ORIGINAL ARTICLE

CONTENTS

Necrotizing enterocolitis in premature infants at different gestation ages

Kateryna Doikova[1], Michael Jerdev[1], Larysa Koval[2], Dmytro Valantsevych[3]

[1]BARUCH PADEH MEDICAL CENTER, PORIA, ISRAEL

[2]ODESA NATIONAL MEDICAL UNIVERSITY, ODESA, UKRAINE

[3]COMMUNAL NONPROFIT ENTERPRISE "CITY CLINICAL HOSPITAL №11" ODESA CITY COUNCIL, ODESA, UKRAINE

ABSTRACT

Aim: To compare X-ray signs in different gestational and body weight groups of patients with NEC.

Materials and Methods: We conducted a retrospective study, enrolling 52 preterm newborns with symptoms of NEC regardless of onset time, who underwent treatment at Neonatal Intensive Care Units in Municipal Non-commercial enterprise "City Children Hospital №2", Odesa. The patients were split into 3 clinical groups: very preterm newborns (VPN), moderately preterm newborns (MPN), and moderately preterm newborns with intrauterine growth restriction (MPN+IUGR).

Results: In the VPN group NEC was diagnosed at stage II (58,82±12,30) % and III (41,18±12,30) % by Bell MJ, p>0,05. In the group MPN+IUGR, NEC stage II (33,33±14,21) % and stage III (66,66 ±14,21) %, p>0,05, were equally observed. In the MPN group, NEC was diagnosed at stage I (41,67±10,28) % and II (58,33±10,28) %, p>0,05, without prevalence of any. Also only localized forms were observed. In VPN, we observed localized forms in most cases, while diffuse forms were diagnosed in (11,76±8,05) % cases, p<0,05. In the MPN+IUGR group, we found diffuse form of the NEC in half of the cases – (50,00±15,08) %. In the VPN and MPN+IUGR groups, NEC developed at 13,23±0,39 and 14,33±1,19 days, respectively. However, in MPN without IUGR, NEC developed at 17,75±0,55 days, significantly later than in the MPN+IUGR group, p<0,05.

Conclusions: We have described distinct features of NEC in MPN with IUGR. Compared to MPN without IUGR, NEC had more severe course and earlier manifestation in such neonates.

KEY WORDS: preterm infants, abdominal radiographs, low birth body mass

Wiad Lek. 2024;77(3):409-416. doi: 10.36740/WLek202403106 DOI

INTRODUCTION

Necrotizing enterocolitis (NEC) is one of the life-threatening conditions in newborn infancy. NEC treatment is one of the most complex and crucial for better outcome in Neonatal Intensive Care Units (NICU) [1,2].

Incidence rate of NEC in preterm infants population is significantly higher compared to full-term [3]. It is typical in NEC that the lower gestational age and birth body mass, the latter is the expected onset, higher complications rates and worse outcome [4]. Reviewed literature provides that gastrointestinal perforations incidence rate in newborns is at 20-30% [5]. Mortality rate and spread of this disease appear to be increasing in the last decades, mostly due to increase of underweight preterm babies in the population [6]. Incidence rate is reported at the level of 1-5% in all NICU patients and 5-10% for extremely low birth weight newborns [7]. Clinical onset often appears asymptomatic [8]. The mortality rate of NEC in newborns varies and is estimated to be 10-60% [9-12].

The problem of estimating probability of NEC development, early and timely diagnosis became even more significant with introduction of governmental program for protection and care of newborns with very low and extremely low birth weight in Ukraine [13].

The distribution of NEC incidence rate in the world is mostly even and is about 2-13% in newborns with very low and extremely low birth weight [4]. For instance, multicentric studies in US and Canada reported average incidence of 7% in newborns with birth weight 500-1500 g [12]. This significant variation can be attributed as much to nutritional protocols in different countries as to different survival rates of newborns from this group across centers within the same country.

NEC can be divided into following categories by triggering mechanisms:

- Posthemotransfusion – onset is typically within 48 hours after erythrocytic mass transfusion.
- Triggered by lactose or cow protein intolerance in bottle-feeding newborns.
- Triggered by bacteria [14].
- Triggered by viral infection.
- NEC because of hypoxia or ischemia longer than 72 hours.

