CLINICAL FEATURES OF PROTRACTED INTESTINAL INFECTION ASSOCIATED WITH *KLEBSIELLA PNEUMONIAE* IN AN INFANT

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The development of complex criteria for the diagnosis, differential diagnosis, and optimization of treatment of infectious diarrhea associated with opportunistic *Enterobacteriaceae* is a pressing issue of pediatric research and practice. The paper reports a clinical case of protracted intestinal infection associated with *Klebsiella pneumoniae* in the form of moderate hemorrhagic enterocolitis in an infant, which is explained by the decrease in specific resistance due to unfavorable maternal obstetric and gynecological history, perinatal CNS injury, iron deficiency anemia, protein-energy malnutrition. The disease relapse associated with secondary norovirus infection was reported after the first hospitalization. Three courses of intestinal antiseptics and probiotics were required to achieve a beneficial treatment outcome, although usually in such a situation one course of such drugs is enough. The recovery process was accompanied by the nutritional status improvement, hemorrhagic colitis relief, normalization of gut microbiota.

Keywords: intestinal infections, infants, opportunistic enterobacteria, diagnosis, treatment

Author contribution: Gonchar NV — manuscript writing and editing; Skripchenko NV — manuscript editing; Kopersak AK, Razdyakonova IV, Podlipnaya YuA — patient management, manuscript writing.

Compliance with the ethical standards: the informed consent to publication of case report was obtained from the patient's parents.

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Received: 29.11.2023 **Accepted:** 26.01.2024 **Published online:** 20.03.2024

DOI: 10.47183/mes.2024.006

КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ЗАТЯЖНОГО ТЕЧЕНИЯ КИШЕЧНОЙ ИНФЕКЦИИ, АССОЦИИРОВАННОЙ С *KLEBSIELLA PNEUMONIAE*, У РЕБЕНКА ГРУДНОГО ВОЗРАСТА

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Разработка комплексных критериев диагностики, дифференциальной диагностики и оптимизации лечения инфекционных диарей, ассоциированных с условно-патогенными энтеробактериями, — одна из важных задач научной и практической педиатрии. Представлен клинический случай затяжного течения кишечной инфекции, ассоциированной с *Klebsiella pneumoniae*, протекавшей в виде геморрагического энтероколита в среднетяжелой форме, у ребенка грудного возраста, что объяснялось снижением неспецифической резистентности по причине неблагоприятного акушерско-гинекологического анамнеза матери, перинатального поражения ЦНС, железодефицитной анемии, белково-энергетической недостаточности. После первой госпитализации на фоне присоединения норовирусной инфекции отмечали рецидив заболевания. Для достижения положительного эффекта лечения потребовалось проведение трех курсов кишечных антисептиков и пробиотиков, хотя обычно в подобной ситуации достаточно одного курса данных препаратов. Процесс выздоровления сопровождался улучшением состояния питания, купированием гемоколита, нормализацией микробиоты кишечника.

Ключевые слова: кишечные инфекции, дети раннего возраста, условно-патогенные энтеробактерии, диагностика, лечение

Вклад авторов: Н. В. Гончар — написание и редактирование статьи; Н. В. Скрипченко — редактирование статьи; А. К. Коперсак, И. В. Раздьяконова, Ю. А. Подлипная — ведение пациента, написание статьи.

Соблюдение этических стандартов: от родителей пациента было получено добровольное информированное согласие на публикацию клинического случая.

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Статья получена: 29.11.2023 **Статья принята к печати:** 26.01.2024 **Опубликована онлайн:** 20.03.2024

DOI: 10.47183/mes.2024.006

The incidence of acute intestinal infections (AII) is a pressing issue. According to the World Health Organization (WHO), more than a billion AII cases are reported annually, among them 20 million are severe and 1/2 of fatal cases occur in children under the age of 5 years [1]. Furthermore, the percentage of AII cases associated with opportunistic enterobacteria is 12.8% [2].

Today, *Klebsiella pneumoniae* is the leading opportunistic pathogen causing AII [3, 4]. The majority of patients is represented by infants with underdeveloped gut microbiota and immature immune system showing signs of chronic nutritional disorders and anemia that adversely affect the nonspecific resistance [5–7] and contribute to the protracted course of AII followed by the development of gastrointestinal disorder [8–11].

