Norovirus Infection in Older Adults
Epidemiology, Risk Factors, and Opportunities for Prevention and Control

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BACKGROUND

Norovirus is the leading cause of acute gastroenteritis across all age groups in the United States.1 It is also a frequent cause of outbreaks in health care settings, including long-term care facilities (LTCFs) and acute care hospitals.2 The total burden of disease is high; norovirus is estimated to cause approximately 21 million total illnesses annually across all age groups in the United States.1 Certain populations

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KEYWORDS

- Norovirus • Gastroenteritis • Long-term care • Vaccine • Older adults

KEY POINTS

- Estimates indicate that a vast majority (90%) of norovirus-associated deaths in the United States occur among persons greater than or equal to 65 years of age.
- In the United States, long-term care facilities are the most commonly reported setting for norovirus outbreaks.
- Norovirus can spread through many routes, including person-to-person contact, contact with contaminated surfaces, and airborne dissemination of vomitus.
- Transmission-based precautions are among the most effective means of interrupting transmission.
- Antiviral therapy is not yet available for norovirus gastroenteritis, but research to identify antiviral treatment strategies for norovirus is in progress.
are at higher risk of infection and severe illness, including those at the extremes of age. In high-income and upper-middle-income (HI/UMI) countries, between 2000 and 13,000 norovirus-associated deaths occur in older adults greater than 65 years of age. Infection with norovirus is also costly to society. Annual hospitalization costs in the United States are estimated at $493 million and outpatient and emergency department visits at $284 million. For patients greater than 65 years of age, total hospitalization costs for norovirus and gastroenteritis are higher compared with younger age groups. Additionally, all foodborne norovirus illness, including productivity losses, are estimated at $2 billion per year in the United States. This review summarizes knowledge on norovirus infection in older adults.

VIROLOGY AND VIRAL DIVERSITY

The norovirus genome is composed of a linear, positive-sense RNA that is approximately 7.6 kb in length. The 3 open reading frames (ORFs), ORF-1, ORF-2, and ORF-3, encode 8 viral proteins (VPs); ORF-2 and ORF-3 encode the structural components of the virion, VP1 and VP2. ORF-1 encodes nonstructural proteins, including the norovirus protease and RNA-dependent RNA polymerase.

Noroviruses belong to the family *Caliciviridae* and are divided into 7 genogroups based on the viral capsid gene. Three of these genogroups, GI, GII, and GIV, include strains that infect humans. Noroviruses are classified further into genotypes, and there are at least 21 genotypes in GII and 8 genotypes in GI. Globally, GII.4 viruses are the predominant pathogen, include new variants that emerge every 2 to 4 years, and are associated with greater symptom severity in the young and elderly, resulting in more hospitalizations and deaths. In the most recent United States norovirus season, from September 1, 2016, to April 21, 2017, of 502 samples tested, the predominant strain was GII.P16-GII.4 Sydney, accounting for 60% of outbreaks; other strains included GII.2 (14% of outbreaks), GI.3 (7% of outbreaks), GII.6 (4% of outbreaks), and GII.Pe-GII.4 Sydney (3% of outbreaks); other genotypes accounted for the remaining 12%.

CLINICAL PRESENTATION AND DISEASE COURSE

After an incubation period of 12 hours to 48 hours, the classic symptoms of norovirus disease include sudden onset of vomiting, abdominal cramps, and watery diarrhea. Constitutional symptoms, including low-grade fever, generalized myalgias, malaise, headache, and chills, frequently accompany the gastroenteritis. Vomiting and diarrhea are usually present together, but either can be seen alone. Most patients experience a brief, self-limited infection with symptoms resolving within 2 days to 3 days. The clinical spectrum of illness is varied, however, and up to one-third of those infected are asymptomatic. On the other end of the spectrum, the most vulnerable include those with underlying medical conditions, the very young, the elderly, and the immunocompromised, who are at greater risk for severe symptoms and complications, such as acute renal failure leading to hemodialysis, cardiac complications including arrhythmias, acute graft organ rejection in transplant recipients, and death.

Complications among healthy adults are less common. Transient postinfectious inflammatory bowel syndrome has been reported up to 3 months postonset of symptoms compared with controls as well as long-term sequelae among US military recruits who experienced gastroenteritis during norovirus outbreaks, including dyspepsia, constipation, and gastrointestinal reflux disease. Neurologic symptoms are rare but have been observed. Headache, neck stiffness, photophobia, and
obtundation were observed together with gastrointestinal symptoms in 3 British military personnel; 1 of these patients also had disseminated intravascular coagulation, and 2 patients required ventilator support. Other infrequent complications have been reported among healthy people, including necrotizing enterocolitis, seizures, and postinfectious arthritis in the pediatric population as well as individual case reports among adults of ischemic colitis, transient hepatocellular injury, and hemolytic uremic syndrome.

