



Paper Accepted\*

ISSN Online 2406-0895

Original Article / Оригинални рад

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differences between rotavirus and norovirus infections – practical or only  
academic significance?**

Етиологија вирусних гастроентеритиса међу хоспитализованим  
болесницима: разлике између Рота и Норовирусне инфекције – практични  
или само академски значај?

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Received: September 26, 2016

Revised: December 12, 2016

Accepted: December 13, 2016

Online First: March 17, 2017

DOI: 10.2298/SARH160926079D

\* **Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. *Srp Arh Celok Lek*. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal.

The date the article was made available online first will be carried over.

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## The etiology of viral gastroenteritis in patients requiring hospitalization: differences between rotavirus and norovirus infections – practical or only academic significance?

Етиологија вирусних гастроентеритиса међу хоспитализованим болесницима: разлике између Рота и Норовирусне инфекције – практични или само академски значај?

### SUMMARY

**Introduction/Objective** Viral gastroenteritides (VGEs) have great infectious potential and may occur in all age groups. Loss of fluid due to vomiting and diarrhea represent a special risk, and may result in a more severe clinical presentation in children, the elderly and people with chronic diseases.

The aim of the study was to explore the causes of VGE among hospitalized patients, as well as to evaluate the severity of clinical symptoms in rotavirus and norovirus infections.

**Methods** The observational prospective study included 191 patients aged 2–88 years who were treated over a two-year period. Testing of stool samples for viral agents was done by the RT-PCR method. Positive findings were found in 59 patients.

**Results** Of the 59 patients with confirmed viral gastroenteritis, in 31 (52.5 %) it was caused by rotavirus, in 17 (28.8 %) by norovirus, 3 patients (5.1%) had other viral causes, while co-infection with two viruses was found in 8 (13.5 %) patients. The severity of clinical manifestations as expressed with Vesikari score did not differ with regard to infectious agents ( $p=0.353$ ). However, patients with rotavirus infection had a higher incidence of fever ( $p=0.043$ ), longer duration of diarrhea ( $p=0.015$ ) and dehydration (0.014), and longer need for hospital treatment ( $p=0.030$ ).

**Conclusion** The most common cause of VGE in our hospitalized patients was rotavirus. There was no difference in the severity of clinical symptoms between rotavirus and norovirus infections.

**Keywords:** norovirus; rotavirus; gastroenteritis; hospitalization; length of stay

### САЖЕТАК

**Увод/Циљ** Вирусни гастроентеритиси имају велики инфективни потенцијал и могу се јавити у свим узрасним групама. Нарочит ризик представља губитак течности услед повраћања и пролива што може дати тежу клиничку слику код деце, старијих и особа са хроничним обољењима.

Циљ овог рада је да утврди дистрибуцију узрочника вирусних гастроентеритиса код хоспитализованих болесника и утврди разлике у тежини клиничке слике између Рота и Норовирусне инфекције.

**Метод** Спороведено је опсервационо проспективно испитивање код 191 болесника узраста 2–88 година лечених у двогодишњем периоду. Тестирање узорака столице на вирусне узрочнике рађено је методом *RT-PCR*. Позитиван налаз на вирусе забележен је код 59 болесника.

**Резултати** Од 59 болесника са потврђеним вирусним гастроентеритисом, код 31 (52,5%) узрочник је био Ротавирус, код 17 (28,8%) Норовирус, код 3 (5,1%) болесника доказани су остали вирусни узрочници, а коинфекција са два вируса забележена код 8 (13,5%) болесника. Тежина клиничке слике изражена кроз Весикари скор није се разликовала у односу на узрочника инфекције ( $p=0,353$ ). Болесници са ротавирусном инфекцијом имали су већу инциденцу температуре ( $p=0,043$ ), дуже трајање дијареје ( $p=0,015$ ) и дехидратације ( $p=0,014$ ) и дужу потребу за болничким лечењем ( $p=0,030$ ).

