



## Characteristics of norovirus infection in Serbia

### Karakteristike norovirusne infekcije u Srbiji

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#### Abstract

**Background/Aim.** Norovirus (NoV), formerly Norwalk-like virus is the most common cause of acute gastroenteritis in humans of all ages. It is known that 90% of viral gastroenteritis and about 60–85% of all outbreaks of gastroenteritis, especially in the territory of United States of America, Europe and Japan are caused by this virus. For the countries of the northern hemisphere, individual cases and outbreaks of acute NoV gastroenteritis appear in seasonal pattern, mainly during the winter months. The aim of this study was to describe characteristics of acute gastroenteritis with the established NoV etiology in Serbia. **Methods.** The study group included 88 patients with the symptoms of acute gastroenteritis, throughout the year 2010 and 2011. From all the patients, stool samples were taken less than three days from the onset of symptoms. Detection of NoV in stool samples was performed by commercial qualitative immunochromatography assay. Statistical analysis included application of  $\chi^2$  test, Mann–Whitney *U*-test, Kruskal–Wallis's test, Spearman's rank correlation test and logistic regression analysis. **Results.** Outbreaks of acute gastroenteritis caused by NoV were recorded to be the most common in children with the incidence of infection of 50% in the age group 0–15 years. Analysis of individual symptoms in the NoV proven infection, showed that diarrhea was the most common symptom, followed by vomiting especially in small children, while abdominal pain was most common in elderly ( $\geq 65$  years). The presence of frequent vomiting, more than 4 times/day, indicated NoV infection in the women, while for men the infection was always presented with diarrhea. **Conclusion.** The obtained results confirmed that small children and elderly are the most susceptible to NoV infection and that outbreaks are more frequent in the winter months. Those who consumed food in restaurants and other public facilities were not at higher risk for NoV infection.

#### Key words:

norovirus; gastroenteritis; incidence; risk assessment; disease outbreaks; serbia.

#### Apstrakt

**Uvod/Cilj.** Norovirus (NoV), raniji naziv virus koji je sličan Norwalk virusu, najčešći je uzročnik akutnog gastroenteritisa kod ljudi svih starosnih doba. Poznato je da je 90% virusnih gastroenteritisa i oko 60–85% svih epidemija gastroenteritisa uzrokovano ovim virusom, posebno na teritoriji Sjedinjenih Američkih Država, Evrope i Japana. Za zemlje severne hemisfere, norovirusne epidemije i pojedinačni slučajevi akutnog gastroenteritisa pokazuju sezonski obrazac pojavljivanja, uglavnom tokom zimskih meseci. Cilj ovog rada bio je da se opišu karakteristike akutnog gastroenteritisa sa utvrđenom norovirusnom etiologijom kod bolesnika u Srbiji. **Metode.** Studijskom grupom bilo je obuhvaćeno 88 bolesnika sa simptomima akutnog gastroenteritisa tokom 2010. i 2011. godine. Od svih bolesnika, uzimani su uzorci stolice najviše tri dana od pojave simptoma infekcije. Za otkrivanje NoV u uzorcima stolice korišćen je komercijalni kvalitativni imunohromatografski test. Za statističku obradu podataka korišćeni su  $\chi^2$  test, Mann–Whitney *U*-test, Kruskal–Wallis test, Spirmanov test korelacije ranga i metode logističke regresije. **Rezultati.** Slučajevi akutnog gastroenteritisa uzrokovanog NoV najčešće su zabaleženi kod dece, sa incidencijom od 50% u grupi od 0–15 godina starosti. Analizom simptoma kod bolesnika sa dokazanom norovirusnom infekcijom zaključeno je da je dijareja bila najčešći simptom, zatim, po učestalosti, sledilo je povraćanje, posebno kod manje dece, dok je abdominalni bol bio karakterističan za ispitanike starije od 65 godina. Prisustvo učestalog povraćanja, preko četiri puta dnevno, ukazivalo je na NoV infekciju kod žena, dok je kod muškaraca infekcija bila uvek manifestovana dijarejom. **Zaključak.** Rezultati istraživanja su potvrdili da su manja deca i starije osobe najosetljivije grupe za NoV infekciju i da su epidemije češće u zimskim mesecima. Bolesnici koji su se hranili u restoranima ili ustanovama za javnu ishranu nisu imali veći rizik od razvoja NoV infekcije.

