Norovirus Infections and Preventive Measures

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Abstract

Characteristics of the ribonucleic acid (RNA) virus family: Viruses with RNA as genetic material with a potential for rapid spread, cause severe or potential lethal diseases in both animals and humans. They are responsible for well-known human diseases such as measles, polio, hepatitis C, influenza, and gastroenteritis. Preventive measures against RNA viruses can be challenging, especially the development of vaccines, due to their high mutation rate compared to DNA viruses.

N*orovirus specific features:* Noroviruses, also referred to as Norwalk-like viruses, are non-enveloped, single-stranded RNA viruses. Their multiple transmission routes (faecal-oral, contaminated water, contact to contact), low infectious dose, high shedding titre as well as their environmental stability confer them their high virulence status.

E*pidemiology of Norovirus infections:* Outbreaks of human norovirus infections, detected in all age groups, have become in recent years one of the major health issues, causing sporadic and acute gastroenteritis. Norovirus gastroenteritis infections characterized by rapid onset of symptoms such as diarrhoea, vomiting, short duration and short incubation period, represent today a significant rise of medical and financial costs worldwide.

Preventive measures: In this review, we discuss norovirus infections, and their preventive measures. Vomiting and toilet flushing following diarrhoea can result in the formation of droplets and aerosols, contributing to the transmission of the virus. Importance of environmental disinfectants, hand hygiene options, and limited exposure to infectious individuals are crucial factors in preventing further outbreaks. Moreover, the development of a vaccine against this pathogen may provide the population with a sustainable solution against spreading of infections.

Key words: Noroviruses, Non-enveloped single-stranded RNA viruses, multiple transmission routes, low infection dose, preventing outbreaks

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INTRODUCTION

Human norovirus is nowadays, in all age groups, especially in children, the leading cause of sporadic and epidemic gastroenteritis (Prasad et al., 2016). This inflammation of the gastrointestinal tract, particularly affects the stomach and small intestine (Munnink and Hoek, 2016).

Noroviruses are infectious, non-enveloped, single-stranded RNA viruses, subdivided into seven genogroups, furthermore divided into multiple genotypes based on their capsid proteins. Genogroups GI, GII, and GIV have been detected in humans, with GII.4 being the predominant cause of gastrointestinal outbreaks (Hall et al., 2011). Its counterpart, GV, has been identified in the murine family.