Clinical Symptoms and Severity of Norovirus in Older Adults (Greater Than or Equal to 65 Years of Age)

Older adults form a high-risk group for severe symptoms and clinical outcomes. Norovirus outbreak investigations have reported a longer duration of diarrhea, from 3 days to 9 days, in older adults and even slower recovery from illness in patients greater than or equal to 85 years of age, with almost half of those affected still symptomatic after 4 days. Clinical symptoms other than diarrhea may also be prolonged in this age group; 1 study reported persistent headache, thirst, and vertigo as long as 19 days postonset of illness in 10 individuals 79 years old to 94 years old in an aged-care facility, although the diarrhea and vomiting had resolved by day 4 postonset.

If they are hospitalized with norovirus infection, older adults are more frequently admitted to an ICU. Also, compared with younger hospitalized patients, older adults who are hospitalized for other conditions are more likely to acquire a nosocomial norovirus infection. This propensity for ICU care–acquired and hospital-acquired infections could be due to longer hospital stays and increased exposures, but it could also be secondary to increased susceptibility to the virus due to age-related changes in B-cell and T-cell function and immunosenescence or underlying chronic conditions and comorbidities.

These age-related factors are also likely contributors to the high mortality rate in this age group from norovirus-associated illness. It is estimated that a vast majority (90%) of norovirus-associated deaths in the United States occur among persons greater than or equal to 65 years of age (Fig. 1). In a study of norovirus outbreaks in nursing homes, all-cause mortality was higher in outbreak periods compared with nonoutbreak periods. When norovirus-associated deaths do occur, most infections are acquired in LTCFs and hospitals; a global review in developed countries found that immediate causes of death in these scenarios included sepsis, aspiration pneumonia, and cardiac complications.

Prolonged Infection and Complications in the Immunocompromised

Immunocompromised hosts, including those who are immunosuppressed due to congenital or acquired immunodeficiencies, transplant, receipt of immunosuppressive therapy, and cancer, are at increased risk for prolonged and more severe norovirus illness. Several studies have demonstrated chronic infection and prolonged shedding of norovirus for months to years after solid or liquid organ transplant and prolonged illness in individuals with leukemia and lymphoma. Duration of symptoms and viral excretion in immunocompromised hosts has ranged from 6 days to 420 days and 11 days to 420 days in hematopoietic stem cell transplant recipients, respectively, and 24 days to 1004 days and 6 days to 898 days in renal transplant recipients. Immune compromised patients who are chronically infected with norovirus potentially transmit the infection to immunocompetent adults, although nosocomial outbreaks stemming from immunocompromised patients are rare.

Norovirus infections in renal transplant patients have also been shown to result in more severe symptoms compared with gastroenteritis due to bacteria or parasites,
including greater weight loss, 8.7-fold longer duration of symptoms, more frequent medication adjustments, prolonged viral shedding, and post-transplant chronic diarrhea potentially complicated by severe kidney graft impairment.\textsuperscript{40} In some cases, immunosuppressive therapy has been temporarily suspended in renal transplant patients because of the severity of clinical symptoms, including severe dehydration and cardiovascular instability.\textsuperscript{20} Further complicating the care of norovirus-infected immunocompromised patients is a potential delay in diagnosis that can result from overlapping clinical symptoms experienced by oncologic patients undergoing therapy with those typical for acute norovirus infection.\textsuperscript{41} Norovirus-associated deaths in patients with varying degrees of immunosuppression have been reported\textsuperscript{37} as well as deaths directly attributable to norovirus in immunocompromised patients.\textsuperscript{18,45}

VIRAL SHEDDING AND TRANSMISSION

Norovirus is highly contagious, and the infectious dose can be small (18–2800 viral particles).\textsuperscript{46,47} The most common route for transmission is person to person, either directly through the fecal-oral route, by ingestion of aerosolized vomitus, or by indirect exposure via fomites or contaminated environmental surfaces.\textsuperscript{9} Foodborne transmission is also common and can occur by contamination from infected food handlers or directly from contaminated foods. Foods often implicated in norovirus outbreaks include leafy greens, fresh fruits (such as raspberries), and shellfish (such as oysters), but any food that is served raw or handled after being cooked can be contaminated.\textsuperscript{48–52} Waterborne transmission is also possible, particularly when drinking or recreational water are not chlorinated. In health care settings, the most common mode of transmission is through direct contact with infected persons or contaminated equipment.