**Закључак** Најчешћи узрочник акутних вирусних гастроентеритиса код хоспитализованих болесника био је ротавирус. Није нађена разлика у тежини клиничке слике између рота и норовирусне инфекције.

**Кључне речи:** ротавирус; норовирус; гастроентеритис; дужина болничког лечења

### INTRODUCTION

Acute gastroenteritis (AGE) mostly represent mild, self-limiting disease, which usually does not require going to the doctor [1]. In a small percentage of cases, depending on the different characteristics of the pathogen and the host and their interrelationship, AGE will require hospital care. Although the proportion of severe clinical forms is small, the ubiquity and high incidence of this disease, especially in countries with poor socioeconomic conditions, gives this disease a great practical significance [2].

In triage settings, the most important is certainly the assessment of severity of disease and indications for hospitalization, as well as differentiation between viral and bacterial AGE. The practical importance of differentiation between causes of viral gastroenteritis is often overlooked by general practitioners [3]. The reasons for this include primarily the treatment approach that is symptomatic in all cases of viral gastroenteritis, as well as the price of the diagnostic tests, which are still based on molecular techniques and therefore usually unaffordable for patients in developing countries [4]. However, literature data indicate that there are differences in the incidence of individual causes of viral gastroenteritis, as well as in the severity of clinical symptoms, and it has been observed that these differences depend on geographic area, as well as socioeconomic status and hygienic habits of the study population [1, 3-6].

The aim of this study was to determine the distribution of causes of viral gastroenteritis among patients requiring hospitalization in our institution, as well as to determine whether there are differences in the clinical presentation between rotavirus and norovirus infections.

## **METHODS**

This observational prospective study included 191 patients aged 2-88 years, who were treated at the Clinic for Infectious Diseases in Novi Sad over a period of two years (between January 1<sup>st</sup> 2014 and December 31<sup>st</sup> 2015). A viral etiology of the disease was confirmed in 59/191 patients.

### **Data sources**

Referrals to laboratory testing for causes of viral gastroenteritis contained basic demographic data, epidemiological data, present symptoms and signs, and disease duration. Medical records included data on personal history, clinical course, response to treatment, and disease outcome.

### **Clinical definition of viral gastroenteritis**

The clinical definition of a case of acute viral gastroenteritis presupposed the presence of the following symptoms:  $\geq 3$  watery stools/24h and/or  $\geq 2$  episodes of vomiting/24h, abdominal pain, and fever. The study excluded patients with comorbidities in the gastrointestinal tract, patients in whom the complaints lasted more than 48 hours prior to hospitalization, patients previously treated with antimicrobial therapy as well as those with a positive stool test for bacterial pathogens.

### **Laboratory diagnostics**

Stool samples for molecular diagnostics were taken not later than 48 hours after the onset of symptoms and before initiation of treatment, and transported in a manual refrigerator (from +4 to +8°C) to the laboratory. Virus isolation from stool was done at the Center for Virology of the Public Health Institute of Vojvodina, Novi Sad. The extraction of viral nucleic acids was carried out with commercially available minispin column kit for the isolation of RNA (Ribo Virus, Sacace, Biotechnologies, Italy). Testing of samples of viral nucleic acids was done using real-time polymerase

chain reaction (RT-PCR) a commercial kit by Sacace (Sacace, Biotechnologies, Italy). Amplification and detection of viral RNA was done using APPLIED BIOSYSTEMS - 7500, USA.

Bacteriological examination of stool to common intestinal pathogens (*Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Yersinia* spp, *E. coli* O: 157) was performed at the Center for Microbiology of the Public Health Institute of Vojvodina, Novi Sad.

Routine laboratory blood and urine tests were performed at the Center for Laboratory Medicine of the Clinical Center of Vojvodina.

The study was approved by ethical committee of the Clinical Center of Vojvodina. All the participants in the study have signed the informed consent.