The development of complex criteria for the diagnosis, differential diagnosis, and optimization of treatment tactics for infectious diarrhea, including that caused by opportunistic pathogens, aimed to improve outcomes in children is a pressing issue of pediatric research and practice [3, 12–14].

The study was aimed to assess clinical features of protracted AII associated with *K. pneumoniae* in an infant in order to reveal the diagnosis and treatment problems.

Clinical case

The clinical case of AII associated with *K. pneumoniae* in an infant admitted three times to the department of intestinal infections of the Pediatric Research and Clinical Center for Infectious Diseases of FMBA of Russia is reported. When making a diagnosis, we assessed medical history, clinical symptoms, results of objective examination and laboratory tests (complete blood count, blood biochemistry test, urinalysis, coprogram), instrumental screening data (ECG, ECHO; abdominal, renal, bladder ultrasound; neurosonography, EEG). The AII etiology was verified by fluorescent polymerase chain reaction (PCR) using the AmpliSens® OKI-screen-FL kit (FBIS CRIE; Russia) for qualitative detection and differentiation of bacterial DNA of *Shigella spp*. and enteroinvasive *E. coli* (EIEC), *Salmonella spp*., and thermophilic *Campylobacter spp*. in fecal samples, as well as DNA of *Adenovirus* F and RNA of *Rotavirus* A, genotype 2 N*orovirus*, astroviruses; bacteriological testing of feces for bacteria of the typhoid-paratyphoid-dysentery group, *Campilobacter spp*., opportunistic *Enterobacteriaceae*; enzyme-linked fluorescence assay involving determination of *C. difficile* A and B toxins in the feces; serological testing aimed to reveal antibodies against *S. sonnei*, *S. flexneri*, *Salmonella spp*., *Y. enterocolitica* O3, *Y. enterocolitica* O9. Gut dysbiosis was detected based on the abundance of atypical *E. coli* in the feces (lg CFU/mL).

The boy M. aged 2 months 17 days arrived by ambulance on 13.03.2023 complaining of diarrhea with blood and mucus.

Medical history. Had been sick for 2 weeks; amid the onset of profuse regurgitation and intestinal colic, the appetite loss, weight loss, large amounts of mucus in watery bowel movements (3–4 a day) were observed. Regurgitation became more frequent, and blood streaks in stool (3–4 times a day) emerged in the last three days (Table 1).

Life history. The child was born to a primagravida having gestosis and threatened miscarriage during pregnancy. Delivery at term. Birth weight 3060 g, body length 50 cm. Normal neonatal period. The child was breastfed. Weight gain in the first 2 months was 900 g per month. Vaccinated against tuberculosis and hepatitis B in the maternity hospital. No hereditary burden.

The infant's condition at admission was of moderate severity. Body temperature 36.0 °C. Body length 60 cm (4 points). Body weight for stature 5270 g (2 points). Clear consciousness. Skin and mucous membranes were pale pink and clean. Nutritional status is moderately reduced (weight deficit exceeding 10%). No skin turgor decrease. The degree of dehydration according to the WHO clinical scale was mild. No hyperemia

Table 1. Features of the course of AII associated with *K. pneumoniae* in an infant

