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Clinical and epidemiological features, therapy issues of norovirus infection in children

14.00.10 – Infectious diseases

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Relevance of the research topic

Acute intestinal infections (AII) is one of the important health issues in both developing and developed countries, being the next widespread among mass infectious diseases after respiratory infections. Despite the progress made in improving diagnostics and treatment tactics, acute intestinal infections are widespread - they are transferred annually by at least 500,000 children (Onishchenko G.G., 2006; Uchaikin V.F., 2007; Feklisova L.V., 2007). In recent years there has been a clear trend in etiological significance of pathogens causing acute intestinal infections in children (Gorelov A.V., Milutin L.N., 2006). There is no doubt that among them a leading role in the world belongs to viruses causing 50-80% of AII in children (Glass R., 2005; Parashar V., 2003; Podkolzin A.T., 2005). AII represent the greatest danger for the children in the first years of life due to high rates of morbidity and mortality worldwide (Sharapova O.V., Korsun A.A., 2003; Glass R.I. et al, 2000; Wilhelmi I. 2003.).

One of the new DCI viral pathogens are noroviruses. Thus, in our pediatric experience viral diarrhea has not been studied enough, particularly true role of noroviruses in the structure of the AII has not been determined, no official examination has been made. According to foreign literature, norovirus infection takes the leading place among viral diarrhea adults, and is a major causative agent of nosocomial outbreaks (Shuji Nakata et al.).

According to Russian researches published in recent years, in the structure of acute intestinal infections in children in Saint - Petersburg, Novosibirsk, Arkhangelsk noroviruses of genotypes I and II are 11.1%, 13.5% and 26.5%, respectively, with a predominance of noroviruses of genotype II (Krasnova E.I., 2004; Sergeeva N.V., 2004; Bulanov I.A., 2008). A large outbreak of norovirus infection has been described in one of the schools in the city of Penza. (Podkolzin A.T., 2007).

Upon literature analysis the fact is noteworthy that calicivirus infection studies have concentrated on epidemiological and diagnostic aspects of the problem, while there are extremely few works dedicated to a detailed description of clinical symptoms in the age aspect, differential diagnosis, and treatment.

In the recent years, it has been convincingly demonstrated that the timeliness and adequacy of therapy in acute intestinal infections depend on the duration of the disease and its outcomes (Maleev V.V., 2007). Still stereotyped antibiotics therapy is used in our country in 70% of AII, regardless of the etiology of patients (A.T. Podkolzin, 2002, Grekov A.I., 2007).

All the foregoing underlines the urgency of improving diagnostics and updates of clinical laboratory, epidemiological features of norovirus infection in children, depending on age and development of optimal treatment approaches.

Materials and methods

The present study included data of 997 patients aged from 1 month to 14 years treated in the Department of children's acute intestinal infections, Hospital of Infectious Diseases No. 5, Moscow (DIB №5) 2005-2008 (the chief doctor - Zolotavina S.V.). In these patients etiologic structure of acute intestinal infections was defined by PCR. Patient selection was carried out randomly throughout the seasons. A prerequisite examination of patients was a fence material on bacteriological seeding and PCR on the first day of admission to beginning of causal treatment. Of these, 401 children examined as routine methods (ELISA) to detect rotavirus.

As a result of a comprehensive survey diagnosis norovirus infection (NV) is set in 168 (16.8%) children with acute intestinal infections. The age structure of NV patients is shown in table 1.

Table 1 Distribution of patients with NV infection by age and sex, n = 168

Age	1-12 months	1-3 years	3-6 years	Older than 6 years	Significance
Boys	23(13,6%)	44(26,1%)	18(10,7%)	5(3%%)	p>0.05
Girls	19(11,3%)	30(17,8%)	22(13%)	7(4,1%)	
Total	42 (25%)	74 (44%)	40 (23,8%)	12 (7,1%)	

As can be seen from table 1, young children under three years dominated - 69%, there were slightly more boys than girls in this age group.

Patients with monovirus infection (131 children) were divided into groups matched by age, therapies, severity:

- To identify the clinical features of NV infection in children, depending on the age we have examined 24 children aged up to 1 year, 42 patients aged from 1 year to 3 years and 22 children from 3 to 6 years.
- To assess the effectiveness of therapies - for a group of children receiving therapy:
 - Oral rehydration + sorbents- 22 children (Enterosgel, neosmectin)
 - Oral rehydration + kipferon- 24 children,
 - Oral rehydration + probiotiki- 24 children (Acypol, Linex)
 - Oral rehydration + antibiotics - 29 children (amikacin, cefazolin, nevigramon).

To identify differentially diagnostic differences of norovirus infections and rotavirus - an additional in-depth analysis of current norovirus infection (56 patients), and rotavirus infection (50 patients) was performed in comparable clinical and laboratory parameters of the group.

All patients were examined in the acute stage of the disease with the date of admission to the hospital before his discharge. The assessment of AII gravity was conducted on the basis of approval by the Ministry of Health and Social Development of the Russian Federation for the benefit of doctors' clinical recommendations for diagnosis and treatment of acute intestinal infections in children (Gorelov A.V., Milutin L.N., Usenko D.V., 2005).

Clinical observation: For every patient a special patient card we have developed was filled in, which marked daily data of the disease course, clinical and laboratory examination, as well as anamnesis: during pregnancy, full-term, the nature of feeding for children, mixed and artificial feeding, age of transition to artificial food, its form.

During the observation of the child daily somatic status was assessed, as well as the child's emotional state (sleep, activity, reaction to the medical examination et al.), appetite. In the appointment of new drugs carried a child surveillance the nature of its portability, efficiency, attitude to the child for him the new drug. When considering the clinical course of the disease into account the development of complications of the disease (exsiccosis, toxemia). Examines in detail the beginning and during the present illness: length of hospital stay, the duration of intoxication, normalization of body temperature as possible, timing recovery of appetite,

vomiting, and the dynamics of the relief of diarrhea, abdominal pain, flatulence, intestinal cramps, rumbling on its course, and other manifestations of DCI.

Clinical efficacy was evaluated comprehensively in the following criteria: "good" - with complete disappearance of the clinical manifestations of the disease on the 3rd day of treatment; "satisfactory" – reduction of clinical manifestations of the disease by 4-5 days of treatment; "lack of effect" - with an increase in the intensity of the clinical manifestations of the disease that entailed replacement etiotropic drug.

Standard examination included CBC and urinalysis, scatological study for blood, and determination of acid-base composition of the blood. Clinical Laboratory diagnosis was made on the basis of laboratory No. 5 Moscow (Head of the laboratory – G.V. Melnikov).

In order to establish the etiology of acute intestinal infection a number of studies was carried out.

On admission to the hospital is one triple-culture and feces on the testimony - gastric lavage. Isolation and differentiation of *Enterobacteriaceae* was performed by a standard scheme (USSR Ministry of Health Order from April 22, 1985. No. 535) with the identification of *Shigella*, *Salmonella*, *Escherichia*, *Yersinia* microorganisms, opportunistic microorganisms in the reactions of agglutination with generic and group agglutinating sulfur production of RAO "biological product" (St. Petersburg), as well as culture was carried out on the environment "Kampilobaktagar" production «Himedia» (India), to create microaerophilic conditions using gas packages CampyPakPlus (Becton Dickinson, USA). Cultures were incubated during 3 days at temperature 42° C (Head of laboratory Gulidov E.P.). in all patients with haemocolitis syndrome and watery diarrhea microbiological research was conducted to identify pathogens of Enterohaemorrhagic escherichiosis (Coli 0157: H7).