### Statistical analysis

Statistical analysis was done using the software package IBM SPSS v.23.0. Categorical variables were presented as numbers and percentages, and differences between groups were investigated by the chi-square test. After examination of the distribution of continuous variables, it was found that the distribution of most of the variables differed significantly from a normal distribution, and also that most of the variables showed significant heterogeneity of variance between groups; therefore, data was presented as a median and an interquartile range, and differences between the groups were investigated using Mann-Whitney U test. Significance of correlations between the variables was tested using a non-parametric approach (Spearman rank correlation).

## RESULTS

In the observed two-year period at the Clinic for Infectious Diseases of the Clinical Center of Vojvodina, with symptoms of acute gastroenteritis were hospitalized a total of 261 patients. All patients underwent stool analysis for viruses and bacteria, and patients with proven bacterial pathogens (n=65) and those with mixed viral and bacterial infection (n=5), were excluded from further analysis. The remaining 191 patients were included in the study. A proven viral pathogen was found in 59/191 patients (30.9%), while stool testing for both viruses and bacteria was negative in 132/191 (69.1%) patients.

Among the 59 patients with confirmed viral gastroenteritis, in 31 (52.5%) patients the cause was rotavirus, in 17 (28.8%) it was norovirus, 3 patients (5.1%) had other viral causes of AGE, and co-infection with two viruses was found in 8 (13.5%) patients. Patients with all stool analyses negative for pathogenic causes (n=132) as well as patients with co-infection with two viruses (n=8) and patients with confirmed viral aethiology other than Noro or Rota virus (n=3) were classified as a non-rota/non-noro group (a total of 143 patients).

Further analysis included only patients with proven viral and non-rota/non-noro gastroenteritis.

Demographic data are presented in Table 1, while clinical and laboratory characteristics of study patients are shown in Table 2.

**Table 1. Demographic characteristics of patients included in the study.**

	Non-rotavirus/ Non-norovirus (n = 143)	ROTA (n = 31)	NORO (n = 17)	N/R	Non/N	Non/R
Age	22 (10.5–31)	19 (4.5–32)	19 (17–25)	0.627	0.831	0.400
Under 5 yrs.	21 (14.7%)	9 (29.0%)	1 (5.9%)			
5–18 yrs.	38 (26.6%)	6 (19.4%)	6 (35.3%)	0.132	0.528	0.265
Adults	84 (58.7%)	16 (51.6%)	10 (58.8%)			
Sex – male	74 (51.7%)	13 (41.9%)	6 (35.3%)	0.653	0.305	0.322
Comorbidity	0 (0%)	9 (29.0%)	6 (35.3%)	0.654	-	-
Takeaway & restaurant food	32 (22.4%)	4 (12.9%)	2 (11.8%)	0.909	0.220	0.238
Similar symptoms in family	34 (23.8%)	8 (25.8%)	3 (17.6%)	0.776	0.793	0.994

**Table 2. Comparison of clinical and laboratory characteristics between rotavirus, norovirus and non-rotavirus/non-norovirus AGEs.**

