ISSN 2221-2582

UDC 616.34-022-036.111-008.87-053.3+579.253.4+578.81+579.8+615.33+616.9-07
DOI: 10.56871/CmN-W.2023.90.13.008

CLINICAL AND LABORATORY FEATURES OF ACUTE INTESTINAL INFECTIONS CAUSED BY *KLEBSIELLA PNEUMONIAE* IN CHILDREN

© Natalya V. Gonchar[1, 2], Alena K. Kopersak[2], Irina V. Razd`yakonova[2], Elena I. Ermolenko[3], Stepan G. Grigor`ev[2, 4], Alina M. Moskalyuk[2], Sabina Abuzarova[1]

[1] North-Western State Medical University named after I.I. Mechnikov. Kirochnaya str., 41, Saint Petersburg, Russian Federation, 191015
[2] Children's Research and Clinical Center for Infectious Diseases of the FMBA of Russia. Professor Popov str., 9, Saint Petersburg, Russian Federation, 197022
[3] Institute of Experimental Medicine. Academician Pavlov st., 12, Saint Petersburg, Russian Federation, 197376
[4] Military Medical Academy named after S.M. Kirov. Akademician Lebedeva St., 6, Saint Petersburg, Russian Federation, 194044

Contact information:
Natalya V. Gonchar — MD, PhD, Doctor of Medical Sciences, Professor, Department of Pediatrics and Neonatology; Leading Researcher. E-mail: nvgonchar@yandex.ru ORCID ID: 0000-0002-5938-2934

For citation: Gonchar NV, Kopersak AK, Razd`yakonova IV, Ermolenko EI, Grigor`ev SG, Moskalyuk AM, Abuzarova S. Clinical and laboratory features of acute intestinal infections caused by *Klebsiella pneumoniae* in children. Children's medicine of the North-West (St. Petersburg). 2023; 11(3): 110-119. DOI: https://doi.org/10.56871/CmN-W.2023.90.13.008

Received: 06.06.2023 **Revised: 21.07.2023** **Accepted: 12.09.2023**

Abstract. The *aim* of the work is to study the clinical and laboratory features of intestinal infections caused by *Klebsiella pneumoniae* in combination with viruses and other enterobacteria to optimize their diagnosis, prognosis and therapy in young children. *Patients and methods*. In the department of intestinal Infections of the Children's Scientific and Clinical Center for Infectious Diseases of the FMBA of Russia in the period 2019–2021, 65 young children who were on inpatient treatment for AII caused by *K. pneumoniae* were observed. Depending on the etiological forms of the disease, the patients formed 4 groups: *K. pneumoniae* monoinfection — group "Kp" (n=29); combination of *K. pneumoniae* with intestinal viruses — group "Kp+V" (n=14); combination of *K. pneumoniae* with opportunistic enterobacteria (OEB) — group "Kp+OB" (n=14); combination of *K. pneumoniae* with intestinal viruses and OEB — group "Kp+V+OEB" (n=8). Clinical and laboratory data were evaluated in all children. The degree of intestinal dysbiosis, in addition to the generally accepted criteria, was characterized by the content of atypical *E. coli* in feces (lg CFU/g). Etiological diagnosis of AII was performed using the bacteriological method and polymerase chain reaction. During statistical processing, the average values of indicators, the average frequency of deviations of indicators from the norm (M±σ; P±σ) were determined, differences in groups were revealed using the t-test and Pearson's criterion χ^2; they were considered reliable at $p < 0.05$. Methods of variance and discriminant analysis were used. *Results*. The higher age of children in the groups "Kp+V" and "Kp+V+OEB" was revealed. The association of *K. pneumoniae* with viruses in these groups was accompanied by an increase in the frequency of diarrhea ($p < 0.05$). The frequency of thrombocytosis and monocytosis differed in the groups of children ($p < 0.05$) and was maximal in the groups "Kp+OEB" and "Kp+V", respectively. The content of atypical *E. coli* in faeces in the "Kp" group was lower than in the "Kp+OEB" group ($p < 0.05$). The duration of inpatient treatment was longer in the "Kp" and "Kp+V+OEB" groups. The discriminant model included the following signs: age of children (p=0.0015); complaints of lethargy (p=0.02); complaints of vomiting (p=0.08); platelet count in the hemogram (p=0.006); amylorrhea in the coprogram (p=0.0008); stool pH (p=0.12); duration inpatient treatment (p=0.004); combination of *K. pneumonia*e with OEB ($p < 0.00001$). The overall diagnostic significance of the model was 89.2%. *Conclusion*. Using discriminant analysis, it was found that the features of clinical and laboratory signs of acute intestinal infections caused by *K. pneumoniae* in young children are more determined by the combination of *K. pneumoniae* with opportunistic enterobacteria than by the combination with viruses.

Key words: *intestinal infections; children; early age; Klebsiella pneumoniae; intestinal viruses; opportunistic enterobacteria; clinical and laboratory features; diagnostics.*

КЛИНИКО-ЛАБОРАТОРНЫЕ ОСОБЕННОСТИ ОСТРЫХ КИШЕЧНЫХ ИНФЕКЦИЙ, ВЫЗВАННЫХ *KLEBSIELLA PNEUMONIAE*, У ДЕТЕЙ

© Наталья Васильевна Гончар[1, 2], Алена Константиновна Коперсак[2], Ирина Владимировна Раздьяконова[2], Елена Игоревна Ермоленко[3], Степан Григорьевич Григорьев[2, 4], Алина Михайловна Москалюк[2], Сабина Абузарова[1]

[1] Северо-Западный государственный медицинский университет им. И.И. Мечникова. 1911015, г. Санкт-Петербург, ул. Кирочная, 41
[2] Детский научно-клинический центр инфекционных болезней ФМБА России. 197022, г. Санкт-Петербург, ул. Профессора Попова, 9
[3] Институт экспериментальной медицины. 197022, г. Санкт-Петербург, ул. Академика Павлова, 12
[4] Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6

Контактная информация:
Наталья Васильевна Гончар — д.м.н., профессор кафедры педиатрии и неонатологии; ведущий научный сотрудник.
E-mail: nvgonchar@yandex.ru ORCID ID: 0000-0002-5938-2934

Для цитирования: Гончар Н.В., Коперсак А.К., Раздьяконова И.В., Ермоленко Е.И., Григорьев С.Г., Москалюк А.М., Абузарова С. Клинико-лабораторные особенности острых кишечных инфекций, вызванных *Klebsiella pneumoniae*, у детей // Children's medicine of the North-West. 2023. Т. 11. № 3. С. 110–119. DOI: https://doi.org/10.56871/CmN-W.2023.90.13.008

