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Review Article

Norovirus: Epidemiology, Clinical Impact, Transmission, and Strategies for Prevention and Control

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Abstract

Norovirus is a member of the family Caliciviridae. The family of Caliciviridae consists of several distinct groups of viruses that were first named after the places where outbreaks occurred. These small, non-enveloped single-stranded RNA viruses cause self-limiting disease in healthy individuals within 10-51 hours after exposure. Norovirus infection can cause the sudden onset of vomiting and diarrhea. It is highly contagious and commonly spreads through food or water that is contaminated. The primary mode of transmission is fecal-oral. Sources include ingestion of contaminated water or food or direct transmission from a contaminated surface or infected person. The virus is resistant and can stay on surfaces even after disinfecting. Common symptoms of norovirus infection include nausea, vomiting, and diarrhea. These could lead to clinically significant dehydration, requiring hospitalizations. In addition to clinical effects, norovirus also has a major financial impact in developed nations. The spread of the infection is facilitated by its low-infecting dose (between 20 and 1,000 viral particles to infect a person), prolonged excretion in stools (up to 2-4 weeks) and relative stability in the environment, food and water, as compared to other viruses. Generally to prevent norovirus: Clean environment, Isolation of infected people, Frequent and clean hand washing, Avoid contaminated food and water, Well cleaned fruits and vegetable, void oysters, omit or feaces should be cleaned and disinfected, Surrounding should be neat and clean, Disinfect virus containing area, Stay home from work, Avoid traveling, Wash and clean the items like bedding clothes which may contain viruses, wide range of product like disinfectant and antimicrobial solutions are registered at EPA, which gives better results.

Keyword

Caliciviridae, Environment, Norovirus

1. Introduction

Norovirus (previously called “Norwalk-like virus” or NLV) is a member of the family Caliciviridae [13, 55]. The name derives from the Latin for chalice-calyx-meaning cup-like, and refers to the indentations of the virus surface [55]. The family of Caliciviridae consists of several distinct groups of viruses that were first named after the places where outbreaks occurred [44]. The first of these outbreaks occurred in 1968 among schoolchildren in Norwalk, Ohio [14]. Norovirus (NoV) is well established as a major cause of viral gastroenteritis across all age groups [1].These small, on-enveloped

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single-stranded RNA viruses cause self-limiting disease in healthy individuals within 10-51 hours after exposure [18]. Norovirus infection can cause the sudden onset of vomiting and diarrhoea. It is highly contagious and commonly spreads through food or water that is contaminated [19, 34]. Chance of infection increases through close contact with infected persons [53, 49].Generally the infection begins after 1248 hrs after exposure. Symptoms last to 3 days. Most cases recovery is possible without treatment. Peoples, specially adults and infants require medical care and attention [9, 24].

Common symptoms of norovirus infection include nausea, vomiting, and diarrhea. These could lead to clinically significant dehydration, requiring hospitalizations. In addition to clinical effects, norovirus also has a major financial impact in developed nations [47, 43]. Replication of NoV may not be restricted to enterocytes. Of all the potential experimental models studied to better understand the pathogenesis of noroviruses, the only norovirus which replicates in vitro is the murine NoV. This agent replicates in macrophages and dendritic cells derived from cultures of bone marrow cells and in mouse macrophage cell lines (RAW 264.7) [59]. The murine NoV-1 infection in knockout mice for recombination-activating gene 2 (RAG2) and signal transducer and activator of transcription 1 (STAT-1) genes, RAG2/STAT-1, showed tropism for haematopoietic cell (macrophages and dendritic cells) and development of systemic disease. Clinical signs include pneumonia, hepatitis, encephalitis, and vasculitis in brain capillaries and can be observed even in inoculation in serial passages [27, 58, 46]. It was also demonstrated that the murine NoV can naturally infect wild and immune deficient mice. The infection also occurs following oral or intranasal inoculation. However, although other strains of murine NoV have already been isolated from faecal samples of infected mice, it is not yet clear whether this virus is an effective enteric pathogen in this animal species [21].