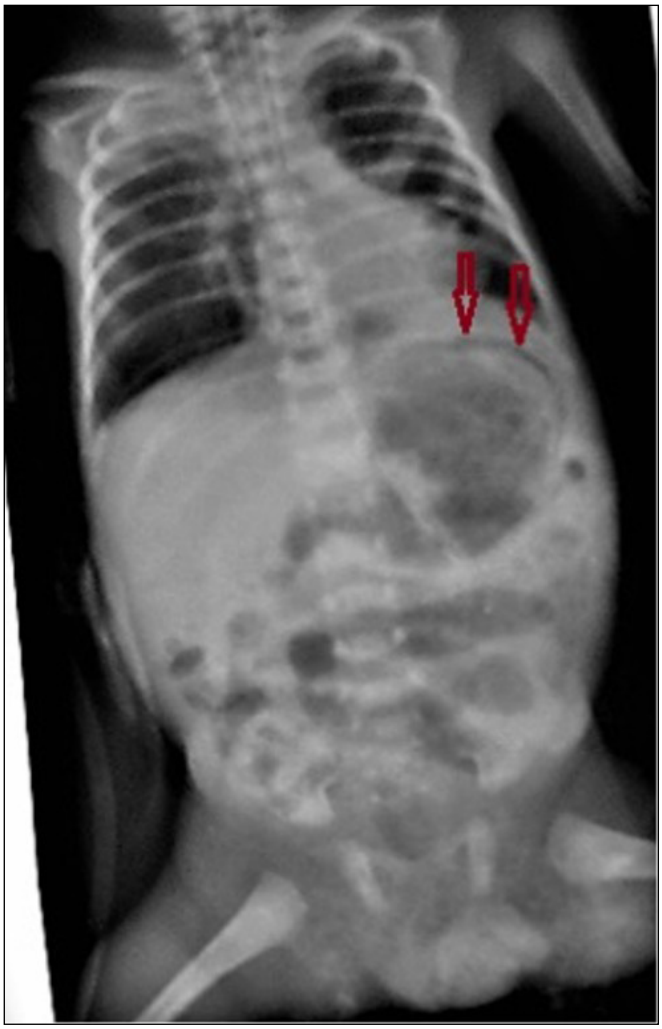

Fig. 1. Chest and abdominal X-ray, upright. Localized gastric substage of NEC. Neonate 11d, birth body weight 1600 g. 30 weeks gestation, VPN group (Oxygen dependent. Endotracheal tube, Nasogastric tube).
Right upper lobe atelectasis. Endotracheal tube at carina level. Bilateral hyperventilation. Flattening of right hemidiaphragm, right lateral sinus partially opaque. Left lateral sinus deepened due to slightly elevated left hemidiaphragm. Nasogastric tube is touching gastric wall at major curvature. Gastric wall at fundus is noticeably thickened with intramural gas shown as a linear translucency (arrows). Intestinal loops are located atypically, intermittent pneumatosis and reduced pneumatization. Liver somewhat rounded with inferolateral margin round.

– NEC resulting from cold stress in preterm babies with body weight less than 2 kg.
– NEC in twins.
– Triggered by gastroschisis.
– Related to congenital heart diseases and anomalies.
– Related to other congenital diseases and anomalies.

We would also like to emphasize that NEC is not a single disease but a collective term covering multiple pathomorphologically similar diseases with different pathogenesis [5].

In general, all factors that cause blood circulation centralization and/or disruption of blood flow in superior mesenteric artery system regardless of development mechanisms favor the NEC development, such as:

– Intrauterine fetal stress and asphyxia.
– Maternal drug addiction (especially cocaine).
– Congenital immunodeficiency in newborns.
– Gramm-negative bacteria translocation through mucinous membrane of intestines, resulting in ischemia and intestinal wall necrosis.

In clinical setting, when estimating probability of NEC, it is determining to consider gestational underdevelopment of preterm intestines, circulation centralization (not necessarily leading to mesenteric steal syndrome), intestinal wall oxygenation pathologies, which may also be caused by preserving intrauterine features of intestinal circulation (immature circulation) [4, 5].

Timely medical imaging is a significant factor for improvement clinical course prognosis since radiological symptoms appear earlier than clinical. In turn, this allows for early feeding adjustments and timely therapy start [8].

Everything stated above transform the task of setting a timely and validated diagnosis of NEC in the NICU setting into a multiparametric problem. It requires a systemic and interdisciplinary team approach. In the case of our hospital, collaboration of neonatologists, pediatricians and radiologists was essential.