Поступила: 06.06.2023 **Одобрена: 21.07.2023** **Принята к печати: 12.09.2023**

Резюме. *Цель работы* — изучить клинико-лабораторные особенности кишечных инфекций, вызванных *Klebsiella pneumonia,* в сочетании с вирусами и другими энтеробактериями для оптимизации их диагностики, прогнозирования и терапии у детей раннего возраста. *Пациенты и методы*. В отделении кишечных инфекций ДНКЦИБ ФМБА России в период 2019–2021 гг. наблюдали 65 детей раннего возраста, находившихся на стационарном лечении по поводу ОКИ, вызванных *K. pneumoniae*. В зависимости от этиологических форм заболевания пациенты образовали 4 группы: моноинфекция *K. pneumoniae* — группа «Кр» (n=29); сочетание *K. pneumoniae* с кишечными вирусами — группа «Кр+В» (n=14); сочетание *K. pneumoniae* с условно-патогенными бактериями (УПЭ) — группа «Кр+УПЭ» (n=14); сочетание *K. pneumoniae* с кишечными вирусами и УПЭ — группа «Кр+В+УПЭ» (n=8). У всех детей оценивали клинико-лабораторные данные. Степень дисбиоза кишечника дополнительно к общепринятым критериям характеризовали по содержанию атипичной *E. coli* в фекалиях (lg КОЕ/г). Этиологическую диагностику ОКИ выполняли при помощи бактериологического метода и полимеразной цепной реакции. При статистической обработке определяли средние значения показателей, среднюю частоту отклонений показателей от нормы (M±σ; P±σ), выявляли различия в группах с помощью t-критерия и критерия χ^2 Пирсона; считали их достоверными при p <0,05. Использовали методы дисперсионного и дискриминантного анализа. *Результаты*. Выявлен более высокий возраст детей в группах «Кр+В» и «Кр+В+УПЭ». Ассоциация *K. pneumoniae* с вирусами в этих группах сопровождалась увеличением частоты диареи (p <0,05). Частота тромбоцитоза и моноцитоза отличалась в группах детей (p <0,05) и была максимальной в группах «Кр+УПЭ» и «Кр+В» соответственно. Содержание атипичной *E. coli* в фекалиях в группе «Кр» было ниже, чем в группе «Кр+УПЭ» (p <0,05). Длительность стационарного лечения была больше в группах «Кр» и «Кр+В+УПЭ». В дискриминантную модель вошли признаки: возраст детей (p=0,0015); жалобы на вялость (p=0,02); жалобы на рвоту (p=0,08); количество тромбоцитов в гемограмме (p=0,006); амилорея в копрограмме (p=0,0008); pH кала (p=0,12); длительность стационарного лечения (p=0,004); сочетание *K. pneumoniae* с УПЭ (p <0,00001). Общая диагностическая значимость модели составила 89,2%. *Заключение.* С помощью дискриминантного анализа установлено, что особенности клинико-лабораторных признаков ОКИ, вызванных *K. pneumoniae,* у детей раннего возраста в большей степени определяются сочетанием *K. pneumoniae* с УПЭ, чем сочетанием с вирусами.

Ключевые слова: *кишечные инфекции; дети, ранний возраст; Klebsiella pneumoniae; кишечные вирусы; условно-патогенные энтеробактерии; клинико-лабораторные особенности; диагностика.*

INTRODUCTION

In the etiological structure of the incidence of acute intestinal infections (AIE) in Russian children in recent years, the importance of opportunistic pathogens has remained significant, among which the leading role belongs to *Klebsiella pneumoniae* [1, 2]. Attention to the study of *Klebsiella* etiology was attracted by its severity and tendency to defeat children in the early age group. The increase in the incidence of Klebsiella, the similarity of local changes in

the gastrointestinal tract with other intestinal infections makes it important to study this pathology. This especially relevant in the appearance of carbapenem resistant strains of *Klebsiella* [3].

When the *Klebsiella* invasion nature of AII is established, the disease is more often diagnosed as a mono-infection [4, 5]. The majority of hospitalized patients with this pathology are young children with unformed intestinal microbiota and immature immune system. Moreover, they have other constitutional anomalies, deficiency conditions, feeding disorders, which reduce the non-specific resistance of the body and predispose to manifestation of AII [6–9].

In the study of epidemiology AII described combinations of Klebsiella infection with other conditionally pathogenic representatives of the family Enterobacteriaceae (conditionally pathogenic enterobacteria — CPE). As well as the combination of CPE with respiratory viruses in young children [10]. As concomitant infections increase [11], the problem of AIIs remains unresolved since AIIs are caused by the combination of conditionally-pathogenic pathogens with intestinal viruses in children [12]. There is a very few information on resistance of *K. pneumoniae* of extra-hospital to antibiotics and Bacteriophages that cause intestinal infections young children [13]. The laboratory feature of out-of-hospital AII caused by Klebsiella and other pathogens of bacterial and viral nature remain poorly studied.

AIM

To study clinical and laboratory features of acute intestinal infections caused by *Klebsiella pneumoniae* in combination with viruses and other enterobacteria to optimize their diagnosis, prognosis and treatment in young children.

MATERIALS AND METHODS

65 children aged from 1 month to 3 years were observed in hospital treatment for AII associated with *K. pneumoniae* in the period 2019–2021, in the Department of Intestinal Infections of the Children's Research and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency of Russia. The sampling was based on the diagnosis of AII mono- and combined etiology associated with *K. pneumoniae*. Patients formed four groups: "Kp group" (n=29) — monoinfection with *K. pneumoniae*; "Kp+V group" (n=14) — combined AII caused by *K. pneumoniae* and intestinal viruses; "Kp+CPE group" (n=14) — AII caused by the K. pneumoniae and other CPEs; and "Kp+V+CPE" group (n=8) — combined AII caused by the *K. pneumoniae*, intestine viruses and CPE.

The etiological significance of *K. pneumoniae* and CPE in AII genesis was determined when detected in feces. The condition was the detection of at least 5 lg CFU/g and the absence of other bacterial pathogens in the bacteriological method. Results of fecal studies by PCR method using the set of reagents "AmpliSens® OKI screen-FL", intended for molecular-genetic diagnosis of bacterial (Shigella, Salmonella, Yersinia, Campylobacter, Escherichia coli) and viral (Rotavirus, Norovirus, Enterovirus, Astrovirus, Adenovirus) pathogens. Value determined by serological response in the diagnosis of indirect hemagglutination in some cases [14].