The spread of the infection is facilitated by its low-infecting dose (between 20 and 1,000 viral particles to infect a person), prolonged excretion in stools (up to 2-4 weeks) and relative stability in the environment, food and water, as compared to other viruses [14, 30]. Generally to prevent norovirus: Clean environment, Isolation of infected people, Frequent and clean hand washing, Avoid contaminated food and water, Well cleaned fruits and vegetable, Avoid oysters, omit or feaces should be cleaned and disinfected, Surrounding should be neat and clean, Disinfect virus containing area, Stay home from work, Avoid traveling, Wash and clean the items like bedding clothes which may contain viruses, wide range of product like disinfectant and antimicrobial solutions are registered at EPA, which gives better results (Centers for Disease Control and Prevention [7].

2. Literature Review

2.1. Etiology

There are seven known genogroups of norovirus, but only genogroups I and II are responsible for the vast majority of human cases. An extremely small number of cases are attributed to norovirus GIV. While both genogroups I and II are both clinically relevant, a specific strain from genogroup II, norovirus GII.4, is responsible for the majority of human outbreaks. Additionally, illness produced by GII.4 strains tends to be more severe and is associated with higher mortality than illness from other strains. Studies have shown that waterborne outbreaks tend to be associated with genogroup I strains, while healthcare-related and winter outbreaks are more likely to have genogroup II strains as a causative agent. Noroviruses are classified into genogroups and genotypes based on amino acid diversity in VP1 and ORF1 proteins [33].

The primary mode of transmission is fecal-oral. Sources include ingestion of contaminated water or food or direct transmission from a contaminated surface or infected person. The virus is resistant and can stay on surfaces even after disinfecting. The virus also has a low viral inoculum to cause infection. As few as ten viral particles are needed to cause infection [4]. Highly contagious virus are shed in the faeces and vomit of infected person, Eating/drinking contaminated food or water, Touching your hand to mouth after contact with contaminated substances, He breathe of the infected person with has virus particles, Unhygienic habits like unwashed hands, uncleaned washrooms [40].

2.2. Epidemiology

The transmission of NoV occurs predominantly by the faecal-oral route for both human and animals. Differently of other viruses that depend on high virus concentrations for causing disease, NoV requires a low infectious dose (<10-100 virions) to establish the infection [3]. NoV showed a long-term survival in suspensions at environmental temperature, indicating that transmission by routes involving surface or drinking water, moisture fomites, or workplace surfaces is possible [10].

Additionally, the respiratory tract has been considered as another natural route of NoV transmission by the inhalation of aerosolised particles in vomitus [3]. NoV is considered a waterborne virus of primary concern, together with other virus agents, such as hepatitis A virus, hepatitis E virus, adenovirus, astrovirus, enterovirus, and rotavirus [14]. Outbreaks of human NoV infection were associated with contaminated drinking water in different countries [10]. Studies revealed a widespread occurrence of human enteric viruses in both individual and municipal wells, showing that groundwater can be pathogen contaminated, including with NoV, and that groundwater-sourced public water systems

producing water without disinfection can represent a risk of waterborne illness [12], including for animals.

The faecal contamination in water, food, and fomites and the direct individual- to- individual contacts are responsible for the major occurrence of gastroenteritis outbreaks determined by NoV. Since the surface/drinking water and groundwater quality can be affected by multiple sources of pathogens, vegetables also can be contaminated with NoV by irrigation with contaminated water. The food may be contaminated with virus particles since its production or crop, as in the case of oysters and fresh produce, or is contaminated on site preparation by means of handling by infected people, as in the case of cold food, sandwiches, and salads [3]. High rates of secondary attacks (≥30%) among people who had contact with infected individuals lead the outbreak amplification in places where there is overcrowding, such as hospital wards, cruise ships, and shelters [4].

In addition to the low infectious dose required for NoV transmission, continuous NoV infection is a result of the difficult elimination of the virus due to its resistance to disinfectants and many chemical products, the facilitated survival by organic debris of the clinical specimens (faeces/vomitus) in which the virus is shed, and the NoV aggregate formation that protects the virus from the environmental conditions [52]. In symptomatic animals, the virus shedding appears shortly before or during the first clinical signs and is prolonged, even after resolving of the symptoms [46]; the individuals with asymptomatic NoV infection also shed the virus. The period of virus shedding may range between 5 and 60 days, with a medium of 30 days. In human NoV infection, the virus is excreted in high amounts; the peak of virus RNA titres may vary from 109 to 1012 genomic copies per gramme stool and may be 1-2 log lower in symptomatic and asymptomatic individuals, respectively [36]. These facts and the NoV infectious stability for weeks or months in the environment may facilitate the NoV persistence and the virus transmission among infected and susceptible hosts [33].