The characteristics of norovirus shedding also play a role in transmission dynamics, although the infectivity of the virus beyond the symptomatic period is not well

Fig. 1. Proportion of annual norovirus burden in the United States that occurs in older adults greater than or equal to 65 years old, by outcome. \textsuperscript{a}Hall and colleagues,\textsuperscript{35} 2012; \textsuperscript{b}Lopman and colleagues,\textsuperscript{4} 2011; \textsuperscript{c}Gastañaduy and colleagues,\textsuperscript{5} 2013; and \textsuperscript{d}Grytdal and colleagues,\textsuperscript{102} 2015.
Shedding occurs primarily in stool but can also be present in vomitus. Although peak viral shedding occurs 2 days to 5 days after infection, viral RNA has been detected in stool samples for up to 4 weeks to 8 weeks in otherwise healthy individuals. Higher viral loads have been reported in symptomatic patients compared with those who have been asymptomatic for at least 3 weeks, but other studies have shown timing of onset, peak, and resolution of shedding was similar for inoculated participants whether or not they developed clinical gastroenteritis. Because the highest period of infectivity is believed to coincide with clinical symptoms and the period shortly thereafter, the Centers for Disease Control and Prevention recommends excluding sick health care personnel, food workers, and caregivers for 48 hours to 72 hours after symptoms resolve.

IMMUNITY

Immunity to norovirus is complex and an ongoing field of research; both acquired immunity and innate host factors and are thought to contribute to susceptibility to infection. Data from volunteer challenge studies indicate a pattern of short-term, acquired immunity, with protection against the same norovirus strain lasting for weeks up to 2 years. Modeling studies suggest a slightly longer duration of protection (4–9 years). As a result, immunity to norovirus is thought to be of limited duration, with most individuals experiencing several infections throughout their lifetime.

Antibodies from natural infection have been studied as possible markers of immunity. Antibody prevalence correlates with increasing age; 1 study of hospitalized patients with acute gastroenteritis demonstrated that infants had the lowest GII.4-specific IgG and IgA prevalence, increasing with age up to 100% prevalence in adults. Although antibody seroprevalence to norovirus in adulthood is high, this does not necessarily correlate with protection from disease. At the same time, other studies have indicated high blocking ability of antibodies is correlated with protection against infection.

Immunity to norovirus seems to be homotypic, with greater protection to strains within genogroups compared with between genogroups and could be one reason why high seroprevalence to norovirus does not necessarily equate with protection from disease. Challenge studies have indicated protection against homologous strains but lack of cross-protection to heterologous strains. Even within a genogroup, protection might be incomplete; studies have shown that although repeat infections by the same genotype are rare, repeat infections by the same genogroup occur commonly.

In addition to acquired immunity, innate host factors play an important role in immunologic protection. Intrinsic susceptibility to norovirus infection is mediated by histo-blood group antigens (HBGAs), including ABO, secretor, and Lewis types. HBGAs have been demonstrated to serve as a docking site or receptor for noroviruses and are believed to play a role in virus entry to the gut mucosal epithelial cells. The expression of HBGAs is regulated in part by the FUT2 gene, which encodes an alpha(1,2) fucosyltransferase to generate H-antigens, which are catalyzed to produce A or B blood group antigens. Those individuals who possess a functional FUT2 gene, which results in ABH glycans secreted into bodily fluids, are known as secretor-positive individuals and have been found to have a higher risk of norovirus infection. Conversely, individuals with polymorphisms in FUT2 that can result in a homozygous nonsense mutation are known as nonsecretors; these mutations vary by ethnicity and occur in approximately 5% to 50% of different populations worldwide. Protection may not be complete, however, based on FUT2 status alone, because...
secretor-negative individuals can be infected with norovirus, with some demonstrated differences in susceptibility to certain genotypes.\textsuperscript{67–69}

**DIAGNOSIS**

Individual cases of norovirus gastroenteritis can be suspected on the basis of clinical manifestations. Routine laboratory tests in affected individuals are generally nonspecific, although peripheral white blood cell counts can be slightly elevated with increased polymorphonuclear cells and relative lymphopenia.\textsuperscript{16} Renal and hepatic function is generally normal unless dehydration ensues.

Confirmation of norovirus as an infectious agent in patients requires laboratory testing of stool specimens. Whole-stool samples are the preferred clinical specimen for detection of norovirus and ideally are collected during the acute phase of illness, but norovirus can also be detected from rectal swabs and vomitus. Serum specimens are not recommended for routine diagnostics\textsuperscript{9}; although several serologic markers, including norovirus-specific IgA and IgG titers, HBGA-blocking antibodies, and mucosal and fecal IgA, are being explored in the context of research and vaccine trials,\textsuperscript{10} correlates of protection for use in the clinical setting are still under development.

