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# PROMISING AREAS OF SCIENTIFIC RESEARCH ON THE PROBLEMS OF INTESTINAL INFECTIONS

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***Abstract.*** The solution of modern problems of diagnosis and treatment of intestinal infections in children is determined by the most important areas of scientific research, among which are the molecular genetics and clinical features of viral diarrhea pathogens, improvement of therapy methods for acute gastroenteritis of viral etiology, molecular diagnostics of toxin-producing bacterial intestinal pathogens, biological safety and intestinal infections, prediction of antibiotic-associated diarrhea and treatment approaches, clinical significance of diarrhea of conditionally pathogenic bacterial etiology in children, antibiotic resistance of *Enterobacteriaceae* and the effectiveness of phage therapy, personalized symbiont therapy of convalescents of intestinal infections.

***Key words:*** *intestinal infections; children; etiology; diagnosis; treatment*

# ПЕРСПЕКТИВНЫЕ НАПРАВЛЕНИЯ НАУЧНЫХ ИССЛЕДОВАНИЙ ПО ПРОБЛЕМАМ КИШЕЧНЫХ ИНФЕКЦИЙ

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***Резюме.*** Решение современных проблем диагностики и лечения кишечных инфекций у детей определяет важнейшие направления научных исследований, в ряду которых стоят молекулярно-генетические и клинические особенности возбудителей вирусных диарей, совершенствование методов терапии острых гастроэнтеритов вирусной этиологии, молекулярная диагностика токсинпродуцирующих бактериальных кишечных патогенов, биологическая безопасность и кишечные инфекции, прогнозирование антибиотик-ассоциированной диареи и подходы к лечению, клиническое значение диареи условно-патогенной бактериальной этиологии у детей, антибиотикорезистентность энтеробактерий и эффективность фаготерапии, персонифицированная симбионтная терапия реконвалесцентов кишечных инфекций.

***Ключевые слова:*** *кишечные инфекции; дети; этиология; диагностика; лечение*

## RELEVANCE OF RESEARCH ON THE PROBLEMS OF ACUTE INTESTINAL INFECTIONS

The years 2022–2031 have been declared the Decade of Science and Technology in Russia (Decree of the President No. 231, April 25, 2022). The aim of the Decade is to strengthen the role of science and technology in solving the most important problems of the development of society and country.

The relevance of scientific research on the problems of acute intestinal infections (AII) in the world is confirmed by statistical data on scientific publications in PubMed for the last 10 years, indicating an increase in the number of annual publications devoted to acute gastroenteritis. Also there was no decrease in number of publications devoted to rotavirus and norovirus gastroenteritis, as well as salmonellosis (Fig. 1).

The topics of publications and thesises allow us to identify the following priority areas of scientific research on the problems of AII in children in the domestic and foreign literature: Molecular genetic characteristics and clinical picture of intestinal infections of viral etiology [1–4]; intestinal infections of bacterial etiology (typhoid fever, shigellosis, salmonellosis) [5–10]; intestinal infections caused by opportunistic Enterobacteriaceae [11, 12]; healthcare-associated viral intestinal infections [13, 14]; immunopathogenesis, gut microbiota and optimization of therapy for intestinal infections [15–17].

Acute gastroenteritis. Norovirus gastroenteritis in children. Rotavirus gastroenteritis in children. Salmonellosis in children.

## MOLECULAR GENETIC FEATURES OF VIRAL PATHOGENS CAUSED DIARRHEA

The relationship between molecular genetic features of viral pathogens caused diarrhea and severity of clinical manifestations of the disease is being actively studied. Thus, comparison of the genetic structure of circulating rotavirus strains in Qatar [18] and Indonesia [19] in 2015–2019 years revealed the similarity of dominant genotypes — G3P [8]. According to the Vesikari scale for severity of AII, severe forms of rotavirus infection in Qatar, including diarrhea and vomiting, were most frequently caused by G3P [8], and less frequently caused by other genotypes.