The murine NoV is one of the most prevalent pathogens of murine, being a causative agent of systemic infection and lethal disease in immunodeficient laboratory mice [27]. However, murine NoV strains were also identified from immunocompetent laboratory mice with silent infection [21, 59]. As the murine NoV is the only norovirus that replicates in cell culture, this virus is considered an excellent model to comprehend the basic mechanisms of norovirus replication in vitro and in vivo [58]. NoV has been detected in diarrhoeic and non-diarrhoeic faecal samples of beef and dairy cattle with young animals being more frequently described with the infection. High seroprevalence of bovine NoV has been reported from cattle herds in Europe and North America. The bovine NoV GIII.2 was prevalent in most of the studies. The porcine NoV was first reported in Japan, where the virus RNA was recovered from caecum content of asymptomatic pigs [50].

2.3. Transmission

HuNoVs are resistant in the environment and can be transmit-ted faecal-orally via different routes, notably by the consumption of contaminated food or water, by contact with contaminated people, objects or surfaces, or even via vomit-derived aerosols [33]. Although NoVs have been detected in animal feces, no evidence of zoonotic transmission has been reported so far [33]. River waters are at risk for HuNoV contamination as they usu-ally receive effluents of wastewater treatment plants, which aremore efficient for removal of bacteria rather than viruses. Several studies throughout the world have detected HuNoV in river water used for irrigation as well as in drinking water [33]. While in the Amazon region, HuNoVs have been molecularly detected only at low frequencies in stream water samples from the city of Man-aus, they have been shown to be responsible for AGE outbreaks following consumption of contaminated water from the river, poor hygienic behavior, or recreational activities in contaminated water [33]. In Guatemala, an AGE outbreak occurred in a student group after a school trip and its origin was traced to contaminated water consumption [48].

HuNoVs have been also detected in water from Argentinean river with 7.7% of positive samples from the Luj án-River and up to 80.8% of positive samples from the Matanza-Riachuelo River in Buenos Aires [33]. This study also showed that faecally contaminated waters frequently involve multiple genetically divergent strains. In the same country, in a study conducted on eight AGE outbreaks due to HuNoVs, three outbreaks were attributed to a waterborne origin [28], confirming that HuNoVs can constitute an issue for safe water supply. Also in Colombia, HuNoVs have been detected in two samples from freshly treated potable water [10]. In the region of Antofagasta, Chile, AGE cases have beenreported wherein HuNoVs were found both in stool samples and in environmental samples, leading to a revision of the rules concern-ing wastewater usage for irrigation of vegetables, especially those habitually consumed raw [25]. In Mexico, the virus was detected during spring in estuary waters [19].The different stages of the food production (at pre-harvest, harvest and post-harvest levels) are at risk for HuNoV contamination [33]. In Rio de Janeiro, Brazil, HuNoVs were detected in six out of nine lettuce samples collected from supermarkets, food services and restaurants [19], mirroring previous observations in other countries [56, 52]. In Chile, foodborne AGE outbreaks often occur following consumption of contaminated seafood products [42]. Seafood constitutes a major food supply in Latin American countries and shellfish, in particular, have been shown to concentrate HuNoVs in their digestive tissues by filtration and concentration through specific binding [41, 29].

Moreover, an underestimation of the real burden of foodborne and waterborne HuNoV infections probably exists due to the frequent absence of an active surveil-lance system to identify and report HuNoV outbreaks in most Latin American

countries [44]. Due to their low infectious dose and high environmental stability, HuNoVs are highly transmissible, rendering the person-to-person transmission route the most efficient, especially in (semi)-closed communities [33]. Sharing the same contaminated environment can obviously facilitate the transmission of this virus as exemplified by an AGE outbreaks with highly efficient person-to-person transmission reported in Peru [15], in Argentina [31] and in Brazil [29].

