Clinical Challenges
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Norovirus in Immunocompromised Patients

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While undergoing a routine mammogram, Mrs. B, age 76 years and in good health, was found to have right axillary adenopathy. A core biopsy confirmed the diagnosis of follicular lymphoma and she was referred to an oncologist who recommended treatment with six cycles of bendamustine, mitoxantrone, and rituximab. She tolerated the treatment fairly well except for mild lower abdominal discomfort for three to four days following infusion of chemotherapy. Prior to her fifth cycle of therapy, she reported chills, vomiting, and watery diarrhea without fever. Mrs. B volunteered one day per week at a nursing home and she noted that a stomach virus had circulated among the residents. Her symptoms resolved five days after her initial episode occurred and she proceeded with her fifth cycle of therapy.

Six days later, Mrs. B called the clinic to report a two-day history of severe abdominal cramping and watery diarrhea with as many as seven stools daily. She denied nausea or vomiting. She was seen in the clinic and was afebrile with normal complete blood count, electrolytes, blood urea nitrogen, and creatinine. Her abdomen was soft, slightly tender to palpation; she had positive bowel sounds in all four quadrants. A stool specimen was noted to be normal for C. difficile, ova and parasites, and norovirus by reverse transcription polymerase chain reaction (RT-PCR). Mrs. B was encouraged to increase her fluid intake and to take antidiarrheal medication to decrease her risk of dehydration. Several days later, the clinic was notified that the stool sample was positive for norovirus. Mrs. B was notified of the result and encouraged to continue with aggressive oral hydration and antidiarrheal medication.

Mrs. B completed chemotherapy two months after developing norovirus gastroenteritis. She continued to experience watery diarrhea and abdominal cramping for the next eight months, with resolution of her symptoms for several days followed by recurrence. Stool samples were repeated at three, five, and six months, and remained positive for norovirus. During the course of her illness, Mrs. B lost 54 pounds and was hospitalized twice for dehydration and failure to thrive. Empiric therapy with IV metronidazole, vancomycin, and IV immunoglobulin did not alleviate her symptoms. Ten months after the development of symptoms, the abdominal cramping and diarrhea resolved. A stool specimen obtained at 11 months was negative for norovirus.

Norovirus

First identified as the cause of a gastroenteritis outbreak in Norwalk, OH, in 1968, noroviruses are small, nonenveloped viruses with a single-stranded RNA genome that make up the genus *Norovirus* in the family Caliciviridae. The viruses are divided into five major genogroups, designated GI through GV. Genogroups I, II, and IV infect humans, whereas III and V infect pigs and cows (Hall et al., 2011). Norovirus cannot be grown in cell cultures and no small animal models exist, which presents a major challenge in norovirus research. Despite these challenges, the application of molecular techniques has led to a greater understanding of the clinical significance of noroviruses (Estes, Prasad, & Atmar, 2006).

Incidence and Transmission

Noroviruses are the leading cause of food-borne disease outbreaks worldwide (Koo, Ajami, Atmar, & DuPont, 2010). The viruses cause infection throughout the year, although the peak incidence occurs in the winter months (Atmar & Estes, 2006). In the United States, an estimated 21 million people suffer from norovirus-induced gastroenteritis annually, which constitutes 60% of the illness burden caused by known enteric pathogens (Scallan et al., 2011). Noroviruses are primarily transmitted through the fecal-oral route. Fecal contamination of food, water, and contaminated surfaces, as well as direct person-to-person spread, account for most outbreaks. Airborne transmission of norovirus also occurs in infectious aerosols generated by vomiting. Because no lasting immunity takes place, and because the virus can be transmitted by a number of routes, outbreaks can occur in a wide variety of institutional settings (Atmar & Estes, 2006). Healthcare facilities, including hospitals and nursing homes, are the most commonly reported settings of norovirus outbreak within the United States (Hall et al., 2011). Other risk groups include immunocompromised individuals, older adults, restaurant patrons, young children, military
personnel, cruise ship passengers, and travelers to developing nations (Koo et al., 2010). Factors that facilitate the spread of norovirus are presented in Figure 1.

**Clinical Presentations**

Norovirus can cause acute gastroenteritis in people of all ages, although as many as 30% of people infected are asymptomatic. The illness typically begins after an incubation period of 12–48 hours and is characterized by an acute onset of nonbloody watery diarrhea, vomiting, nausea, and abdominal cramping. A portion of patients experience only nausea and vomiting. Low-grade fever and body aches also can be associated with infection (Hall et al., 2011). In immunocompetent adults, norovirus is a self-limiting disease lasting 24–60 hours in the majority of cases. Prolonged norovirus infection and illness have been reported in people who are immunocompromised as a result of congenital immunodeficiency, immunosuppressive therapy for maintenance of an organ allograft, cancer chemotherapy and biologic therapy, and infection with HIV. In these populations, the disease course often is severe and can include dehydration, weight loss, renal failure, disseminated intravascular coagulation, malnutrition, and even death (Koo et al., 2010).

A retrospective study of the clinical, epidemiologic, and virologic features of norovirus gastroenteritis in 12 adult patients undergoing hematopoietic stem cell transplantation was conducted by the Department of Haematology at University College Hospital in London, England (Roddie et al., 2009). The study found that most patients presented with vomiting of short duration and almost all were receiving immunosuppressive therapy. Six patients required enteral or parenteral nutrition for severe weight loss, and two patients died from malnutrition. The diarrhea lasted for a median of three months (range = 0.5–14 months), with high levels of virus shed throughout in the majority of patients (Roddie et al., 2009).