The study of molecular epidemiology of rotavirus infection have practical implications: in the East Java region (Indonesia), in September 2015 — March 2018 [19], a shift from group A rotavirus equine-like strains (G3) to human strains (G1/G3) was observed amid a sharp drop in rainfall intensity (Figure 2). Comparison of the population of group A rotavirus (RVA) genotypes by whole genome sequences in different periods of the study shows differences in the set of genome segments during the change of genotypes (Fig. 3).

According to the results of observations of the Reference Center for Monitoring of Acute Intestinal Infections, in the Russian Federation in 2021 [20]

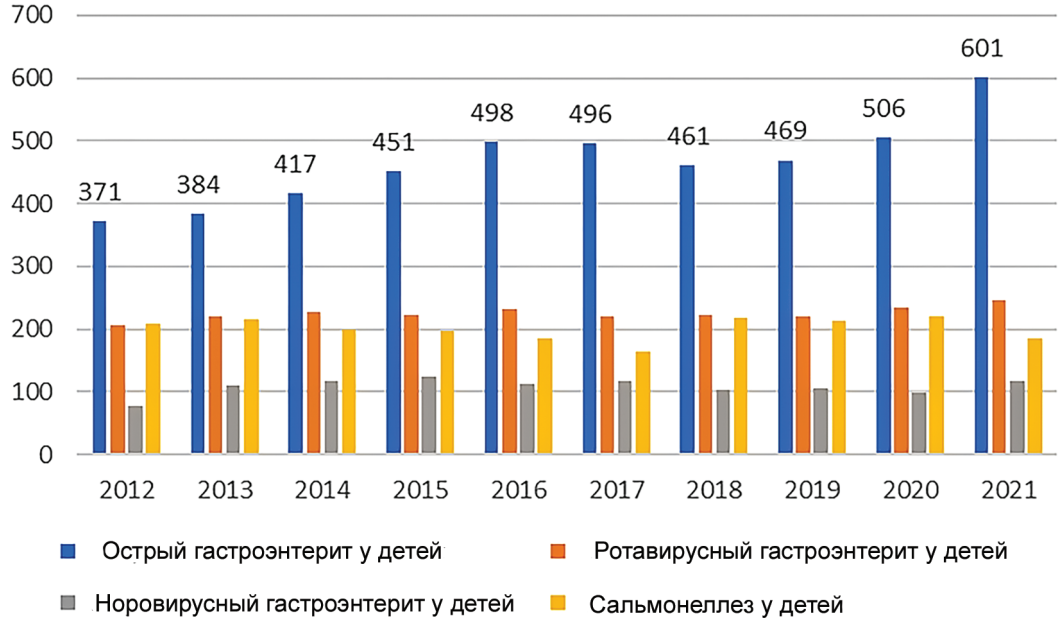


Fig. 1. Number of annual publications on "Acute intestinal infections in children" in PubMed (2012–2021)

Рис. 1. Число ежегодных публикаций по теме «Острые кишечные инфекции у детей» в PubMed (2012–2021)

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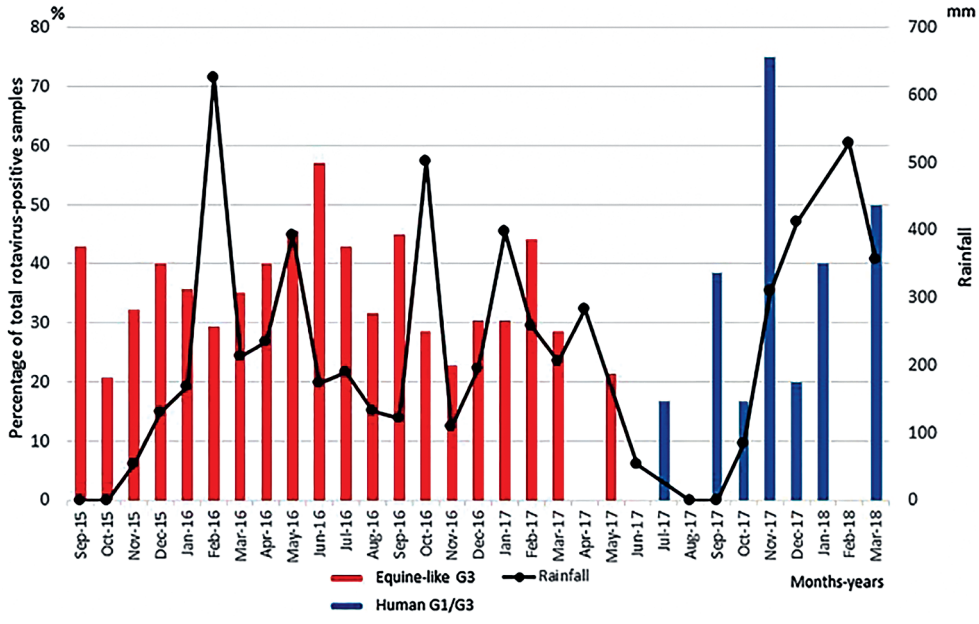