Molecular tests, including conventional reverse transcription (RT)–polymerase chain reaction (PCR) and real-time RT-PCR are most sensitive and currently the gold standard for norovirus detection but are usually only available in public health laboratories and research facilities (\textit{Table 1}). RT-quantitative (q)PCR afford several advantages, because it is the most sensitive assay available, can detect GI, GII, and GIV strains simultaneously and in several types of specimens (stool, vomitus, food, water, and environmental) and through use of an internal extraction control can reduce false-negative results.\textsuperscript{70,71} It can also provide an estimate of viral load based on the cycle threshold value; some data suggest that patients with higher viral loads excrete virus longer.\textsuperscript{71} One consideration when using RT-qPCR is that norovirus is frequently detected in stool samples of healthy and asymptomatic individuals, which can complicate interpretation of results; however, detection of norovirus in asymptomatic controls seems more common in developing countries.\textsuperscript{72} Laboratory diagnostics in the clinical setting have only recently become more widely available. Molecular-based assays for multiple enteric pathogens, such as xTAG GPP (Luminex, Toronto, Canada), FilmArray gastrointestinal panel (BioFire Diagnostics, Salt Lake City, Utah), and Verigene Enteric Pathogens Test (Nanosphere, Northbrook, Illinois), can detect multiple viral, bacterial, and parasitic pathogens simultaneously within a few hours.\textsuperscript{71} The equipment and testing can be expensive, however, and interpretation of positive results with mixed infections can pose challenges for appropriate treatment and management of patients.

Other diagnostic tests include electron microscopy assays, enzyme immunoassay, and immunochromatographic lateral flow assays. Electron microscopy can detect multiple viral pathogens but is expensive and insensitive and generally only used in reference laboratories.\textsuperscript{71} Enzyme immunoassay and immunochromatographic assays are commercially available, allow for rapid results and have high specificity, but, because of large genetic and antigenic variation among noroviruses and variable viral loads in stool samples, they have low sensitivity (35%–76%) and are not recommended for individual patients.\textsuperscript{71,73–75} They can be useful, however, for rapid screening of multiple samples, such as in an outbreak setting.\textsuperscript{75} Negative tests should still be confirmed by a second technique in an outbreak setting, such as RT-qPCR.

In an outbreak setting, and in situations where stool samples are not available for testing but rapid diagnosis is paramount, norovirus infections can be suspected
<table>
<thead>
<tr>
<th>Method</th>
<th>Characteristics</th>
<th>Availability</th>
<th>Use in Clinical Setting?</th>
<th>Use in Outbreak Setting?</th>
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<tbody>
<tr>
<td>Conventional RT-PCR, real-time RT-PCR</td>
<td>• Gold standard test</td>
<td>Public health and reference laboratories</td>
<td>Not widely&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
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<td></td>
<td>• High sensitivity</td>
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<td></td>
<td>• Frequently detects specimen in asymptomatic and healthy patients</td>
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<tr>
<td>Multiple enteric pathogen tests (xTAG GPP, FilmArray gastrointestinal panel, and Verigen Enteric Pathogens Test)</td>
<td>• Detects multiple viral, bacterial, and parasitic pathogens simultaneously</td>
<td>Public health and clinical laboratories</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td>• High sensitivity</td>
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<td>• Expensive</td>
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<tr>
<td>Enzyme immunoassay, immunochromatographic</td>
<td>• Low sensitivity, high specificity</td>
<td>Public health and clinical laboratories</td>
<td>Not recommended for individual patients</td>
<td>Yes, for rapid screening of multiple samples</td>
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<tr>
<td>Electron microscopy</td>
<td>• Detect multiple viral pathogens</td>
<td>Reference laboratories</td>
<td>No</td>
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<td>• Low sensitivity</td>
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<sup>a</sup> Individual patient specimens can be tested such as in an outbreak at a reference laboratory and positive specimens genotyped, but due to lack of availability in the clinical setting is unlikely to provide results back to the patient in a timely fashion. Some commercial diagnostic laboratories, however, offer their own in-house RT-PCR as do some tertiary care hospitals.
based on the clinical and epidemiologic profile. The Kaplan criteria provide the means to discriminate between outbreaks due to norovirus and due to bacterial agents and include (1) vomiting in more than half of affected persons, (2) mean (or median) incubation period of 24 hours to 48 hours, (3) mean (or median) duration of illness of 12 hours to 60 hours, and (4) no bacterial pathogen in stool culture. These criteria are highly specific (99%) but less sensitive (68%) in discriminating between outbreaks due to bacteria versus norovirus. Other clinical and epidemiologic profiles have been suggested to help discriminate norovirus outbreaks from non-norovirus gastroenteritis outbreaks, including an increased vomiting to fever ratio and decreased diarrhea-to-vomiting ratio. These clinical definitions are of particular importance in nursing homes and assisted living facilities, where diagnostic testing might not be obtained and could lead to delays in diagnosis and implementation of control measures.