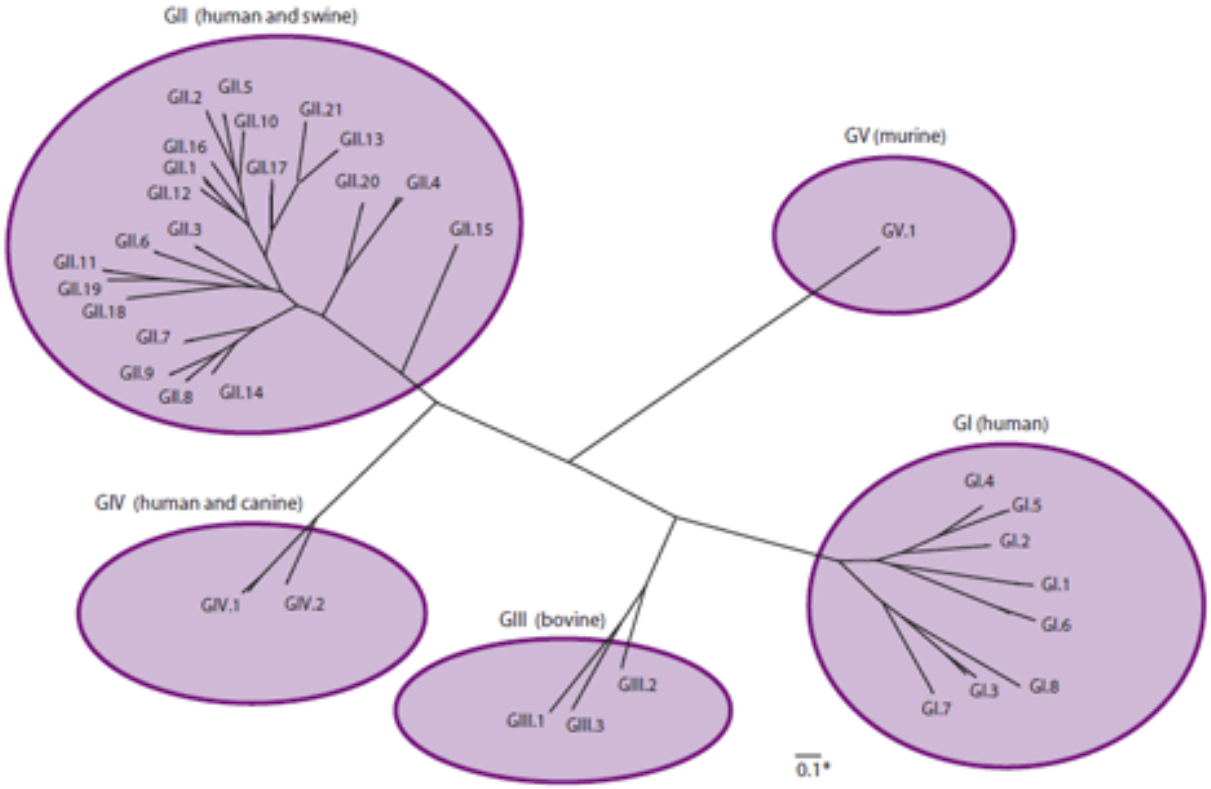

Figure 1: Classification of noroviruses into 5 genogroups (GI--V) and 35 genotypes based on sequence diversity in the complete capsid protein VP1 (human strains cluster within GI, GII, and GIV) (Hall et al., 2011)

Noroviruses use different strategies to reduce the efficiency of the immune system. Such strategies include the actions of p22 and p48, which are non-structural proteins to impair cellular protein trafficking and secretory pathways. p48 and p22 possess anti-secretory properties. Both contribute to Golgi apparatus disassembly and inhibition of the cellular secretory pathway. Disruption of the secretory pathway results in an imbalance of ions and fluids between the epithelial barrier and the intestinal lumen, leading to the diarrhoeal symptoms.

Additionally, another possible mechanism is via VF1 protein, which inhibits cytokine induction and the ability of minor structural protein VP2 to regulate antigen presentation (Karst, 2010).

People that failed to develop last-long protective immunity against human norovirus developed lasting symptoms. This is the case for immunocompromised patients (patients suffering from diabetes, HIV, etc.) and elderly. However, symptoms in healthy individuals are non-lasting, but they continue to shed low levels of virus for several weeks indicating an incomplete clearance by the immune system, thus diagnostic relevance of viral load.

Norovirus infections also represent an important global economic burden, with an estimation of cost approximately equal to US$ 44 billion, from which US$ 4.2 billion being associated with healthcare systems (Bartsch et al., 2016).

EPIDEMIOLOGY

Human norovirus infections affect both children and adults and can be life-threatening, especially in immunocompromised and elderly patients due to their immune system inability to fight infections. Following the development of the vaccine against rotavirus in children, norovirus has become the most common pathogen that causes gastroenteritis in this age group.
The transmission of the virus is through faecal-oral, oral-oral, direct person-to-person or indirect through faecal or emesis droplets, contamination of food, water, fomites and environment (de Graaf et al., 2017).

Norovirus, once within the organism, attaches to histo blood group antigen (HBGAs) that it recognizes as cellular attachment factors (Mallagaray et al., 2015).

Asymptomatic infections are most commonly occurring in children. This virus means usually a year-round type of infection, with an increased frequency of occurrence during the winter season. The virus has a short incubation period (from 6 to 48 hours) and the disease typically lasts for approximately 12 to 60 hours. This virus causes approximately half of all infectious foodborne outbreaks, with roughly 23 million cases per year (Karst, 2010).

Figure 2 shows the total number of norovirus outbreaks reported between 2009 and 2018 in some states of the USA. It can be observed that in the first week of August there were approximately 10 outbreaks, which steadily increased throughout the months, until a peak of 90 outbreaks during March. Following this subsequent peak, outbreaks began to decrease.

There were approximately 775 norovirus outbreak cases reported between August 1, 2017 and February 12, 2018 in certain US states only. Contrasting to these numbers, in the last whole year around 770 outbreaks were reported. The number of outbreaks reported this year is higher than the ones reported during the past 7 years, confirming the rapid spreading of infections (Centers for Disease Control and Prevention, 2018).