AIM

The aim of this study is to compare X-ray signs in different gestational and body weight groups of patients with NEC.

MATERIALS AND METHODS

We conducted a retrospective study, enrolling 52 preterm newborns with symptoms of NEC regardless of onset time, who underwent treatment at NICU in Municipal Non-commercial enterprise "City Children Hospital №2", Odesa in the period 2014-2022 years. The included 52 patients (males (48,08±6,93) %, females (51,92±6,93) %) were split into 3 groups (Table 1). Entry criteria: Gestational age 29-36 weeks (dated by antenatal ultrasound or clinically). We excluded the patients with radiological signs suspicious of NEC without further clinical confirmation or development from this work. Other exclusion criteria include: lethal congenital anomaly, twin-twin transfusion, significant multi-organ failure prior to trial entry, symmetric IUGR.

Imaging performed using X-ray machine Multimobile 2.5 (Siemens LTD, India, Germany), mobile X-ray system ULTRA 200A (EcoRay, Seoul, South Korea). In order to ensure proper patient positioning, reduce patient

Table 1. Clinical groups

Clinical group	Number of patients (n, %)
Very preterm newborns (VPN) (29-32 weeks) with very low birth body mass (<1500 g)	16, (32,08±6,41) %
Moderately preterm newborns (MPN) (33-36 weeks) with low birth body mass (<2500 g)	24, (45,28±6,84) %
Moderately preterm newborns (33-36 weeks) with intrauterine growth restriction (MPN+IUGR)	12, (22,64±5,75) %

Table 2. Clinical characteristic of patients

Measures Groups	Gestation, weeks (M±m)	Weight, g (M±m)	Onset of NEC, days (M±m)
VPN, (n=16)	30,52±0,23	1358,82±16,10[1]	13,23±0,39[1]
MPN, (n=24)	33,91±0,190	2010,01±56,44[1,2]	17,75±0,55[1,2]
MPN+IUGR, (n=12)	34,16±2,84	1471,16±122,63[2]	14,33±1,19[2]

[1] – the significance of difference between groups VPN and MPN: p<0,001, [2] – the significance of difference between groups MPN and MPN+IUGR: p<0,01.

Table 3. Radiological changes structure in preterm neonates with NEC

Stage by Bell MJ	Substage		Number of patients (n, %)
Neonates from the VPN group			
Stage II	Localized	Gastral	3 (17,65±9,53) %
		Intestinal	5 (29,41±11,39) %
		Multiple segments	2 (11,76±8,05) %
Stage III	Localized	Gastral	4 (23,53±10,60) %
		Intestinal	1 (5,88±5,86) %
	Diffuse		2 (11,76±8,05) %
Neonates from the MPN group			
Stage I	Localized	Intestinal	10 (41,67±10,28) %
Stage II	Localized	Intestinal	12 (50,00±10,43) %
		Multiple segments	2 (8,33±5,76) %
Neonates from the MPN+IUGR group			
Stage II	Localized	Multiple segments	4 (33,33±14,21) %
Stage III	Localized	Multiple segments	2 (16,67±11,24) %
	Diffuse		6 (50,00±15,08) %

dose, protect staff from radiation, and enhance X-ray unit productivity, we utilized the Oniko (ONIKO Ltd, Ukraine) X-ray patient stand, equipped with a special holder for children up to 1 year old. This table facilitates the upright suspension of children without causing any strain on the body. Additionally, we designed a custom plastic insert to enhance limb security, improved skin protection with a soft cotton surface, and included additional spine and body supports. The custom plastic base is then placed in foam rubber-filled holders on a metal base with adjustable radiation protection covers. This device enables safe upright diagnostic imaging for children under 1-2 years old, weighing less than 15 kg, with all body parts securely positioned and fixed without harm to the patient.

All newborns also underwent abdominal ultrasound to evaluate mesenterial circulation, and suspected intestinal ischemia, infiltrative changes, ascites, pneumatosis portalis, which was not reflected in this paper. For image reporting, we used modified NEC classification by Bell MJ [15].

All newborns admitted to NICU had a chest and abdominal X-ray performed during the first 24 hours. The imaging was repeated at least after 6 hours from the initial imaging for those newborns with indications. In the case with erythrocyte mass transfusion, all patients underwent an abdominal X-ray after 24 hours regardless of symptoms.