Fig. 2. Frequency of isolation of group A rotavirus equine-like strains (G3) and human strains (G1/G3) in East Java region from September 2015 to March 2018 [19]

Рис. 2. Частота выделения лошадиноподобных штаммов ротавируса группы А (G3) и человеческих штаммов (G1/G3) в регионе Восточной Явы в период с сентября 2015 г. по март 2018 г. [19]

| Name of strain | Genotypes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | VP 7 | VP4 | VP6 | VP1 | VP2 | VP3 | NSP1 | NSP2 | NSP3 | NSP4 | NSP5 |
| RVA/Hu-tc/USA/Wa/1974/G1P1A[8] | G1 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| RVA/Hu-tc/USA-DS-1/1976/G2P[4] | G2 | P[4] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/D05/2013/G1P[8] | G1 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/D13/2013/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/D37/2013/G1P[8] | G1 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/D63/2013/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/GRV60/2014/G1P[8] | G1 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/GRV67/2014/G1P[8] | G1 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/GRV68/2014/G1P[8] | G1 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM004/2015/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM008/2015/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM009/2015/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM044/2015/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM050/2015/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM102/2016/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM147/2016/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM169/2016/G3P[6] | G3 | P[6] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM182/2016/G3P[6] | G3 | P[6] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM197/2016/G3P[6] | G3 | P[6] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM230/2016/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM369/May2017/G3P[8] | G3 | P[8] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM387/July2017/G1P[8] | G1 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | - | H1 |
| RVA/Human/IDN/STM415/2017/G3P[6] | G3 | P[6] | I2 | R2 | C2 | M2 | A2 | N2 | T2 | E2 | H2 |
| RVA/Human/IDN/STM453/2018/G1P[8] | G1 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |
| RVA/Human/IDN/STM457/2018/G1P[8] | G1 | P[8] | I1 | R1 | C1 | M1 | A1 | N1 | T1 | E1 | H1 |

Fig. 3. Comparison of the population of RVA genotypes by whole genome sequences in different periods of the study (23 Indonesian strains) [19]

Рис. 3. Сравнение совокупности генотипов RVA по последовательностям всего генома в разные периоды исследования (23 индонезийских штамма) [19]

the prevalence of the G9P [8] genotype was maintained and proportion of the G3P [8] genotype of rotaviruses increased. Among the genotypes that do not have a global distribution, circulation of the G8P [8] genotype has been established.

Against the background of an introduction of routine rotavirus vaccination, the study of genotypic and clinical features of norovirus infection (NVI) is important. The structure of circulating norovirus strains in many countries is dominated

by the GII strain, but data on the clinical features of NVI caused by the same strains of the pathogen vary from country to country. For example, in Ghana, the clinical picture of NVI in children infected with GII.4 and non-GII.4 strains did not differ [21], and in children in Canada, the clinical picture of NVI caused by GII.4 strain was characterized by higher scores on Vesikari scale and longer duration of diarrhea and vomiting compared with the clinical picture of NVI caused by non-GII.4 strains [22].