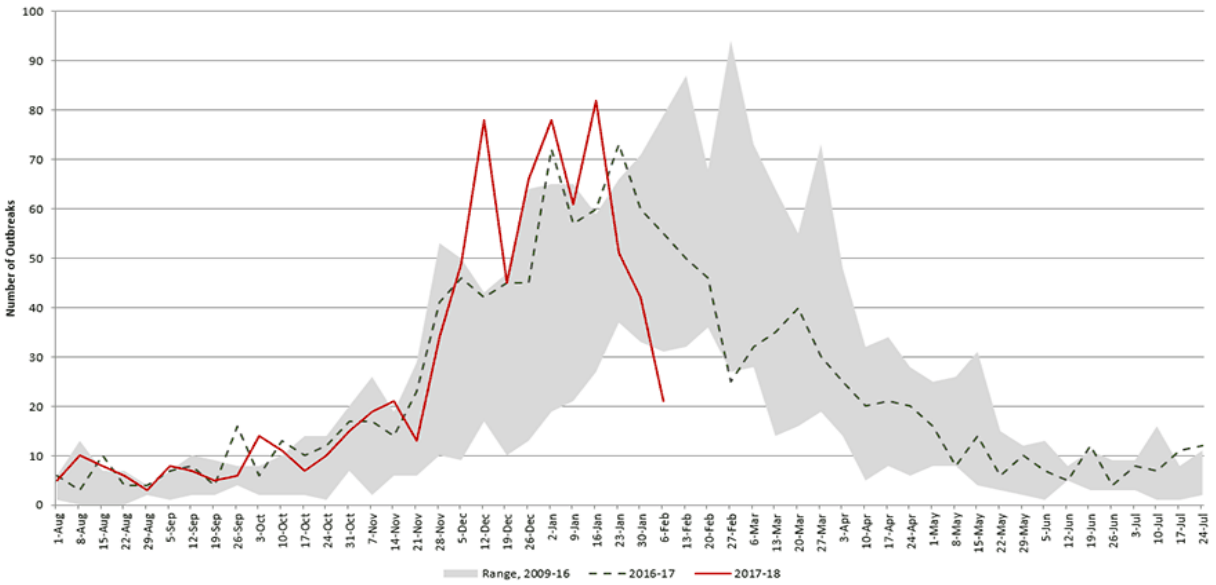

Figure 2. Suspected and confirmed Norovirus outbreaks reported by the State Health Departments in Massachusetts, Michigan, Minnesota, Ohio, Oregon, South Carolina, Tennessee, Virginia, and Wisconsin to the National Outbreak Reporting System (NORS) by week of illness onset, 2009-2018† (Centers for Disease Control and Prevention, 2018)*

Norovirus outbreaks can occur in many different settings *(Table I),* mainly closed ones, such as health care facilities, where there are infected patients, staff members, visitors and contaminated food. Illnesses caused by this virus can be more severe and possibly fatal among immunocompromised patients such as the elderly or those with underlying diseases such as diabetes and HIV patients. In restaurants and catered events, norovirus can be transmitted from contaminated foods while on cruises due to close proximity with infected individuals, similarly to schools or other institutional settings.

Table I

Setting of Norovirus outbreaks reported through the National Outbreak Reporting System (NORS), 2009-2012

Exposure settings	Number of outbreaks	Percentage of outbreaks
Health care facility	2189	62.7%
Restaurant or banquet facility	771	22.1%
School or day-care facility	214	6.1%
Private residence	69	1.9%
Other / multiple settings	251	7.2%

Data on specific settings are restricted to outbreaks with a single exposure setting; for foodborne outbreaks, setting refers to the setting where the implicated food was consumed (Source: Hall et al., 2011)

CLINICAL FINDINGS

In acute conditions, there is a sudden onset of projectile vomiting (more than two episodes in 24 hours), watery and non-bloody diarrhoea (more than 3 times in 24 hours), abdominal cramps, nausea and low grade fever. Norovirus is a mild and self-limiting illness. However, in immunocompromised patients, especially after transplants, the illness may be severe due to the decreased immune system response (Lopman et al., 2004).