Other cases when abdominal X-ray was performed:

- in cases when one of the twins/triplets had symptoms of NEC, imaging of apparently healthy child (children) was obligatory
- in patients with congenital heart pathology during clinical worsening or deterioration
- in bottle-fed newborns preventively

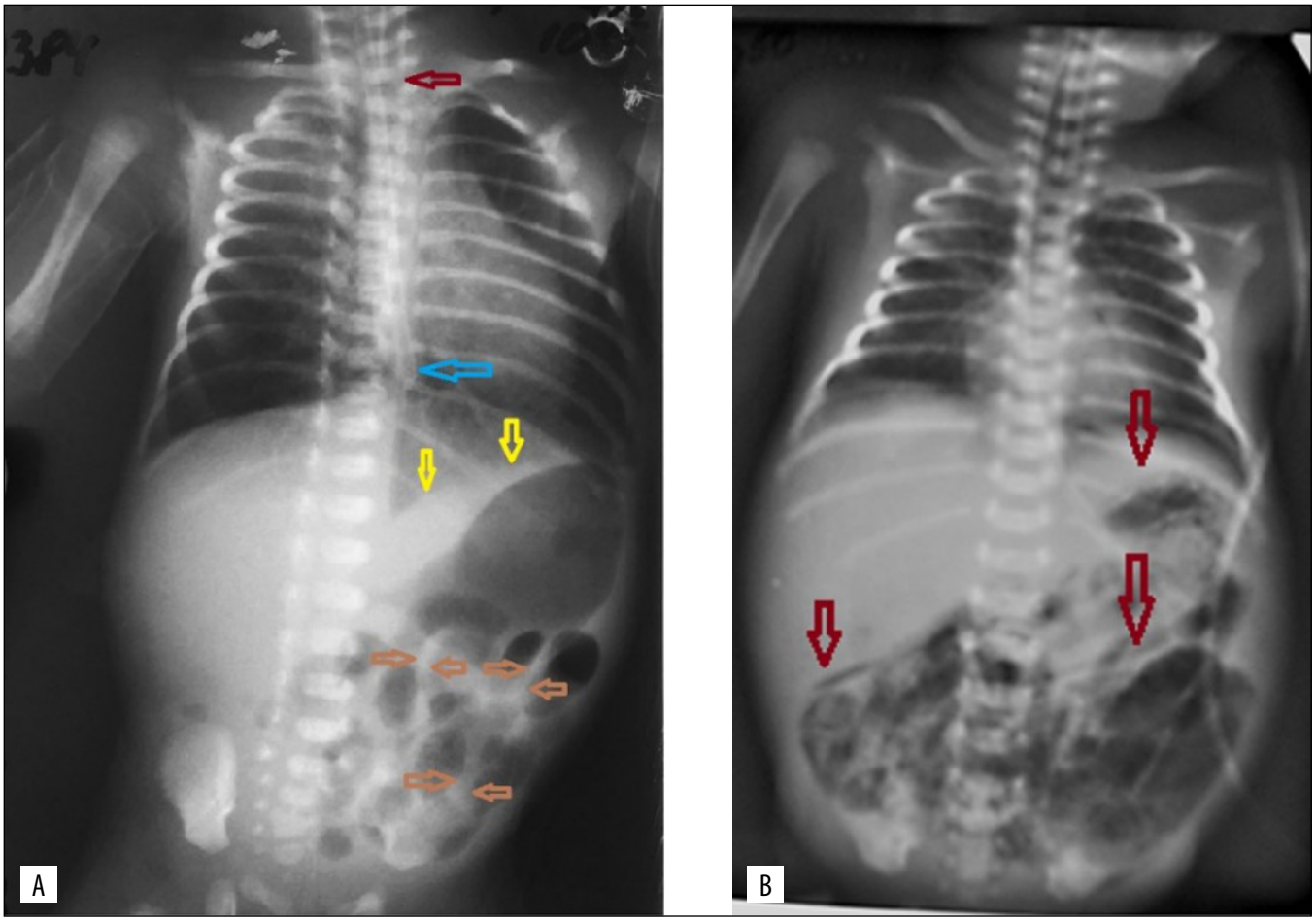

Fig. 2.A. Chest and abdominal X-ray, upright, slight rotation to the left. Suspected NEC Neonate 15d. Suspected NEC. Neonate 15d, body birth weight 1350 g, 32 weeks gestation. VPN group.
Endotracheal tube (red arrow) is located distally. Bilateral hyperventilation: posterior-basal margin of left lung (yellow arrows) is moved caudal, causing not enlarged spleen to visualize significantly lower. Tip of nasogastric tube (blue arrow) is located above cardia in esophagus. Gastrointestinal hyperpneumatosis. Some spaces between loops are widened. Intestinal walls are thickened on significant duration of intestine (brown arrows). The liver has a rounded shape, slightly enlarged.
On cardiac ultrasound: perimembranous ventricular septal defect, open oval window, open arterial duct (not shown). Clinical presentation: NEC symptoms, remittent fever, diffuse intravascular coagulation, bloody stool. No lab results abnormalities.
B. Chest and abdominal X-ray, upright. Diffuse form of NEC. (Same patient as in figure 2A) 35 days (as image F-G). VPN group.
Endotracheal tube, Nasogastric tube. Diffuse hyperpneumatosis of the stomach and intestines. Linear radiolucencies are caused by intramural gas (red arrows). The liver is enlarged and has a rounded shape.

