REVIEW ON: WINTER VOMITING DISEASE (NOROVIRUS)

[1]Deep G. Agrawal, [2]Divya I. Sahejwani, [3]Amol V. Sawale

[1,2] Students, [3]Assistant Professor,
Vidyabharti college of Pharmacy, Amravati (MH) INDIA 444-602
Corresponding author: Deep G. Agrawal

***Abstract*- Although noroviruses (NoVs) were the first viral agents linked to gastrointestinal disease, for a long time they have been considered secondary cause of gastroenteritis, second torota viruses as etiologic agents. The development of molecular techniques in diagnosing NoV provided a clearer insight into the epidemiological impact of these viruses, which are currently recognized not only as the leading cause of non-bacterial gastroenteritis outbreaks, but also as a major cause of sporadic gastroenteritis in both children and adults. This review focuses on the required knowledge to understand their virology, diagnosis, transmission, pathogenesis, and control. Since no vaccine is available, prevention of NoV infection relies mainly on strict community and personal hygiene measures.**

KEYWORDS: Outbreak, Norovirus, Norwalk virus, Capsid protein, diarrhea

INTRODUCTION

Human Norovirus, previously known as Norwalk virus, was first identified in stool specimens collected during an outbreak of gastroenteritis in Norwalk, OH, and was the first viral agent shown to cause gastroenteritis [1]. Illness due to this virus was initially described in 1929 as "winter vomiting disease" due to its seasonal predilection and the frequent preponderance of patients with vomiting as a primary symptom [2].

The 1968 outbreak that led to the identification of the virus affected 50% of students at an elementary school in Norwalk and manifested primarily as nausea, vomiting, diarrhea, and low grade fever[3]. Among primary cases, 98% complained of nausea, and 92% vomited, while 58% had abdominal cramps, 52% complained of lethargy, 38% had diarrhea, and 34% had fever. The occurrence of secondary cases in 32% of family contacts allowed the estimation of a 48-h incubation period. The illness lasted 24 h, with complete recovery in all cases.

OUTBREAK

Water borne Norovirus was first reported as the causative agent of a waterborne gastrointestinal disease outbreak by Kaplan et al. in 1982. The outbreak affected 1,500 people in a small community in Georgia, with the highest attack rates occurring in geographic areas closest to points of interconnection between industrial and municipal water systems, where the industrial water was noted to contain coli form contamination. Evidence of norovirus was determined by increased antibody titers to Norwalk virus in patient serum [4]. The diversity of waterborne sources implicated in norovirus outbreaks ranges widely, indicating the ubiquitous distribution of the virus. Outbreaks have been linked to potable water sources at camps, municipal water systems, commercial ice consumption, and recreational water exposure during rafting and swimming [5–10].Norovirus outbreaks have been reported in a variety of settings and are uniquely suited to areas of close living quarters, shared dining facilities, and difficult environmental maintenance.

STRUCTURE OF NORO VIRUS

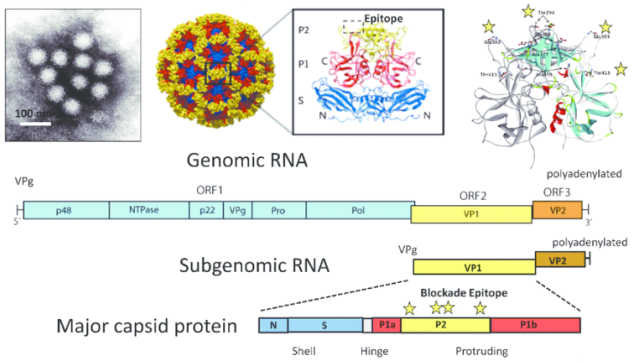

Fig.1 Structure of noro virus

- It has a buoyant density of 1.33–1.41 g/cm3, an inability to propagate in vitro.
- Characteristically, Norwalk virus possesses a single capsid protein.
- The genome is a non-segmented, single-stranded, positive polarity RNA genome.
- Ten prominent spikes and 32 cup-shaped depressions can be seen on the virion by microscopy.
- The structure of the capsid protein is organized into two domains joined by a flexible hinge.

- The inner shell (S) domain is composed of the N-terminal 225 residues and is involved in the formation of the icosahedra capsid shell.
- The protruding (P) domain forms prominent structures extending from the surface of the shell and is formed from the C-terminal half of the protein.
- The P domain is further organized into two sub domains (P1 and P2), and it has been suggested that these structures may be involved in binding to cellular receptors and may also be the determinants of strain specificity.[11]

MODES OF TRANSMISSION

Noroviruses are non-enveloped RNA viruses belonging to the virus family Caliciviridae. They can survive for long periods in the environment.

