Kozishkurt E. V. Prevalence of acute intestinal infections and their role in human pathology (review). Journal of Education, Health and Sport. 2019;9(9):1308-1323. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3687260
http://ojs.ukw.edu.pl/index.php/johs/article/view/7694

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.09.2019. Revised: 16.09.2019. Accepted: 30.09.2019.

PREVALENCE OF ACUTE INTESTINAL INFECTIONS AND THEIR ROLE IN HUMAN PATHOLOGY (REVIEW)

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Abstract

Acute intestinal infections (AII) are one of the most common infectious diseases, the eighth most important cause of annual mortality among all age groups, and the fifth most common cause of death among children under 5 years of age worldwide. From 3 to 5 million children are affected each year, with nearly 446.000 fatalities. This is facilitated by: international migration, the interstate exchange of food products and raw materials of animal origin, the intensification of industrial production of livestock and poultry products, urbanization, activation of recreational processes, climate change, environmental degradation. Viruses are the dominant etiological factors, both during the period of a seasonal increase in the incidence of AII (65-76% of cases) and according to the analysis of sporadic cases (62.6%). The most common and significant viral agents of the causative agent of AII rota-, calici, adeno- and astroviruses. In most acute respiratory infections, the immune response formed in childhood is sufficient protection against infection in more advanced adulthood. The main reason for the absence or insufficiency of immune defense is a significant genetic and antigenic diversity of viral pathogens. The only means of identifying viruses are molecular genetic methods.

Currently, there are no effective measures to deal with outbreaks of AII. The quality of drinking water remains the most important way of their prevention, which is a very difficult task for many countries. The development of vaccines for most viral pathogens is difficult.

One of the promising methods for preventing the incidence of AII is the use of boiled water and the development of food processing technologies with a high risk of virus contamination, which include seafood, fresh vegetables and ready-to-eat foods.

Key words: acute intestinal infections; rotaviruses; noroviruses; prevention

Acute intestinal infections (AII) are found everywhere in the world and are one of the most common infectious diseases. By the number of registered cases, they are second only to acute respiratory tract infections [1].

Numerous materials on record indicate extremely negative impact of this group diseases on the health of the population and on the demographic processes occurring in different territories. So, according to C. Troeger et al., AII is the eighth most important cause of annual mortality among all age groups, leading to more than 1.6 million deaths, and the fifth cause of death among children under 5 years of age worldwide [2]. According to WHO, in 2010 58% of deaths worldwide among children under 5 years of age were due to infectious diseases. Their 11% were due to diarrheal infections, and in European Region among children under 5 years old, they caused 13% of fatalities [3].

Chow C. M. et al. report that diarrheal diseases annually affect from 3 to 5 million children, while almost 446 000 die [2, 4]. In developing countries, the incidence and mortality from gastroenteritis is increasing, being one of the main public health problems. The causes of AII are bacteria, protozoa and viral pathogens [5].

G. Mayindou et al. indicate that diarrheal diseases remain the leading cause of death in Africa [6]. They are supported by J. Hyun et al. and other researchers, arguing that diarrhea is the second leading cause of death among children under five y. o. on the continent [7-11].

A high incidence of diarrhea is promoted by: population international migration, interstate exchange of food and raw materials of animal origin, intensification of industrial production of livestock and poultry products, urbanization, activation of recreational processes, climate change, environmental degradation and, as a result, negative changes in humans immune status [12, 13].

The ubiquitylation of these diseases, defeat of the able-bodied population, occurrence of nosocomial and epidemic outbreaks, leading to the development of severe and / or complicated forms, imperfection of diagnostic methods, absence of specific treatment and prevention methods indicate their high epidemiological and socio-economic importance.