Furthermore, the person-to-person transmission route facilitates geographical extension of outbreaks caused by contaminated food as observed in Antofagasta, Chile [14], and in outbreaks involving Latin American travelers [54, 20]. In Chile, a prevalence of 12.3% for HuNoVs in AGE outbreaks has been found, with positive detection in samples from wastewater treatment plants but negative results in potable water samples collected from households [38]. In this country, several outbreaks caused by HuNoVs have been reported from closed communities such as childcare centers, schools and hospitals, while a smaller fraction was reported to occur in restaurants [5].

2.4. Pathogenesis

After norovirus was taken orally to the body, it replicates in the upper intestinal tract (duodenum and upper jejunum). A broadening and blunting of the villi of the intestine occurs. Norovirus infection alters enzyme activity in infected intestinal cells. Transient malabsorption of fat, d-xylose, and lactose is reported during experimentally induced norovirus illness [17, 11]. Major shedding of norovirus from infected cells goes to intestinal lumen, but norovirus RNA is detected in serum and cerebrospinal fluid also [23]. Although the usual/actual method of norovirus pathogenesis is yet needed to be elucidated, it is thought that enteric infection in gnotobiotic piglets and primates when administered by the intravenous or oral route causes gastroenteritis [23, 42]. Expression of HBGA on intestinal cells is needed for virus attachment. Relation between HBGA and norovirus is complicated: the types of HBGA, norovirus strains, volume of norovirus and binding activities in host are interrelated. Non secretor of HBGA is less susceptible to norovirus infection. GII.4 strains, such as GII.4 2006b (Den Haag) and GII4 2012 (Sydney) strains, which cause outbreak worldwide, usually bind to all types of HBGA. However, how HBGA facilitates norovirus to enter into target cells, whether it is an attachment ligand only, and whether it plays a critical role of functional receptor, is not yet clear [17, 52, 60]. Human immune response to norovirus infection also remains unclear. One reason for this obscurity is that human norovirus does not grow in cell culture. Unlike rotavirus infection, adults are found susceptible to recurrent norovirus infection even they have antibodies to norovirus. Probably, neutralizing antibodies to norovirus do not persist for long time, or antibodies to one genotype/strain may not be effective against others. Paradoxical evidence has demonstrated that norovirus infected volunteers suffering from diarrhea showed high level of antibody in convalescent sera compared to those without diarrhea [16]. Recent study showed that antibody avidity and blocking antibody are surrogate measurement of protecting norovirus [18, 16, 51, 22].

2.5. Clinical Sign of Norovirus

NoV infection can be symptomatic or asymptomatic; however, the pathogenesis of norovirus in humans and animals is not fully clarified. The incubation period after exposure to NoV is short, varying between 24 and 48 h. Symptoms of infection include acute enteritis with non-haemorrhagic diarrhoea, vomitus (characteristic sign in outbreaks), nausea, anorexia, abdominal pain, and mild fever. However, asymptomatic infections occur in one third of individuals experimentally infected. The disease duration is short (12-60 h) and self-limiting; however, immunosuppressed patients may have chronic diarrhoea and excrete viruses for months or years [28]. Previous studies with NoV performed in volunteers showed that the target cells for virus replication are primarily enterocytes of the proximal portion of the intestine, leading to mal absorption diarrhoea. Although the intestinal epithelium appears to remain intact, there are specific histo pathological lesions by infection of human NoV in the jejunum, including atrophy in intestinal villi, breakdown of intestinal epithelial cells, hyperplasia crypt cells, and vacuolated and mononuclear inflammatory infiltrate in the lamina propria of villi.

The mal absorption is related to the shortened microvilli and decreased brush border enzyme activity, both observed in acute infection [28]. Bovine NoV has been detected in diarrhoeic and non-diarrhoeic cattle faecal samples. Newborn calves that were inoculated with the bovine NoV GIII.1 (Jena agent) by the oral route presented severe diarrhoea in a very short incubation period [41]. Experimental infection with the bovine NoV GIII.2 (Newbury agent-2) showed calves presenting diarrhoea 3-4 days postinoculation (dpi), withshort duration (1 day), and no diarrhoea was observed after the re-challenge of the calves [25]. This and other bovine NoV experimental-based studies showed that infected calves presented reduced appetite at the fourth and fifth dpi, non-haemorrhagic enteritis, mild to moderate diarrhoea, transient anorexia, and/or xylose malabsorption; discrete or no diarrhoea was observed in conventionally kept calves at 1-8 days of age. The rectal temperatures were between 37 and 40 ℃, with pulse and respiratory rates kept within normal ranges [25, 41].