Signs of the disorder	Follow-up periods					
	hospital stay		hospital stay		hospital stay	
	13.03	21.03	03.04	13.04	18.05	24.05
Age	2 months 17 days		3 months 10 days		4 months 24 days	
Body lengh, cm (points)	60.0 (4)	60.0 (4)	60.0 (4)	60 (3)	60 (2)	60 (2)
Body weight for stature, kg (points)	5.270 (2)	5.300 (3)	5.720 (4)	5.920 (4)	5.740 (4)	5.850 (4)
Body temperature, °C	36	36.7	36.3	36.5	36.5	36.7
Fatigue		–		–		–
Loss of appetite	+ 2 weeks	–	+ c 31.03	–	+ starting from 17.04.23	–
Decrease in weight gain	+ 2 weeks	–	±	+	+	–
Profuse spitting up, rare vomiting	+	–	+	–	–	–
Intestinal colic		–		–		–
Flatulence		–		–		–
Watery stool	2 weeks, 3–4 times a day	mushy	+ starting from 01.04.23	mushy	dilute, 1–2 times a day	–
Large amounts of mucus in watery stool	2 weeks, 3–4 times a day	–	+ starting from 01.04.23	–	±	–
Traces of blood in liquid stool	3 days, 3–4 times a day	–	+ starting from 01.04.23	–	–	–
Diuresis	preserved	normal	preserved	normal	preserved	normal
Primary clinical diagnosis	A04.8 — Other specified bacterial intestinal infections. Acute gastroenterocolitis associated with *K. pneumoniae* of moderate severity		A08.1 — Acute gastroenteropathy due to norovirus. Acute gastroenteritis of moderate severity		A09 — Other and unspecified enterocolitis, mild form	
Secondary diagnosis	D50.9 — Iron deficiency anemia, mild form. E44 — Protein-energy malnutrition of moderate and mild degree		A04.8 — Other specified bacterial intestinal infections. Acute enteritis, hemorrhagic colitis associated with *K. pneumoniae*, moderate form, protracted course. D50.9 — Iron deficiency anemia, mild form		D50.9 — Iron deficiency anemia, mild form	
Complications of primary condition	E87 — Other disorders of fluid, electrolyte and acid-base balance, exicosis of I degree		E87 — Other disorders of fluid, electrolyte and acid-base balance, exicosis of I degree			

Table 2. Data of laboratory testing of an infant having AII associated with *K. pneumoniae* acquired during treatment in hospital settings

Parameters	Normal	Testing dates				
		hospital stay		hospital stay		hospital stay
		13.03.23	20.03.23	03.04.23	11.04.23	18.05.23
Complete blood count						
White blood cells, 10^9/L	6.0–17.5	5.6	6.3	11.12	12.25	8.5
Red blood cells, 10^{12}/L	3.6–4.9	3.2	3.4	3.26	3.25	3.85
Hemoglobin, g/L	110–135	96	100	89	90	102
Hematocrit, %	33.0–47.5	27.6	28.1	26.6	26.7	29.9
Mean corpuscular volume, fl	70.0–84.0	86.1	84.1	81.7	82.1	77.8
Platelets, 10^9/L	180–400	398	635	483	470	438
Thrombocrit, %	0.10–0.40	0.34	0.55	0.44	0.43	0.4
Neutrophils, %	15.5–49.0	30.4	29.3	22.8	27	26.2
Lymphocytes, %	38.0–72.0	61	75	67.7	61.4	64.6
Monocytes, %	2.0–12.0	1	1	7	7.3	6.2
Eosinophils, %	0.0–6.0	1	5	2.5	4.3	3
Eosinophils, 10^9/L	0.10–1.00	0.06	0.15	0.28	0.53	0.25
ESR, mm/h	2–17	25	10	18	7	3
Blood biochemistry test						
ALT, U/L	0.00–55.0	28		41.6		35
Urea, mmol/L	2.78–8. 07	3.66	2.35	1.67		1.87
Total bilirubin, μmol/L	0.00–21.00					3
Creatinine PAP, μmol/L	15.0–37.0	41	22	35		24
Glucose, mmol/L	3.5–5.8	5.1		5.2		5.2
Amylase, U/L	28.0–100.0	9		12		15
C-reactive protein	0.0–5.0			1.4		
Iron, μmol/L	9.5–30.0			8		8.3
Blood electrolytes						
Potassium, mmol/L	3.7–5.7	6	5.7	5.6		4.7
Sodium, mmol/L	130–145	135	134	135		136
Calcium, mmol/L	1.00–1.29	1.28		1.27		1.27
Coprogram						
Fecal occult blood		+	–	–	–	–
Color		greenish yellow	greenish yellow	yellowish brown	yellowish brown	greenish yellow
Texture		mushy	mushy	loose	mushy	mushy
pH		6	6	6	7	6
White blood cells in mucus		18–20	8–10	–	–	3–5
Red blood cells		–	–	–	–	–
Mucus		+++	+++	–	–	+
Bacteriological testing of feces						
Testing dates		13.03.23	20.03.23	03.04.23	11.04.23	18.05.23
Klebsiella pneumoniae, CFU/mL		10^6	10^5	10^6		10^4
E. coli, nontypeable, non-lactose fermenting, CFU/mL		10^6		10^6		
E. coli, nontypeable, lactose fermenting, CFU/mL			10^3			10^3