The severity of intestinal dysbiosis was assessed indirectly by the excretion of atypical *E. coli* from the feces in a quantity of not less than 5 lg CFU/g.

There has been performed evaluation of patients' complaints (weakness, fever, vomiting, diarrhea), medical history (duration of pre-hospital stage of disease, treatment) and life (food allergies, atopic dermatitis, past illnesses, vaccination history), objective status, results of clinical tests of blood and urine, biochemical blood tests (ALT, C-reactive protein, glucose, urea, electrolytes), stool test data. The severity of exicosis in children with AII was assessed on the basis of clinical recommendations.

K. pneumoniae sensitivity to antibacterial drugs (ampicillin/sulbactam, ceftriaxone, gentamicin, nalidixic acid, nitrofurantoin, trimetoprim/sulfamethoxazole) was determined by microdiffusion on Muller-Hinton agar using standard ACS strains 700603. The sensitivity of K. pneumoniae to bacteriophages ("Bacteriophage Klebsiella polyvalent purified" and "Bacteriaphage Klebsiella pneumoniae purifying" JSC "NGO "Mikrogen"", Ufa) was studied. The lithium activity of bacteriophages was assessed using the "sterile spot" method according to MP 3.5.1.0101–15.

Treatment of children with AII was carried out according to clinical recommendations of the Ministry of Health of Russia. The results of treatment in different children's groups were evaluated. According to the duration of hospitalization and outcomes (recovery, improvement).

During statistical processing, the average values of indicators, the average frequency of deviations of indicators from the norm (M±σ; P±σ) were determined, differences in groups were revealed using the t-test and Pearson's criterion χ^2; they were considered reliable at $p < 0.05$. To prove the possibility of separating groups of children with AII of mono- and combined etiology associated with *K. pneumoniae*, the discriminant

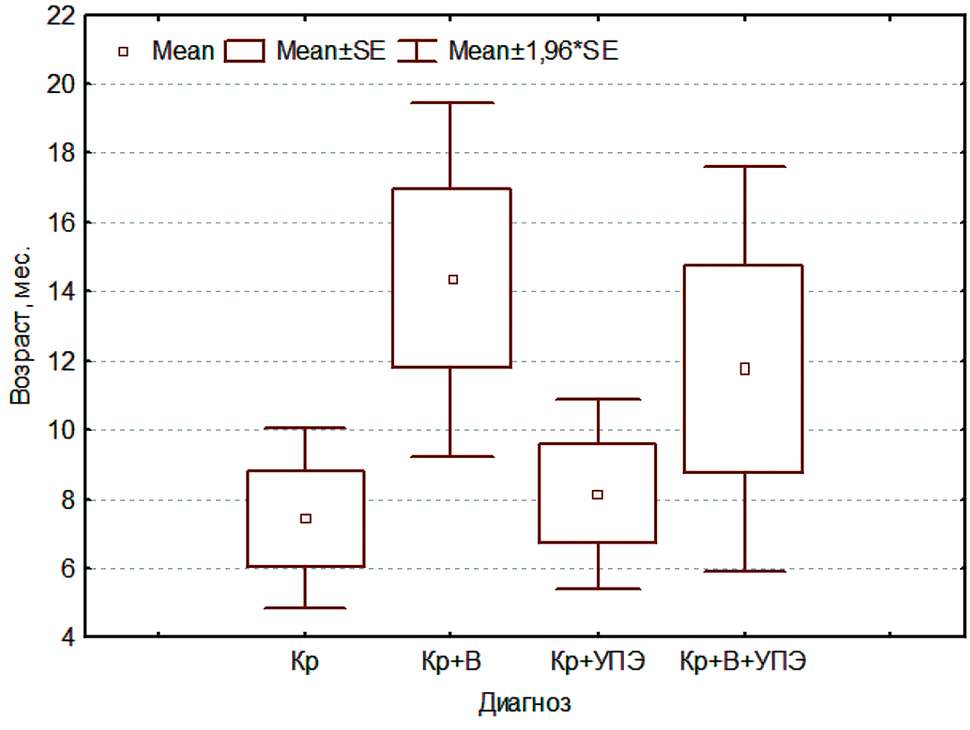

Fig. 1. Average values of the age of children in groups (number of months)
Рис. 1. Средние значения возраста детей в группах (число месяцев)

analysis method was used. By identifying the signs of determinants that significantly influence the assignment of a particular patient to one of the four groups, coefficients were calculated for the identified signs and subsequent solution of discriminant functions.

RESULTS AND DISCUSSION

The gender composition of the children in the sample shows a small predominance of boys in the group in the "Kp+V" and "Kp+CPE" groups (48.3%; 64.3%; 57.1%; 37.5%; χ^2=1.82; p=0.61). (These groups are presented here and will be listed in the following order: "Kp", "Kp+V", "Kp+CPE", "Kp+V+CPE"). The age composition was characterized by a relatively high proportion of children of the first year of life in the "Kp" and "Kp+CPE" groups (79.3%; 50%; 85.7%; 62.5%; χ^2=05.83; p=0.12) (Fig. 1), when visiting children's organized groups, it is normal for children older than one year to have more contact with viral infectious agents [15]. A comparison of the median age values of children revealed differences between the "Kp" and "Kp+V" groups (7.4±7.3 and 14.4±9.7 months; p=0,007) and the "Kp+V" and "Kp+CPE" groups (14.4±9.7 and 8.1±5.3 months; p=0.036) (Fig. 1).

In children in the grip "Kp+V" rotavirus was detected in 50% of cases, norovirus — in 35.7%, enteroviruses — in 7.15%. The combination of rotaviruses with norovírus — in 7,15%. In children in the group "Kp+V+CPE" rotavirus was detected in 25% of cases, norovirus — in 50%, adenovirus — in 12.5%. In this group the combination of rotaviruses with noroviruses — in 12,5%.

The frequency of discharge of different CPE in stool was at high titers in children in the "Kp+CPE" and "Kp+V+CPE" groups decreased in the following rows: *S. aureus* (45,8%); *P. mirabilis* (20,8%); *Enterobacter* (12,5%); *C. freundii* (8.3%); *H. alvei* (4.2%); *A. baumani* (4.2%); *P. aeruginosa* (4,2%).