In recent decades, the use of high-tech diagnostic methods for AII has led to new developments in the establishment of a clinical diagnosis. Modern advances in molecular biological diagnostics have made it possible to identify new etiological agents that affect the human gastrointestinal tract, namely enteropathogenic viruses. The spectrum of pathogens of AII is quite large. It includes a significant amount of both bacterial and viral infectious agents. The etiological structure of diarrheal diseases does not depend so much on the region where the studies were conducted, but on the methods and techniques of pathogens detection. So, according to researchers made in Russian Federation and Belarus, in 12.0-33.0% of cases, AII are caused by bacteria (usually opportunistic microorganisms), in 35.3-71.7% by viruses, and in 17.1-28. 0% of cases etiology is unknown [14-16].

Viruses are the dominant etiological factors both during the period of seasonal increase in AII morbidity (65-76% of cases), and according to the analysis of sporadic cases (62.6%). In 47.9% of cases it was monoinfection, and in 7.5 - 14.7% of cases - mixed infections [14].

In studies conducted in Tajikistan, bacterial pathogens, rotaviruses (RV), adenoviruses (ADV) and astroviruses (ASV) were determined in samples of native material. In 27.0% of cases AII are bacterial, and in 52.0% of cases they are of viral origin [17]. In Ukraine, etiological confirmation has predominantly RV gastroenteritis [18].

The list of viral agents that cause intestinal upsets is constantly growing.

Today, representatives of at least 8 different virus families are associated with acute gastroenteritis (AGE): *Reoviridae* (genus *Rotavirus),* *Caliciviridae* (genus *Norovirus, Sapovirus),* *Adenoviridae* (genus *Mastadenovirus*), *Astroviridae* (genus *Astrovirus*), *Picornaviridae* (genus *Enterovirus, Parechovirus, Kobuvirus),* *Coronaviridae* (genus *Coronavirus, Torovirus),* *Parvoviridae* (genus *Bocavirus),* *Picobirnaviridae* (genus *Picobirnavirus)*

The spectrum of possible etiological agents of human gastroenteritis continues to expand as far as isolation of previously unknown viruses. The diseases caused by them are less studied, since their detection was carried out mainly in the framework of scientific research [19, 20].

Many researchers believe that on a global scale, the most common agents for diarrheal diseases are *Campylobacter sp., Cryptosporidium sp.*, enterotoxigenic *Escherichia coli* and *Shigella sp*. and enteropathogenic viruses (rotaviruses A, noroviruses of genogroup II, astroviruses) [21].

At the same time, in the 21st century, significant changes occurred in the etiological structure of intestinal infections. If at the end of the twentieth century the leading role in the occurrence of diseases belonged to bacterial pathogens, then over the past decades there has been a clear dominance of viruses. Currently, viral diarrhea accounts for up to 80% of all intestinal infections in childhood [22–25].

Viral diarrhea differs from bacterial diarrhea in that they spread rapidly with a rapid onset, with the development of exsiccosis. The epidemic process is characterized by a large number of asymptomatic carriers of infection, the absence of specific clinic manifestation and difficulties in laboratory diagnosis, pathogens are extremely stable in the environment [26, 27].

According to the data of foreign researchers, the most common and significant viral causative agent of AII include rota-, calici, adeno- and astroviruses [28-33]. They cause diarrheal diseases, occurring mainly in the form of acute gastroenteritis. Diseases caused by various types of intestinal viruses are very similar, but there are differences inherent in a particular infection.

The scale of the population outreach by these diseases can be evidenced by the fact that, for example, in Kenya about 2.8-3.3 million people annually suffer from infection caused by noroviruses; 0.45-0.54 million from sapovirusama and 0.77-0 , 95 from astroviruses [34]. Enserink R. et al. indicate the leading role of enteroviruses in the occurrence of acute GE in children in the Netherlands [35].

Intestinal viruses (IV) belong to the class of highly pathogenic agents that pose a serious danger to human health when they go into the drinking water.

This danger is due to severe polymorphism and severity of diseases, duration of virus's survival in environmental objects, high resistance to disinfectants, low infectious dose. The epidemic significance of virus-contaminated water is confirmed by water outbreaks and epidemics of AII, which are often recorded in the world [36, 37].

According to multicenter foreign studies, rotavirus infection (RVI) has a leading place in the structure of AII [22, 26, 28]. RVI is widespread and is registered in both economically developed and developing countries.