DIAGNOSTIC TESTS

Definitive diagnosis based solely on clinical findings cannot be made as most symptoms are non-specific, therefore identification and confirmation is made by detection of viral capsid antigens in stool samples using Enzyme-Linked ImmunoSorbant Assay (ELISA). Specimen collection involves the collection of fresh stool sample in a clean container that needs to be refrigerated at 4°C after collection. Diagnostic methods focus on detecting viral RNA antigen and majority clinical virology labs use Real-Time Reverse Transcription- Polymerase Chain Reaction (RT-qPCR) assays (Rabenau, 2003; Vinjé, 2014).

The sensitivity of this method has the ability to detect from a range of 10 to 100 norovirus copies per reaction. Viral identification focuses on differentiating between genogroup I and genogroup II norovirus by using a set of different oligonucleotides primer sets to visualize and observe hybridization. This assay provides us with a quantitative estimate of viral load (responsible for the difference between symptomatic and asymptomatic patients (Kabue, 2016) by using a range of specimens such as stool, vomitus, and food (Kirby et al., 2016).

TREATMENT

Treatment of a noroviral infection is symptomatic only. Therefore, as one of the symptoms is diarrhoea, the treatment includes rehydration by oral and intravenous (IV) fluids. Subsequently, since electrolytes are lost during diarrhoeal episodes, electrolyte replacement therapy would be a possible treatment to maintain the osmotic balance of blood and extracellular fluid (Division, 2008).

SOLUTIONS

Infection control principles of noroviruses infections include protective and disinfection methods and the development of antiviral drugs and vaccines.

CHALLENGES

On the one hand, the cellular targets of the virus in the host organism intestinal mucosa are still not completely defined, making the development of antiviral drugs challenging (Kaufman, 2014).

On the other hand, there has been no vaccine developed due to the genetic and antigenic diversity of noroviruses. Due to their high mutation rate, contrasting with DNA viruses, the targeting of specific strands is strenuous. Moreover, the absence of passive immunity in patients that have been affected also represents a challenge in the development of effective vaccines (Kaufman, 2014).

OUTCOMES

The best preventive measure of noroviral infections is hygiene. Appropriate hand hygiene remains one of the most important steps in preventing norovirus infections and controlling its transmission. This is achieved by appropriate handwashing with running water, together with plain or antiseptic soap, for at least 20 seconds.

In addition, isolation of the infected patients and limited contact with the outside environment interrupts transmission of the virus and further propagation of the contamination to the population, which potentially could have led to outbreaks due to uncontrolled spread of the virus.

Chemical disinfectants, particularly containing sodium hypochlorite, are used to discontinue the spread from contaminated environmental surfaces, particularly from bathrooms, handles and kitchen surfaces. Norovirus remains viable for up to 12 days in carpeting and other environmental surfaces.

Staff members can also help prevent the spread of norovirus by wearing masks and gloves when cleaning areas, which could be contaminated by faeces or vomitus (Barclay, 2014).

Murine noroviruses are used as a model for research in development of antiviral drugs and vaccines. This is due to the similarities between human and mouse infections, in terms of genetics, molecular and pathogenic properties, thereby making murine norovirus models the ideal candidate for antiviral and vaccine research (Kaufman, 2014).

Development of antiviral drugs is based on targeting the norovirus glycan-binding site. In effect, norovirus, once within the organism, attaches to the histo blood group antigens (HBGAs) that it recognizes as cellular attachment factors (Mallagaray et al., 2015). Blocking those sites would make binding of the virus to the intestinal mucosa not possible and therefore prevent infection by the virus.

Promising vaccine development relies on recombinant vaccines based on diverse genotypes.

As of today, two vaccines Takeda's TAK-214 injectable vaccine – GI.1/GII.4 Bivalent Virus-Like Particle and Vaxart's oral vaccine - still under clinical trial, are the two most promising vaccines against Norovirus.

CONCLUSION

Appropriate hygiene procedures constitute nowadays the leading preventive measure against norovirus infections. However, focus on antiviral drugs discovery and vaccine development is today a promising way in reducing and preventing norovirus infections. Antiviral therapy, especially in immunocompromised individuals, will not only contribute to the decrease of the burden on patients, but also to avoid further spreading of the disease to high risk patients. It could also be used as prophylactic measure, especially in individuals living in closed environments (Kaufman, 2014).

The development of a vaccine against this family of pathogens may provide the population with a sustainable solution against spreading of infections. However, due to the virus high mutation rate, a new norovirus vaccine would need to be developed every couple of years in order to keep up with the rapidly changing strains.

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