

# CLINICAL CHARACTERISTICS OF ROTAVIRUS-INDUCED GASTROENTERITIS IN INFANTS

Sofija Lugonja<sup>1</sup>, Jelena Zivic<sup>2,3</sup> and Natasa Zdravkovic<sup>2,3</sup>

<sup>1</sup>Division of Gastroenterology, Department of Internal Medicine, General Hospital "Djordje Jovanovic", Zrenjanin, Serbia

<sup>2</sup>Clinic of Internal Medicine, Clinical Center Kragujevac, Kragujevac, Serbia

<sup>3</sup>University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine, Kragujevac, Serbia

## KLINIČKE KARAKTERISTIKE GASTROENTERITISA KOD MALE DECE ČIJI JE UZROČNIK ROTAVIRUS

Sofija Lugonja<sup>1</sup>, Jelena Živić<sup>2,3</sup> i Nataša Zdravković<sup>2,3</sup>

<sup>1</sup>Odeljenje za gastroenterologiju, Klinika za internu medicinu, Opšta bolnica "Đorđe Jovanović", Zrenjanin, Srbija

<sup>2</sup>Klinika za internu medicinu, Klinički centar Kragujevac, Kragujevac, Srbija

<sup>3</sup>Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za internu medicinu, Kragujevac, Srbija

Received/Primljen: 27.01.2020.

Accepted/Prihvaćen: 08.02.2020.

### ABSTRACT

Rotavirus is the most common cause of acute infectious diarrhea in infants and young children up to the age of five. The disease is characterized by profuse watery diarrhea, vomiting and fever. The major complications of rotavirus gastroenteritis (RVGE) are dehydration, middle ear inflammation and upper respiratory tract infection. The basis of treatment is compensation for fluid loss and administration of probiotics. The aim of this study was to analyze the clinical characteristics of rotavirus gastroenteritis in infants. The study was conducted by the type of retrospective-prospective clinical study on infants with rotavirus gastroenteritis diagnosed on the basis of a positive Rotalax test (Orion Diagnostica Finland) and exclusion of other etiological factors at the University Children's Clinic in Belgrade, from April 2005 to December 2010. In addition to the detailed medical history and clinical examination, relevant laboratory analyzes were performed in all patients. Descriptive and analytical statistical methods were applied in the study. Among the descriptive methods, we used grouping, tabulation, graphing, calculating measures of central tendency, calculating measures of variability and calculating relative numbers. Of the analytical statistical methods, distribution normality testing,  $\chi^2$  test, Mann-Whitney U test and T test were used. Statistical significance will be taken to mean  $p < 0.05$ . The average infant mortality was  $6.7 \pm 3.7$  months. All respondents were divided into two groups according to the age. The first group consisted of infants aged 0 to 5 months (46%), the second group consisted of infants aged 6 to 12 months (54%). The incidence of aqueous diarrhea (100%), vomiting (84%) and fever (74%) in infants suffering from rotavirus gastroenteritis was analyzed. The significance of the age on the symptomatology of rotavirus gastroenteritis as well as on the importance of using probiotics has been demonstrated.