At the time of admission at the hospital, the majority of the children in all groups had exicosis of the 1 degree (65,5%; 78.6%; 57.1%; 62.5%; χ^2=3.88; p=0.69), exicosis of the 2 degree — 6.9% of "Kp" children and 14.3% of the "Kp+CPE". The combination of AII with acute respiratory infection was diagnosed in children in all groups (37.9%; 28.6%; 21.4%; 33.3%; χ^2=1.42; p=0.70), of which 10.3%; 14.4%; 7.1%; 12.5% cases (χ^2=0.40; p=0.94). Febrile seizures were observed in children in the groups "Kp", "Kp+V", "Kp+CPE" (3.4%; 7.1%; 7,1%; χ^2=8.40; p=0.49). Urinary tract infections were diagnosed in a small part of children in all groups (6.9%; 7.1%; 7,1%; 12.5%; χ^2=8.40; p=0.49). Atopic dermatitis was detected in children in the "Kp", "Kp+V", "Kp+V+CPE" groups (20.7%; 7.1%; 25%; χ^2=4.75; p=0.19).

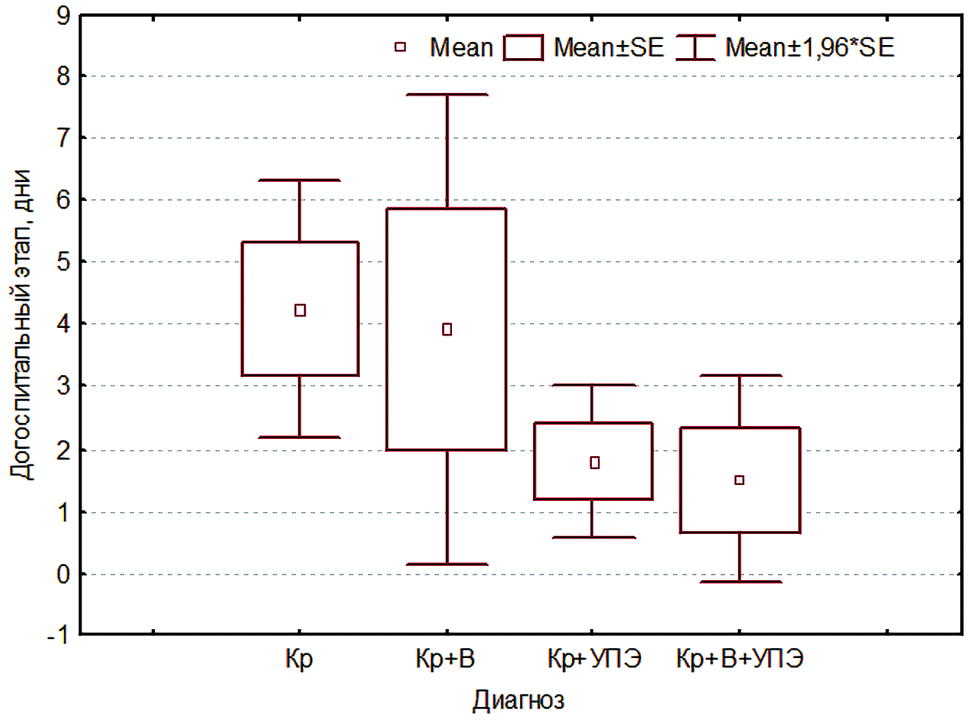

Fig. 2. The average duration of the prehospital stage of treatment of children in groups (number of days)

Рис. 2. Средняя длительность догоспитального этапа лечения детей в группах (число дней)

The pre-hospital stage by time was slightly greater in children in the "Kp" and "Kp+V" groups (4.2±5.7 days; 3.9±7.2 days) compared to those in the "Kp+CPE" and "Kp+V+CPE" groups (1.8±2.3 days; 1.5±2.4 days) (p >0.05) (Fig. 2). Nifuroxazide treatment was equally often during this period in all groups: 6.9%; 14.3%; 7.1%; 25%; χ^2=2,51; p=0.47; Antibiotic treatment was received by 13.8% of children in the "Kp" group, 7.1% of those in the "Kp+V" group and 7.1% in the "Kp+CPE" group (χ^2=1.68; p=0.64).

The incidence of diarrhea in the children's groups was high: 79.3%; 100%; 71.4%; 100% (p_{1-2} <0.05; p_{1-4} <0.05) and the incidence of vomiting was lower than 44.8%; 71.04%; 50%; 87.5% (χ^2=6.0; p=0.099). The incidence of lethargy (24.1%; 50%, 64.3%, 37.5%) and fever (41.4%; 64.3%; 50%; 75%) in the children's groups did not differ significantly (χ^2=4,0; p=0,27 and χ^2=2,92; p=0,40).

Inflammatory changes in the blood analysis were manifested by leukocytosis in children in the "Kp" and "Kp+V+CPE" groups (13.8%; 37.5%; χ^2=11.66; p=0.07), leukopenia in children of the "Kp", "Kp+V", "Kp+CPE" groups (20.7%; 14.3%; 28.6%; χ^2=11. 66; p = 0.07), thrombocytosis — frequently in children from the "Kp" and "Kp+CPE" groups (37.9%, 21.4%, 57.1%, 7.5%; χ^2=12.8; p=0.46), monocytosis — significantly frequently among children of "Kp+V" and "Kp+CPE" groups (6.9%, 42.9%, 28.6%, 12.5%; χ^2=8.61; p=0.34). Children in the "Kp" and "Kp+V+CPE" groups experienced increases in ESR more frequently (20.7%; 7.1%; 7,1%; 37.5%; χ^2=8.42; p=0.21).

Increases in C-reactive protein in the blood were frequently in the "Kp", "Kp+V", "Kp+V+CPE" groups (20.7%; 21.4%; 7.1%; 37.5%; χ^2=3.0; p=0.39). An increase in the level of alanine transaminase — an indicator of reactive changes in the liver in All. Increase ALT was slightly more commonly observed in the groups "Kp+CPE" and "Kp+V+CPEs" (6.9%; 7.1%; 21.4%; 50%; χ^2=2.3; p=0.51). An increase in urea was also found slightly more frequently in the group "Kp+CPE", "Kp+V+CPE" (44.8%; 42.9%; 50%: 50%; 50%, χ^2=0.2; p=0.97). Dehydration-related elevated potassium blood levels associated with electrolyte disorders were a little less common in the "Kp" group (3.4%; 14.3%;14.3%; 12.5%; χ^2=2.1; p=0,55).