Infections with both bovine NoV genotypes lead to the villus atrophy and crypt hyperplasia in the proximal small intestine [20, 41]. Other enteric virus agents, such as bovine rotavirus and Torovirus, infect primarily the tips and bases of villi; however, an experimental study with the bovine NoV GIII.1 showed that this virus infects all the enteroabsorptive cells. Since the bovine NoV GIII.1 causes severe villus atrophy and loss of mature enterocytes, it was suggested that these

facts may limit the infection duration due to the reduction in the number of susceptible cells to the virus infection [41]. On the other hand, the bovine NoV GIII.2 experimental studies showed that calves shed the NoV in faeces for at least 30 days after inoculation, regardless of the faecal consistency (diarrhoeic or not) and the duration of the clinical signs [25, 26]. Diarrhoea and prolonged faecal shedding of bovine NoV GIII.2 were observed even in calves that were not presented with major histological changes in the intestine, including no necrosis of intestinal epithelium, villous atrophy, or inflammatory lesions [26].

The importance of the porcine NoV as diarrhoea-causative agent in pigs is not yet fully understood. In an experimental challenge of piglets, the porcine NoV incubation period was of only 1 dpi, and the diarrhoea persisted for 2-6 days. Piglets presented mild to moderate villous atrophy and mild to moderate and multifocal villous fusion in the small intestine [48]. Previously, an experimental study inoculated piglets with the human NoV strain GII.4. The incubation period varied from 24 to 48 h; the diarrhoea was mild and self-limiting, persisting for 1-3 days. As well, the virus shedding was shown to be short, from 1 to 4 days. The virus antigen was detected in the cytoplasm of the small intestine cells. The histopathological lesions that were multifocal atrophy of the intestinal villi, enterocytes infected with low columnar morphology, and oedema of the lamina propria duodenal occurred at low frequency and were considered to be of low intensity.

Another finding of this study was the increase in the number of apoptotic enterocytes [8]. Replication of NoV may not be restricted to enterocytes. Of all the potential experimental models studied to better understand the pathogenesis of noroviruses, the only norovirus which replicates in vitro is the murine NoV. This agent replicates in macrophages and dendritic cells derived from cultures of bone marrow cells and in mouse macrophage cell lines (RAW 264.7) [58]. The murine NoV-1 infection in knockout mice for recombination-activating gene 2 (RAG2) and signal transducer and activator of transcription 1 (STAT-1) genes, RAG2/STAT-1, showed tropism for haematopoietic cell (macrophages and dendritic cells) and development of systemic disease. Clinical signs include pneumonia, hepatitis, encephalitis, and vasculitis in brain capillaries and can be observed even in inoculation in serial passages [27, 59, 46]. It was also demonstrated that the murine NoV can naturally infect wild and immunodeficient mice. The infection also occurs following oral or intranasal inoculation. However, although other strains of murine NoV have already been isolated from faecal samples of infected mice, it is not yet clear whether this virus is an effective enteric pathogen in this animal species [21].

2.6. Diagnostic Methods

Researchers have succeeded in culturing norovirus in human intestinal cells. But this has not be implemented in action till date. Diagnostic methods focus on detecting viral RNA or antigen. Most public health and clinical virology laboratories can test for norovirus using real-time reverse transcription-polymerase chain reaction (RTqPCR) assays.

2.6.1. RT-qPCR Assays

RT-qPCR assays are the preferred laboratory method for detecting norovirus. These assays are very sensitive and can detect as few as 10 to 100 norovirus copies per reaction. They use different primers to differentiate genogroup I and genogroup II norovirus. RT-qPCR assays are also quantitative and can provide estimates of viral load. The assays may be used to detect norovirus in stool, vomitus, foods, water, and environmental specimens. [37, 6].