In Ukraine, statistical accounting of RVI incidence was introduced in the 90s of the last century. RVI is the most common cause of AII in children, mostly young children, and accounts for up to 60% of all intestinal hospitalizations [1, 39]. The main source of infection is a sick person or carrier. Infected individuals secrete RV in significant amounts for more than 30 days. Children under 3 y. o. are most susceptible to infection. Post-infectious

immunity is short-lived; therefore, up to 70% of children who previously had the disease are re-ill before the age of two [33].

Pathogens are extremely stable in the environment. Foe example, they can persist more than 2 months in tap water and in feces - up to 7 months, at various environmental objects - up to 1 month, on vegetables in a refrigerator - up to 30 days. The virus dies when boiled and treated with strong detergents, for example, 95% ethanol [1].

Rotavirus gastroenteritis (RVG) is registered everywhere, in tropical countries - all year round, with a slight increase in the rainy season, in our country - throughout the year with seasonal increases in January-April. So, in 2011 RV caused 6 outbreaks in various settlements, including Odessa. More than 120 people suffered, and 97 of them were children. During a major epidemic outbreak of RV infection in Odessa in 2000-2001 more than 1300 people were taken. The leading factor in pathogen transmission was contaminated drinking water [27].

In approximately 70% of sick children, virus excretion occurs up until the twentieth day of clinical manifestations, there are cases when the virus is excreted for more than thirty days, and with prolonged diarrhea, up until 450 days. This explains carrier state in healthy children, who are significantly dangerous in the matter of epidemiology [40].

Risk of RV infection among people of different ages was calculated In the USA. It amounted to 0.01% for the general population, 1.0% for elderly persons and 50.0% for humans with various immunodeficiencies. A high level of risk occurs when one drinks water from surface water sources in which RVs are often found [19]. Among AII of viral etiology RVI prevails, however, the limited range of studies that are carried out in practical health care institutions only with the detection of bacterial, opportunistic flora leads to incomplete and insufficient verification of AII cases [16, 38].

RV of group A are the most common cause of severe gastroenteritis in young children in most countries of the world. According to WHO data almost every child during the first five years of life come through RVG, regardless of race and socio-economic status. More than 100 million cases of RVG are registered annually in the world, which result in 600 000 of fatalities [40-42].

C Celik et all. (2015) in line with a long-term observation (2006–2012) studied the influence of climatic parameters (average monthly temperature, minimum monthly temperature, average monthly humidity) on RV A prevalence among patients under 5 y.o. It was found that with a decrease of minimum monthly temperature by 1°C, the detection rate of RVG patients increases by 0.523% ($p < 0.001$). The researchers concluded that weather

changes and related thereto population's receptiveness changes, affect the intensity of RV infections spread [43].

At lenght it was believed that RV affects only the mucosa of the small intestine. However, already at the end of the 70s of the XX century, information appeared about extraintestinal manifestations of RV infection. RNA and RV antigen were detected in children with rotavirus etiology diarrhea blood samples, which can damage to any organ, including the central nervous system. Kubota T.et al. (2011) describe rotavirus encephalitis with cerebellum's damage confirmed by head MRI [44]. Vorobyova M. A. et al. describes a clinical case of rotavirus meningitis in a four-year-old girl, confirmed by the detection of virus RNA in cerebrospinal fluid by PCR, while the virus was detected in the feces by ELISA [45]. Heart damage, increased activity of hepatic transferases are also not ruled out.

Thus, modern data show that the pathogenetic manifestations of RVI are systemic in nature. Taking into account the foregoing, it should be noted that the severity of RVI, as a disease with localized lesions of the mucous membrane of the small intestine and relatively mild course, requires some re-evaluation taking into account

its possible generalization and the formation of extraintestinal manifestations in general and damage to the central nervous system in particular.

Due to the high morbidity and mortality associated with RVI, Rotarix® vaccine was introduced in Brazil. Immunization has helped reduce the prevalence and mortality caused by this agent among children.