#### Ključne reči:

norovirus; gastroenteritis; incidenca; rizik; procena; epidemije; srbija.

## Introduction

Norovirus (NoV), formerly Norwalk-like virus is the most common cause of acute gastroenteritis in humans of all ages<sup>1, 2</sup>. It is known that 90% of viral gastroenteritis and about 60–85% of all outbreaks of gastroenteritis especially in the territory of the United States of America (USA), Europe and Japan is caused by this virus<sup>3, 4</sup>. For the countries of the northern hemisphere, individual cases and outbreaks of acute NoV gastroenteritis appear in a seasonal pattern, mainly during the winter months<sup>4–6</sup>. Outbreaks usually occur in closed collectives such as hotels, hospitals<sup>7</sup>, homes for the elderly<sup>8</sup>, kindergartens, schools and cruise ships<sup>4</sup>.

Humans are the only reservoir of infection and common routes of transmission including fecal contamination of food and water, direct contact with an infected person, spreading the virus in the form of aerosol and contact with contaminated surfaces in the environment. High resistance to environmental factors, the low infectious dose (10–100 viral particles enough to develop symptoms of disease) and the lack of long-term immunity are important factors contributing to the rapid spread of NoV<sup>1</sup>.

The disease occurs after an incubation period of 12–48 h accompanied by diarrhea, nausea, vomiting and abdominal cramps. In most cases the infection ends with complete recovery after 4–6 days. In 30% of cases, it passes as asymptomatic infection<sup>9, 10</sup>, while in 10% of infected it is manifested as severe form of disease that requires hospitalization<sup>11, 12</sup>. Fatal outcome was recorded more frequently in the group of preterm born children, and in persons older than 65 years. On the United States territory, 90% of annual death outcomes associated with NoV were recorded in patients older than 65 years<sup>13</sup>.

The virus is shedded by feces or vomits where it can be detected during 4 weeks after infection, with a peak of shedding in 2–5 days following the onset of symptoms<sup>9</sup>. Most microbiology laboratories in industrialized countries use molecular techniques for routine and confirmatory detection of norovirus, but for the rapid screening of NoV infections, it is faster and cheaper to use immunochromatography tests for the detection of NoV antigen in stool samples. These tests enable identification of the virus with the specificity of 87.5% compared to polymerase chain reaction (PCR)<sup>14</sup>. In Serbia, NoV infection has not so far been considered as causative agent of acute gastroenteritis, so there are no previously published data on the prevalence of these infections in outbreaks or in sporadic cases of acute gastroenteritis. The Public Health Institute of Belgrade was the first to investigate NoV as a cause of acute gastroenteritis according to epidemiological indications. The aim of this study was to describe the characteristics of acute gastroenteritis with the established NoV etiology in Serbia.

## Methods

The study group included 88 patients with the symptoms of acute gastroenteritis, throughout the year 2010 and 2011. A total of 88 stool samples was conducted in the

Microbiology Laboratory of Public Health Institute of Belgrade. They were divided in subgroups defined on the basis of epidemiological data.

Testing for NoV infection was conducted according to indications set by The Epidemiological Control Department of Public Health Institute of Belgrade. The study included testing for NoV infection in: 15 sporadic cases (13 cases from the general city population during summer months, 2 from the gerontology center); and in 6 suspected outbreaks as follows – two in the nursery (14 cases), three in restaurants (31 cases) and one in a medical institution (28 cases).