There were variations found in the kids' rates of decline in the groups' percentage relative urine density (44.8±14.4%; 42.9±22.1%; 64.3±16.9%; 0%; χ^2=15.1; p=0.19; $p_{"Kp" -"Kp+V+CPE"}$ <0.01; $p_{"Kp +CPE" - "Kp+V+CPEs"}$ <0.01). This was explained by the difference in the kidney concentrating capacity, since the age of children in groups «Kp» and «Kp+CPE» was lower than in the group «Kp+V» and "Kp+V+CPE» (Fig. 1). There was a difference in the frequency of detection of ketones in urine (10.3%;

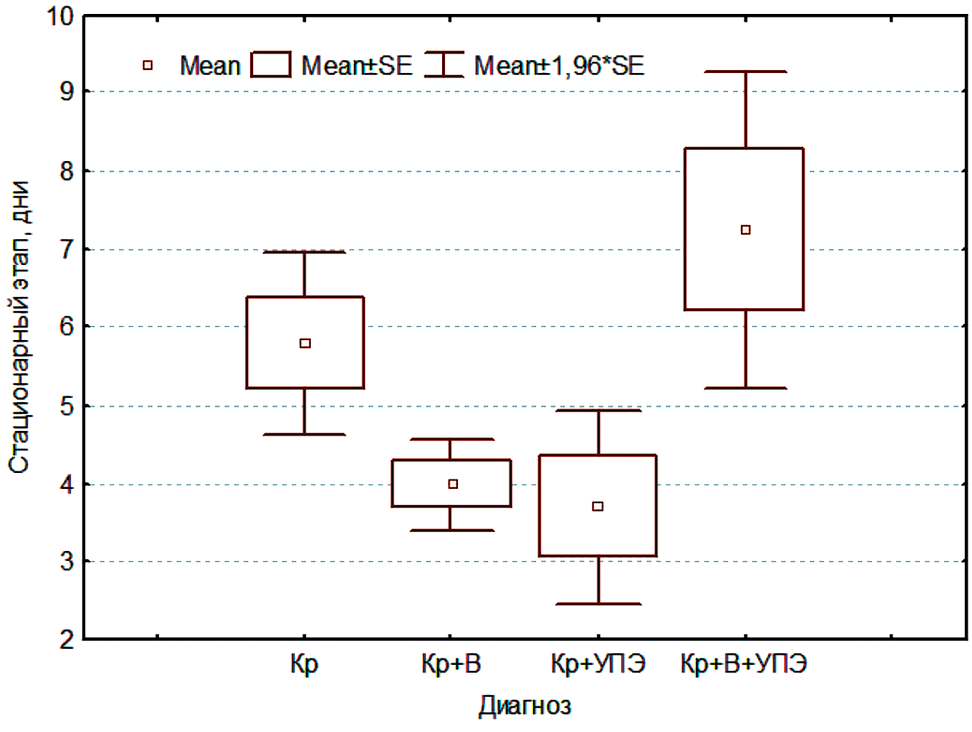

Fig. 3. Average duration of inpatient treatment of children in groups (number of days)

Рис. 3. Средняя длительность стационарного лечения детей в группах (число дней)

28.6%; 7.1%; 37.5%; χ^2=19,4; p=0,080). This indicating a more frequent acidosis in children of the "Kp+V" and "Kp+V+CPE" groups, in which intestinal infections were involved in the combination AII. Elevated leukocyte counts in the urine were somewhat more frequently seen in children in the "Kp" and "Kp+V+CPE" groups (41.4%; 21.4%;21.4%; 62.5%; χ2=5.4; p=0.14).

The changes in the stool test were characterized by a relatively more frequent decrease in fecal pH in children in the "Kp", "Kp+V", "Kp+CPE" groups (69%; 78.6%; 92.9%; 50%; χ^2=6.86; p=0.33). This due to fermentation dyspepsia with malabsorption in the small intestine. In the "Kp" (17.2% of cases) and "Kp+CPE" (14.3%) groups, amylorrhea was noted, and in 6.9 and 7.1% of cases, respectively, steatorrhea type 2. All child groups showed signs of colitis syndrome in stool test with high leukocyte detection (58.6%; 28.6%; 35.7%; 25%; χ^2=5.4; p=0.14) and mucus abundance (69%; 35,7%; 50%; 37.5%; χ^2=5.46; p = 0.14).

A high titer of atypical *E. coli* was observed in the overwhelming majority of children in all groups (65,5%; 71.4%; 78.6%; 75%; χ^2=0.87; p=0.83). In the same time the average titer for atypic *E. coli* in the feces in the "Kp" group was lower than in the "Kp+CPE" group (4.7±1.9 and 5.8±0.4; t=2.1; p <0.05). This confirmed a more pronounced microbiocenosis disorder in AII caused by the combination of *K. pneumoniae* with CPE than in monoinfection with *K. pneumoniae*.

Multiple antibiotic resistance to *K. pneumoniae* (to three or more drugs) was detected only in "Kp" (6.9±4.7%) and "Kp+V" (14.3±9.7%) children (p >0.05). In all child groups, *K. pneumoniae* resistance to bacteriophages was noted (48.3%; 21.4%; 42.3%; 62.5%; χ^2=11.3; p=0.51).

The duration of hospital treatment for children was maximum in the "Kp" and "Kp+V+CPE" groups (5.8±3.2 days; 4.0±1.1 days; 3.7±2.4 days; 7.3±2.9 days; $p_{"Kp" - "Kp+V"}$=0.04; $p_{"Kp"-"Kp+CPE"}$=0.02; $p_{"Kp+V" - "Kp + V+CPE"}$=0.008; $p_{"Kp + CPE"-"Kp+V+CPE"}$= 0.004) (Fig. 3). Most of the kids in the groups were discharged from the hospital "with improvement" (75.9%; 85.7%; 100%; 75%; χ^2=4.4; p=0.22).