**Keywords:** rotavirus, gastroenteritis, infant.

### SAŽETAK

Rotavirus je najčešći uzročnik akutne infektivne dijareje u dobi odojčeta i malog deteta uzrasta do pet godina. Bolest karakteriše profuzna vodena dijareja, povraćanje i povišena telesna temperatura. Osnovne komplikacije rotavirusnog gastroenteritisa (RVGE) su dehidracija, upala srednjeg uha i infekcija gornjih respiratornih puteva. Osnovu lečenja čini nadoknada gubitka tečnosti i primena probiotika. Cilj ove studije bio je analiza kliničkih karakteristika rotavirusnog gastroenteritisa u dobi odojčeta. Sprovedena je studija po tipu retrospektivno-prospektivne kliničke studije na odojčadima sa rotavirusnim gastroenteritisom dijagnostikovanim na osnovu pozitivnog Rotalax testa (Orion Diagnostica Finland) i isključenju drugih etioloških činilaca u Univerzitetskoj dečjoj klinici u Beogradu, u periodu od aprila 2005. godine do decembra 2010. godine. Pored detaljne anamneze i kliničkog pregleda, kod svih bolesnika sprovedene su relevantne laboratorijske analize. U studiji su primenjene deskriptivne i analitičke statističke metode. Od deskriptivnih metoda korišćeno je grupisanje, tabeliranje, grafičko prikazivanje, izračunavanje mera centralne tendencije, izračunavanje mera varijabiliteta i izračunavanje relativnih brojeva. Od analitičkih statističkih metoda korišćeno je testiranje normalnosti raspodele,  $\chi^2$  test, Mann-Whitney U test i T test. Pod statističkom značajnošću podrazumevaće se vrednost  $p < 0,05$ . Prosečna starost odojčadi izosila je  $6,7 \pm 3,7$  meseci. Svi ispitanici su bili podeljeni u dve grupe u odnosu na starosnu dob. Prvu grupu su činila odojčad starosti od 0 do 5 meseci (46%), drugu grupu činila su odojčad starosti od 6 do 12 meseci (54%). Analizirana je učestalost vodene dijareje (100%), povraćanja (84%) i povišene telesne temperature (74%) kod odojčeta obolelog od rotavirusnog gastroenteritisa. Dokazan je značaj uzrasta na simptomatologiju rotavirusnog gastroenteritisa kao i značaj upotrebe probiotika.

**Ključne reči:** rotavirus, gastroenteritis, odojče.



UDK: 616.33/.34:616.98-053.2/.4

Ser J Exp Clin Res 2020; 21 (4): 291-297

DOI: 10.2478/sjecr-2020-0003

Corresponding author:

Natasa Zdravkovic

Svetozara Markovica 69, 34000 Kragujevac, Serbia

Tel.: +381604401776/

E-mail: natasasilvester@gmail.com



## INTRODUCTION

Rotavirus is the most common single cause of acute infectious diarrhea in infants and young children up to five years of age (1, 2, 3). The incidence rate of hospitalized infants and children under 5 years of age due to rotavirus gastroenteritis in Europe is 300 per 100.000 children of the same age (1, 4). Rotavirus infections occur more frequently in winter and spring (5, 6). The disease is transmitted by feko-oral route, also thought to be a drip infection (6, 7). The virus is present in a very high concentration in the stool (1011 viral particles in only one gram) of the diseased person and is excreted the day before and 8-10 days after the manifestation of the clinical picture of the disease, and in immunocompromised persons, even 2-3 weeks after the manifestation of the clinical picture. The duration of virus excretion does not correlate with the severity of clinical picture of the disease.

The clinical picture of rotavirus gastroenteritis (RVGE) can range from a subclinical form to a very severe form that can lead to the death of a patient. Whether the infection will proceed symptomatically or asymptotically depends on the characteristics of the virus itself as well as the susceptibility of the host. The most important factor is the age of the host (8). The clinically manifested form of the disease is rare within the first 3-6 months of birth due to passive immunity acquired prenatally (2, 9). The disease is characterized by a profuse watery diarrhea, vomiting and fever (1, 2, 3, 10).

The conditions associated with chronic rotavirus infection are severe immunodeficiency, X-linked agammaglobulinemia, acquired immunodeficiency syndrome (AIDS), and DiGeorge syndrome (11).

The complications of RVGE are dehydration, upper respiratory tract infection, middle ear inflammation, febrile convulsions, bowel invaginations while other complications are rare. Expressed dehydration is the most common reason for hospitalization of the diseased children and the cause of more than 90% of deaths due to rotavirus infection.

The ELISA test and latex agglutination are most commonly used in the diagnosis of rotavirus infection (2).

There is no specific antiviral treatment for rotavirus gastroenteritis. The basis of treatment is a quick and effective compensation for the loss of fluid, water and electrolytes, as well as the use of probiotics.

## MATERIALS AND METHODS

The study is a retrospective-prospective study conducted at the University Children's Clinic in Belgrade from April 2005 to December 2010. The study included 50 infants who had a confirmed diagnosis of rotavirus gastroenteritis.