Acute onset of diarrhea, vomiting, nausea and abdominal pain, were considered typical symptoms of acute gastroenteritis, while malaise, fever, chills, muscle pain, headache and dizziness, were considered nonspecific. The information about water and food supply during 48 h before the onset of acute gastroenteritis was also gathered.

The study included only samples that met the following criteria: stool samples taken less than three days from the onset of symptoms; stools with no visible traces of blood, without fixatives or preservatives; samples available in sufficient quantity volume of 2 mL or 2 g; samples transported and stored in accordance with the Good Laboratory Practice.

Detection of NoV in stool samples was performed by commercial qualitative immunochromatography assay RIDA<sup>®</sup>QUICK Norovirus (R-Biopharm, Darmstadt, Germany), that utilizes specific monoclonal antibodies to norovirus antigens GG I and GG II.

## Statistical analysis

Data statistical analysis were performed using the SPSS software package 20.0 (IBM SPSS Statistic for Windows, Amonk, NY, USA). Individual characteristics between the groups were compared using Mann Whitney and Kruskal-Wallis's test for continuous variables and  $\chi^2$  test for categorical data. The receiver operating characteristic (ROC) curve was used for determination of NoV markers. Spearman's rank correlation test was utilized to evaluate the relationship between variables. Logistic regression analysis was used for determination of odds ratio (OR) for diarrhea in men and risk estimation parameters for NoV infection in childhood. Statistical significance was defined by the value of  $p \leq 0.05$ .

## Results

NoV antigen was detected in stool samples of 37 (42%) out of 88 patients suffering from acute gastroenteritis. The majority of NoV positive cases was discovered in sporadic cases of gastroenteritis (73.3%,  $n = 11/15$ ) and among the patients in healthcare facilities (42.9%,  $n = 12/28$ ). The incidence in outbreaks of NoV infection was 35.6%.

In the group of patients with proven NoV infection, 44 (50%) were aged 0–15 years, approximately 1/3 [28 (31.8%)] were aged  $\geq 65$  years, while those aged 15–64 years (16 patients) accounted for only 18.2%.

Among the patients with proven NoV infection, the recorded symptoms were: diarrhea (35), followed by vomiting

(29), nausea (19), abdominal pain (19), malaise (19), fever (11), chills/shivering (4), dizziness (1). None of the patients with the proven NoV infection had headache or muscle pain. The frequency (%) of specific and nonspecific symptoms of NoV infection was shown in Figure 1.

Analysis of individual symptoms showed that diarrhea was the only symptom that was significantly more present in NoV proven infection compared to acute gastroenteritis without proven NoV infection (94.6%,  $n = 35/37$  vs 78.4%,  $n = 40/51$ , respectively;  $p = 0.035$ ). All the children aged 0–7 with the proven NoV infection had vomiting (100%,  $n = 13/13$ ), while vomiting was present in only 50% of children with non-NoV acute gastroenteritis [ $\chi^2 (19.1) = 7.72$ ,  $p = 0.021$ ; OD 5.33, CI 95% 1.92–14.7].

In the group of patients aged  $\geq 65$  years, abdominal pain was significantly more frequent in proven NoV infection (84.6%,  $n = 11/13$ ) than in patients with no NoV present

years, men were more present (84.6%,  $n = 11/13$ ) than women. The women were more often infected in the age group 16–65 years (66.7%,  $n = 4/6$ ). In childhood NoV infection was equally present in both sexes.

The women with proven NoV infection were shown to have more severe vomiting. In fact, more than 4 vomiting *per* day in women was significantly correlated with the presence of NoV antigens (sensitivity 75% and specificity of 81.2%,  $p = 0.030$ , area 0.777).

The men with NoV infection suffered from diarrhea in all the cases (100%,  $n = 25/25$ ), while the men with NoV negative acute gastroenteritis had this symptom in 77.8% ( $n = 21/27$ ), [ $\chi^2 (52.1) = 6.28$ ,  $p = 0.012$ ]. The number of unformed stools in 24 h was not significantly more present in the patients with NoV infection than in those without it.