The genomic organization of the genus *Norovirus* is being studied. Norovirus RNA contains three open reading frames that encode eight viral proteins (https://viralzone.expasy.org/194). The first classification of the genus Norovirus is based on the assessment of nucleotide sequence diversity obtained by sequencing the ORF 1 or ORF 2 regions. In 2013, a universal standardized system of norovirus nomenclature and typing was proposed, according to which, in 2019, 10 genogroups (GI-GX) and 48 genotypes were distinguished, and changes were made to the designation of norovirus strains because frequent recombination events in the norovirus genome cause data on the number of genotypes quickly become outdated. The diversity of circulating norovirus genotypes, rapid variability of the genome, and Its ability to cause outbreak morbidity indicate the need for continuous monitoring of NVIs [23].

According to the observations of the Reference Center for Monitoring of Intestinal Infections, in the Russian Federation in 2021 [20], genotypes / genogroups of noroviruses in foci of group and sporadic morbidity differ. The results of genotyping of isolates in outbreak and sporadic morbidity indicate the diversity of norovirus genotypes / genogroups.

## INTESTINAL INFECTIONS CAUSED BY UNIDENTIFIED PATHOGENS

Intestinal infections caused by unidentified pathogens are characterized by significant medical, social and economic importance, and Its morbidity rates have remained high for many years [20]. It accounts for more than 30% in the etiologic structure of AII according to data of Children's research and clinical center for infectious diseases of the FMBA of the Russian Federation. Reducing the proportion of infectious diarrheas of unidentified etiology can be achieved by expanding the range of diagnosable pathogens.

In recent years, the number of studies demonstrating the association of acute gastroenteritis (AGE) with "non-intestinal" adenoviruses have increased worldwide. The etiologic role of adenovirus genotype B3 has been proven in infants and children with diarrhea; genotypes C1, C2, and C5 are also frequently identified in patients with AGE. In addition, genotypes A12, A18, A31 and G52 are capable of causing symptoms of AGE [24]. In Italy, the incidence of adenoviral gastroenteritis in hospitalized children is 7.1%, which is consistent with the results of studies in Thailand, Japan, China and India. A predominance of adenovirus genotypes C (91.2%) and B (8.8%) was detected by molecular typing. However, F40 and F41 genotypes, which are most common in patients with AGE, were not identified in this study [25]. Since most commercial systems detect only the "intestinal" strains F40 and F41, new rapid and reliable detection methods should be developed for all known adenovirus genotypes at present.

Human parechoviruses (HPeV), which, like enteroviruses (EV), are members of the family *Picornaviridae*, should also be considered in the verification of viral diarrhea. The genus *Parechovirus* is divided into 2 species: *Parechoviruses* A and B. *Parechovirus* A species consists of 16 types [26].

The incidence of parechovirus infection is not precisely known because it is not reportable, but is assumed to correspond to the incidence of enterovirus infection [26]. Unlike EV infection, HPeV infection is rare in older children and adults. Serologic data show that more than 90% of children under 2 years of age are infected with at least one type of HPeV. The primary sites of EV and HPeV replication are epithelial cells of the oropharynx and intestinal mucus membrane, followed by viremia and secondary infection of various organs and tissues. Most studies have focused on the pathogenicity of HPeV genotypes 1 and 3. The clinical manifestations due to different HPeV genotypes are thought to be due to differences in their biological properties. Most commonly, circulating HPeV genotype 1 causes mild gastrointestinal and respiratory complaints, although more severe disease may be detected in young children. HPeV genotype 3 is a more pathogenic type associated with paralysis, neonatal sepsis and sudden death in infants [27]. The PCR-RT method is recognized as the "gold standard" for the diagnosis of HPeV infection [26].

## PROBLEMS OF TREATMENT FOR ACUTE GASTROENTERITIS AND ROTAVIRUS VACCINATION

Probiotics are used as medicines that can accelerate the symptomatic relief of acute gastroenteritis. However, recent clinical studies have questioned their efficacy [28]. It was shown that there were no differences in the efficacy of treatment for AII of viral, bacterial, and combined viral-bacterial