• **Person-to-person:** This is the primary mode of transmission of infection due to noroviruses. These viruses may be spread from person to person by the faecal–oral route and by vomiting (air–oral/mucous membrane spread), probably by causing widespread aerosol dissemination of virus particles, environmental contamination and subsequent indirect person-to-person spread. In some situations, particularly hospitals, transmission via vomiting may be more important than the established faecal–oral route of infection associated with other enteric pathogens. In addition, fomites have been shown to be another important method of transmission.

• **Food borne:** Foods that are handled and are not subjected to further cooking such as cold meats, saladsor sandwiches are commonly implicated in food borne norovirus infection.[13] Bivalve molluscan shellfish such as oysters can harbour the viruses due to filter feeding in sewage-contaminated water.[12] However any food item can potentially transmit norovirus if it is handled or comes in contact with an infected food handler or is exposed to environmental contamination.

• **Waterborne:** Water and ice are being increasingly recognized as vehicles for transmission of norovirus.[14]The factors that may promote transmission of norovirus within healthcare settings include:

- Frequent, close patient-staff contact
- Susceptible pool of hosts (elderly, small children)
- Movement of patients (transfers from ward to ward and to other departments, such as Radiology, Physiotherapy or the Laboratory)
- Movement of staff (normal [esp. medical], locums, agency nurses)
- Staff hygiene if sub-optimal (hand washing etc)
- Environmental hygiene if sub-optimal
- High occupancy rates may leave no surge ward capacity to allow more effective cohorting
- Throughput of visitors and other staff (catering, ancillary, retail)

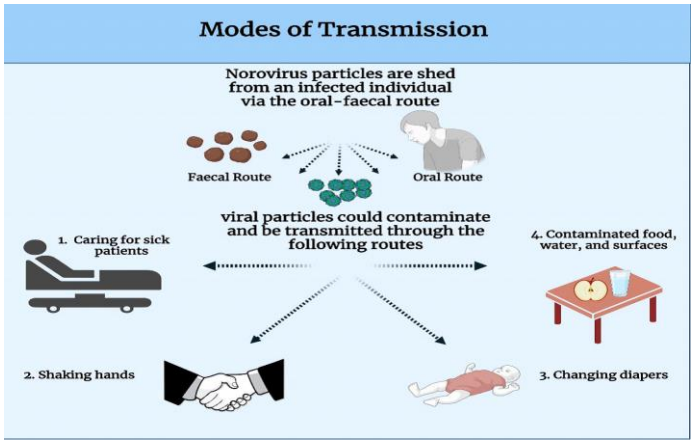

Figure 2. Transmission Modes of NoV

VIROLOGY

- Primarily in stool, but can also be present in vomitus
- Shedding peaks 4 days after exposure
- In some individuals, shedding may occur for at least 2-3 weeks
- May occur after resolution of symptoms
- Infectivity of shed virus in environment unknown
- Shedding in asymptomatic individuals is common but their role in transmission in not known

SYMPTOMS

Norovirus symptoms begin a median of 33 (range, 12–48) hours after exposure to the virus.

Symptoms may include:

- Vomiting
- Diarrhea, typically watery and without blood
- Nausea
- Low-grade fever
- Abdominal cramps
- Malaise

- Chills

DIAGNOSIS

Laboratory diagnosis

The classic diagnosis method is electron microscopy (EM), detecting virus particles with 27 to 30 nm in diameter, the so-called SRSV. This method is used in public health laboratories in many countries; however, it requires a highly qualified microscopist and very expensive equipment, making epidemiological or clinical studies impracticable[16].

The immune enzymatic method (ELISA) to detect the virus antigen uses norovirus capsid proteins expressed on baculo virus as a reactant in immune enzymatic tests[15]. This method has been recently made commercially available to diagnose NoV directly from feces (Dako Cytomation, Ely, UK 2001; Denka Seiken, Tokyo, Japan, 2002; R-Biopharm AG, Germany 2004). These kids have low diagnostic sensitivity, as reported by Bulletal.[17]. However, the development of new kit generations, such as RIDASCREEN 3rd Generation kit (R-Biopharm AG, Darmstadt, Germany), which is more sensitive and specific, entailed benefits for NoV quick diagnosis, mainly targeting outbreaks[18].