of the oropharyngeal mucosa. No peripheral lymph node enlargement, painless lymph nodes. Normal musculoskeletal system. Pulse rate 138 bpm. BP 90/64 mmHg. No expansion of cardiac borders, tone was clear, rhythmic. Respiratory rate 26 breaths per minute. Puerile respiration. Percussion sound is pulmonary. The abdomen was soft and painless. The liver was palpated at 1–1.5 cm below the costal margin; no enlargement of the spleen. Yellow-green liquid stool with mucus and traces of blood (examined). Preserved diuresis.

The complete blood count test revealed decreased counts of white blood cells, red blood cells, decreased levels of hemoglobin, hematocrit, decreased counts of monocytes, eosinophils, increased erythrocyte sedimentation rate (ESR) (Table 2), which were indicative of inflammation and grade 1 anemia. Blood biochemistry test revealed elevated creatinine, potassium levels, along with the decreased amylase level, which were considered to be manifestations of acute kidney injury and decreased secretory function of the pancreas resulting

Table 3. Features of treatment of an infant having All associated with *K. pneumonia*

Therapy	hospital stay 13.03–21.03	outpatient clinic	hospital stay 03.04–13.04	outpatient clinic	hospital stay 18.05–25.05	outpatient clinic
Feeding	breastfeeding	breastfeeding + lactose-free formula supplementation	breastfeeding + lactose-free formula supplementation	breastfeeding + lactose-free formula supplementation	breastfeeding + weaning foods on water	breastfeeding + weaning foods
Oral rehydration	rehydration solution for children	–	rehydration solution for children	–	rehydration solution for children	–
Sorbents	–	–	–	–	hydrolytic lignin	–
Probiotics	+	+	+	+	+	+
Intestinal antiseptics	nifuroxazide 5 days	nifuroxazide 5 days	nifuratel 4 days	nifuratel 6 days	–	–
Antifoam agents	simethicone 6 days	simethicone when required	simethicone 9 days	–	–	–
Prokinetic agentы	–	–	domperidone 6 days	–	–	–
Digestive enzymes	dietary supplement being the source of lactase	–	–	–	–	–
Iron supplements	–	iron(III)-hydroxide polymaltose complex	iron(III)-hydroxide polymaltose complex	iron(III)-hydroxide polymaltose complex	iron(III)-hydroxide polymaltose complex	iron(III)-hydroxide polymaltose complex

from the intoxication and dehydration syndromes. Occult blood was revealed in the feces by the Gregersen fecal occult blood test; white blood cells up to 20 per field of view, large amounts of mucus, and the lack of red blood cells were revealed by microscopy. Bacteriological testing revealed growth of *K. pneumoniae* in the diagnostically significant titer of 10^6 CFU/mL (susceptibility to amoxicillin, ceftriaxone, gentamicin, nalidixic acid, nitrofurantoin, trimethoprim; resistance to the *Klebsiella K. pneumoniae* polyvalent bacteriophage were reported), which provided the basis for the following etiological diagnosis: A04.8 — Other specified bacterial intestinal infections. Acute gastroenterocolitis associated with *K. pneumoniae* of moderate severity (Table 1). The growth of nontypeable non-lactose fermenting *E. coli* in a high titer, 10^6 CFU/mL, was observed that was indirect evidence of gut dysbiosis.

According to the instrumental diagnostic screening data (ECG, ECHO; abdominal, renal, bladder ultrasound), the following was revealed: incomplete right bundle branch block; hemodynamically insignificant patent foramen ovale, left ventricular accessory chord; gallbladder deformity, moderate enlargement of the liver, fluid filled bowel loops, bowel wall thickening up to 2 mm.