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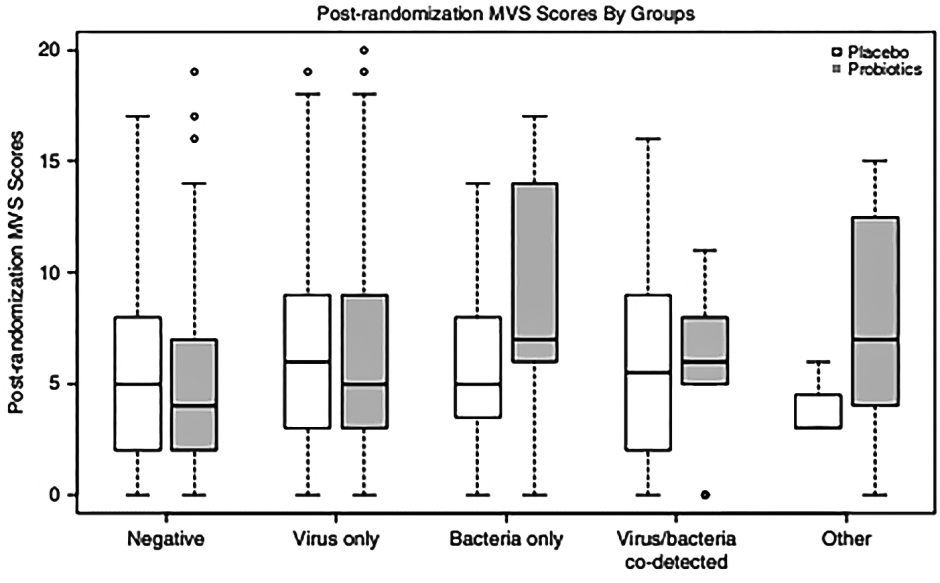


Fig 4. Comparison of severity of acute gastroenteritis according to the Vesikari scale in children (n=816) in groups with different treatment (5-day use of probiotics *L. rhamnosus+L. helveticus* or placebo) and groups with diseases of different etiology [28]

Рис. 4. Сравнение тяжести острых гастроэнтеритов по шкале Везикари у детей (n=816) по группам лечения (5-дневный прием пробиотиков *L. rhamnosus+L. helveticus* или плацебо) и группам этиологии заболевания [28]

etiologies, previously vaccinated against rotavirus infection, according to the criteria for assessing a severity of the disease (Vesikari scale). It was shown in group of children who were treated with a 5-day course of probiotics (*L. rhamnosus+L. helveticus*) and in group of children treated with platinum-based probiotics (*L. rhamnosus+L. helveticus. Helveticus*) and in the placebo group (Fig. 4). Also, the absence of differences in the terms of norovirus elimination was established, when assessment of dynamics and count of norovirus in faces in three described groups was done.

The explanation for these facts may be the change of leading pathogens after routine use of rotavirus vaccine and insufficient study of the therapeutic effects of probiotics in AGE of non-rotavirus etiology.

The analysis of changes in fecal viral load in patients with AGE represents a new unique approach to diagnosis and assessment of therapy efficacy. A higher viral load reflects a greater degree of intestinal epithelial damage and contributes to the development of a more severe disease [29]. A high viral load in feces of patients does not exclude the possibility of intestinal viruses spreading outside the intestine into the bloodstream (viral antigenaemia) and manifestation of extraintestinal signs of AGE [30].

New strategies for the prevention and treatment of viral diarrhea are being developed. It has been established that certain representatives of the gut microbiota are capable of exerting an inhibitory or stimulatory effect on the infectivity of intestinal viruses *in vitro*. In particular, it has been shown that the bacterial taxa *Ruminococcus* and *Oxalobacter* can inhibit rotavirus infection [31].

## ISSUES OF ETIOLOGY OF FOODBORNE INTOXICATION

As it was noted in the State Report of Russian Agency for Health and Consumer Rights, the incidence of foodborne intoxication of unspecified etiology in the Russian Federation, in 2021–2020, increased by 17.5%, not exceeding the average annual level (336.11) [20]. Also, in 2020, botulism affected 112 people, 7 of them had a fatal outcome. In the first 9 months of 2021, botulism affected 92 people, in whom 15 cases were fatal. Botulism develops by eating products containing toxin produced by vegetative forms of *Clostridium botulinum*, characterized by paresis and paralysis of striated and smooth muscles, which in the initial period of the disease is sometimes accompanied by gastroenteritis. The infectious nature of the disease is clearly manifested in cases of botulism in children of the first year of life and in extremely rare cases of botulism in adults, when the incubation period exceeds 4–5 days [32].