NoV infection was more often detected in winter than summer (Figure 2).

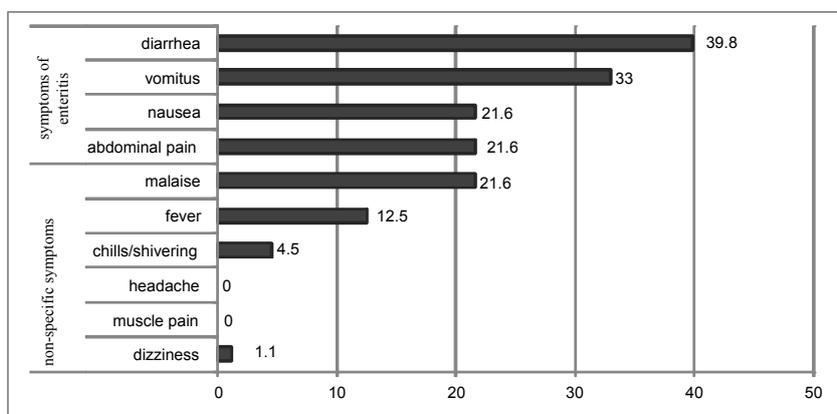


Fig. 1 – The frequency of specific and nonspecific symptoms of acute gastroenteritis in the norovirus positive patients

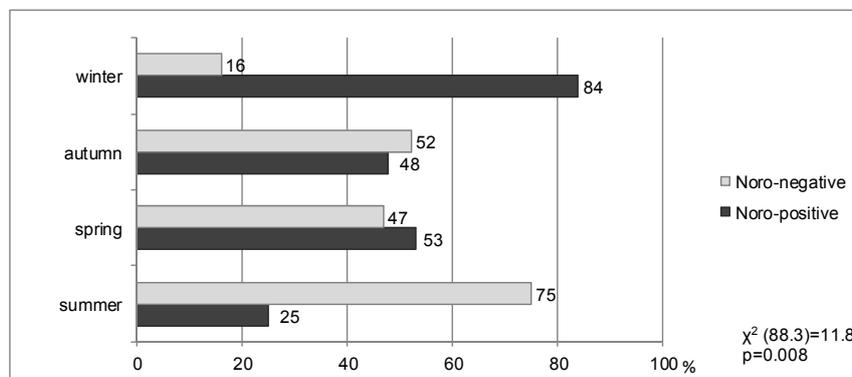


Fig. 2 – The percent of patients diseased in different seasons.

(40%,  $n = 6/15$ ), [ $\chi^2 (28.1) = 5.81$ ,  $p = 0.020$ ; OR 8.25, CI 95% (1.33–51.26)]. The most severe clinical manifestations with  $\geq 10$  stools/24 h and/or  $\geq 10$  vomits/24 h and  $t \geq 39$  °C were encountered in 28 patients (15 NoV positive and 13 NoV negative), and the majority (57.1%,  $n = 16/28$ ) of them were children aged 0–15 years (NoV positive 56.3%,  $n = 9/16$ , NoV negative 43.7%,  $n = 7/16$ ).

There was no statistically significant difference in the incidence of proven NoV infection by gender (women 33.3%,  $n = 12/36$  vs men 48.1%,  $n = 25/52$ ;  $\chi^2 (88.1) = 1.9$ ,  $p = 0.168$ ). In the group of NoV-positive patients aged  $\geq 65$

#### Water and food in the last 48 h before symptoms

None of the patients used well water, bottled water was used by one, local water supply by 14 and urban water supply by 73 patients. The frequency of NoV infection among the patients who used local water supply was 50% ( $n = 7/14$ ), urban water supply 38.7% ( $n = 29/73$ ) and there was no statistically significant difference between these two groups [ $\chi^2 (87.1) = 0.511$ ,  $p = 0.475$ ].