In the second week of illness serological testing of blood was conducted by PHA to *Salmonella*, *Shigella* and *Yersinia* diagnosticums (Head of laboratory Gulidov E.P.).

For the detection of rotavirus antigen ELISA method was used with test systems, "Roth-analysis" JSC "Bioimmunogen" (Moscow). Material for study were feces of sick children with acute gastroenteritis collected in the first days after onset. Feces was conducted in test tubes with a capacity of 10 ml in ¼ of the tubes. The study was conducted by Kosorotikova AI, doctor-virologist, lab DIB No. 5.

On the first day of admission we performed initial testing of faeces of patients for the presence of pathogens of intestinal infections with PCR diagnostic test systems with electrophoretic detection products amplification of the family "AmpliSens." To elucidate the etiology of acute intestinal infections in patients performed once the feces, at a time not later than 3 days from the beginning disease and the first day of hospital stay (to avoid possible nosocomial infection). Samples of native constituents in a volume of 1 ml (Vesom1 c.) Were collected in sterile disposable plastic bottles s1.5 ml a transport medium containing a cryoprotectant and a preservative. If it is impossible their delivery to the laboratory during 6 hours prior to further storage. The research carried out at a temperature of not more than 1-1.5 -15-20°S months.

The samples were transported in the cold chain. Only once before the thawing the material research was allowed. After conducting research fecal samples were banked under conditions of freezing temperature 70 ° C.

Assembled a collection of fecal samples was tested at the Center molecular diagnosis of infectious diseases FSIS "CRI Epidemiology" Rospotrebnadzor (Moscow) using kits FSIS reagents production "CRI of Epidemiology" Rospotrebnadzor (License № 99-04-000058). For

isolation of nucleic acid from feces use the kit reagents "Ribo-Sorb" and "DNA sorbitol" said producer. Preparation of complementary DNA was produced using Reagent Kit "Reverte-L» (head of laboratory Ph.D. Podkolzin AT). Some sample underwent parallel testing using set of reagents for the multiplex hybridization-fluorescence detection of the most common causative agents of AEI - "AmpliSens Oxides screen "(Head. Podkolzin A.T., laboratory - MD, PhD Head of the Department Shipulin GA).

Statistical processing of the data was carried out on computer using parametric and nonparametric tests. To assess the significance of differences using Student's t test, Mann-Whitney, Fisher et al. Mathematical processing was performed by standard statistical algorithms using licensed software Microsoft Excel, included in the package programmOffice XP operating sredyWindows XP, as well as the statistical package Biostat. Determined percentage of the number of data (%), the arithmetic mean (M) and standard deviation (s).

Differences were considered significant at $p < 0.05$, highly reliable – with $p < 0,01$ and $p < 0.001$, insignificant- at $p > 0.05$.

The main results and discussion

Place of norovirus infection in etiological structure of acute intestinal infections in children, admitted to hospital

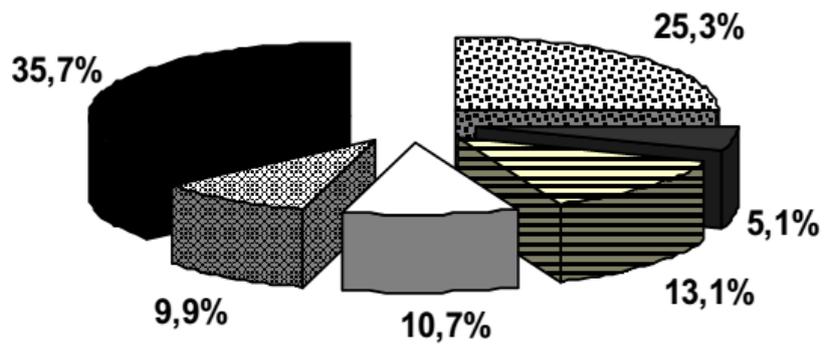
All etiology was established in 641 patients using PCR (64.2%).

Table 2 shows the frequency of detection of different pathogens in patients with acute intestinal monoinfections and combined infections (n = 997).

Table2 Incidence of different pathogens in patients suffering with AII using PCR, n = 997

Agent	Total frequency	Monoinfection	Combined infection
Rotaviruses	322 (32,2%)	253 (25,3%)	69 (6,9%)
Noroviruses	168 (16,8%)	131 (13,1%)	37 (3,7%)
Other viral agents	92 (9,2%)	51 (5,1%)	41 (4,1%)
<i>Salmonellae</i>	70 (7%)	52 (5,2%)	18 (1,8%)
Campylobacter	69 (6,9%)	48 (4,8%)	21 (2,1%)
Shigellae, EIEC	10 (1%)	7 (0,7%)	3 (0,3%)
Unexplained intestinal infections	356 (35,7%)		

As can be seen from Table 2, the dominant group in the AII structure were viral diareas - 58.3%. Rotaviruses prevailed, which were discovered in 322 (32.2%) samples (Figure 1, Table 2), and detected significantly more often than noroviruses ($p < 0,001$, the criterion $-\chi^2$). Norovirus infection was as monoinfection diagnosed in 131 (13.1%) patients. In 35.7% of the samples, none of the investigated pathogens were identified. But this does not exclude the presence of these pathogenic bacteria and other, less common viruses that can cause acute intestinal infections.



- Rotaviruses
- Noroviruses
- Mixed infections
- Other viral agents
- Bacterial infections
- Unexplained intestinal infections

Fig.1. Role of norovirus infection in etiological structure of acute intestinal infections after PCR, n = 997 (2006-2008).

Figure 2 shows etiological structure of acute intestinal infections deciphered in children. No significant differences in the frequency of detection of noroviruses (20.4%) vs other pathogens have been identified. Significantly more often in AII structure only rotavirus was identified 39.4% ($p < 0,001$, test χ^2). Combined infections amounted to 15.4% in AII structure and were found in 99 identified patients.

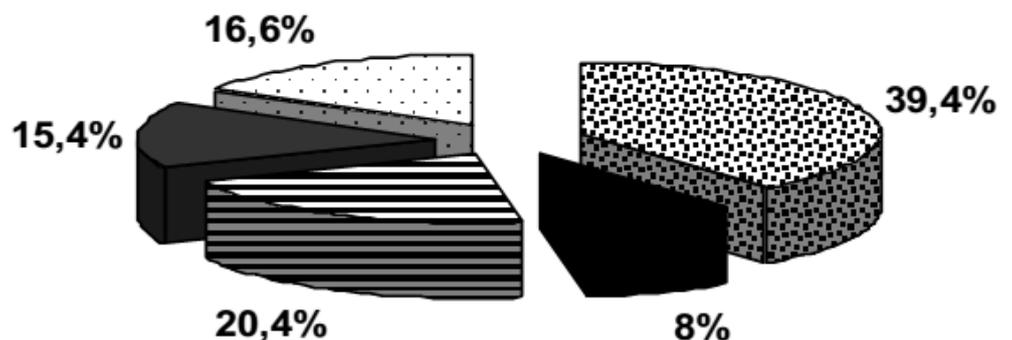


Figure 2. Etiological AII structure deciphered in children, n=64

- Rotaviruses
- Noroviruses
- Mixed infections
- Other viral agents
- Bacterial infections

■ Mixed infections

Noroviruses were most often found in conjunction with rotavirus - 67.5%, noroviruses + other viral agents were found significantly less frequently - 16.2% cases, *Salmonella* + noroviruses - 3 (8.1%), *Campylobacter* + noroviruses – 2 (5.4%) cases, *Shigella* + noroviruses + enteropathogenic escherichiosis - 1 (2.7%) (Fig. 3).