- in patients with umbilical catheterization longer than 3 days, within the first 24 hours after its removal regardless of symptoms.

To compare patient characteristics, we determined distribution types and applied appropriate descriptive statistics methods. We determined the arithmetic mean (M), the arithmetic mean error (m), and parametric Student test with a p-value <0.05 was considered statistically significant. The statistical analyze was performed with GNU Project (2015) (GNU PSPP (Version 0.8.5) [Computer Software]. Free Software Foundation. Boston, MA).

This study was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association "Ethical principles for medical research involving human subjects". The informed consent was taken from parents and guardians of all children involved in the study.

RESULTS

Results evaluation revealed a significant discrepancy in clinical course of NEC in neonates from the MPN+IUGR group. Compared to the neonates without IUGR, children from this group had a much earlier onset, similar to the VPN group (Table 2).

Further analysis of radiological signs of NEC in different clinical groups revealed several features. In the VPN group, radiological picture was of the stage II (58,82±12,30) % (Fig. 1., Fig. 2. a, b) and III

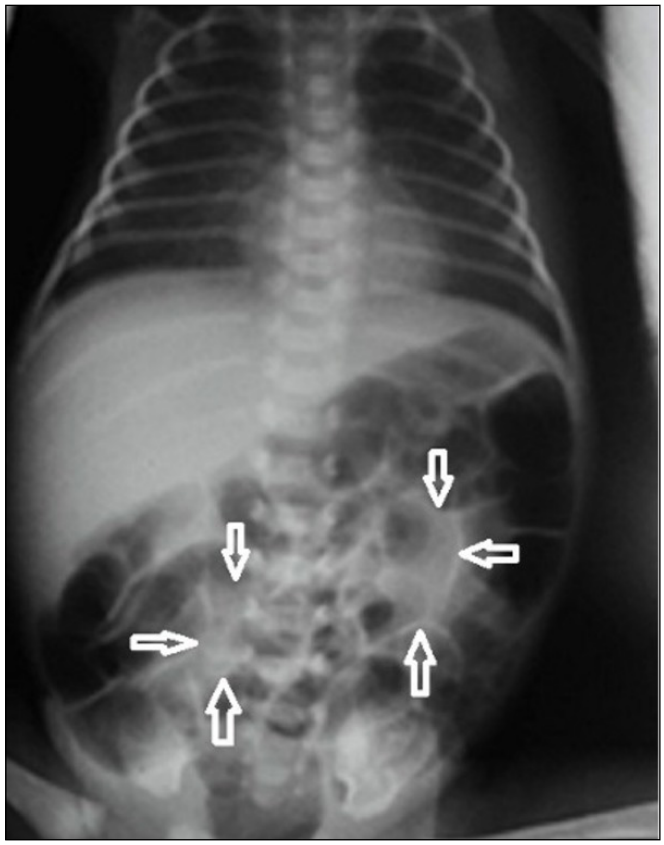

Fig. 3. Chest and abdominal X-ray, upright. Suspected NEC. Neonate 14d, birth body weight 1350 g, 33w gestation age. First of the triplets. MPN+IUGR group
Intestinal pneumatosis. Local widening of interloop spaces caused by fluid collection (arrows). No signs of hepatosplenomegaly.