Treatment included diet therapy (breastfeeding reduced per actual body weight), oral rehydration, intestinal antiseptics (nifuroxazide, 100 mg 3 times a day), probiotic, enzyme products (dietary supplement being the source of lactase), symptomatic therapy (simethicone) (Table 3). Treatment resulted in feeling better, relief of vomiting and profuse spitting up regurgitation, resolution of flatulence, stool back to normal; however, the weight gain was insufficient. Red blood counts improved; white blood cell counts and ESR were back to normal; the increase in platelet counts, thrombocrit, relative lymphocyte counts was reported. The creatinine, potassium levels were back to normal; however, there was a significant decrease in urea levels being an indirect evidence of inhibition of synthetic function of the liver under the influence of infection [8].

The patient was discharged after 7 days due to clinical improvement, his body weight was 5300 g (+ 30 g; 3 points); the follow-up bacteriological testing of the feces revealed the decrease in the *K. pneumoniae* titer to 10^5 CFU/mL, the lack of nontypeable non-lactose fermenting *E. coli*, and the emergence of nontypeable lactose fermenting *E. coli* in a titer of 10^3 CFU/mL. It was recommended to continue treatment in outpatient settings.

The second hospitalization took place 13 days later. The child was admitted due to referral from local pediatrician complaining of bloating, intestinal colic, spitting up regurgitation, vomiting, recurrent breast refusal, watery bowel movements (3–4 a day) since 30.03.2023, fatigue since 31.03.2023, increase in body temperature to 37.5 °C since 02.04.2023. Starting from 24.03.2023, blood streaks in stool were noted; the child had been receiving nifuroxazide for 5 days, 100 mg 3 times a day, showing improvement. Blood streaks in stool were noted again starting from 01.04 (Table 1).

The condition at admission was of moderate severity. Body temperature 36.4 °C. Body length 60 cm (4 points). Body weight for stature 5720 г (4 points) (Table 1). Clear consciousness. Skin and mucous membranes were pale pink and clear. Nutritional status is satisfactory. No skin turgor decrease. The degree of dehydration according to the WHO clinical scale was mild. No hyperemia of the oropharyngeal mucosa. No peripheral lymph node enlargement, painless lymph nodes. No apparent abnormality of the musculoskeletal system. Pulse rate 148 bpm. BP 90/57 mmHg. No expansion of cardiac borders, tone was clear, rhythmic. Respiratory rate 34 breaths per minute. Puerile respiration. Percussion sound is pulmonary. The abdomen was soft and painless. The liver was palpated at 1–1.5 cm below the costal margin; the spleen was not palpable. Yellowish brown loose stool with no abnormal foreign matter (examined). Preserved diuresis.

Laboratory testing revealed grade 1 anemia, moderate thrombocytosis, increased ESR, decreased serum levels of iron, urea, amylase. Normal coprogram. A norovirus antigen was detected in the feces; growth of *K. pneumoniae* in a high titer of 10^6 CFU/mL (with the antibiotic susceptibility and bacteriophage resistance similar to that revealed during the first hospitalization) was observed; growth of nontypeable non-lactose fermenting *E. coli* in a titer of 10^6 CFU/mL was reported, which, in aggregate, made it possible to establish the diagnosis of acute norovirus gastroenteritis of moderate severity

combined with protracted AII (enteritis, hemorrhagic colitis) associated with *K. pneumoniae*, which took place against the background of gut dysbiosis (Table 1). Abnormal foreign matter typical for colitis was visually detected in the feces starting from days 6–7 of hospital stay.

Based on the neurological assessment and neurosonography data it was reported that the child had perinatal CNS injury, moderate hypotonia, and was through early recovery period.

Treatment included diet therapy (breastfeeding with lactose-free formula supplementation), oral rehydration, probiotic, intestinal antiseptics (nifuratel in a dose of 10 mg/kg 3 times a day), symptomatic therapy (simethicone, domperidone), iron supplement (iron (III) — hydroxide polymaltose complex) (Table 3).

The patient was discharged after 10 days due to clinical improvement. It was recommended to continue treatment in outpatient settings.