The RT-PCR molecular technique, developed to identify NoV, is sensitive and specific, enabling epidemiological studies to identify gastroenteritis outbreaks[19]. International collaborative studies[20] demonstrated that, among several primer pools developed for regions ORFs 1, 2, and 3, those showing the best results were primers in POL region of ORF 1 (preserved region). Phylogenetic analysis of 145 nucleotides in the POL gene region was used as a pattern to identify genotypes. NoV sequencing has assisted in epidemiological investigations relating clinical cases to determine a common source and to differentiate outbreaks that could be wrongly related[20].

REAL-TIME TaqMan[21],[22] RT-PCR and SYBR Green[23] techniques quantify specific DNA or RNA sequences in clinical samples and the gene expression from emitted fluorescence detection since the first amplification cycle. These methods have advantages over regular PCR, such as higher specificity, sensitivity, and reproducibility, in addition to allowing real-time monitoring; quicker cycling; lower RNA amount in RT-PCR reactions; and elimination of post-PCR product handling, thus reducing contamination[20]

TREATMENT

Stopping transmission is the first strategy for prevention, especially in hospitals and day-care centers. A number of precautions, such as hand washing with water and soap before and after contacting the patient or objects used by him/her, must be taken when caring for a patient diagnosed with an acute gastroenteritis. It is also required to clean all surfaces with 2% hypochlorite[24], as NoV persist in dry inanimate surfaces over eight hours to seven days[25].To avoid secondary transmissions, prevention of food contaminations during the preparation by a continuous hand washing is required. Those who handle food must wear plastic gloves when preparing raw food[26]. Affected workers must not prepare food for a minimum period of three days after the disease to avoid gastroenteritis outbreaks[27].

As there is no strengthened antivirus agent to treat norovirus diseases, the focus consists of prevention and treatment of the secondary dehydration. Fluid therapy is usually maintained orally with isotonic fluids. Hospitalization in cases of a severe dehydration may be required, although this is rare. Symptoms such as headache, myalgia, and nausea can be treated with analgesic and antipyretic drugs[28].

In 2006, Rossignol[29] analyzed a new drug, the nitazoxanide, indicated to treat diarrhea caused by virus gastroenteritis. In this study, the drug efficacy in several patients with symptoms and positive diagnosis for rotavirus, enteric adenovirus, norovirus, and astro virus was observed. However, higher drug effectiveness was found against rotavirus, compared with other viral pathogens.

Future of NoV Treatment

Ever since the application of VLPs has been introduced in studying NoVs, they have formed an attractive vehicle for vaccine development. There are currently many vaccine candidates in development and clinical trial phases, and the majority of them administer VLPs. One of the main challenges faced in the development of a NoV vaccine is their heterotypic nature and ability to mutate rapidly [30]. This highlights the need for a NoV vaccine to be bivalent against the two main infectious genotypes GI.1 and GII.4.Studies have shown that immunization against one genotype also provided immunity against other genotypes, which could allow us to conclude that a bivalent vaccine protecting against more than one NoV variant is possible [30, 31, 32]. The emergence of a new strain of GII.4 every 2–4 years also presents an issue when developing a vaccine. This is a similar issue as the one faced by Influenza virus, and would require for the vaccine to evolve as the new variants emerge [33]. An ideal NoV vaccine would protect against multiple variants asides from what it was designed for, and the possibility of that is likely as suggested in the previous paragraph. One vaccine developer suggested a strategy which would involve the development of a vaccine against the major capsid protein of a combination of three GII.4 variants [34].

PREVENTION AND CONTROL

Several studies, with various degrees of evidence quality, on infection prevention and control practices to interrupt the transmission of norovirus in health care settings have been reported. Many of these results are summarized in the HICPAC (Healthcare Infection Control Practices Advisory Committee) guidelines for the prevention and control of norovirus gastroenteritis outbreaks in health care settings published in 2011 and in a recent review of norovirus infection control measures[35,36]. The three main strategic areas included staff and patient policy development, hand hygiene, and proper environmental disinfection. Despite the breadth of existing literature on norovirus outbreaks and mitigation strategies, a recent survey of infection preventionists showed clear room for improvement in their knowledge of both prevention and control practices [37].