(41,18±12,30) % by Bell, p>0,05. Moreover, localized substages with isolated gastric (Fig. 1.) and intestinal involvement were observed in a similar number of patients (Table 3).

In the MPN group, imaging symptoms typical for stage I and II were observed equally (41,67±10,28) % and (58,33±10,28) %, respectively p>0,05, with predominantly localized intestinal substage. Multiple segments involvement was observed only in 2 cases (Table 3).

As with the VPN group, children from MPN+IUGR group (Figure 3) also had prevalence of stages II and III by Bell, although type III was observed more often (66,66 ±14,21) % compared to stage II (33,33±14,21) %, p >0,05. From distinct features, we found that localized substage of NEC manifested with multiple segments involvement only (Table 3).

Another distinctive feature in the MPN+IUGR group was that half of the patients (50,00±15,08) % had a diffuse stage III clinical presentation (Fig. 4. a-d), which was significantly more often than in the VPN group (11,76±8,05) %, p<0,05, (Fig. 2. a, b). In the MPN group similar radiological presentation was not observed (Table 3).

DISCUSSION

Our study focused on researching NEC presentation with IUGR. Majority of authors, who studied NEC, considered IUGR as a risk factor for NEC in preterm neonates [15]. In our study however, we stress the distinct features of NEC clinical course and radiological features in neonates from this group.

Our colleagues research shows that most NEC cases in preterm neonates were observed at stage III by Bell, considering all gestational age groups, extremely low birth weight included [16]. In our study we separately observed children with NEC and different grades of prematurity. A distinct feature of NEC clinical manifestations in the MPN group is absence of cases with stage III by Bell, while in children with the same gestational age and IUGR, such patients represented half of the cases (50,00±15,08) %. To some extent our research is supported by paper by Hassan et al., who concluded that low birth weight in preterm neonates is a risk factor for NEC [17]. The clinical onset we found is similar to that from referenced sources. In particular it was reported to be on 14.44 (4.75–21.25) day with average gestation age 33.06 (30.25–36.14) [18]. However, different median of 22 days [16] with gestation age median at 33 weeks [19] was also reported. Overall, onset estimation in different sources is characterized by a marked variability and typically consider all preterm neonates regardless of the prematurity grade. Our research has shown that depending on gestation ages, there is a difference in NEC onset time as much as clinical symptoms. Considerations for IUGR also have demonstrated that NEC clinical manifestations were different from a similar patient group without IUGR as well.

The methodological limitations of the current study include relatively small size of the clinical groups. Thus, we were unable to consider neonates with congenital heart anomalies separately.

As a future perspective we consider studying radiological features of NEC in full-term neonates with normal birth weight and IUGR.

CONCLUSIONS

1. NEC in children from VPN and MPN+IUGR groups manifested in a similar timeline at 13,23±0,39 and 14,33±1,19, p >0,05 days, respectively.
2. In VPN and MPN+IUGR groups, radiological findings were represented exclusively by stages II and III by Bell, while in the MPN group – by stages I and II.
3. In MPN group, NEC manifested with only localized substage. In MPN+IUGR group, a diffuse stage III cases were observed more often than in the VPN group.