The control of foodborne intoxication is accompanied by measures on hygiene of children's food, implemented through the system of dissemination of medical knowledge. Molecular diagnostics of toxin-producing intestinal pathogens in contaminated food for children's feeding play an important role and make it possible

to significantly increase the etiologic interpretation of infections caused by toxin-producing bacteria [3].

## BIOSECURITY AND INTESTINAL INFECTIONS

The VII (current) cholera pandemic began in 1961 in South Asia, spread to Africa in 1971, and to America in 1991. Currently, cholera is an endemic disease (in 2020, 323,369 cases were registered in 24 countries). In Mariupol, the first 3 cases of cholera were reported on May 29, 2011, and the outbreak ended on August 19. Laboratory tests confirmed 54 cases, including 22 cases of carriage. A toxigenic strain of *V. cholera eltor* of Ogawa serovar, resistant to tetracycline and levomycetin, was isolated in all infected persons. The most important factors of cholera transmission were fish cutting and eating (48.1% cases in total) [33]. The annual isolation of non-toxigenic *V. cholera* indicates the need to determine the potential and real risks of contamination of water with V. cholera of O1/O139 serogroups and elimination of pathogens [34].

## PREDICTION PROBLEMS, ETIOLOGY AND TREATMENT APPROACHES FOR ANTIBIOTIC-ASSOCIATED DIARRHEA

The study of a heterogeneity of diarrhea in 981 patients with COVID-19 allowed us to distinguish early antibiotic-associated diarrhea (AAD) — viral etiology (9.3% of patients) and late AAD — bacterial etiology (16.7% of patients). This fact suggests the use of different methods of treatment [35]. Toxin-producing *C. difficile* strains were detected in 70.5% of adult patients with COVID-19 and late diarrhea, but it was not found in patients with early diarrhea. Risk factors for the development of late AAD were identified: use of oral amoxiclav (OR=2.2) or clarithromycin (OR=3.8), and glucocorticoids (OR=4.4). Late AAD was associated with an increased risk of death after 20 days of illness (OR=4.7). Before the development of late AAD, the decrease in C-reactive protein level and increase in the number of lymphocytes stopped, but the number of leukocytes and neutrophils in the blood increased (sensitivity 82.0%, specificity 70.8%).

According to modern studies, the frequency of detection of toxin-producing *C. difficile, C. perfringens, K. oxytoca*, and *S. aureus* during AAD in hospitalized adult patients is 19.6, 14.9, 27, and 5.2%, respectively. At the same time, high resistance of *C. difficile* was found to ciprofloxacin, and low resistance to chloramphenicol, vancomycin, and metronidazole [36].

Nowadays, new methods of treatment for antibiotic-associated colitis associated with *C. difficile* are being developed and implemented — transplantation of intestinal microbiota of healthy donors [37].

## DIARRHEA OF OPPORTUNISTIC ETIOLOGY IN CHILDREN

AII caused by opportunistic Enterobacteriaceae (OE) in children under 1 year of age account for 60% of the total number of AIIs of specified bacterial etiology [38], where *Klebsiella pneumoniae* plays a leading role among the causative agents [39]. OE diarrhea more often proceeds as a mild monoinfection [38].

