What is the reason for such a patient's condition? Directions of pharmacotherapy.

3. The patient arrived at the hospital in a difficult condition, in the mind. The relatives found out that a man had a foot injury injury to the foot with contaminated land during field work in the field a few days ago. At examination, trism is observed with the transition to tonic tension of the muscles of the back, chest,

limbs.

What can a previous diagnosis be? Directions of pharmacotherapy in prehospital and hospital periods.

4. The hospital was contacted by a veterinarian with complaints that the skin of her hands appeared as itchy spots, which then turned into papules and bubbles in a few hours, swelling of the hands, which spread rapidly in the proximal direction, symptoms of intoxication. During the survey, it was found that a day later, the patient was conducting an autopsy of a dead animal with an unclear diagnosis, during the autopsy were small injuries to the brushes.

What can a previous diagnosis be? Directions of pharmacotherapy.

Test tasks

1. What group of drugs is most effective against the causative agent of anthrax:

1. penicillins
2. tetracycline
3. fluoroquinolones
4. aminoglycosides
5. macrolides

2. When prescribing antibacterial drugs in patients with urinary tract infection, it is necessary to take into account:

1. Spectrum of antimicrobial action.
2. Ur urine.
3. Sensitivity of microflora in bacteriological seed cultures of urine.
4. Degree of nephrotoxicity of the drug.
5. All of the above is true.

3. In the case of an allergic reaction to a medicine in the history:

1. it is necessary to prescribe this medication in the half dose
2. Never appoint this drug.
3. It is possible to appoint this drug in case if the allergic reaction was a long time
4. it is necessary to appoint a drug with adrenaline
5. it is necessary to appoint a medicamentous drug together with preparations of calcium.

4. In what clinical situations prescribe antibiotics for bronchial asthma?

1. in the presence of a multitude of dry wheezing on both sides
2. in the presence of signs of bacterial infection in the broncho-pulmonary system
3. with severe exacerbation of asthma
4. When exacerbation of asthma caused by respiratory viral infection
5. when exacerbated by asthma in the elderly.

5. Select a group of antibacterial drugs that are most effective in meningococcal meningitis:
1. Macrolides
2. Penicillin
3. Fluoroquinolone
4. Aminoglycosides
5. Tetracyclines.

6. Toxic effects of medicinal products are the result of:
1. Changes in the kinetics of the drug.
2. Increased activity of hepatocytes.
3. Overdose of drugs.
4. Genetically determined by enzymopathy.
5. Low range of therapeutic drug concentrations.

7. The development of diarrhea after the course of antibiotic therapy is:
1. An allergic reaction.
2. The reaction of Yarish-Herxheimer.
3. Idiosyncrasy.
4. The manifestation of the toxic effect of the antibiotic.
5. Violation of immunobiological properties of the organism.

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