- **Hand Hygiene**

One of the primary recommended control strategies to interrupt norovirus transmission during outbreaks is appropriate hand hygiene, although this is based primarily on descriptive data [46]. Use of soap and running water for a minimum of 20 s is recommended after patient contact with confirmed or suspected cases at a category IB level (strong recommendation and low-quality evidence) [35]. Evaluation of disinfectants has proven challenging due to the limited ability to cultivate human norovirus in cell culture. Several viral proxies have been evaluated, including feline calicivirus (FCV) and murine noroviruses (MNVs), to assess the effectiveness of various disinfectants in hand contamination models [47]. Researches in Germany, using FCV as a surrogate for human noroviruses, measured the virus-inhibitory effect of three types of alcohol (ethanol, 1-propanol, and 2-propanol) in vitro and in vivo with artificially contaminated fingertips. This study showed that ethanol and 1-propanol had higher log10 viral reduction values than did 2-propanol, which was not considered adequate by those authors [48]. This study also demonstrated declining log10 viral reductions with increased concentrations of alcohol in each type of solution, which the authors theorized was related to the minimum amount of water necessary to achieve viral inactivation. Additionally, an FCV fecal hand contamination model supported the use of higher-concentration ethanol-based hand rubs rather than propan-1-ol-containing products [49]. In one study of experimental human norovirus hand contamination, liquid soap wash and water rinse were superior to ethanol-based sanitizers based on viral recovery through quantitative RT-PCR [50]. Triclosan-containing soaps and several other alcohol based-hand rubs showed inadequate levels of virus reduction [51]. Overall, additional research on specific human noroviral inactivation by various common cleaning and sanitizing products is needed [35].

- **Isolation and Personal Protective Equipment Procedures**

Symptomatic patients with vomiting and/or diarrhea should be placed in contact isolation (single room, gowns, and gloves) pending results of testing. After confirmation of norovirus infection, several descriptive studies support the use of continued contact precautions until some time period after the resolution of diarrhea, typically 48 h[38, 44, 45, 52]. Enforcement of standard precautions throughout health care settings experiencing a nosocomial norovirus outbreak is thought to reduce transmission [40]. The data in favor of gown and glove use for the prevention of norovirus transmission are derived primarily from observational or descriptive studies. Mask use is recommended only for staffs who anticipate exposure to vomitus [42, 40].

- **Environmental Disinfection**

Environmental persistence of norovirus has been reported in several settings, and its role in propagating outbreaks has been described in settings ranging from health care environments to food products and preparation sites to a concert hall [53–54]. A large proportion of the evidence on environmental disinfection is derived from studies using FCV or other surrogate viruses, and direct correlation with success in disinfecting human noroviruses is unknown [35, 55]. In general, hypochlorite (bleach) solutions of at least 1,000 ppm are the preferred disinfectants for contaminated surfaces and objects and must be used for an appropriate contact time [35, 56, 57]. Quaternary ammonium compounds are also under investigation but have been somewhat less effective than bleach solutions [36,57]. Both the type of sanitizer and method of application can have an impact on virucidal success [58]. In health care and non-health care settings, studies have focused on cleaning of high-touch surfaces, such as patient bathrooms, tables, chairs, computers, and commodes, in addition to floors and carpets [43,39,40,53]. Descriptive evidence supports rapid attention to and remediation of contaminated floors and patient care items and steam cleaning of carpets, although these data are of limited generalizability [35, 38, 40, 41]. Additional steps, such as discarding all unused patient care items after discharge of a norovirus patient, disposing of curtains, and changing mop heads and cleaning solution after every three rooms, have been described and may be performed, but these steps are without direct correlation to a shortening of the duration of nosocomial outbreaks [35, 38, 39, 40, 55]

CONCLUSION

Norovirus is an important cause of morbidity due to acute gastroenteritis both within health care institutions and in the broader community. Although mortality is typically limited to the extremes of age, the disease exacts a significant toll on the health care system. Therapeutic management is usually supportive, and advances in molecular diagnostics may lead to the earlier identification of outbreaks and a reduction in person-to-person transmissions, particularly in vulnerable patient populations. Ongoing global reporting initiatives will be enhanced by improved diagnostic methods. Additionally, global control efforts will benefit from the growing knowledge of the clinical implications of various norovirus strains. Several advances into understanding the relationship among the viral strain, the host human blood group antigen type, and disease susceptibility have recently been elucidated, but this work has not yet been extended to clinical practice.

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- SRSV : Spencer flu and Snow Mountain virus
- ELISA : enzyme-linked immunosorbent assay
- RT-PCR : Real-Time Reverse Transcription – Polymerase Chain.
- ORF : Observer Research Foundation
- SYBR : dsDNA binding dye
- VLPs : Virus like particles

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