The third hospitalization took place after 37 days. The infant's parents contacted the clinic without any referral from the local physician. Loss of appetite, sometimes watery stool with mucus (1–2 times a day), bloating, restlessness were observed starting from 17.05.2023; dilute stool with small amounts of mucus (up to 3–4 times a day), fatigue were reported starting from 18.05.2023.

The condition at admission was of moderate severity. Body temperature 36.5 °C. Body length 60 cm (2 points). Body weight for stature 5740 g (4 points) (Table 1). Clear consciousness. Skin and mucous membranes were pale pink and clean. Nutritional status is satisfactory. No dehydration according to the WHO scale. No hyperemia of the oropharyngeal mucosa. No peripheral lymph node enlargement, painless lymph nodes. No evident musculoskeletal system abnormality. Pulse rate 142 bpm. BP 80/50 mmHg. No expansion of cardiac borders, tone was clear, rhythmic. Respiratory rate 42 breaths per minute. Puerile respiration. Percussion sound is pulmonary. Soft and painless abdomen. The liver was palpated at 1–1.5 cm below the costal margin; no enlargement of the spleen. Greenish yellow and mushy stool, large amounts of mucus (examined). Preserved diuresis.

Testing revealed the signs of grade 1 anemia, moderate thrombocytosis, slight upward trend in blood levels of iron, preserved low serum levels of urea and amylase. Normal coprogram. A significant decrease in the *K. pneumoniae* titer (to 10^4 CFU/mL) together with the presence of nontypeable lactose fermenting E. coli in a titer of 10^3 CFU/mL in the feces was observed, which suggested the child's recovery from AII associated with *K. pneumoniae*, gut microbiota composition improvement. Primary clinical diagnosis at discharge: A09 — Other and unspecified enterocolitis, mild form (Table 2).

The treatment applied during the last hospitalization included diet therapy (breastfeeding, weaning foods on water), oral rehydration, enterosorbent (hydrolytic lignin), probiotic, iron supplement (iron (III) — hydroxide polymaltose complex) (Table 3).

The child was discharged after 6 days due to general health improvement and stool back to normal.

Clinical case discussion

This clinical case demonstrates typical features of protracted AII associated with *K. pneumoniae* in the form of gastroenterocolitis (hemorrhagic colitis). The disease onset was associated with the decrease in nonspecific resistance resulting from unfavorable maternal obstetric and gynecological history, perinatal CNS injury with decreased muscle tone, iron deficiency anemia, protein-energy malnutrition, which was largely compliant with the data reported by other researchers [3, 4, 6]. The gut dysbiosis accompanying perinatal abnormalities and deficiencies in infants also contributed to the protracted course of AII associated with the opportunistic representative of *Enterobacteriaceae* [3, 5] and showed remarkable persistence, despite the repeated courses of probiotic therapy. It is clear that the hemorrhagic colitis relapse during the second hospitalization was caused by activation of opportunistic gut microbiota associated with norovirus infection layering. Recovery was accompanied by the nutritional status improvement, hemorrhagic colitis relief, switch from mixed feeding to breastfeeding due to restoration of lactation in the mother, however, the child's physical development was still disharmonious, which was explained by persistence of iron deficiency anemia and metabolic disorder. It seems that the child's third hospitalization resulted from the functional gastrointestinal disorder, not from the new episode of AII of unknown etiology.

CONCLUSION

In modern conditions, when there are no clinical guidelines on management of infants with intestinal infection associated with opportunistic Enterobacteriaceae, practitioners rely on the experts showing the possibility of etiological and differential diagnosis of this disorder. However, the issue of *K. pneumoniae* significance in community-acquired pediatric AII is still not completely resolved.

Treatment of patients traditionally includes diet therapy, rehydration, enterosorption, probiotics. Intestinal antiseptics are prescribed according to indications, one of which is hemorrhagic enterocolitis; however, the etiotropic treatment efficacy is not always sufficient. It seems that this problem can be solved through testing and implementation of personalized treatment approaches based on autoprobiotics and/or *Klebsiella bacteriophages* being an alternative to antibacterial agents used against *K. pneumoniae*.

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