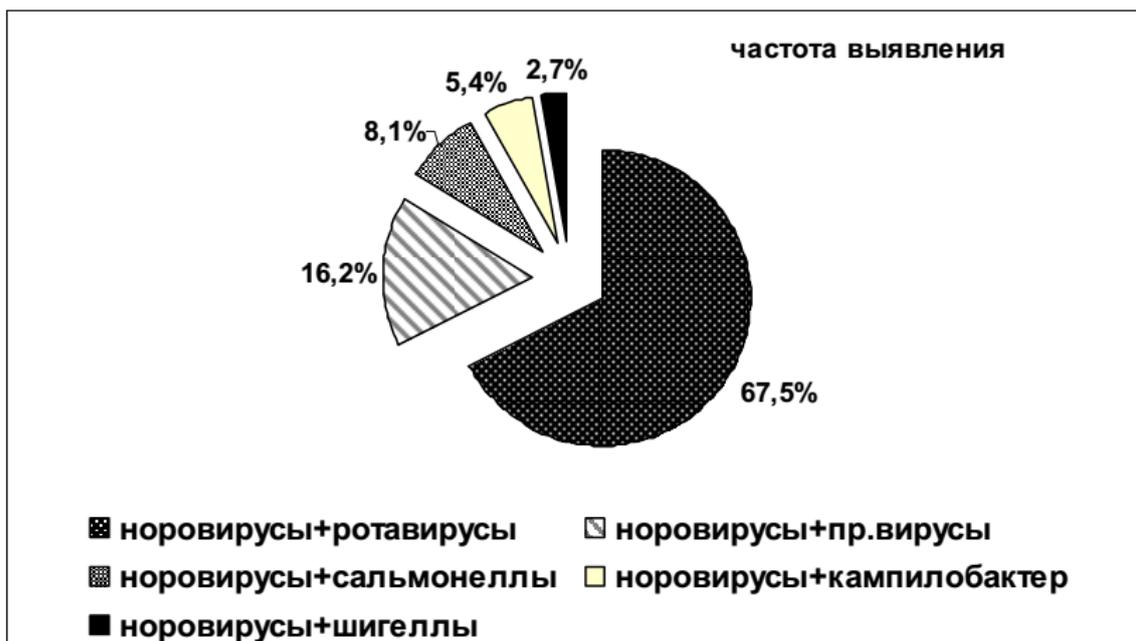


Fig. 3 Structure of mixed norovirus infection, n = 37, 2006-2008.

- - noroviruses + rotaviruses
- - noroviruses + *Salmonellae*
- - noroviruses + *Shigellae*
- - noroviruses + other viruses
- - noroviruses + *Campylobacter*

As can be seen from Figure 4, in different age groups AII pathogens were met with varying frequency. Viral diarrhea accounted for half of all AII children under 6 years and only 1 / 3 – in children older than 6 years ($p < 0.001$, test- χ^2).

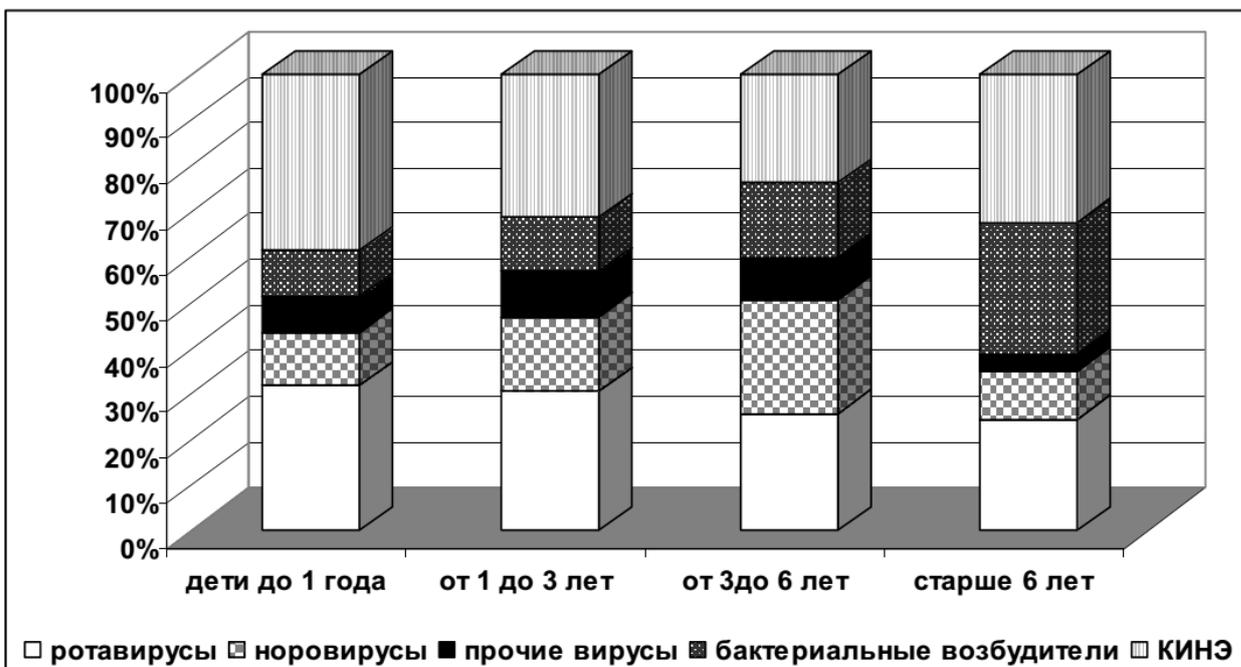


Figure 4. Etiological AII structure in children of various age groups, n=997.

- rotaviruses
- noroviruses
- other viruses
- bacterial agents
- Unexplained intestinal infections

The structure of AII norovirus infection was detected significantly more frequently in children aged from 3 to 6 years compared to children under 1 year and older than 6 years, 27.7%, vs 12% and 11,8%, ($p < 0.001$, test- χ^2).

Rotavirus was most frequently recorded at the age from 1 to 3 years compared to children under 1 year, from 3 to 6 and over 6 years (34.5% vs. 32.8%, 28.4% and 26.7%, respectively, $p < 0,001$). Other viruses are determined approximately with the same frequency in children under 1 year, 1 - 3 years and 3 - 6 years (8%, 11.2%, 10.4%, respectively) and significantly less frequent – in a group of children older than 6 years (4,9%, $p < 0,001$).