The aim of this study was to analyze the clinical features of infantile rotavirus gastroenteritis and to determine the

significance of the age on the expression of this pathological condition.

The criteria for inclusion in the study were: infants with gastroenteritis signs referred to the University Children's Clinic for the treatment and proven to have Rotalex test infection and infants diagnosed with Rotalex test hospitalized at the Department of Gastrointestinal and Nutritional Disorders primarily due to another pathological condition (intolerance to cow's milk proteins, gluten enteropathy, urological tract infection, etc.). The exclusion criteria were: infants with chronic diarrhea, infants with acute diarrhea who demonstrated bacterial and / or parasitic antigens in a stool sample, infants with a positive Adenolex test, infants with previous gastroenterological operations, immunodeficiency antibodies, infants with a probiotic or any other medication for diarrhea at least 7 days before the admission to hospital and infants with other infections (sepsis, pneumonia). All patients included in this study were thoroughly analyzed for their anamnesis (heteroanamnesis) data, clinical findings, as well as relevant laboratory parameters and therapeutic procedures. A latex agglutination test, the Rotalex test (Orion Diagnostica Finland), was used to demonstrate rotavirus infection or presence of rotavirus in the stool. In heteroanamnesia, the attention was paid to infant problems. The following symptoms and signs of the disease were investigated: diarrhea, vomiting and fever.

Relevant laboratory blood tests were performed in each infant to assess the severity and follow-up of the disease, such as: the acid-base status, urea level, creatinine,) and the leukocyte count with a differential formula. The use of relevant clinical-laboratory parameters in all infants has registered presence of dehydration. Dehydration, as a basic complication, was followed by presence of other complications. Finally, the analysis of the patient's rehydration (intravenous, oral) and probiotic administration was made.

The data were analyzed using modern descriptive methods (grouping; tabulation; graphical representation; calculation of central tendency measures: arithmetic mean, median, mode; calculation of variability measures: standard deviation; calculation of relative numbers: percentages) and analytical statistics (distribution normality testing,  $\chi^2$ -squared test, Mann-Whitney U test, T test) with computer support and SPSS 12.0 software package. Statistical significance was taken to mean  $p < 0.05$ .

## RESULTS

Rotavirus infections occurred throughout the year as shown in Figure 1. The clinical characteristics of infants suffering from rotavirus gastroenteritis are shown in Table 1. We divided all respondents by the age into two groups. The first group consisted of 23 infants aged 0 to 5 months, which is (46%), and the second group consisted of 27 infants aged 6 to 12 months, which is (54%). The clinical characteristics

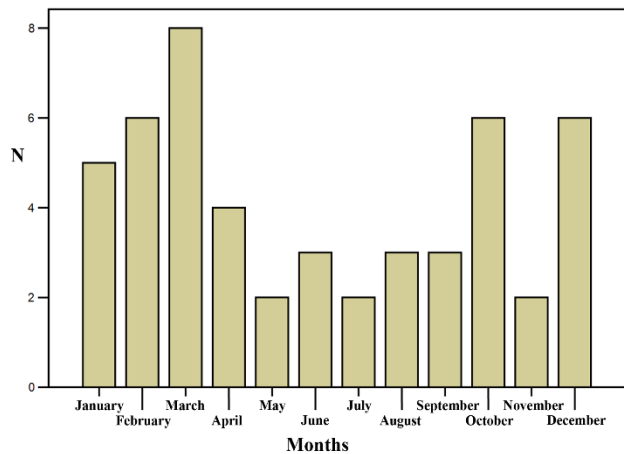


of infants with rotavirus gastroenteritis with the age were analyzed and the results are shown in Table 2.

Based on the results of the test, we proved that there is a statistically significant difference between the age groups of infants considering the average values of fever for a period of 24 hours ( $p=0.002$ ), but that there is no statistically significant difference between the age groups of water diarrhea for a period of 24 hours ( $p=0.571$ ) or considering the average number of vomits over a 24-hour period ( $p=0.788$ ).