The analysis of food taken 48 h before the onset of symptoms revealed that the NoV positive result was most

frequently detected in the patients who ate at home and in kindergarten, while the restaurants were the least common places connected with the infection (Figure 3).

Totally 73.7% of the the children aged 0–7 years had meals in kindergarten 48 h before the onset of acute gastroenteritis 21.1% of the children ate only at home, while 5.3% ate in restaurants. Most patients aged  $\geq 65$  years ate in a medical institution (92.9% , n = 26/28), while only 7.1% at home (n = 2/28).

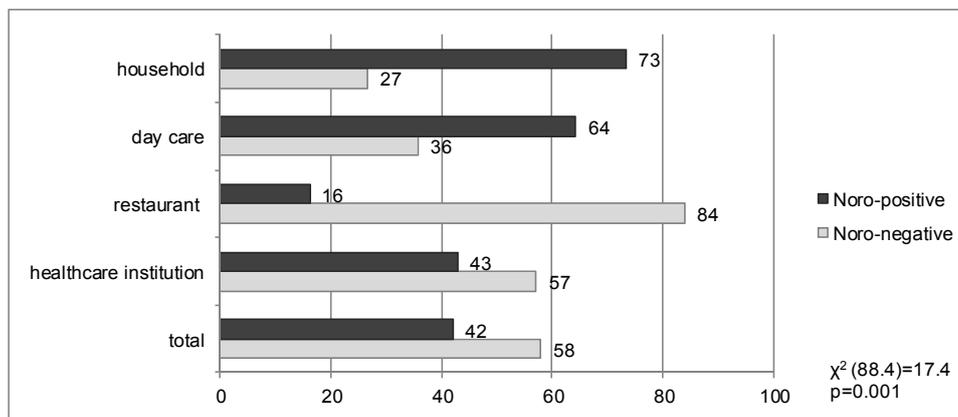


Fig. 3 – The percentage of patients regarding the places of having meal in 48 h before the onset of symptoms.

## Discussion

NoV infect persons of all ages, often causing epidemic outbreaks of acute gastroenteritis as well as sporadic cases. The frequency of NoV infection in outbreaks and sporadic cases of acute gastroenteritis in the South Eastern Europe region ranges from 15% in Bulgaria<sup>15</sup> to 57% in Greece<sup>4</sup>. The results of this study show that overall incidence of NoV infection was 42%; in sporadic cases it was 75%, while in the outbreaks 35.6%.

Outbreaks of acute gastroenteritis caused by NoV were recorded to be the most common in children (two in kindergarten and two in school-aged children in the recreational classes). A high incidence of NoV infection in children aged 5–11 years was also shown in Spain<sup>16</sup>. Similarly, in Greece 57% of patients was NoV positive in the age less than 15 years<sup>4</sup>. This is in agreement with the results of this study where the incidence of infection was 50% in the age group 0–15 years. However, most of NoV-positive children were of even younger age (4–7 years) in outbreaks that have occurred in kindergartens. Sanitary and hygienic conditions in the kindergarten were good, but the characteristics of NoV (resistance in the environment, low infectious dose) probably contributed to the spread of infection by direct contact between the children. In a survey conducted by Bernard et al.<sup>17</sup>, most cases of disease were observed in hospitals (32%), elderly care centers (28%), households (24%) and centers for the care of children (10%).

The other age group at risk for developing NoV infection is people older than  $\geq 65$  years<sup>16</sup>. The outbreak in the medical institution in this study was manifested by acute NoV gastroenteritis mostly in elderly people, mean age of 72

years, who were hospitalized because of exacerbation of their chronic disease. The highest percentage of NoV-positive patients in this outbreak was found in patients with chronic cardiovascular (83.3%, n = 5/6), and neurological diseases (62.5%, n = 5/8). It was pointed out by different authors<sup>18–20</sup> that viral contamination of the environment, the existence of asymptomatic cases (approximately 12%<sup>7</sup>) and prolonged excretion of the virus (up to 10 days) are the most common factors that contribute to infection of elderly patients in he-

alth institutions and elderly care centers.