Bacterial pathogens were most frequently detected in children older than 6 years - 31.6%. in children from 3 years to 6 noroviruses were determined significantly more often than bacterial agents ($p < 0,001$, criterion $-\chi^2$). Combined AII of unknown etiology in children under 1 year was the highest among all age groups - 39.7%.

Depending on the season, there has been considerable variation in the etiological structure of acute intestinal infections in children (Figure 5).

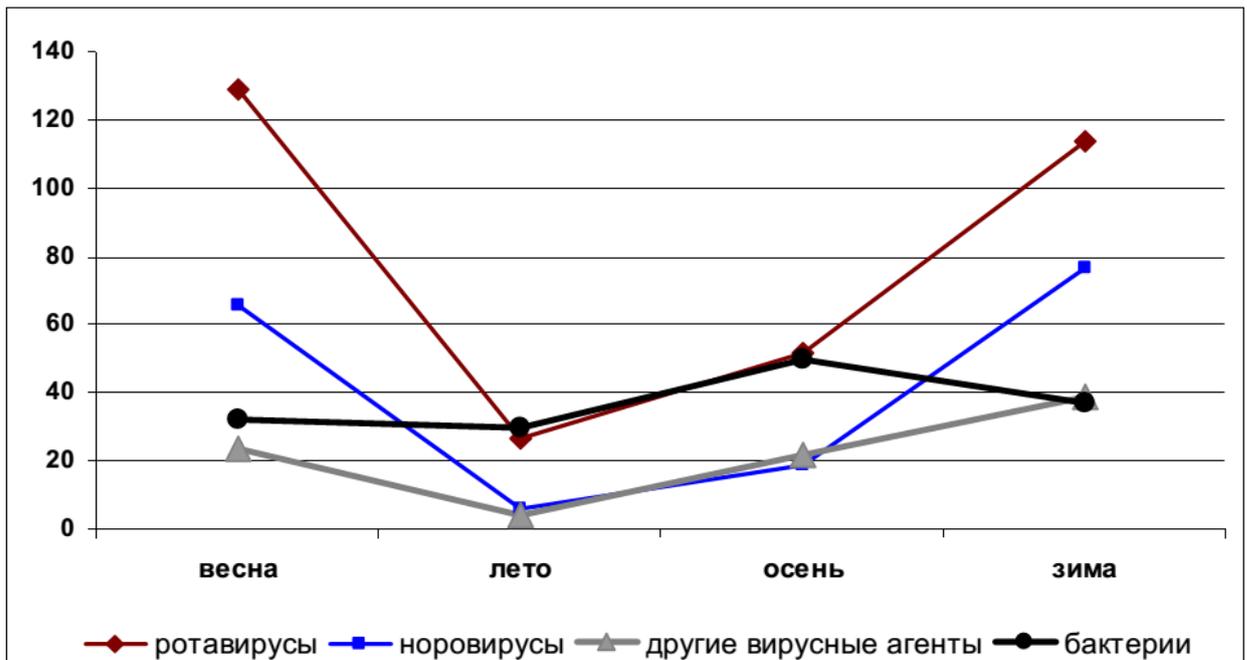
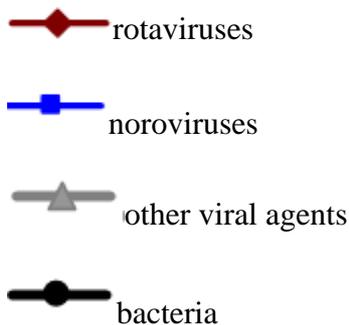


Figure 4. Seasonality OCI various etiology (2006-2008.) (vertical axis - absolute values, abscissa axis shows seasons of year).

Spring – summer – autumn – winter



Norovirus infection was detected significantly more often in winter and spring months and was found in 77 (46%) and 66 (39.2%) patients, respectively, whereas in the summer and autumn months it was detected much less - 6 (3.5%) and 19 (11,3%) ($p < 0,001$, criterion- χ^2). It was marked by pronounced seasonal and rotavirus, the peak being registered in spring - 129 (40%) and winter months - 115 (35.4%). Other viral agents were commonly found in winter - 39 (42.3%), and detected significantly more often than in the summer period- 4 (4,3%) ($p < 0,001$, the criterion- χ^2).

However, contrary to popular belief, viral diarrhea were recorded in summer. Bacterial infections were most often found in autumn and winter months (50 (33.5%) and 37 (24.8%), respectively). Norovirus infection had pronounced seasonality with two peaks of morbidity attributable in the winter and spring months (Figure 4).

We analyzed the frequency of norovirus infection for the entire research period by months. It was found that the most frequent norovirus infection was detected in 2006- 2007., in December

and March, 9.5% and 10.1% respectively, and for the period of 2007 - 2008. - in January and March (9% and 9%, resp.) (Figure 5).

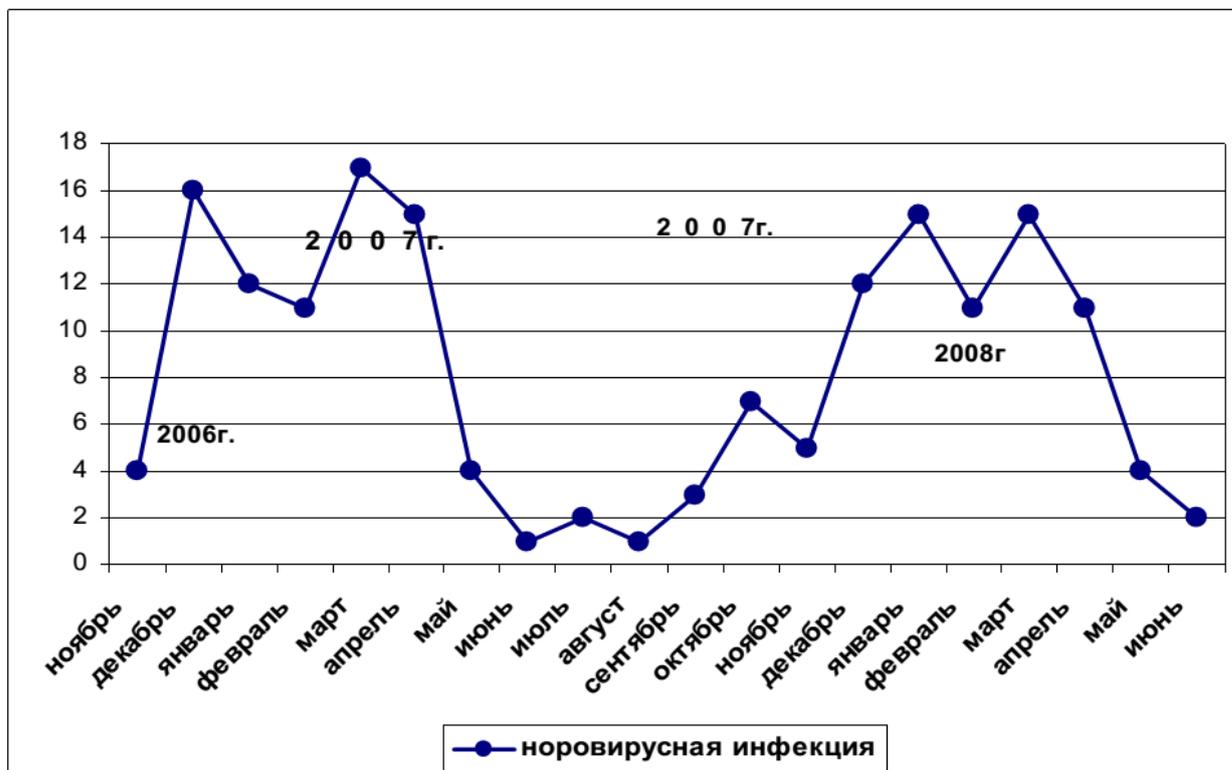


Figure 5. Monthly incidence of norovirus infection, 2006-2008.