Analyzing the influence of age on the use of probiotics in the treatment of rotavirus gastroenteritis, it was found that there was a highly statistically significant difference between the age groups of infants with rotavirus gastroenteritis considering the use of probiotics ( $p=0.006$ ). More probiotics were used in the older age group

**Figure 1.** Monthly occurrence of RVGE



**Table 1 - Clinical characteristics of infants with rotavirus gastroenteritis**

Clinical characteristics of infants	infants with rotavirus gastroenteritis
average age	6,7±3,7
sex	
M	30 (60%)
F	20 (40%)
type of infection primary	
primary	34 (68%)
intra-hospital	16 (32%)
clinical symptoms	
diarrhea	50 (100%)
vomiting	42 (84%)
fever	37 (74%)
average number of diarrhea in 24 hours	6,5±3,9
average number of vomiting in 24 hours	5,1±2,5
average fever for 24 hours	38,6±0,5
dehydration	48 (96%)
metabolic acidosis	29 (58%)
serum potassium value	
physiological range	37 (74%)
hypokalemia	10 (20%)
hyperkalemia	3 (6%)
serum urea value	
physiological range	24 (48%)
increased value	14 (28%)
reduced value	12 (24%)
serum creatinine value	
value physiological range	50 (100%)
blood leukocyte value	
physiological range	43 (86%)
leukocytosis	7 (14%)
complications	24 (48%)
respiratory tract infection	17 (34%)
middle ear inflammation	7 (14%)
rehydration	
i.v.	35 (70%)
per os	15 (30%)
probiotic	40 (80%)



Table 2 - Clinical characteristics of infants with rotavirus gastroenteritis in relation to age

Clinical characteristics of infants	age groups of infants with RVGE		
	0-5 months	6-12 months	p value
N	23 (46%)	27 (54%)	
clinical symptoms			
diarrhea	23 (100%)	27 (100%)	1,000
vomiting	18 (78,3%)	24 (88,9%)	0,526
fever	15 (65,2%)	22 (81,5%)	0,191
average number of diarrhea in 24 hours	6,3±4,1	6,7±3,9	0,571
average number of vomiting in 24 hours	5,0±3,6	5,2±3,2	0,788
average fever for 24 hours	38,3±0,3	38,7±0,5	0,002
dehydration	22 (95,7%)	26 (96,3%)	0,446
metabolic acidosis	12 (52,2%)	17 (63%)	0,400
serum potassium value			
physiological range	3 (13,0%)	7 (25,9%)	
hypokalemia	18 (78,3%)	19 (70,4%)	0,204
hyperkalemia	2 (8,7%)	1 (3,7%)	
serum urea value			
physiological range	10 (43,5%)	14(51,9%)	
increased value	7 (30,4%)	7 (25,9%)	0,966
reduced value	6 (26,1%)	6 (22,2%)	
blood leukocyte value			
physiological range	20 (87%)	23 (85,2%)	1,000
leukocytosis	3 (13%)	4 (14,8%)	
complications	14 (60,9%)	13 (48,1%)	0,982
rehydration			
i.v.	16 (69,6%)	19 (70,4%)	0,976
per os	7 (30,4%)	8 (29,6%)	
probiotic	14 (60,9%)	26 (96,3%)	0,006

## DISCUSSION

In the United States, about 50.000 patients report having RVGE hospital treatment each year, with 20 to 40 patients dying from complications during the year, while the number of deaths in some European countries ranges from 7 to 87 (2).

A systematic review of RVGE in children under the age of five in Asia has determined that rotavirus is associated with approximately 145.000 deaths per year (12).

RVGE is the cause of 25 million doctor visits, 2 million hospitalizations and 180.000-450.000 deaths in children under five years of age, annually. In the European Union, rotavirus is estimated to cause about 3.6 million episodes of acute gastroenteritis, 700.000 doctor visits, 87.000 hospitalizations and 231 deaths in children under five (13).

In our study, Rotavirus infection occurred throughout, with statistically significant occurrence in March. The results of compatibility with ours were obtained by Shrestha et al. who conducted his research in the territory of Nepal (12), Aristegui et al. in the territory of Spain (14), as well as Nahari

et al. in the territory of Saudi Arabia (15). Different results from ours were reported in Thailand, where the highest incidence was recorded in the summer months (16) as well as during the summer rains in Ethiopia (17).