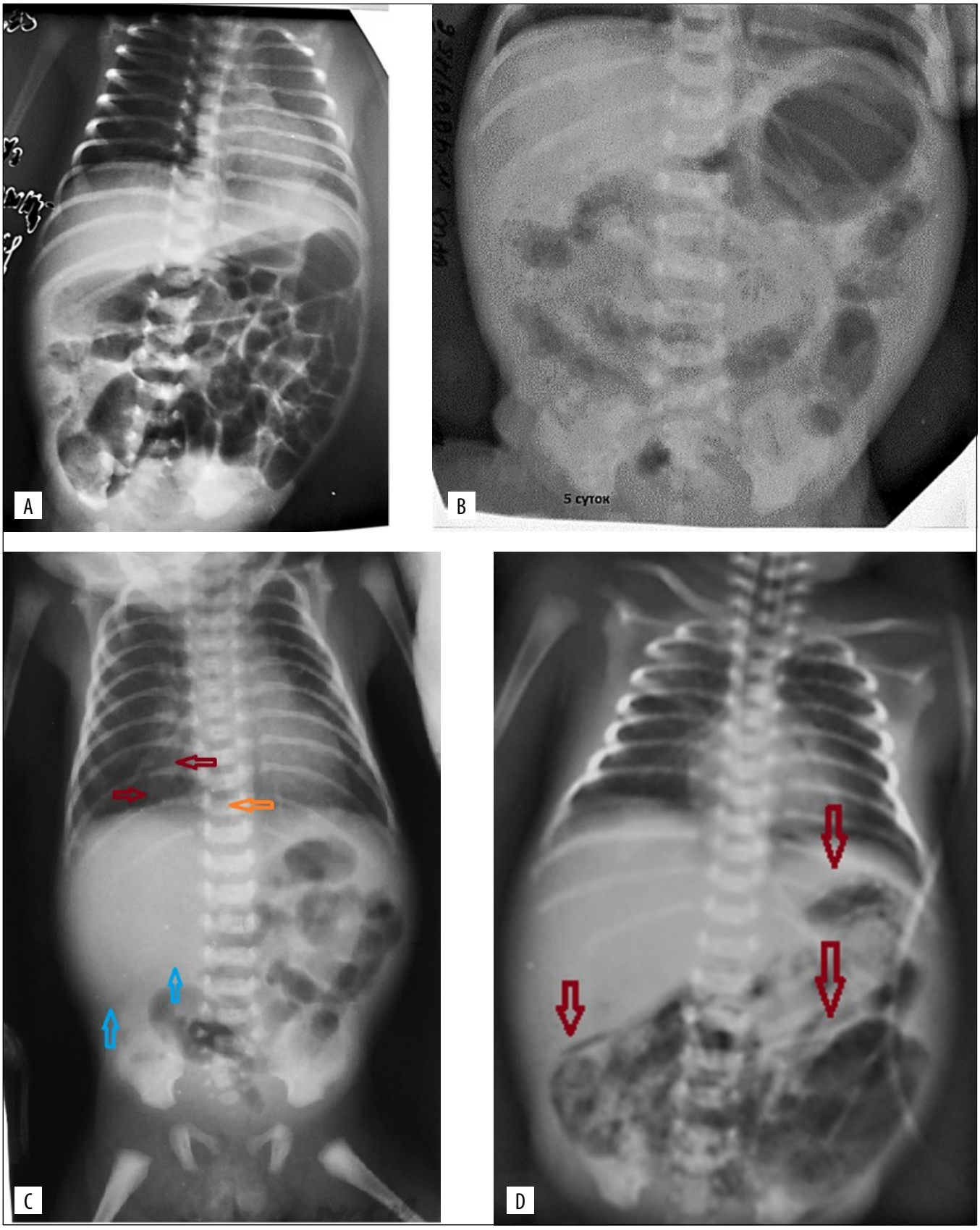

Fig. 4. A. Chest and abdominal X-ray, upright. Suspected NEC. Neonate 7d, birth body weight 1120 g, 33w gestation age, first of the twins. Received parenteral feeding. MPN+IUGR group.
Intestinal hyperpneumatosis. Small and large bowel proportion is changed. Colon may not be followed in all parts; certain levels of displacement and haustration can be seen. B). Abdominal X-ray, upright. Diffuse form of NEC, Pre-perforation phase. Neonate, 15 d (Same patient as in figure 3A). MPN+IUGR group.