Figure captions: /November-December-January-February-March-April-May-June-July-August-September-October-November-December- January-February-March-April-May-June/

Table 3 shows the incidence of different pathogens in children using complex routine diagnostic methods (bacterial culture and ELISA), n = 401 (2006-2008.). As can be seen from Table 3, among the acute intestinal infections the most frequently detected were rotaviruses – 19.7%.

Table 3 The incidence of different pathogens in patients with acute intestinal infections according to routine diagnosis, n = 401 (2006-2008).

Agent	Total frequency	Monoinfection	Combined infection
Rotaviruses	79 (19,7%)	77 (19,2%)	2 (0,4%)
Bacteria	61 (15,2%)	58(14,4%)	3 (0,7%)
Unexplained intestinal infections	261 (65%)	-	-

Routine methods allowed to define etiological structure of acute intestinal infections only in 140 (35%) patients in the form of monoinfection, bacterial infections have been found in 58 (14.4%) patients. No significant difference between rotavirus and bacterial agents were detected ($p > 0,05$, the criterion- χ^2).

Thus, by using molecular genetic techniques (PCR) etiological structure of acute intestinal infections was found in 64.2% of children, whereas, routine methods made it possible to establish the cause of the disease in only 35% cases. It was shown that AII in children were often caused by pathogens of viral than bacterial origin, with a predominance of combined noroviruses and mixed infections. Viral agents were detected throughout the year, but dominated with the cold weather (rotaviruses and noroviruses- in spring and winter). Rotavirus diarrhea was most frequently reported in children at the age of 1 - 3 years, whereas norovirus - - from 3 to 6 years.

Clinical features of acute intestinal infections of norovirus etiology in children and the factors they affect.

During 2006-2008 we examined 131 children aged from 1 month to 14 years in the hospital of infectious diseases in Moscow, in which norovirus monoinfection was diagnosed. The distribution of patients by sex and extent gravity are shown in Table. 4.

Table 4 Distribution of patients with norovirus monoinfection by gender and severity degree of the disease, n = 131

Forms	Patients with norovirus infection		
	Total n, %	Boys n, %	Girls n, %
Mild	28 (21,4%)	13 (10%)	15 (11,4%)
Moderate	99 (75,6%)	53 (40,4%)	46 (35,1%)
Severe	4 (3%)	2 (1,5%)	2 (1,5%)
Total	131 (100%)	68 (52%)	63 (48%)

Moderate forms of the norovirus infection in children admitted to hospital were more frequent - 99 (75.6%) cases. In 28 (21.4%) children norovirus infection was mild, severe form was diagnosed in 4 (3%) cases.

We studied peculiarities of norovirus monoinfection children different age groups: under 1 year (24), 1-3 years (42), and 3-6 years (22).

Start of norovirus infection in all children was acute, with fever, vomiting, and diarrhea. The most frequently registered clinical option for children in all age groups was gastroenteritis: under 1 year - 66.6%, 1-3 years - 61.9%, 3-6 years - 63.6%. in children under 1 year and 1 year to 3 years gastritis was often- 16.6% and 19%, respectively, but in children of 3-6 years it was significantly more often- 27.2%. Gastroenterocolitis in children up to 1 year and 1-3 years occurred in 12.5% and 12%, respectively. Enteritis was detected in only 2 age groups and was in children under 1 year - 4.1%, from 1 to 3 years - 7.1%. Enterocolitis, and colitis were not detected in either group. No significant differences in levels of shock syndrome in the study group were established.

The syndrome of intoxication in norovirus infection was characterized by lethargy, decreased appetite, pale skin, and was most pronounced symptoms of intoxication were in children under 1 year (lethargy, decreased appetite, pallor - 100%, 87.5%, 75%, respectively).

The least pronounced these symptoms were in children of 3 - 6 years – appetite reduction was observed in 63.6% of patients, lethargy - 81.8%, pallor - 54.5%. For children of 1-3 years lethargy was present in 90,4% cases, appetite loss - 81%, pale skin - 73,8% of children.

Most fever was also observed in children under 1 year (91.6%), especially higher than 39°C (45.8%), compared with children from 1 do3 years ($p < 0,05$). In children aged 1 to 3 years increase in body temperature was fixed in 81% cases, it ranged from 37 to 37,9°C- in 45,2%, which was significantly more often in comparison with children under 1 year. 38 – 38,9°C - 19%, above 39°C - 16.6% of children. Less often the rise in temperature observed in children of 3-6 years (77.2%). The temperature rise in the range 37 – 37,9°C and higher 39°C was with the same frequency- 22.7% for 38, 31.8% for 38,9°C.

Catarrhal symptoms were scarce in all age groups, the most often recorded was throat congestion and mild symptoms of rhinitis. Hyperemia was significantly more common in children under one year (66.6%) in relation to children from 1 to 3 years (33.3%). Exsiccosis grade I was identified in 72 children (62%) under 3 years.

Table 5 Terms of relief of intoxication symptoms during norovirus infection in children

Symptoms	Children under 1 year, n=24		Children aged 1-3 years, n=42		Children aged 3-6 years, n=22	
	%	(M+s)	%	(M+s)	%	(M+s)
Fever	91,6	3,4±0,4*	81	2,8±0,6 *	77,2	2,1±0,26*
Loss of appetite	87,5	2,1±0,8*	81	1,9±0,6*	63,6	1,4±0,41 *
Apathy	100	1,9±0,8*	90,4	1,5±0,5*	81,8	1,4±0,51*

* Significant differences, $p < 0.05$, criterion- χ^2

The duration of intoxication symptoms in different age groups was different, but clearly shows that the younger the age, the relief timing symptoms of intoxication duration (tab. 5). In children, symptoms of 3-6 years, intoxication disappeared significantly faster than in all other investigated age groups, fever persisted in average $2,1 \pm 0,26$ days, anorexia - $1,4 \pm 0,41$, apathy - $1,4 \pm 0,51$ days.

Involvement of the gastrointestinal tract was shown a number of symptoms: vomiting, loose stools, abdominal pain, flatulence. Vomiting was frequently recorded in children from 3 to 6 years- 100% of children (children under 1 years- 95.8%, from 1 year to 3 years- 90.4%). Frequency of vomiting in children up to 1 year did not exceed 10 times a day, whereas in children between 1 - 3 years and 3 to 6 years multiplicity of emesis was over 10 times (11,9% and 9%, respectively).

Diarrhea occurred with equal frequency in the age groups up to 1 year and from 1 year to 3 years and it was 83,3%, respectively, in children from 3 to 6 years- 68.1%.