**Diagnosis**

RT-PCR of diarrheal stools or emesis for norovirus is the diagnostic test of choice (Koo et al., 2010). Although many laboratories use electron microscopy to screen stools for potential viral infection, this method has a sensitivity of less than 25% when compared with molecular detection assays (Atmar & Estes, 2006). Whole stool specimens should be collected for laboratory diagnosis of norovirus infection and are preferred over rectal swab because of the higher viral load detected in stool. Vomit also may be collected, although the sensitivity of molecular assays in such samples is unknown (Hall et al., 2011). Unfortunately, many clinical laboratories are unable to perform the testing using RT-PCR. In outbreak settings where microbiologic outbreak evaluation is not possible, the Kaplan criteria have been used successfully to identify probable norovirus outbreaks. The criteria include a duration of illness (mean or median) of 12–60 hours, an incubation period (mean or median) of 24–48 hours, more than 50% of affected persons experiencing vomiting, and no bacterial cause being identified. These criteria, established by Kaplan, Feldman, Campbel, Lookabaugh, and Gary (1982), are based on an in-depth analysis of 38 norovirus outbreaks from 1976–1980 (Koo et al., 2010).

**Treatment and Management**

No specific therapy is in place to treat norovirus infection (Atmar et al., 2011; Patel, Hall, Vinje, & Parashar, 2009). The mainstay of treatment includes supportive care measures with oral rehydration with electrolytes (Koo et al., 2010). Patients presenting with signs and symptoms of significant dehydration and those unable to tolerate oral fluids may require parenteral fluids with electrolyte replacement. In addition, no role exists for antibiotic therapy (Patel et al., 2009).

Administration of hyperimmune human immunoglobulin parenterally or orally has been suggested, but has not been studied in a clinical trial (Glass, Parashar, & Estes, 2009).

The Centers for Disease Control and Prevention (CDC) has developed management and disease prevention guidelines for norovirus (Healthcare Infection Control Practices Advisory Committee, 2011). Hand washing with soap and water for at least 20 seconds is the single-most important method to prevent norovirus infection and control transmission. The efficacy of alcohol-based and other hand sanitizers is controversial. Isolation is used to minimize contact with people during the most infectious periods of their illness, including the acute phase and the recovery period when a person is still shedding high levels of virus (usually 24–72 hours). Exclusion of incubating or asymptomatic individuals also is used to minimize transmission of the virus. For example, in healthcare settings, such people should not be transferred to or work in infected areas for 48 hours after exposure to infected patients. The CDC offers additional information at www.cdc.gov/norovirus/index.html.

The use of chemical disinfectants is another important component of interrupting the spread of norovirus from contaminated surfaces. Sodium hypochlorite (chlorine bleach), at a concentration of 5–25 tablespoons per gallon of water, has been found to be effective in eradicating the virus from environmental surfaces. In hospital settings, all disinfecting and cleaning products must be Environmental Protection Agency–registered and have label claims for use.

Noroviruses are extremely contagious, with an estimated infectious dose as low as 18–100 viral particles. Secondary attack rates of greater than 30% occur in close contacts and family members.

Viral shedding precedes the onset of illness in as many as 30% of exposed people and can persist for as long as five weeks after resolution of symptoms.

Noroviruses have a vast diversity of strains, resulting in a lack of complete cross protection and long-term immunity, which can lead to repeated infections throughout life.

The norovirus genome easily undergoes a mutation that causes antigenic shift and recombination, resulting in the evolution of new strains of the virus that are able to infect susceptible hosts.

Noroviruses can withstand a wide range of temperatures, from freezing to 60°C, and can persist on environmental surfaces, in recreational and drinking water, and in a variety of food items.

**Figure 1. Factors Facilitating the Spread of Norovirus**

*Note. Based on information from Atmar et al., 2008; Glass et al., 2010.*
Norovirus

**Description**
- Small nonenveloped viruses with a single-stranded RNA genome that make up the genus *Norovirus* in the family *Caliciviridae* (Hall et al., 2011)
- Major pathogen responsible for infectious gastroenteritis in both immunocompromised and immunocompetent hosts
- Leading cause of gastroenteritis worldwide and extremely contagious
- Vast diversity of strains, resulting in lack of complete cross protection and long-term immunity
- Primarily transmitted through fecal-oral route (Atmar & Estes, 2006)

**Clinical Presentation**
- Symptoms begin during an incubation period of 12–48 hours.
- Immunocompetent individuals: self-limiting lasting 24–60 hours in a majority of cases.
- Acute onset of nonbloody watery diarrhea
- Nausea, vomiting, and abdominal cramping
- Low-grade fever and body aches also can be associated with infection (Hall et al., 2011).
- Immunocompromised individuals: can last for weeks to years. Often severe and can lead to dehydration, weight loss, renal failure, disseminated intravascular coagulation, malnutrition, and even death (Koo, Ajami, Atmar, & DuPont, 2010).

**Prevention and Treatment**
- No known treatment and no role for antibiotic therapy (Koo et al., 2010; Patel, Hall, Vinje, & Parashar, 2009)
- Supportive care with oral or IV rehydration and electrolyte replacement
- Handwashing is the most important method to prevent and control transmission.
- Exclusion and isolation of infected people
- Cleaning of surfaces with sodium hypochloride (chlorine bleach) or other Environmental Protection Agency–approved agent (Hall et al., 2011)

**References**