	Non-rotavirus/ Non-norovirus (n = 143)	ROTA (n = 31)	NORO (n = 17)	N/R	Non/N	Non/R
Vomiting	118 (82.5%)	24 (77.4%)	16 (94.1%)	0.138	0.854	0.507
>5x per day	48 (33.6%)	11 (35.5%)	7 (40.2%)	0.696	0.532	0.838
Duration*	1 (1–2)	1 (1–2)	1 (1–1)	0.643	0.824	0.726
Diarrhea	136 (95.1%)	31 (100%)	16 (94.1%)	0.758	0.860	0.451
>5x per day	92 (64.3%)	17 (54.8%)	9 (52.9%)	0.926	0.406	0.213
Duration*	3 (1–4)	3 (2–4)	2 (1–3)	0.015	0.105	0.407
Fever	93 (65%)	25 (80.6%)	9 (52.9%)	0.043	0.523	0.092
Duration*	1 (1–3)	2 (1.5–3)	2 (1–2)	0.052	0.703	0.031
Max. BT	38.1 (37.2–38.8)	38.2 (37.6–38.9)	37.6 (37.2–38.3)	0.078	0.245	0.482
Bloody stool	5 (3.5%)	3 (9.7%)	0 (0%)	-	-	0.309
Abd. Pain	97 (67.8%)	20 (64.5%)	13 (76.5%)	0.597	0.653	0.884
SBP	110 (100–120)	110 (100–120)	110 (100–120)	1.00	0.534	0.638
WBC	54 (37.8%)	8 (25.8%)	4 (23.5%)	0.862	0.375	0.292
CRP	25 (8–121)	52 (7–168)	18 (15.5–21)	0.540	0.583	0.593
Potassium	4 (3.7–4.3)	4 (3.7–4.3)	4 (3.8–4.3)	0.863	0.939	0.096
Vesikari score	12 (10–14)	12 (11–13)	12 (10–12)	0.353	0.430	0.835
Mild	1 (0.7%)	1 (3.2%)	0 (0%)			
Moderate	46 (32.2%)	7 (22.6%)	4 (23.5%)	0.755	0.713	0.305
Severe	96 (67.1%)	23 (74.2%)	13 (76.5%)			
Duration of complaints before hospitalization*	1 (1–2.5)	1 (1–3)	1 (1–1)	0.154	0.262	0.481
Duration of hospitalization*	3 (2–5)	4 (3–5)	3 (2–4)	0.030	0.225	0.174
Duration of I.V. Th*	4 (3–5)	4 (4–5)	4 (3–4)	0.014	0.382	0.025

\*Duration is expressed in days. Data are presented as number of cases (percentage) for categorical variable, and median (interquartile range) for continued variable. BT – body temperature, SBP – systolic blood pressure, WBC – white blood cells, CRP – C reactive protein.

The results showed no statistically significant difference in the age of patients in relation to the pathogen. However, when the age categories were taken into account, it was observed that rotavirus infection was more common in children under five years of age, while norovirus infection was more frequent in children aged 6–18 years. On the other hand, all three groups (rotavirus, norovirus and non-rotavirus/non-norovirus GE) were similarly prevalent in adults (50–60%). These differences, however, did not reach the level of statistical significance.

It is interesting that of the 143 patients with non-rotavirus/non-norovirus GE, none had associated comorbidities, while in the group with norovirus GE, as many as 35% of the patients (n=6) had comorbidities (4 patients had hypertension, and 2 of them chronic obstructive pulmonary disease). In

the group of patients with Rotavirus infection nine of them had comorbidities (29.0%) – hypertension (n=6), diabetes mellitus (n=1) and obstructive pulmonary disease (n=2).

With respect to the epidemiological data regarding family members suffering from similar symptoms or eating food prepared outside home, there were no statistically significant differences between the observed groups of patients. Food consumption outside home immediately prior to the onset of complaints was reported by 11.8%-22.4% of patients.

An analysis of individual elements used to estimate severity of the clinical picture showed that diarrhea and fever lasted longer in patients with rotavirus infection compared with norovirus infection, while this difference was not found in patients with non-rotavirus/non-norovirus gastroenteritis in comparison to norovirus and rotavirus groups. However, considering the overall severity of the clinical picture as expressed by the Vesikari score, we did not find a statistically significant difference in the severity of clinical symptoms between the three GE groups.

In addition, the group with rotavirus infection had a significantly longer need for parenteral rehydration, compared to both the norovirus and the non-rotavirus/non-norovirus groups, as well as a significantly longer duration of hospitalization.

Laboratory parameters did not differ significantly between the studied groups of patients.

An analysis of demographic parameters (host's characteristics) that might have potentially affected the clinical picture expressed by the Vesikari score in patients with proven viral gastroenteritis showed a statistically significant negative correlation of a moderate intensity (n=59,  $r=-0.305$ ,  $p=0.033$ ) between the Vesikari score and age. In other words, younger patients had a more severe clinical picture. Similarly, patients with comorbidities had a statistically significantly more severe clinical picture compared to those without comorbidities (n=59,  $r=0.311$ ,  $p=0.031$ ).