RVI vaccination has been introduced into national immunization programs in 20 Latin America countries, including Brazil and Mexico, the USA, Australia and South Africa; in Europe Belgium, Luxembourg, Austria and Finland [46, 47] participate in this program.

According to a number of surveys, in Russian Federation 30-40 thousand people are taken ill with RVI per year [22]. This is significantly less than the cases registered in developed countries. This can be explained by insufficient diagnosis and incomplete registration of infection. The number of sick children under 3 y. o. constitutes 20-30 thousand persons per year. Most children become infected with RV between the ages of 3 months and 2 years. By the end of the 3rd year of life, antibodies to RV, group A are found in 90.0% of children. RV infection creates a certain immunity and protection increases with every contact with the virus. Breastfed children are less likely to have RVG and are more likely to experience asymptomatic or mild manifestations of infection [48]. Prevention consists in strict observance of sanitary-hygienic rules, personal hygiene, and boiled water use [27].

Diarrheal diseases caused by various intestinal viruses are highly contagious with multiple transmission routes. They can be manifested by isolated cases, local group cases, or mass outbreaks with the coverage of various population groups in large territories [49, 50].

Norovirus infection (NRI) is a serious problem in the public health system of many countries all over the world. Noroviruses cause 6-17% of acute intestinal infections [51], and rank high position in childish morbidity [52]. In infected individuals, clinical manifestations of gastroenteritis occurring with dehydration are noted, so they need hospitalization. NVI often occurs in elderly people [53, 54].

Significant genetic diversity and rapid molecular evolution of pathogens are typical for these viruses and it leads to global spread of their new epidemic variants in the world [54-56].

NRVs are highly resistant both to physical and chemical factors, and can retain their properties for a long time (more than 28 days) on different surfaces. The results of studies of treated wastewater indicate that 8.2% of the samples contain NRV [52]. It was found that their complete inactivation occurs when the concentration of free residual chlorine is more than 10.0 mg / L.

NRI is characterized by complex genetic diversity and the rapid molecular evolution of pathogens, which has led to the global spread of new epidemic variants in the world [57]. NRVs are divided into 5 gene groups (GI-GV), of which GI representatives are obtained exclusively from native human material, GII and GIV - from humans and animals (while maintaining guest specificity), GIII and GV - only from animals. It has been proven that NRVs GII cause diseases 10 times more often than GI [28]. NRV genogroups are variable and divided into genotypes, which, in turn, have subgenotypes, or genovariants. The evolutionary mechanisms governing the conservation and emergence of new NRV strains in humans are still unknown. NRV GI is found in patients with gastroenteritis in 0.6-17.0% of cases, more often with sporadic morbidity, and is rarely identified with outbreaks. In GI, 8–16 genotypes are distinguished; the most common NRV group is GII. In the structure of NRV infections its share is up to 80-90% of cases. NRV GII is the main etiological agent for outbreaks of gastroenteritis worldwide. Within GII, 19-23 genotypes are identified. NRVs of different genotypes can circulate simultaneously, therefore outbreaks of the disease can be caused by different NRV GII genotypes. HB GII of genotype GII 4 at modern conditions cause AII epidemics [28].

Due to the genetic diversity of NRV and constant formation of new variants, efforts to create a vaccine were not successful [57].

The reservoir and source of NRI is a sick person or carrier. The maximum concentration of viruses in stool samples is found on the 1-2 day of the disease. The allocation of virus from convalescents continues for 5-47 days. HIV patients (4–6 months) and transplant recipients who received immunosuppressive therapy (24 months) remain carriers of the virus for longer [56]. NRV was isolated in 9.1% of employees of kindergartens without signs of infection [30].

NRV infection is a highly contagious disease, but despite this, a significant number of people are insusceptible to it. The only nucleotide mutation (G428A) in the fucosyltransferase gene (FUT2) on the 19th chromosome provides reliable protection against infection in 20% of the Caucasian population [58].

The main mechanism of NRV transmission is fecal-oral, which is realized by contact-household, food and much less often - waterways. The aerosol transmission route is not excluded [59]..