The highest frequency of watery stools, fixed 10 times or more was in children under 1 year- 25 children, up to 1% of patients, whereas in children from 1 to 3 years and from 3 to 6 years- 4,5% and 9.5%, respectively. Abdominal pain was most frequently recorded in children 1 to 3 years in 38% of cases (in children under 1 year - 20.8%, from 3 to 6 years of age - 36.3%).

Flatulence was more common in children younger than 1 year (75%), but was stopped reliably faster than children in other age groups- $1,2 \pm 0,4$ days (children from 1 to 3 years- $2,2 \pm 0,48$, from 3 to 6 years old - $2,1 \pm 0,6$ days) ($p < 0,05$). No significant differences in the frequency of symptoms of gastrointestinal tract in the groups studied did not reveal ($p > 0,05$).

Table 6 Terms of reduction of GIT dysfunction in norovirus infection

Symptoms	Children under 1 year, n=24		Children aged 1-3 years, n=42		Children aged 3-6 years, n=22	
	%	(M+s)	%	(M+s)	%	(M+s)
Vomiting	95,8	$2,3 \pm 0,84^*$	90,4	$2,2 \pm 0,72^*$	100	$1,7 \pm 0,96^*$
Diarrhea	83,3	$3,5 \pm 0,94^*$	83,3	$3,2 \pm 0,9^*$	68,1	$2,2 \pm 0,8^*$
Flatulence	75	$1,2 \pm 0,4$	66,6	$2,2 \pm 0,48$	54,5	$2,1 \pm 0,6$

* Significant difference, $p < 0.05$, criterion- χ^2

In the dynamics of the relief of vomiting significant differences in children under 1 year and from 1 to 3 years have been identified ($2,3 \pm 0,84$ i $2,2 \pm 0,72$, respectively), but in children from 3 to 6 years vomiting stopped significantly faster and an average of $1,7 \pm 0,96$ days ($p < 0.05$, criterion- χ^2) Table. 6).

The average duration of diarrhea in children up to 1 year was $3,5 \pm 0,94$ days in children from 1 year to 3 years- $3,2 \pm 0,9$ days, and significantly earlier (for the whole day before), children from 3 to 6 - $2,2 \pm 0,8$ days ($p < 0,05$, criterion- χ^2), Tabl.6).

Thus, norovirus infection in children of all ages studied had an acute onset, the first signs of which were - vomiting, symptoms of intoxication, diarrhea and scanty catarrhal phenomena. In children under the age of 1 year norovirus infection had more clinical symptoms, such as fever over 39°C (45.8%), lethargy (100%), vomiting (95.8%), diarrhea (83.3%), flatulence (75%).

Significantly longer because of all these clinical symptoms persist fever ($3,4 \pm 0,4$ days) and diarrhea ($3,5 \pm 0,94$ days). The fastest of all clinical symptoms disappeared flatulence - $1,2 \pm 0,4$ days. Abdominal pain in children under 1 year was less common (20.8%) than in children from 1 year to 3 years and 3-6 years. With respect to the entire study group rhinitis and throat congestion detected almost the same frequency (42.8% and 46.5% respectively), but comparing them in the frequency for individual age categories, it should be noted that congestion significantly throat was found more frequently in children up to 1 year.

Norovirus infection in children aged 3 to 6 years proceeded with less pronounced clinical symptoms and currently treated more quickly than children groups comparison. However, the symptom of vomiting were more frequent - 100% than in other age groups, and in 9% incidence of vomiting was 10 or higher. Fervescence was fixed at 77.2% of children in the range of $38 - 38,9^\circ\text{C}$. This character of the fever was noted more often in children of 3-6 years than in other age categories- 31.8%.

Comparative analysis of the clinical features of acute intestinal infections and norovirus rotavirus in children.

Due to the fact that norovirus infection frequency of occurrence among viral diarrhea, ranks second after rotavirus, it was interesting to compare the characteristics of the course of these infections.

For a comparative analysis of the clinical course of rotavirus and noroinfections were studied in detail by us both in groups comparable by age, premorbid background, gravity (in 50 and 56 children).

Children admitted to hospital in the early hours of the onset of the disease norovirus infection in 35.7% of cases, for 2 hours - 39.2% 3 hours - 12.5% and subsequently third day - 10.7% of cases. When rotavirus in the first day of the onset of illness the children received in 20% of the time, almost 16% less than in norovirus infection. Probably due to a sudden, more acute starting of norovirus infection, as multiple abundant vomiting. Children from 1 months to 1 year were 30.3% of rotavirus infection 20,3% - from 1 year to 3 years- 55.3% and 56%, respectively.

The conducted detailed clinical analysis showed that with norovirus infection, gastritis significantly more frequently detected in 13 (23.2%) patients, in contrast to rotavirus infection ($p < 0,05$, criterion- χ^2). Despite the fact that the most common clinical goal in both groups at entry had gastroenteritis during rotavirus he met significantly more frequently (74%) compared to norovirus infection (53,5%) ($p < 0,05$, criterion - χ^2). No significant differences in frequency of gastroenterocolitis and enteritis in norovirus and rotavirus were detected (14.2% and 9 and 16 and 19%, respectively).

In norovirus infections catarrhal phenomena were recorded less frequently (46.4% (26) - hyperemia and 26.7% (15) cases - rhinitis) than rotaviral infection (throat redness marked in 36 (72%) patients, in 19 (38%) - rhinitis). Symptoms of intoxication at both clinically manifested infections was the same (pale skin, loss of appetite, lethargy, raising the temperature), but the temperature rise rotavirus from 37.5 to 38,5°C (68% and 46%, resp.) and all signs of intoxication were detected significantly more often than in the norovirus infection ($p < 0,05$).

Analyzing the dynamics of reduction of intoxication symptoms, depending on infection indicated that the norovirus infection anorexia and lethargy stopped significantly earlier ($1,4 \pm 0,4$), whereas in rotavirus the appetite was restored by the end of the third day ($2,8 \pm 1,64$), and lethargy disappeared by the beginning of the fourth day of the onset of the disease ($3,1 \pm 0,70$) ($p < 0,05$, criterion - χ^2). Terms of normalization of body temperature were significantly shorter in the norovirus infection ($2,6 \pm 1,2$), rather than at rotavirus - $3,4 \pm 1,44$ (tab. 7).

Table 7 Frequency and duration of intoxication symptoms

Symptoms	Norovirus infection, n=56		Rotavirus infection, n=50	
	Frequency, %	Duration, days	Frequency, %	Duration, days
Loss of appetite	76,7	1,4±0,4*	100	2,8±1,64*
Apathy	76,7	1,4±0,54*	100	3,1±0,70*
Fever	87,5	2,6±1,2*	94	3,4±1,44*

* Significant difference, $p < 0.05$, criterion- χ^2

Onset of norovirus infection in all children were sharp, with 91% repeated vomiting on the background of well-being. Vomiting was plentiful, dominated multiplicity vomiting from 5 times a day, and above-31 (60.7%) cases. Frequency of vomiting from 5 just above (up to 10 times) was significantly more frequent in the norovirus infection (60.7%), whereas up to 5 times vomiting (66.6%) was significantly more characteristic of rotavirus. Diarrhea occurred in 76.7% of patients, but stool frequency was substantially higher than 5 times a day (62.7%).