Gladstone et al. in his prospective study, which lasted for three years, monitored the occurrence of RVGE from birth to the third year of life and concluded that the distribution by gender was of no statistical significance (18).

In the study of Shresth et al., the infection was more prevalent in male (31%) than in female (24%) but without statistical significance (12). The results obtained by the RVGE analysis in London are compatible with our results. RVGE was more frequent in the male population (66%) than in the female population (44%), but without statistical significance (13). In the study by Konda et al., conducted in the territory of Japan, the gender distinction is also without a statistically significant difference (19). The compatible results were obtained in the study by Aristegui et al., where there was a higher male representation with 51.9% (14), as in the study by Nahari et al., where there was a higher male representation with 66.6% (15).



Some authors in the youngest age group of 0-5 months either do not have the disease or their number is very low. Gurwith et al. do not have patients at all at that age (20). Holdaway et al. have a frequency of RVGE in the youngest age group of 4.7% (21), while in the study of Nahari et al., the incidence of less than 6 months among the patients with RVGE was 38.2% (15).

Kamia et al. examined the incidence of RVGE in children under 5 years of age in three Japanese cities and concluded that only 4.2% of the total number of children surveyed, were under six months of age and 24.8% of children < 1 year old, ie. infants (22).

The average infant age in our study is  $6.7 \pm 3.7$  months, which is in line with Western European countries. The average age in the territory of Saudi Arabia in a study conducted by Nahari et al., was  $9.8 \pm 10.2$  months (15).

In the multicenter prospective study covering Western European countries, the largest number of hospitalized children due to RVGE was registered at the age of 6 to 11 months (Belgium, France, Germany, United Kingdom) with the exception of Italy, Spain and Sweden, where the age of hospitalized children was in range from 12 to 23 months (23).

Diarrhea in our study was present in all infants 100%, which is identical with the study of Shresth et al. (12). In the study of Karampatsas et al. in London, diarrhea was reported in 86% of cases (13), and in the study by Arístegui et al., the incidence of diarrhea was 97% (14).

The average number of water diarrhea obtained in our study was  $6.5 \pm 3.9$  over a 24-hour period, which is higher than the average number of diarrhea over a 24-hour period recorded in the study by Kondo et al., which was  $3.6 \pm 3.2$  (19).

In our study, vomiting, as a symptom of the disease, was present in 84% of infants with RVGE. The results similar to ours were obtained in their study by Nahari et al., where vomiting was reported as a symptom in 81.3% (15). A slightly lower incidence of vomiting was observed in the study of Karampatsas et al., where it was 74% (13) and in the study by Arístegui et al., where it was 69.1% (14). The lowest incidence of vomiting registered in the study of Shresth et al., was 36% (12).

The average number of returns within 24 hours in our study, was  $5.1 \pm 2.5$  times, which is higher than in the study by Kondo et al., where it was  $3.6 \pm 3.8$  times for a 24-hour period (19).

In our study, fever was recorded in 74% of infants. An identical incidence of fever was registered in the study conducted by Karampatsas et al. (13). In the study of Nahari et al., fever was observed in 81.3% of cases (15), while slightly lower incidences were reported in the study by Arístegui et al., 69.1% (14), and a significantly lower incidence of fever

was registered in the study of Shresth et al., where it was present in 25% of RVGE cases (12).

In our study, dehydration was present in 96% of infants. In the study of Shresth et al., dehydration was present in all cases of RVGE (12). The results different from ours were obtained by Karampatsas et al., where dehydration was present in 44% (13). A lower incidence of dehydration was registered in the study of Arístegui et al., where it was present in 20% of RVGE cases (14) and in the study of Nahari et al., where it was present in only 11.7% of cases (15).

In our study, metabolic acidosis was reported in 58% of RVGE cases while in the study of Nahari et al., it was reported in 68.6% of RVGE cases (15). In our study, complications of rotavirus gastroenteritis were present in 48% of infants. The upper respiratory tract infection was common in 34% of infants while 14% of infants had the middle ear inflammation. Febrile convulsions, intestinal invagination and other possible complications were not recorded in our study. In the study of Karampatsas et al., a higher incidence of neurological complications was reported, whereas the upper respiratory tract infection complications were present in 27% of RVGE cases (13).