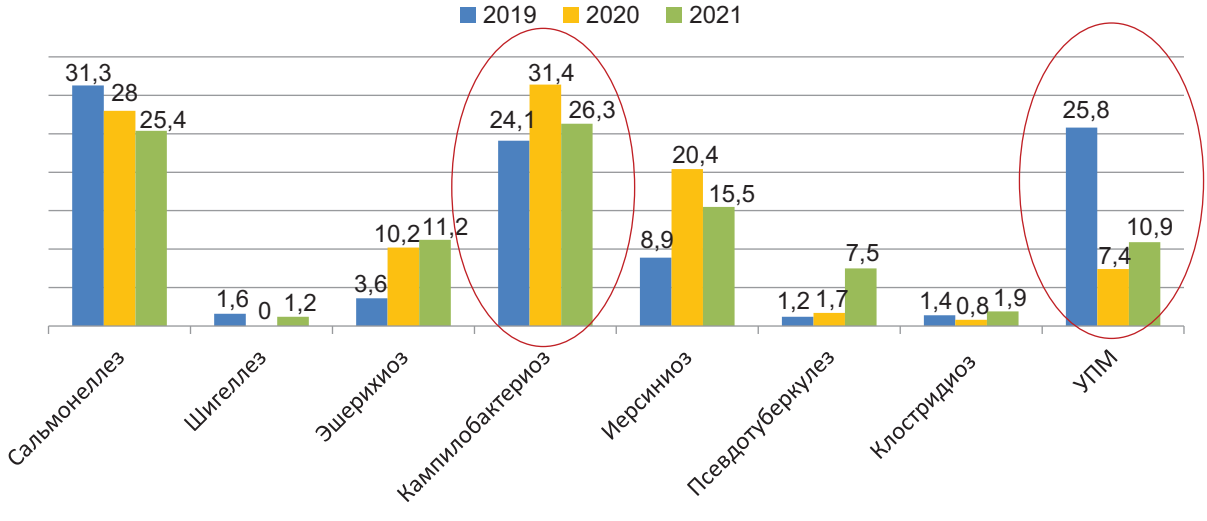


Fig. 5. Dynamics of frequency of diagnostics of bacterial AII of different etiology in children in Children's Research and Clinical Center for Infectious Diseases of the FMBA of the Russian Federation in 2019–2021. OM — opportunistic microbes

Рис. 5. Динамика частоты диагностики бактериальных ОКИ различной этиологии у детей в ДНКЦИБ ФМБА России в 2019–2021 гг. УПМ — условно-патогенные микробы

Klebsiellosis is more common in young children with an unfavorable premorbid background: protein-energy malnutrition, rickets, deficiency anemia. Patients under 1 year of age are characterized by water loss dehydration [40].

Analysis of the dynamics of the frequency of diagnosis of bacterial AII of various etiologies in children in the Children's research and clinical center for infectious diseases of FMBA of the Russian Federation in 2019-2021 shows that AII caused by opportunistic pathogenic microbes (APM) is detected almost as often as campylobacteriosis (Fig. 5).

## ANTIBIOTIC RESISTANCE OF ENTEROBACTERIACEAE AND PHAGE THERAPY

Antibiotic-resistant Enterobacteriaceae (ESCAPE pathogens: *E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. Aeruginosa, Enterobacter*) became a global problem of the Health care. Antibiotic susceptibility testing of 646 Enterobacteriaceae isolates revealed multidrug resistance in 87.3% of cases. β-lactamase genes were detected in 73.2% of isolates [41].

Phages and phage-encoded enzymes are used as etiological therapy for antibiotic-resistant pathogens, which is based on the principles of interaction between phages, pathogenic bacteria, and immune cells (Fig. 6) [42].

## TRENDS IN GROWTH OF PHAGORESISTANCE OF OPPORTUNISTIC ENTEROBACTERIACEAE

In children with impaired gut microbiota, there is a significant frequency of detection of phage-resistant strains of OP. That is why a regular monitoring of sensitivity of these strains to bacteriophages is necessary to improve the effectiveness of phagotherapy prescribed to infants and young children. Data on the sensitivity of OPs to bacteriophages are not stable and may vary depending on the frequency of antimicrobial use in the region. Studies indicate a rather large proportion of OPs (43.5%) resistant to bacteriophages [43].

New therapeutic approaches to overcome phage resistance in OPs are being developed. There is evidence that the use of a combination of an antibacterial drug or antibiotic with bacteriophages increases the effectiveness of treatment for staphylococcal enterocolitis in infants [38].

## IMPROVEMENT OF PATHOGENETIC AND ETIOTROPIC THERAPY FOR ACUTE INTESTINAL INFECTIONS IN CHILDREN

The prospect of new nutritious low-osmolar rehydration mixtures and new enterosorbents-cytomucoprotectors in treatment of children with viral diarrhea has been demonstrated. The use of nutritious low-osmolar rehydration mixtures and cytomucoprotector in children with AII has a rapid detoxification and antidiarrheal effect [44].