When rotavirus infection was the leading symptom of diarrhea, it was significantly more frequent (100%), vomiting in 42 less marked (84%) patients, with its multiplicity not more than up to 5 times sutki- 28 (66.6%) children.

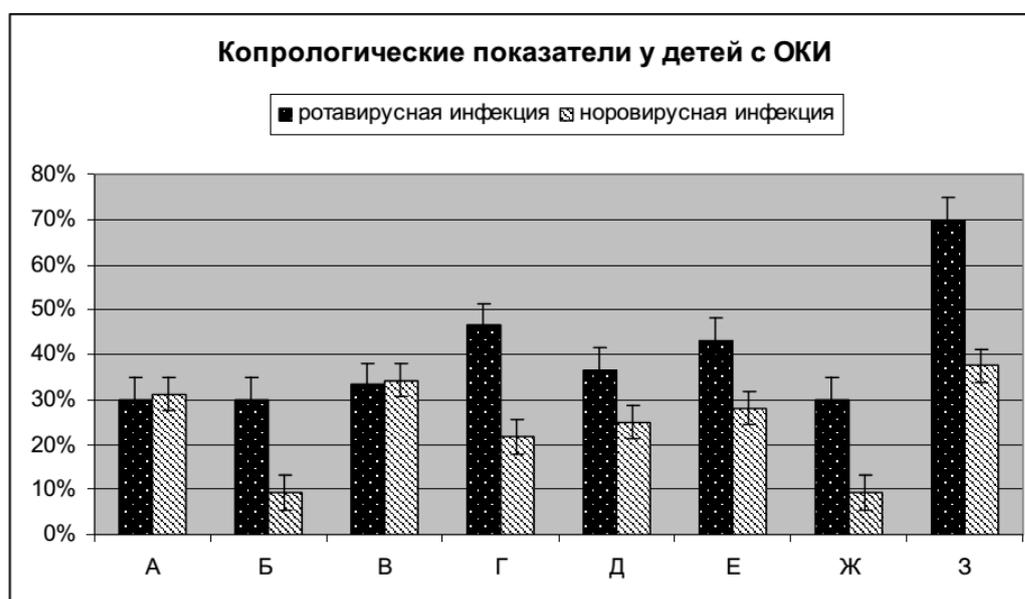
Table 8 Frequency and duration of symptoms of gastrointestinal tract (M + s)

Symptoms	Norovirus infection, n=56		Rotavirus infection, n=50	
	Frequency, %	Duration, days	Frequency, %	Duration, days
Loss of appetite	91	2,1±0,9	84	2,4±0,5
Apathy	76,7	2,7±0,7*	100	3,4±1,3*
Fever	42,8	1,1±0,35*	75,5	2,79±0,7*
Stomach pains	14,2	1,2±0,45	22	1,7±0,32

* significant difference, $p < 0,05$, criterion- χ^2

It was found that at moderate forms of norovirus and rotavirus AII etiology in children, there were no significant differences in terms of relief of vomiting in the two groups (Table 8). However, it may be noted in the norovirus infection in the early stages of reliably reducing diarrhea ($2,7 \pm 0,7 \pm 1,3$ and $3,4$ resp.) and flatulence ($1,1 \pm 0,35$ and $2,79 \pm 0,7$ resp.).

The most common pathological components in coprogram in the acute phase of the disease for norovirus infections were neutral fat (34.3%), starch (28,1%), to the presence of leukocytes in the field of view 10 (43.7%), consistency chair most often is a liquid slurry (62.5%) (Figure 6).



A mucus

B-fatty acids

B- neutral fat

T- digestible fiber

D- leukocytes

E extracellular starch

F- yeast-like fungi

W - watery consistency

Figure 6. Features of coprological indicators in children with norovirus and rotavirus infections

In rotavirus the stool was significantly more watery than the norovirus infection. No significant differences in the incidence of other koprologicheskikh indicators have been identified, but the yeasts, fatty acids and starch were often found in the rotavirus. The duration of preservation of deviations in coprogram was significantly shorter with norovirus infection ($3,5 \pm 0,7$ day) vs. ($5,8 \pm 0,9$ days) $p < 0,05$.

As a result, ultrasound examination of the abdomen and in the specifically pancreas revealed that the size of the pancreas cancer in the acute phase were increased at both infections (due to head of pancreas), but more often with rotavirus than norovirus infection (14 (60.8%) and 8 (40%), respectively). Reduction of echogenicity was also observed in both infections, but the detection rate was higher with rotavirus, norovirus infection than (17 (74%), and 11 (55%), respectively).

Thus, the most common syndrome of shock syndrome in children norovirus and rotavirus gastroenteritis was (53.5% and 74%, respectively), and gastritis were significantly more when norovirus infection and was 23.2% of cases, whereas gastroenterocolitis - met with almost equal frequency. Despite the acute onset at both infections and similar clinical symptoms, with clinical manifestations of rotavirus disease most pronounced. The temperature rise was noted in 94% of pediatric rotavirus patients and 85.7% of children with norovirus infection. At norovirus infection vomiting was more abundant in nature and was more often, the catarrhal phenomena recorded less than in rotavirus infection.

Despite the similar symptoms of both diseases, the dynamics of relief of clinical manifestations shorter when norovirus infection. Terms of reduction of anorexia, lethargy, fever, significantly longer at rotavirus infection than with norovirus infection. Analyzing scatological changes significantly more watery stools was recorded at rotavirus infection 70%, whereas the only norovirus $\sqrt{37,5\%}$ cases.

Signs of exocrine pancreatic insufficiency in the norovirus infection was less severe, that is not marked with the rotavirus. Evidence of inflammation and yeasts often recorded in coprogram well as rotavirus. Much more often detected and ultrasound changes in pancreas of rotavirus infection than the norovirus.

Retrospective evaluation of the effectiveness of different therapy approaches norovirus infection in children retrospectively analyzed the effectiveness of initial therapy norovirus infection in different comparable groups of children (tab. 9).

Table 9 Comparability of the study groups

Comparability of the study groups				
Admission terms	Enterosorbents, n=22 (group 1)	Kipferon, n=24 (group 2)	Probiotic, n=24 (group 3)	Antibiotics, n=29 (group 4)
Day 1	31,8%	37,9%	33,3%	31%
Day 2	59%	50%	54,1%	62%
Day 3	0%	12,5%	8,3%	6,8%
Age groups				
Under 1 year	31,8%	25%	29,1%	20,6%
1-3 years	45,5%	50%	45,8%	49,8%
3-6 years	23,7%	25%	25%	27,5%
Loaded premorbid background	36,3%	41,6%	37,5%	41,3%

Based on the evaluation of the dynamics of the main symptoms of norovirus infection by therapy (Table 10).