Discriminant analysis was applied considering similarities and differences of clinical-laboratory manifestations in groups. It was used to prove the possible separation of AII mono- and combined etiology associated with *K. pneumoniae*. The discriminant model includes the following interrelated signs: children's age (months of life; p=0,0015); complaints of lethargy (0 — no, 1 — yes; p=0,02); complaints of vomiting (0 — none, 1 — yes, p=0,08); platelet count (0 — normal, 1 — lowered, 2 — elevated; p=0,006); amylorrhea in the stool test (0 — not, 1 — yes; P=0,0008); feces pH (0 — normal, 1 — decreasing, 2 — increasing; p=0.12);

Table 1. Complex of clinical and laboratory signs of discriminant model of differential diagnosis of intestinal infections associated with *K. pneumoniae*, codes and coefficients of detected signs

Таблица 1. Комплекс клинико-лабораторных признаков дискриминантной модели дифференциальной диагностики ОКИ, ассоциированной с *K. Pneumoniae*, коды и коэффициенты выявленных признаков

Наименование признаков / Name of signs	Коды / Codes	Коэффициенты признаков линейных дискриминантных функций (ЛДФ) / Feature coefficients of linear discriminant functions (LDF)			
		ЛДФ$_1$ / LDF$_1$	ЛДФ$_2$ / LDF$_2$	ЛДФ$_3$ / LDF$_3$	ЛДФ$_4$ / LDF$_4$
Возраст детей / Age of children	X_1	0,23	0,38	0,69	0,73
Жалобы на вялость / Complaints of lethargy	X_2	–0,12	2,54	–3,59	–1,93
Жалобы на рвоту / Vomiting complaints	X_3	3,00	4,08	0,37	3,37
Количество тромбоцитов в крови / The number of platelets in the blood	X_4	1,77	0,82	5,13	4,17
Амилорея в копрограмме / Amylorrhea in the coprogram	X_5	3,39	–3,33	3,64	0,42
pH кала / Fecal pH	X_6	3,47	4,77	–0,09	0,59
Длительность стационарного лечения / Duration of inpatient treatment	X_7	1,18	0,85	0,68	1,29
Сочетание *K. pneumoniae* с другими условно-патогенными бактериями / Combination of *K. pneumoniae* with other opportunistic bacteria	X_8	–0,92	–1,10	48,20	43,27
Константа / Constant		–8,24	–10,78	–30,95	–32,99

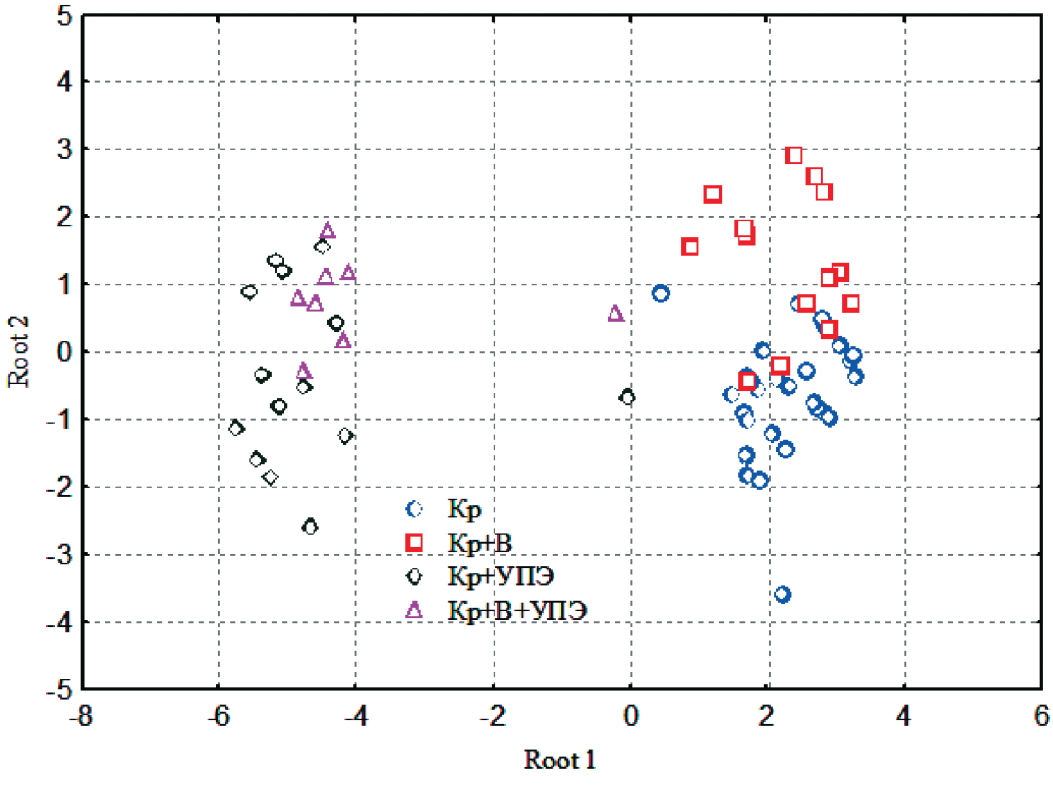

Fig. 4. The position of the objects of the four groups in the coordinates of the first and second canonical LDF

Рис. 4. Положение объектов четырех групп в координатах первой и второй канонических ЛДФ

duration of hospital treatment (days; p=0,004); combination of *K. pneumoniae* with other CPE (0 — no,1 — yes; p <0,00001).

Decisive diagnostic rules expressed as linear discriminatory functions (LDFs): LDF1 (monoinfection of *K. pneumoniae* — "Kp"), LDF2 (AII caused by *K. pneumoniae* and intestinal viruses — "Kp+V"), LDF3 (AII caused by *K. pneumoniae* and other CPE — "Kp+CPE"), LDF4 (AII caused by *K. pneumoniae*, intestinal viruses, and CPE — "Kp+V+CPE"). Table 1 shows the complex of clinical laboratory features affecting the patient's assignment to one of the four groups, the codes and coefficients of these traits.

The following formulae were used to carry out the LDF decision:

$$LDF_1 = -8{,}24 + 0{,}23X_1 - 0{,}12X_2 + 3{,}00X_3 + 1{,}77X_4 + 3{,}39X_5 + 3{,}47X_6 + 1{,}18X_7 - 0{,}92X_8,$$

$$LDF_2 = -10{,}78 + 0{,}38X_1 + 2{,}54X_2 + 4{,}08X_3 + 0{,}82X_4 - 3{,}33X_5 + 4{,}77X_6 + 0{,}85X_7 - 1{,}10X_8,$$

$$LDF_3 = -30{,}95 + 0{,}69X_1 - 3{,}59X_2 + 0{,}37X_3 + 5{,}14X_4 + 3{,}64X_5 - 0{,}09X_6 + 0{,}68X_7 + 48{,}20X_8,$$

$$LDF_4 = -32{,}99 + 0{,}73X_1 - 1{,}93X_2 + 3{,}37X_3 + 4{,}17X_4 + 0{,}42X_5 + 0{,}59X_6 + 1{,}29X_7 + 43{,}27X_8,$$

where X_1–X_8 correspond to the numerical values of the characteristics. The patient is assigned to the group for which LDF will take the maximum value.