At outbreaks, causal mechanisms often fail to be identified [52].

According to some researchers, NRV epidemic process at the present stage is manifested by sporadic incidence with seasonal rises (autumn, winter, spring) and outbreaks regardless of the season [56, 60]. According to others, in winter months they recorded 52.7% of cases of NR infection and 41.2% of outbreaks, in the cooler months - 78.9 and 71.0%, respectively [30]. Other researchers argue that the dynamics of infection does not have significant differences depending on season. Sporadic incidence is characterized by a significant genetic diversity of NRV. Its outbreak is usually caused by a dominant genovariant. In Europe during 2001-2006, 7636 outbreaks of the virus were recorded. In almost all countries GII 4 is a predominant variant. Outbreaks have been reported in kindergartens, educational institutions, medical institutions, tourist groups, and on cruise liners [60].

Clinically, diseases caused by noroviruses are characterized by the sudden onset of vomiting and diarrhea [61]. Symptoms usually last from 2 to 4 days and, in some cases, longer. The peak excretion of the pathogen lasts from 2 to 5 days after infection [62, 63].

Sabria et al. (2016), indicate that both asymptomatic carriers and those who have had norovirus gastroenteritis during outbreaks release the virus up to 3 weeks after the disease [64]. Experimental studies have shown that NRV can survive on the surfaces of objects for a long time without losing pathogenic properties [65]. It is because of the ability of viruses to survive on household items and equipment that outbreaks in nursing homes are caused [66].

Adenoviruses in many cases cause water outbreaks of acute intestinal infections. They are included in the list of water pollutants that are not standardized and are found in wastewater, river water, ocean water, and surface waters; often in number significantly prevail over enteroviruses (EV) [67]. In contrast to diseases caused by other intestinal viruses, seasonal incidence increases are not characteristic for those of acute adenoviral etiology. More often children up to 3 y. o. are sick, diarrhea has a protracted course [68].

According to some epidemiological studies, human astroviruses often cause acute intestinal infections, mainly in young children (mainly under 1 year) and elderly people. Infection is recorded during the year without much seasonality [31 34-36, 49, 50].

According to Russian researchers, 10.8% of preschool workers are carriers of astroviruses with pathogenicity. In many cases, infection does not always lead to the development of the disease, however, an immune response was observed in almost 71% of 3-4 y.o. children under examination, but in their history there were no signs of disease [55, 69].

Among EV, the etiological role in the development of acute intestinal infections is most often belongs to Coxsackie B viruses [18, 20, 21, 22, 24] and ECHO [11, 14, 18]. Outbreaks of EV gastroenteritis are more often local, among young children. According to the researchers, the incidence of EV in the stool samples of children with acute diarrhea is 9.7%. In 5.1% of cases, EV is found in mixed infections with other viruses [28].

Human parechovirus is a common etiological factor in AII and occurs in 13.4% of stool samples in children with diarrhea under 2 y. o. [28, 70].

Thus, the problem of viral etiology AII is relevant in connection with morbidity rate increase, in particular among young children. In most acute intestinal infections, the immune response formed in childhood is sufficient protection against infection in more advanced adulthood. The main reason for the absence or insufficiency of immune protection against rotaviruses and caliciviruses is their significant genetic and antigenic diversity. Serological identification of viral pathogens of acute intestinal infections is difficult due to the lack of common group-specific antigenic determinants. Therefore, the only means of identifying viruses of this group are molecular genetic methods.

Currently, there are no effective measures to deal with AII outbreaks. The quality of drinking water remains the most important way of their prevention, which is a very difficult task for many countries of the world. The development of vaccines for most viral pathogens is difficult due to significant genetic diversity.

One of the promising methods for the prevention of acute intestinal infections is the development of food processing technologies with a high risk of viral pathogen contamination, which include seafood, fresh vegetables and ready-to-eat foods. To expand the ability to combat these pathogens, it is necessary to develop comprehensive research and introduce programs to disseminate knowledge on food virology.

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