Duration of hospitalization and duration of parenteral rehydration did not significantly correlate with either demographic or epidemiological factors.

## DISCUSSION

Rotavirus is considered the most common cause of viral gastroenteritis and accounts for the highest percentage of patients presenting with a more severe clinical picture. This conclusion was reached by analyzing outpatients and hospitalized patients, and it has been found that the most common cause of hospitalization is rotavirus [3, 6-11]. However, studies that included only hospitalized patients, have provided contradictory data about the severity of clinical picture of rotavirus and norovirus infections. Perl and associates [12], analyzing individual symptoms of viral gastroenteritis among children hospitalized in their institution, reported a more severe clinical picture in rotavirus infection compared to other pathogens. On the other hand, Kawada and colleagues [13] reported that in children less than 12 years of age norovirus infection caused vomiting more frequently and that vomiting and diarrhea lasted longer. A prospective study of French researchers showed that rotavirus is by its frequency and severity of the clinical picture the most important

pathogen in hospitalized pediatric patients [6]. Our results showed a higher prevalence of fever in patients with rotavirus infection, as well as a longer duration of fever and diarrhea. However, considering the overall severity of the clinical picture expressed by the Vesikari score, our results did not show a statistically significant difference in the severity of clinical symptoms of gastroenteritis caused by rotavirus and norovirus. Norovirus infections require statistically significantly shorter parenteral rehydration, thereby reducing duration of hospitalization.

The discrepancy of literature data on the severity of the clinical picture and the data indicating that particular symptoms last longer in rotavirus infections [6, 8, 12] may be explained by differences in the host's characteristics, rather than the characteristics of the pathogen. In fact, our results suggest that younger children, in view of age-particular immune response, present with a more severe clinical picture, regardless of the pathogen (severity of the clinical picture does not differ with regard to the cause, but statistically significantly correlates with age). Bearing in mind that children under 5 years of age are the "target group" of rotavirus, this may explain the more severe symptoms and a longer hospital stay. In support of the notion that host factors are the reason for the differences in the severity of clinical symptoms is our finding showing that the presence of comorbidities significantly affected the severity of clinical picture. It is noteworthy that we found as many as 35% of patients with associated diseases in the group with norovirus diarrhea. Considering that the incidence of norovirus increases in immunocompromised and elderly patients, this could have, besides clinical aspects, significant financial effects [13, 14]. Most literature data related to viral gastroenteritis in hospitalized patients comes from pediatric departments [6, 10-13]. Our research included patients of all ages; however, we found that rotavirus infection was significantly more common among children aged up to five years. The observed negative correlation between age and severity of disease as expressed by the Vesikari score may be a result of still insufficiently formed immunity of children who are susceptible to rotavirus infection, rather than the virulence of the pathogen itself.

Viral diarrhea in developing countries is associated with hygienic habits of the population but also with consumption of food in restaurants and takeaways [4]. Only one fifth (11.8%22.4 %) of our patients consumed food outside home immediately before the onset of symptoms.

Although it is the common belief among practicing physicians that detection of causes has no great practical importance, we do not agree with this attitude. In developing countries, where the incidence of viral gastroenteritis is high, costs of hospital care for these patients are not negligible [4]. Research contributing to estimating the prevalence of rotavirus and norovirus infections (1-3) as well as potential further pharmaco-economic research are needed in order to assess the need for preventive vaccination of vulnerable groups (lower socioeconomic conditions, immunocompromised patients), which would contribute to reducing the incidence, decreasing the severity of clinical picture, and indirectly, to a practical increase in the budget of healthcare institutions [15, 16].

## CONCLUSION

The most common cause of AGE in patients in our institution was rotavirus. In comparison to norovirus infection, it was characterized by higher incidence of fever, longer duration of diarrhea and dehydration as well as need for longer hospitalisation. Although the severity of clinical picture in hospitalized patients and the therapeutic approach do not differ with regard to causes of disease, laboratory identification of viral pathogens, in addition to the academic, has an indirect great practical significance.

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