The model's sensitivity for kids in the "Kp" group was 96.6%, 78.6% for the "Kp+V" group, 92.9% for the "Kp+CPE" group, and 75%. The model's overall diagnostic significance was high — 89.2%.

The position of the objects of the four groups in the coordinates of the first and second canonical LDFs (with a level of significance of p <0,001) is shown in Fig. 4. This figure demonstrates that the combination of *K. pneumoniae* with other CPEs, rather than the association of K. pneumoniae with intestinal viruses. In children under three years of age is more determined by the combination of *K. pneumoniae* with other CPE than with intestinal viruses.

The less accurate diagnosis of the discriminatory model for the "Kp+V" and "Kp+V+CPE" groups, representing viral-bacterial variants of AII, is due to the significant overlap of clinical and laboratory symptoms in children of the groups "Kp" and "Kp+V", "Kp + CPE" and "Kp+V+CPE". This shows how similar pairs of groups' manifestations of the disease were influenced by common bacterial pathogens. *K. pneumoniae* was present in groups "Kp" and "Kp+V," as well as *K. pneumoniae* combined with CPE in groups "Kp+V+CPE" and "Kp+V" Put another way, variations in the degree of intestinal dysbiosis clearly explained the features and severity of clinical and laboratory signs of AII in similar pairs of groups.

One article describes intestinal infections that are not associated with hypervirulent Klebsiella [16]. However, more dangerous by pathogenicity factors may appear among the population of community-acquired *Klebsiella*. These strains may not have sensitivity to phages and antibiotics which can cause serious complications. Community-acquired strains of *Klebsiella* are among pathogens that provoke AII in young children, they do not have high pathogenicity and pronounced antibiotic resistance. Community-acquired strains of Klebsiella deserve close attention since they are commonly combined with other infectious agents, including representatives of intestinal microbiocenosis. This increasing the likelihood of adverse outcome of the disease.

The manifestation of intestinal infections caused by *K. pneumonia* and other CPE in young children is associated with an increase in their microbiotic representation. It is accompanied by distinct clinical and laboratory manifestations of inflammatory nature.

CONCLUSION

The conducted study allowed to define the features of clinical laboratory signs of mono- and combined intestinal infections associated with *K. pneumoniae* in young children. This study shows that the nature and severity of these signs to a greater extent determines the combination of *K. pneumoniae* with other conditionally-pathogenic enterobacteria than a combination with intestine viruses. Also it confirms the relationship of the symptoms of these intestinal infections with the gravity of bowel dysbiosis, which is main significant in reducing the non-specific resistance of the organism.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

REFERENCES

1. Pron'ko N.V., Kras'ko Yu.P. Kliniko-epidemiologicheskie osobennosti klebsiellezno j infekcii u detej na sovremennom etapeю. [Clinical and epidemiological features of klebsiella infection in children at the present stage]. Aktual'na infektologiya. 2019; 7(3): 155–9. (in Russian).
2. Murzabayeva R.T., Mavzyutov A.R., Valishin D.A. Kliniko-immunologicheskiye paralleli pri ostrykh kishechnykh infektsiyakh, vyzvannykh uslovno-patogennymi enterobakteriyami [Clinical and immunological parallels in acute intestinal infections caused by opportunistic enterobacteri]. Infektsionnyye bolezni. 2018; 16(4): 79–85. (in Russian).
3. Wiener-Well Y., Rudensky B., Yinnon A.M. et al. Carriage rate of carbapenem-resistant Klebsiella pneumoniae in hospitalised patients during a national outbreak. J Hosp Infect. 2010; 74(4): 344–9. DOI: 10.1016/j.jhin.2009.07.022.
4. Mustayeva G.B. Osobennosti techeniya klebsiyelleznoy infektsii po dannym Samarkandskoy oblastnoy klinicheskoy bol'nitsy. [Features of the course of Klebsiella infection according to the Samarkand Regional Clinical Hospital]. Vestnik nauki i obrazovaniya. 2020; 18-2(96): 81–5. (in Russian).
5. Aftayeva L.N., Mel'nikov V.L., Ondrikova Ye.A., Ondrikov N.A. Etiologiya ostrykh kishechnykh infektsiy u detey. [Etiology of acute intestinal infections in children]. Sovremennaya meditsina: aktual'nyye voprosy. 2017; 4(56): 28–33. (in Russian).
6. Kuz'menko S.A., Brusina Ye.B. Meditsinskiye tekhnologii, vliyayushchiye na infitsirovaniye detey bakteriyami roda Klebsiella, profilaktika infitsirovaniya. [Medical technologies affecting the infection of children with bacteria of the genus Klebsiella, prevention of infection]. Chronos. 2020; 8(46): 39–43. (in Russian).
7. Mazankova L.N. Mikrodisbioz i endogennyye infektsii. [Microdisbiosis and endogenous infections]. GEOTAR-Media Publ.; 2018. (in Russian).
8. Murzabayeva R.T., Dubrovskaya D.N., Kuluyev B.R., Mavzyutov A.R. Geneticheskiye markery patogennosti klinicheskikh shtammov uslovno-patogennykh enterobakteriy i tyazhest' techeniya vyzvannykh imi ostrykh kishechnykh infektsiy u vzroslykh. [Genetic markers of pathogenicity of clinical strains of opportunistic enterobacteria and the severity of acute intestinal infections caused by them in adults]. Mezhdunarodnyy akademicheskiy vestnik. 2016; 2(14): 17–21. (in Russian).
9. Rybak T.G. Kliniko-epidemiologicheskaya kharakteristika kishechnoy infektsii klebsiyelleznoy etiologii u detey. [Clinical and epidemiological characteristics of intestinal infection of Klebsiella etiology in children]. V kn.: Sbornik materialov konferentsii studentov i molodykh uchenykh, posvyashchennoy 100-letiyu so dnya rozhdeniya A.Z. Nechiporenko. Grodno; 2016: 184–5. (in Russian).
10. Kharchenko G.A., Kimirilova O.G. Kliniko-epidemiologicheskiye osobennosti ostrykh kishechnykh infektsiy, vyzvannykh uslovno-patogennymi enterobakteriyami u detey rannego vozrasta. [Clinical and epidemiological features of acute intestinal infections caused by opportunistic enterobacteria in young children]. Lechashchiy Vrach. 2021; 4(24): 37–41. (in Russian).
11. Gonchar N.V., Razd'yakonova I.V., Skripchenko N.V., Grigor'yev S.G. Osobennosti etiologii i epidemiologii sochetannykh ostrykh kishechnykh infektsiy u detey. [Features of the etiology and epidemiology of combined acute intestinal infections in children]. Zhurnal infektologii. 2020; 12(2): 113–8. (in Russian).
12. Tkhakushinova N.Kh., Gorelov A.V. Povtornyye ostryye kishechnyye infektsii rotavirusnoy etiologii u detey: osobennosti techeniya, faktory riska, usloviya razvitiya i iskhody. [Recurrent acute intestinal infections of rotavirus etiology in children: course features, risk factors, developmental conditions and outcomes. infectious diseases]. Infektsionnyye bolezni. 2017; 15(1): 29–34. (in Russian).
13. Shamina O.V., Samoylova Ye.A., Novikova I.Ye., Lazareva A.V. Klebsiella pneumoniae: mikrobiologicheskaya kharakteristika, antibiotikorezistentnost' i virulentnost'. [Klebsiella pneumoniae: microbiological characterization, antibiotic resistance and virulence]. Rossiyskiy pediatricheskiy zhurnal. 2020; 23(3): 191–7. (in Russian).
14. Sanitarno-epidemiologicheskiye pravila SP 3.1.1.3108-13 "Profilaktika ostrykh kishechnykh infektsiy". ["Prevention of acute intestinal infec-