Rehydration, as the primary treatment for RVGE patients, was present in all infants in our study. In 70% of cases, it was intravenous, while in 30% of cases, it was oral.

In the study of Karampatsas et al., intravenous rehydration was present in 50% of cases (13), and in the study by Arístegui et al., intravenous rehydration was present in 68.3% of RVGE cases (14).

Many studies have attempted to demonstrate the importance of probiotic use in RVGE therapy. Grandy et al. demonstrated in his study that the use of probiotics in RVGE therapy in infants and young children significantly reduced the duration of diarrhea by 31.4%, as well as the duration of fever by 73%. The effect of probiotics on vomiting has not been clear yet and the exact mechanism of the effect of probiotics on vomiting length cannot be determined (24). Some studies have reported that the use of probiotics does not affect the length of vomiting, while other authors believe that the use significantly shortens the length of vomiting (25).

In our study, because of the same opinion about the beneficial effect of probiotics on the length of the problems and their alleviation, there is a statistically significant difference in the use of probiotics, ie. a significantly higher number of infants received probiotics, 80%. More probiotics in our study were present in infants of the older age group.

A more severe clinical picture of RVGE is commonly seen in intrahospital infections. In our study, of all registered RVGEs, 32% of RVGEs were due to the intrahospital infection. Different results from ours were obtained by Shrestha et al., where statistically significant was a higher incidence of non-tachospitular RVGE infections compared to the primary rotavirus infections (12). The results obtained by





Karampatsas et al. showed that the incidence of intrahospital RV infection was prevalent in 93% of RVGE cases (13).

## CONCLUSION

Based on the results obtained in the study period, the following can be concluded:

- The mean age of infants with RVGE was  $6.7 \pm 3.7$  months.
- Most infants (68%) were hospitalized for RVGE, while in other infections, they were acquired intrahospitally.
- Infection was more common in March compared to other months of the year.
- RVGE clinical imaging was based on aqueous diarrhea (100%), vomiting (84%) and fever (74%).
- Dehydration is found in 96% of infants.
- Complications (the upper respiratory tract infection and middle ear inflammation) have been reported in 48% of infants with RVGE.