Studies aimed at research of nutritional status in children with infectious diarrhea as a criterion of premorbid background, the dynamics of course of the disease and as a basis for optimizing therapeutic nutrition are relevant. The correlation between severity of infectious colitis and nutritional disorders in children of different age groups was shown [45].

The issues of etiological therapy of campylobacteriosis and its influence on clinical manifestations and gut microbiota in children are studied. It was shown in studies, that in the treatment for severe and moderate-to-severe forms of campylobacteriosis in children, antibacterial drugs of the macrolide group were more effective. The use of

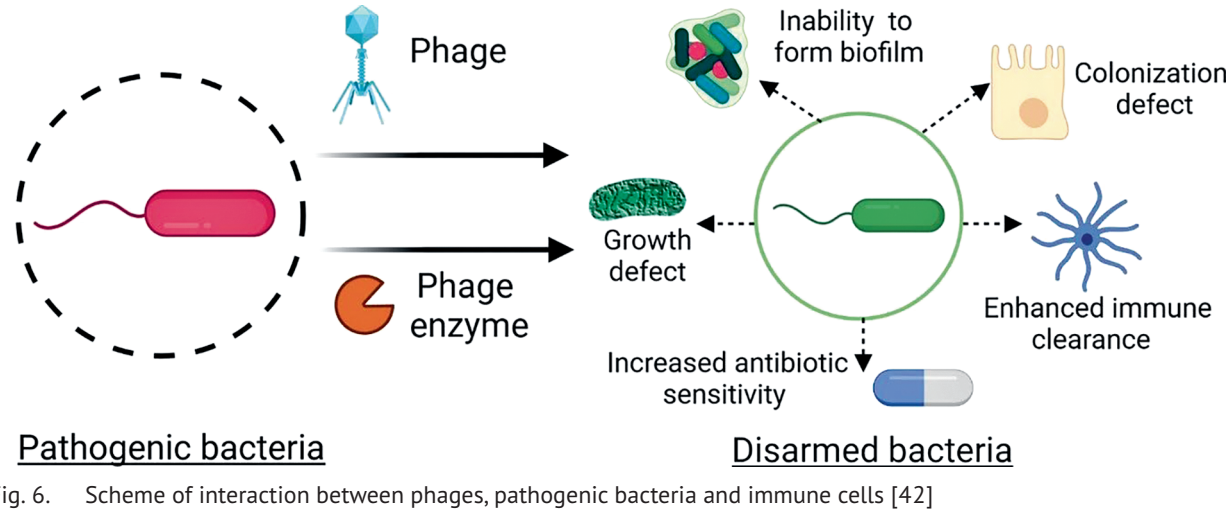


Fig. 6. Scheme of interaction between phages, pathogenic bacteria and immune cells [42]

Рис. 6. Схема взаимодействия между фагами, патогенными бактериями и иммунными клетками [42]

cephalosporins leads to delayed recovery due to significant damage of a gut microbiota [46].

The personalized symbiont therapy of children who had had an AII based on the use of autoprobiotics for the prevention of postinfection gastroenterological pathology is being developed. The introduction of targeted probiotics (autoprobiotics) for the correction of disorders of gut microbiota in children with prolonged course of intestinal infections is a promising way to improve the effectiveness of treatment and prevention of postinfection functional gastroenterological pathology [47].

## CONCLUSION

The relevance of scientific studies on the problems of acute intestinal infections in children is beyond doubt. Promising areas of research today are molecular and genetic features of pathogens, which causes a viral diarrhea, improvement of therapy methods for acute gastroenteritis of viral etiology, molecular diagnostics of toxin-producing bacterial pathogens, biosafety and intestinal infections, prediction of antibiotic-associated diarrhea and approaches to treatment, clinical significance of diarrhea of opportunistic etiology in young children, antibiotic resistance of Enterobacteriaceae and the effectiveness of antibiotic therapy. The introduction of scientific and technical progress in medicine contributes to the improvement of diagnosis, treatment and prevention of infectious diseases.

## 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.

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