tions"]. Prilozheniye. Utverzhdeny postanovleniyem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiyskoy Federatsii ot 05.12.2017 g. № 149. (in Russian).
15. Kanner Ye.V., Pechkurov D.V., Gorelov A.V. Epidemiologicheskaya kharakteristika ostrykh infektsiy s sochetannym porazheniyem dykhatel'noy i pishchevaritel'noy sistem u detey. [Epidemiological characteristics of acute infections with combined lesions of the respiratory and digestive systems in children]. Epidemiologiya i infektsionnyye bolezni. 2019; 2: 24–30.
16. Ageyevets V.A., Ageyevets I.V., Sidorenko S.V. Konvergentsiya mnozhestvennoy rezistentnosti i gipervirulentnosti u Klebsiella pneumoniae. Infektsiya i immunitet. [Convergence of multiple resistance and hypervirulence in Klebsiella pneumoniae]. 2022; 12(3): 450–60. DOI. org/10.15789/2220-7619-COM-1825.

ЛИТЕРАТУРА

1. Пронько Н.В., Красько Ю.П. Клинико-эпидемиологические особенности клебсиеллезной инфекции у детей на современном этапе. Актуальна інфектологія. 2019; 7(3): 155–9.
2. Мурзабаева Р.Т., Мавзютов А.Р., Валишин Д.А. Клинико-иммунологические параллели при острых кишечных инфекциях, вызванных условно-патогенными энтеробактериями. Инфекционные болезни. 2018; 16(4): 79–85.
3. Wiener-Well Y., Rudensky B., Yinnon A.M. et al. Carriage rate of carbapenem-resistant Klebsiella pneumoniae in hospitalised patients during a national outbreak. J Hosp Infect. 2010; 74(4): 344–9. DOI: 10.1016/j.jhin.2009.07.022.
4. Мустаева Г.Б. Особенности течения клебсиеллезной инфекции по данным Самаркандской областной клинической больницы. Вестник науки и образования. 2020; 18-2(96): 81–5.
5. Афтаева Л.Н., Мельников В.Л., Ондрикова Е.А., Ондриков Н.А. Этиология острых кишечных инфекций у детей. Современная медицина: актуальные вопросы. 2017; 4(56): 28–33.
6. Кузьменко С.А., Брусина Е.Б. Медицинские технологии, влияющие на инфицирование детей бактериями рода Klebsiella, профилактика инфицирования. Chronos. 2020; 8(46): 39–43.
7. Мазанкова Л.Н. Микродисбиоз и эндогенные инфекции. ГЕОТАР-Медиа; 2018.
8. Мурзабаева Р.Т., Дубровская Д.Н., Кулуев Б.Р., Мавзютов А.Р. Генетические маркеры патогенности клинических штаммов условно-патогенных энтеробактерий и тяжесть течения вызванных ими острых кишечных инфекций у взрослых. Международный академический вестник. 2016; 2(14): 17–21.
9. Рыбак Т.Г. Клинико-эпидемиологическая характеристика кишечной инфекции клебсиеллезной этиологии у детей. В кн.: Сборник материалов конференции студентов и молодых ученых, посвященной 100-летию со дня рождения А.З. Нечипоренко. Гродно; 2016: 184–5.
10. Харченко Г.А., Кимирилова О.Г. Клинико-эпидемиологические особенности острых кишечных инфекций, вызванных условно-патогенными энтеробактериями у детей раннего возраста. Лечащий Врач. 2021; 4(24): 37–41.
11. Гончар Н.В., Раздьяконова И.В., Скрипченко Н.В., Григорьев С.Г. Особенности этиологии и эпидемиологии сочетанных острых кишечных инфекций у детей. Журнал инфектологии. 2020; 12(2): 113–8.
12. Тхакушинова Н.Х., Горелов А.В. Повторные острые кишечные инфекции ротавирусной этиологии у детей: особенности течения, факторы риска, условия развития и исходы. Инфекционные болезни. 2017; 15(1): 29–34.
13. Шамина О.В., Самойлова Е.А., Новикова И.Е., Лазарева А.В. Klebsiella pneumoniae: микробиологическая характеристика, антибиотикорезистентность и вирулентность. Российский педиатрический журнал. 2020; 23(3): 191–7.
14. Санитарно-эпидемиологические правила СП 3.1.1.3108-13 «Профилактика острых кишечных инфекций». Приложение. Утверждены постановлением Главного государственного санитарного врача Российской Федерации от 05.12.2017 г. № 149.
15. Каннер Е.В., Печкуров Д.В., Горелов А.В. Эпидемиологическая характеристика острых инфекций с сочетанным поражением дыхательной и пищеварительной систем у детей. Эпидемиология и инфекционные болезни. 2019; 2: 24–30.
16. Агеевец В.А., Агеевец И.В., Сидоренко С.В. Конвергенция множественной резистентности и гипервирулентности у Klebsiella pneumoniae. Инфекция и иммунитет. 2022; 12(3): 450–60. DOI. org/10.15789/2220-7619-COM-1825.