Editorial article

*Norovirus* and its increasing clinical importance

*Norovirus y su creciente importancia clínica*

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Over the last two decades, there has been an increasing acknowledgement of the impact on people’s health of infections by *Norovirus*. In the U.S.A. it is considered the most frequent cause of gastroenteritis, producing 19–21 millions of infections, 56,000–71,000 hospitalisations, and 570–800 deaths per year. Moreover, *Norovirus* is considered the main cause of outbreaks and sporadic cases of nonbacterial gastroenteritis in patients of all ages. In industrialised countries, the incidence of this condition among ambulatory patients is estimated to be between 21 and 92 every 10,000 inhabitants, with hospitalisation rates from 1.2 to 2.4 every 10,000 inhabitants and mortality rates from 0.19 to 0.40 every 10,000 inhabitants. Outbreaks mainly take place in health care centres, schools, restaurants, cruises, long-term health care centres, and daytime centres. Only in the U.S.A., the estimated incidence of this disease in cruises is 25.6 every 10,000 inhabitants, constituting the main cause of gastroenteritis.

This disease is more frequently seen in developing countries as a result of poor sanitary and hygienic conditions, although there are discrepancies in terms of rates, probably due to the difficulties in reaching a diagnosis, given the concomitance of other gastrointestinal diseases, both bacterial and parasitic.

At-risk population: the incidence rate of this disease is very high among children under 5 years of age (2140 every 10,000 inhabitants); this virus is responsible for 18% of diarrhoea processes and constitutes the second cause of endemic diarrhoea within this population after rotavirus. Population at risk also includes people over 65 years of age and immunosuppressed patients.

Among humans, the virus has a person-to-person transmission (faecal-oral and vomit-oral) or, indirectly, through the consumption of foods and water or through environmental transmission. Zoonotic transmission is unusual, since this virus is highly selective in terms of its hosts. Person-to-person transmission is responsible for 90% of *Norovirus* outbreaks in health care centres. In order for food and water consumption and environmental transmission to be viable, the food, water or faeces in question must have been previously contaminated with viral particles from an infected human.

In Europe and the U.S.A., an approximate 10% and 26%, respectively, of *Norovirus* outbreaks are estimated to be caused by food transmission, with low hospitalisation and mortality rates (1% and 0.01%, respectively), the main source of food poisoning being the hands of the subject handling food, followed by raw vegetables and molluscs consumption.

*Norovirus* was discovered in 1972, while studying a gastroenteritis outbreak in an elementary school located in Norwalk (Ohio, U.S.A.) by Kapikian et al. It belongs to the *Caliciviridae* family, which includes five other types of viruses: *Sapovirus*, *Lagovirus*, *Vesivirus*, *Becovirus* and *Recovervius*. It is small (27–40 nm), unwrapped and icosahedral viral. Its genome consists of a simple RNA molecule with a 7.5 kb positive polarity, and to date, it has not been possible to isolate or cultivate human *Norovirus* in cellular cultures.

Within the *Norovirus* type of virus, there are six gene groups: GI, GII and GIV are mostly isolated in humans, whereas GIII, GV and GVI are isolated in animals. These gene groups are, in turn, divided into more than 38 genotypes based on the amino acid sequence variation for capsid protein VP1, and those with a variation below 15% belong to the same genotype. Typically, there is a considerable number of different genotypes co-circulating, and they vary significantly year after year; however, due to unknown reasons, a unique and predominant viral strain has appeared, spreading widely and causing most cases. Since 2002, the gene group GII and variants of genotype GII.4 within this group are responsible for most gastroenteritis outbreaks, including pandemics and sporadic cases. However, this does not always take place, as seen in the study by Manso et al., who noted a higher prevalence of gene group GI over II, and the increase of unusual genotypes such as GII.14. During the last decade, new variants of genotype II.4 (thus classified for having differences >5% in the protein VP1 amino acid sequence) have appeared every 2–3 years, replacing viral strains that had prevailed before. A clear example is the global replacement of variant GII.4 New Orleans 2009 for variant GII.4 Sydney 2012. It is believed that genotype II.4 might suffer a sequential evolution process similar to that suffered by flu viruses. Finally, there is an association between genotypes and types of transmission: GI is associated with water or food consumption, but G4.II is associated with person-to-person transmission at health care centres.