2.6.2. Conventional RT-PCR Assays for Genotyping

Conventional RT-PCR followed by sequence analysis of the RTPCR products is used for norovirus genotyping. Typically, a partial region of the capsid gene, such as region D, is used by laboratories participating in CaliciNet, a national laboratory surveillance network for norovirus outbreaks coordinated by CDC. [37, 6].

2.6.3. Enzyme Immunoassays

Rapid commercial assays, such as enzyme immunoassays (EIAs), that detect norovirus antigen have recently been developed. However, these kits have poor sensitivity (50%) and are not recommended for diagnosing norovirus infection in sporadic cases of gastroenteritis. The RIDASCREEN Norovirus 3rd Generation EIA was recently cleared by Food and Drug Administration for preliminary identification of norovirus when testing multiple specimens during outbreaks. However, samples that test negative should be confirmed by a second technique, such as RT-qPCR. Thus, EIA kits should not replace molecular methods during outbreak investigations. [37, 6].

2.7. Treatment

There are no specific anti-norovirus drugs and vaccine at this moment. Treatment focuses on supportive care, especially preventing and treating dehydration. For dehydration, oral fluid or intravenous fluid for replacement therapy is used depending on the severity of the patients [17, 57]. Anti-vomiting drugs are also used. For other complications, individual treatments for each disease are used. Probiotics have shown to be an effective treatment for viral infections in intestinal surface and antibody activation [35]. High titer human IgG or IgA against human norovirus is useful for immunoglobulin deficient patients. Bone marrow transplantation or organ transplant are useful to elevate humoral and cellular immune responses in immune deficient patients [5]. According to the norovirus lifecycle, several candidate drugs have been developed to target the actions of polymerase and protease enzymes [2].

2.8. Prevention and Control

The possibility of suffering from a norovirus infection emerges shortly after birth. Cohort studies demonstrate multiple exposures throughout the life span [39, 45, 32]. The mode of transmission is mainly fecal-oral, in particular for endemic gastroenteritis when a symptomatic person, or quite frequently, an asymptomatic excretor transmits the infection to a susceptible individual. Oral-oral transmission for individuals suffering from vomiting is also viable [29, 56]. Contaminated food and water are the primary sources in outbreaks, followed by person-to-person transmission. The spread of the infection is facilitated by its low-infecting dose (between 20 and 1,000 viral particles to infect a person), prolonged excretion in stools (up to 2-4 weeks) and relative stability in the environment, food and water, as compared to other viruses [14, 30].Generally to prevent norovirus: Clean environment, Isolation of infected people, Frequent and clean hand washing, Avoid contaminated food and water, Well cleaned fruits and vegetable, Avoid oysters, Vomit or feaces should be cleaned and disinfected, Surrounding should be neat and clean, Disinfect virus containing area, Stay home from work, Avoid traveling, Wash and clean the items like bedding clothes which may contain viruses, A wide range of product like disinfectant and antimicrobial solutions are registered at EPA, which gives better results [7].

3. Conclusion and Recommendation

Norovirus is a leading cause of gastroenteritis, both in community and healthcare settings, often causing outbreaks. These are associated with significant morbidity, some mortality and incur substantial costs. Multiple factors (related to virus biological properties, human immune responses or inadequate management modalities) make it a challenging pathogen to control. Until large-scale effective vaccination and specific treatments become available, the safeguarding of food and water supplies and the rigorous and timely application of outbreak management and infection control measures will remain the key to norovirus disease prevention and control. Based on above conclusion the following recommendation is important:

1. To aware the population how norovirus transmitted.
2. To the study the population the effect of norovirus on public health and economic importance.
3. Due to norovirus have no treatment aware the community how they can kept their environment safely and food contamination.

Abbreviations

NLV	Nor Walk-like Virus
NoV	Noro Virus
RBA	Ribonucleic Acid
RAG	Recombination-activating Genes
STAT	Signal Transducer and Activators of Transcription
EPA	Environmental Protection Agency
CDC	Center for Disease Control
AGE	Acute GastroEnterities

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M. M., Review and writing: MS. MK. Editing: Z. M., Z. D. and AA: Material Collection.

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Conflicts of Interest

The authors declare no conflicts of interest.

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