## REFERENCES

1. Saia M, Giliberti A, Callegaro G, Baldovin T, Busana MC, Pietrobon F et al. Hospitalisation for rotavirus gastroenteritis in the paediatric population in the Veneto Region, Italy. *BMC Public Health* 2010; 10: 636.
2. Vuletić B, Obradović S, Stojkovic-Andjelković A, Igrutinović Z, Radlović P. Rotavirus gastroenteritis. *Srp Arh Celok Lek* 2006;134 (3-4): 166-9.
3. Radlović N, Milosavljević S, Deura L. Rotavirus gastroenteritis in children: our clinical experience. *G Mal InfektParasit* 1990; 42: 683-5.
4. Soriano-Gabarró M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. *Pediatr Infect Dis J* 2006; 25 (11): 7-11.
5. Vlastelica Ž, Rogulj M, Krželj V, i sar. Rotavirusne infekcije djece liječene u Kliničko bolničkom centru Split tijekom trogodišnjeg razdoblja. *Paediatr Croat* 2010; 54 (1): 177-81.
6. Vesikari T, Van Damme P, Giaquinto C, Gray J, Mrukowicz J, Dagan R et al; Expert working group; European Society for Paediatric Infectious Diseases/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition evidence - based recommendations for rotavirus vaccination in Europe: executive summary. *J Pediatr Gastroenterol Nutr* 2008; 46 (5): 615-8
7. Dennehy H. Transmission of rotavirus and other pathogens in the home. *Pediatr Infect Dis J* 2000; 19 (10): 103-5.
8. Greenberg B, Estes K. Rotaviruses: from pathogenesis to vaccination. *Gastroenterology* 2009; 136 (6): 1939-51.
9. Asensi T, Martinez-Costa C, Buesa J. Anti-rotavirus antibodies in human milk: quantification and neutralizing activity. *J Pediatr Gastroenterol Nutr* 2006; 42 (5): 560-7.
10. Parashar D, Gibson J, Bresee S, Glass I. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis* 2006; 12 (2): 304-6.
11. Gilger A, Matson O, Conner E, Rosenblatt HM, Finegold MJ, Estes MK. Extraintestinal rotavirus infection in children with immunodeficiency. *J Pediatr* 1992; 120 (6): 912-7.
12. Shrestha S, Thakali O, Raya S, Shrestha L, Parajuli K, Sherchand JB. Acute gastroenteritis associated with Rotavirus A among children less than 5 years of age in Nepal. *BMC Infect Dis* 2019; 22: 19 (1): 456.
13. Karampatsas K, Osborne L, Seah ML, Tong CYW, Prendergast AJ. Clinical characteristics and complications of rotavirus gastroenteritis in children in east London: A retrospective case-control study. *PLoS One* 2018; 13 (3): e0194009.
14. Arístegui J, Ferrer J, Salamanca I, Garrote E, Partidas A, San-Martin M, et al. Multicenter prospective study on the burden of rotavirus gastroenteritis in children less than 3 years of age in Spain. *BMC Infect Dis* 2016; 16 (1): 549.
15. Nahari A, AlGhamdi SM, Alawfi A, Faqeehi H, Alzahrani S, Abu-Shaheen A, et al. The Clinical Burden of Rotavirus Gastroenteritis: A Prospective Study. *Cureus* 2017; 9 (12): e1903.
16. Echeverria P, Ho MT, Blacklow NR, Quinnan G, Portnoy B, Olson JG, et al. Relative importance of viruses and bacteria in the etiology of pediatric diarrhoea in Taiwan. *J Infect Dis*. 1977; 136 (3): 383-90.
17. Stintring G, Malby R, Hobte D. Enterotoxigenic E. Coli and other enteropathogenes in pediatric diarrhoea in Addis Ababa. *Acta Paediatr Scand*. 1982; 909-13.
18. Gladstone BP, Ramani S, Mukhopadhyaya I, Muliylil J, Sarkar R, Rehman AM, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. *N Engl J Med* 2011; 365 (4): 337-46.
19. Kondo K, Tsugawa T, Ono M, Ohara T, Fujibayashi S, Tahara Y. Clinical and Molecular Characteristics of Human Rotavirus G8P [8] Outbreak Strain, Japan, 2014. *Emerg Infect Dis* 2017; 23 (6): 968-972.
20. Gurwith M, Williams A. Gastroenteritis in children: a two-year review in Manitoba. I. Etiology. *J Infect Dis* 1977; 136 (2): 239-47.
21. Holdaway M, Kalmakoff J, Todd BA, Jennings LC. Rotavirus infection in a small community. *J Med Virol* 1985; 15 (4): 389-98.
22. Kamiya H, Nakano T, Kamiya H, Yui A, Taniguchi K, Parashar U. Rotavirus-Associated Acute Gastroenteritis Hospitalizations among Japanese Children Aged > 5 Years: Active Rotavirus Surveillance in Mie Prefecture, Japan. *Jpn J Infect Dis*. 2011; 64: 482-7.



23. Van Damme P, Giaquinto C, Huet F, Gothefors L, Maxwell M, Van der Wielen M. Multicenter Prospective Study of the Burden of Rotavirus Acute Gastroenteritis in Europe, 2004-2005: The REVEAL study. *J Infect Dis* 2007; 195: S4-S16.
24. Fang SB, Lee HC, Hu JJ, Hou SY, Liu HL, Fang HW. Dose-dependent effect of lactobacillus rhamnosus on quantitative reduction of faecal rotavirus shedding in children. *J Trop Pediatr* 2009; 55 (5): 297-301.
25. Grandy G, Medina M, Soria R, Terán CG, Araya M. Probiotics in the treatment of acute rotavirus diarrhoea. A randomized, double-blind, controlled trial using two different probiotic preparations in Bolivian children. *BMC Infect Dis* 2010; 10: 253.