*Norovirus* is considered a highly infectious virus for a number of reasons: the infectious dose is very low (approximately 10 viral particles) and high viral loads are detected in faeces (1 × 10^{10})

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* Please cite this article as: Hernández Porto M, Lecuona M. *Norovirus* y su creciente importancia clínica, Med Clin (Barc). 2015;144:207–208.
* See related content at doi: [http://dx.doi.org/10.1016/j.medcle.2015.05.042](http://dx.doi.org/10.1016/j.medcle.2015.05.042)
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copies of RNA(g). Virus excretion may take place in asymptomatic carriers, in symptomatic carriers before and after clinical manifestation, it may persist up to 2 weeks after symptoms disappeared,\(^5\) diarrhoea may even persist and the virus may even continue to spread during months in transplanted patient.\(^6\) It is a very stable virus under adverse environmental conditions. Due to the fact that its infectious capacity remains in temperatures of \(-60\,\text{°C},\) acid pH, they are relatively resistant to disinfectants such as ethanol and chlorine, and they can survive 2 weeks on surfaces.\(^1,6,7\)

Even though infections take place throughout the year, in temperate climate areas they seem to have a higher incidence during wintertime. However, outbreaks may present different seasonal patterns: in summertime, they are mostly seen in cruises, while in wintertime, they are mostly seen in health care centres.\(^2\) Besides, there are certain seasonal variations according to the gene group of the responsible virus.\(^4\)

The gastroenteritis caused by these viruses appears suddenly after a 24 h incubation period (limits 12–72 h). In general, the clinical condition lasts from 12 to 60 h, and it is characterised by self-limiting diarrhoea, nausea, vomiting and abdominal pain, being vomiting and diarrhoea the more prevalent symptoms among children and adults, respectively, and with cases of vomiting where there is no diarrhoea.\(^7\) Nevertheless, not every infected patient develops the disease;\(^4\) in fact, \textit{Norovirus} is frequently detected in the faeces of healthy subjects.\(^5\)

Infection susceptibility has been associated to the presence of H blood group hydrocarbonated antigens, which also express in gastrointestinal epithelial cells, acting as receptors of the virus in the intestine. Therefore, the absence of secretion of these antigens is associated with the resistance to infection by \textit{Norovirus}.\(^8\)

It is possible to develop immunity to certain genotypes, with an estimated duration of 4–8 years. However, the large variety and the emergence of new viral strains may trigger successive infections during a lifetime.\(^15\) Children are more prone to get infected than adults, due to their lower hygiene level and their higher social contact.\(^15\) Moreover, unlike adults, children tend to get infected by several genotypes at once.\(^11\) All of these elements turn said population into a very important link in the transmission chain, along with health care workers, and thus, developing a vaccine against this virus would be very beneficial, both directly and indirectly.

The laboratory diagnosis may be obtained by means of enzyme-linked immunomethods and/or molecular biology techniques. The former have an elevated specificity, of approximately 100%, and do not present cross reactions with other viruses. However, their sensibility is estimated in 50–80% and varies according to the gene groups causing the disease. Furthermore, the storage conditions of these samples may affect the sensibility of these techniques, improving them when samples are subject to a freezing/unfreezing process, due to the subsequent elimination of inhibitors.\(^16\) Finally, the molecular biology technique from the chain reaction of the reverse transcriptase polymerase is the reference procedure for the diagnosis of infections by \textit{Norovirus}.\(^12\)

\textit{Norovirus} asks for a special mention in health care centres, and, specifically, in long-term stay health care centres. Although the elderly population within the community is not at high risk of contracting this infection, the situation is different for those staying at these health care centres, where the infection rate amounts to approximately 55%, and the mortality rate is elevated\(^9\) (estimated in 6 every 10,000 inhabitants). This is due to the high person-to-person viral transmission, but cases are isolated both in symptomatic and asymptomatic patients and health care workers, as shown by the study conducted by Moreno et al.\(^18\) published in this edition, since comorbidities, cognitive deficits and digestive disorders affecting this population make it difficult to identify cases, it is necessary to amplify studies within these populations to quickly identify cases and intervene accordingly in order to control the infection.\(^19\)

References