REFERENCES

1. Garg PM, Paschal JL, Ansari MAY et al. Clinical outcomes and gestational age based prediction of pneumatosis intestinalis in preterm infants with necrotizing enterocolitis. J Neonatal Perinatal Med. 2022;15(4):803-812. doi: 10.3233/NPM-210971. DOI
2. Aurora M, Keyes ML, Acosta JG et al. Standardizing the Evaluation and Management of Necrotizing Enterocolitis in a Level IV NICU. Pediatrics. 2022;150(4): e2022056616.. doi: 10.1542/peds.2022-056616. DOI
3. Frid G, Reppucci M, Lum T et al. Comparison of Necrotizing Enterocolitis in Pre-mature Infants vs. Term-Born Infants With Congenital Heart Disease. Front Pediatr. 2021;20:9:802607. doi: 10.3389/fped.2021.802607. DOI
4. Alsaied A, Islam N, Thalib L. Global incidence of Necrotizing Enterocolitis: a systematic review and Meta-analysis. BMC Pediatr. 2020;20(1):344. doi: 10.1186/s12887-020-02231-5. DOI
5. Singh DK, Miller CM, Orgel KA et al. Necrotizing enterocolitis: Bench to bedside approaches and advancing our understanding of disease pathogenesis. Front Pediatr. 2023;10:1107404. doi: 10.3389/fped.2022.1107404. DOI
6. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. 2011;364(3):255-64. doi: 10.1056/NEJMra1005408. DOI
7. Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. Drugs. 2008;68(9):1227-38. doi: 10.2165/00003495-200868090-00004. DOI
8. Ahle M, Ringertz HG, Rubesova E. The role of imaging in the management of necrotising enterocolitis: a multispecialist survey and a review of the literature. Eur Radiol. 2018;28(9):3621-3631. doi: 10.1007/s00330-018-5362-x. DOI
9. Alganabi M, Lee C, Bindi E, Li B et al. Recent advances in understanding necrotizing enterocolitis. F1000Res. 2019;25:8:F1000. doi: 10.12688/f1000research.17228. DOI
10. Thänert R, Keen EC, Dantas G et al. Necrotizing Enterocolitis and the Microbiome: Current Status and Future Directions. J Infect Dis. 2021;223(12Suppl2):S257-S263. doi: 10.1093/infdis/jiaa604. DOI
11. Feng B, Zhang Z, Wei Q et al. A prediction model for neonatal necrotizing enterocolitis in preterm and very low birth weight infants. Front Pediatr. 2023;11:1242978. doi: 10.3389/fped.2023.1242978. DOI
12. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med.. 2011;364(3):255–264. doi: 10.1056/nejmra1005408. DOI
13. Mavropulo TK. Nekrotyzuiuchyi enterokolit novonorodzhenykh - problemy diahnostyky. [Necrotizing enterocolitis of newborns - problems of diagnosis]. Neonatolohiya, khirurhiya ta perynatal'na medytsyna. 2017;7:4(26):95-101. doi: 10.24061/2413-4260.VII.4.26.2017.17. (Ukrainian) DOI
14. Tirone C, Pezza L, Paladini A et al. Gut and Lung Microbiota in Preterm Infants: Immunological Modulation and Implication in Neonatal Outcomes. Front Immunol. 2019;10:2910. doi: 10.3389/fimmu.2019.02910. DOI
15. Patel RM, Ferguson J, McElroy SJ et al. Defining necrotizing enterocolitis: current difficulties and future opportunities. Pediatr Res. 2020;88(1):10-15. doi: 10.1038/s41390-020-1074-4. DOI
16. Tewari VV, Dubey SK, Kumar R et al. Early versus Late Enteral Feeding in Preterm Intrauterine Growth Restricted Neonates with Antenatal Doppler Abnormalities: An Open-Label Randomized Trial. J Trop Pediatr. 2018;64(1):4-14. doi:10.1093/tropej/fmx018. DOI
17. El Hassan NO, Tang X, Gossett J et al. Necrotizing Enterocolitis in Infants with Hypoplastic Left Heart Syndrome Following Stage 1 Palliation or Heart Transplant. Pediatr Cardiol. 2018;39(4):774-785. doi: 10.1007/s00246-018-1820-0. DOI
18. Cai N, Liao W, Chen Z et al. The Mean Platelet Volume Combined with Procalcitonin as an Early Accessible Marker Helps to Predict the Severity of Necrotizing Enterocolitis in Preterm Infants. Int J Gen Med. 2022;15:3789-3795. doi: 10.2147/IJGM.S346665. DOI
19. Gong X, Chen X, Wang L et al. Analysis of clinical features of neonates with congenital heart disease who develop necrotizing enterocolitis: a retrospective case-control study. Ann Transl Med. 2022;10(16):879. doi: 10.21037/atm-22-3248. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Larysa Koval
Odesa National Medical University
2 Valikhovsky Lane, 65000 Odesa, Ukraine
e-mail: larikuk87@gmail.com

ORCID AND CONTRIBUTIONSHIP
Kateryna Doikova: 0000-0001-9289-394X A B D F
Michael Jerdev: 0009-0001-6968-9622 A E F
Larysa Koval: 0000-0003-4050-5954 C D
Dmytro Valantsevych: 0000-0002-3882-4529 C E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 14.10.2023
ACCEPTED: 19.02.2024