In this study group there were 39.8% of NoV positive patients with diarrhea, 33% with vomiting, and only 12.5% patients with fever. These symptoms are consistent with previously reported clinical manifestations of NoV infection<sup>16</sup>. The clinical presentation of NoV infection varied in relation to age group. In children under the age of 7 (100%) vomiting was a major symptom of NoV infection. If acute gastroenteritis in children, under the age of 7, was manifested by vomiting, it was 5.3 times more likely to identify NoV in the stool. On the other hand, the occurrence of abdominal pain in the elderly represented 8.2 times greater risk for NoV positivity.

Usually, severe disease occurs in young children, the elderly, and persons with chronic illness<sup>21</sup>. Some authors report that disease can be very serious and sometimes fatal, particularly for the vulnerable population of children under 5 years of age and people  $\geq 65$ <sup>22,23</sup>. The risk for hospitalization and death of patients of  $\geq 65$  years is increased by 20–30% during epidemic outbreaks of NoV, while for the users of centers for care of the elderly, the risk is increased by another 10%<sup>24</sup>. In this study, no deaths from NoV infection were recorded, although difficult cases of acute gastroenteritis were more prevalent in the age group of 0–15 years (with similar frequency of NoV positive and negative cases). These results suggest that the severity of the clinical presentation of viral gastroenteritis is the result of vulnerability of children and elderly for intestinal infections in general.

Although NoV infection occurs with a similar frequency in males and females, present study shows some distinctions associated with gender. The presence of frequent vomiting, more than 4 times, indicated NoV infection in

women with a specificity of 81.4%, while for men the infection was always presented with diarrhea. Similarly, Arias et al.<sup>16</sup> report that abdominal pain and fever were more common in men than women. When analysed according to age groups, men were more often infected in older age ( $\geq 65$  years) and women in the age group including reproductive period (16–65 years). In childhood NoV infection was equally present in both sexes. Since the differences in the number of infected patients according to gender were observed only in adults, the influence of hormonal status on the sensitivity could be expected and might be the subject of future investigation.

The previously published results showed that sporadic cases of NoV infections were more common in the summer months. On the other hand, the season for outbreaks of NoV infection was winter in adults, while in children the outbreaks were reported throughout the year<sup>4, 5, 25, 26</sup>. The occasional amplification of viral activity in the population is explained by the emergence of new viral genotype<sup>27</sup>. In this study, the overall prevalence (sporadic cases and outbreaks) of NoV infection was shown to be higher in winter months.

The present study shows no difference in the incidence of infection in relation to water supply, despite the known fact that hygienic conditions and intense precipitation precede the occurrence of epidemics, especially in summer<sup>4</sup>. A lower recorded incidence of NoV infection after consuming

food in restaurants can be explained by the fact that older children and adults who frequently visit these facilities were less sensitive to NoV in relation to pre-school children and the elderly.

### Conclusion

The results of this study confirm that young children and elderly are the most susceptible to norovirus infection and that infection is more frequent in winter. Diarrhea was the most common symptom followed by vomiting especially in young children. Those who consumed food in restaurants and other public facilities were not at higher risk for norovirus infection.

These results indicate the need for improvement of acute viral gastroenteritis prevention, as well as the need to introduce a better system of surveillance that would include screening for norovirus infection in asymptomatic employees of facilities of collective shelters, and institutions for feeding and medical treatment of children and the elderly. Also, a major contribution to the prevention of viral gastroenteritis outbreaks, can be made through education of physicians in primary health care about vulnerable groups, phenotypic characteristics of norovirus infection in different age groups, as well as the indications and possibilities for rapid testing of this infection.

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Received on January 31, 2014.

Revised on April 3, 2014.

Accepted on April 7, 2014.