Table 10 Comparative characteristics of the relief of the main clinical symptoms of norovirus infection in children, depending on therapy

Comparability of the study groups				
Admission terms	Enterosorbents, n=22 (group 1)	Kipferon, n=24 (group 2)	Probiotic, n=24 (group 3)	Antibiotics, n=29 (group 4)
Loss of appetite	2,8±0,7	2,1±0,74	1,88±0,6	2,85±0,18
Apathy	2,4±0,6	2,3±0,9	1,9±0,7*	3,2±0,18*
Fever	2,7±0,09	2,6±0,72	2,41±0,8	2,6±0,12
Vomiting	1,9±0,9	2,1±0,5	1,60±0,5*	2,7±0,5*
Diarrhea	2,9±0,7	2,6±0,66	2,6±0,6*	4,7±0,42*
Flatulence	2,9±0,5	2,7±0,7	1,33±0,5*	3,4±0,7*
Stomach aches	2,2±0,2	2,2±0,5	2±0,8	3,1±0,22

* Significant difference, $p < 0.05$, criterion- χ^2

As seen from Table 10, in patients receiving probiotics intoxication symptoms such as lethargy and decreased appetite stopped significantly earlier (criterion $-\chi^2$, $p < 0.05$). No significant differences in dynamics of fever reduction were observed, but the trend for earlier reduction was observed in children receiving oral rehydration therapy and probiotic (2.5 and $2,4 \pm 0,5$ days). It should also be noted that similar dynamics of intoxication symptoms was observed in children receiving oral rehydration therapy and Kipferon suppositories. Thus, apathy and loss of appetite were stopped earlier than in children receiving treatment - oral rehydration combined with

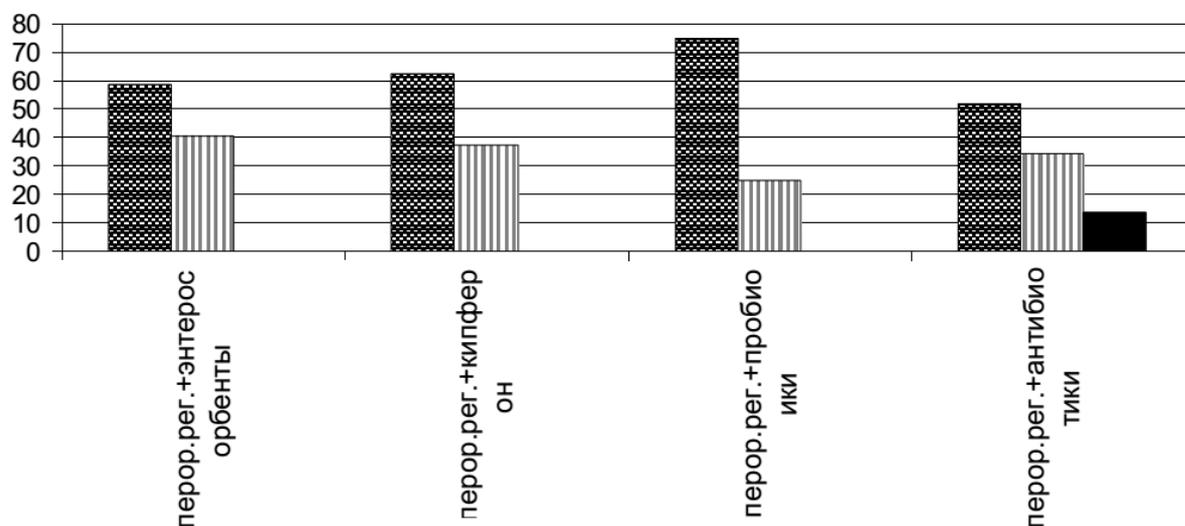
antibiotics and oral rehydration therapy and enterosorbents. Apathy persisted most of all in children treated with the combination of oral rehydration + antibiotics and was 3.2 ± 0.18 days (tab. 10).

GIT dysfunction duration, symptoms such as vomiting, abdominal pain (independent or palpation), flatulence and diarrhea syndrome were the most persistent in children of Group 4 on antibiotic background. In groups 1, 2, and 3 of patients vomiting stopped in most cases already by day 2 of treatment, while in group 4 vomiting continued until 3 days from the start of treatment (Table. 10). Faster reduction of abdominal pain (2 ± 0.8) and relief of flatulence (1.33 ± 0.5 , criterion - X^2 , $p < 0.005$) was observed in children from 3 groups. The duration of vomiting was significantly less in group 3 than in group 4 (1.60 ± 0.5 and 2.7 ± 0.5 days, respectively, criterion- χ^2 , $p < 0.005$) (Table. 10).

The most significant differences occurred in the dynamics of stool normalization - if in the groups 1, 2, and 3 diarrhea mainly stopped after the average of 2.6 - 2.9 days, diarrhea in group 4 persisted on the average for 4.7 ± 0.42 day.

It was also noted that in children receiving antibiotics, the stool was not formed for a long time. Diarrhea stopped significantly earlier in children in the two groups: in group 3 (2.6 ± 0.6) and in group 2 (2.63 ± 0.66).

A comprehensive assessment of the therapy effectiveness of norovirus infection indicated a good therapeutic effect observed in the group of infants receiving probiotics (75%). It also clearly showed that only in the group of children receiving antibiotics therapy, 13.7% of patients noted the absence of the effectiveness of treatment, requiring correction therapy (Figure 7.).



per os rehydration + enterosorbents

per os rehydration + Kipferon

per os rehydration + probiotics

per os rehydration + antibiotics

Figure.7. Complex assessment of efficiency of various therapies of norovirus in children.

Thus, in children with norovirus infection, the main symptoms of the disease stopped most quickly with a combination of oral rehydration and probiotics, and the least - with antibiotics. Our research has once again demonstrated that in the norovirus infection, as with all types viral diarrhea, appointment of antibiotics was not effective. The objective necessity of breaking existing stereotypes in the treatment of acute intestinal infections in children is evident. In norovirus infection tactics of "initial" therapy is more justified and purposeful, involving a combination of oral rehydration and probiotics.

Conclusions

1. The rate of mono and combined norovirus infection is high in the structure of acute intestinal infections in children admitted to the hospital and amounts to 16.8% and 13.1%, respectively. It ranks second in frequency after rotavirus. Most often norovirus infection affects children aged 3-6 years.
2. There is a distinct seasonality of norovirus infection, which coincides with that of rotavirus infection. Frequently noroviruses cause disease in winter and spring months (December, January, March).
3. The clinical picture of norovirus infection is characterized by acute onset, with repeated vomiting, intoxication symptoms, mild catarrhal symptoms, gastrointestinal lesions by gastroenteritis type, and exsiccosis, degree I-II. Reliably and quickly clinical symptoms stopped in children older than 3 years of age. The younger the child's age, the higher severity of clinical symptoms.
4. Norovirus and rotavirus infections have significant differences in clinical manifestations. Rotavirus is marked with wider clinical symptomatology, persisting for a longer time compared with norovirus infection. In norovirus infection the stool is significantly less watery than in rotavirus infections, while repeated vomiting is observed more frequently.
5. The use of antibiotics in the treatment of norovirus infection in children is inappropriate. The optimal therapy is a combination of oral rehydration and probiotics, reducing the duration of intoxication symptoms and providing more rapid relief of GIT symptoms.

Practical advice

1. For the purpose of diagnosing norovirus infection in the hospital, it is advisable to use PCR to conduct the survey all year long, without a break for the summer months.
2. The use of antibiotics in the treatment of norovirus infection is not justified, as well as in other viral diarrheas.
3. To enhance the effectiveness of treatment of patients with norovirus infection in complex treatment, it is advisable to combined probiotics (Acypol, Linex) from the first days of the disease in age doses for 14-21 days.