TREATMENT

As with other causes of viral gastroenteritis, treatment is primarily supportive with replenishment of intravascular depletion of volume and electrolytes as well as unrestricted nutrition. Oral rehydration remains the first-line therapy for uncomplicated illness and intravenous fluids for severe vomiting and dehydration. Older adults with signs of hypovolemia are at greatest risk for complications and are more likely to require hospitalization. Symptomatic treatment with analgesics, antimotility, antiemetic, and antisecretory agents can be used as adjuncts in adults, depending on the type and severity of symptoms and necessity of continued performance, such as work and travel. One study demonstrated that bismuth salicylate improved symptoms from gastroenteritis in Norwalk virus–infected volunteers but had no effect on the number or consistency of stools or rates of viral shedding. A more recent study found that in vitro, bismuth subsalicylate and bismuth oxychloride slightly reduced the level of Norwalk replicon-bearing cells. Loperamide has been shown to reduce the duration of diarrhea from a variety of causes compared with placebo and has few side effects, although constipation was reported in 1 study in adults greater than 70 years old. In adults with diarrhea for less than 24 hours, diphenoxylate-atropine [Lomotil] was superior to placebo in reducing the rate of bowel movements in the 24 hours after treatment, but there was no statistically significant difference in median time to last loose or watery stool.

Antibiotics are not recommended for the treatment of uncomplicated viral gastroenteritis, and no Food and Drug Administration–approved antiviral therapies are available for norovirus gastroenteritis, but research to identify antiviral treatment strategies for norovirus is in progress. Nitazoxanide, a broad-spectrum thiazolide anti-infective licensed for use against Cryptosporidium spp and Giardia lamblia, has been used off-label as a treatment of norovirus infection in transplant recipients and immunocompromised patients, and a small clinical trial demonstrated significant reductions in time to resolution of symptoms of norovirus diarrhea in immunocompetent adults and adolescents treated with nitazoxanide. Other investigational agents, including the antiviral favipiravir, under development for influenza treatment, have shown modest potency against norovirus replication. Human alpha-interferon and ribavirin also reduced replication of a human norovirus replicon in cell culture. Probiotics and vitamin A are also being explored for their antiviral effects; reductions in incidence and shorter duration of diarrhea and viral shedding have been demonstrated with probiotic regimens in pigs inoculated with human norovirus. Until recently, lack of a robust and reproducible in vitro cultivation system hampered research and
development for therapeutics, but a human intestinal enteroid culture system has been described to support human norovirus replication in vitro\textsuperscript{96} and is expected to yield new insights for antivirals as well as in diagnostics and vaccine development.

**ENDEMIC DISEASE**

Studies of endemic norovirus gastroenteritis have elucidated some important trends. In the United States, norovirus is the leading cause of gastroenteritis in the community, outpatient setting, and emergency departments in all age groups, accounting for 19 million to 21 million cases annually.\textsuperscript{1} Estimates of the total number of cases in adults greater than or equal to 65 years of age in the United States have not previously been reported; extracting a recently reported community incidence rate in this age group and multiplying by the total number of persons greater than or equal to age 65 in 2015\textsuperscript{97} results in an estimated 3.7 million total cases of norovirus annually in the United States in older adults (Fig. 2). Additionally, norovirus cases in older adults account for an estimated 320,000 outpatient visits; 69,000 emergency department visits; 39,000

![Fig. 2. Estimated annual norovirus cases in older adults (≥65 years old) in the United States in 2015, by outcome. To generate case counts, incidence rates by outcome were obtained or calculated from existing literature (\textsuperscript{a}Hall and colleagues,\textsuperscript{35} 2012; \textsuperscript{b}Lopman and colleagues,\textsuperscript{4} 2011; \textsuperscript{c}Gastañaduy and colleagues,\textsuperscript{5} 2013; and \textsuperscript{d}Grytdal and colleagues,\textsuperscript{102} 2015) and multiplied by the US population estimate for older adults in 2015 (47.8 million). For deaths and emergency department visits, 95% CIs are shown in parentheses; for outpatient visits, the average from 2 studies is shown; for hospitalizations, high and low seasonal estimates from 1996 to 2007 are shown; for total illnesses, 95% credible intervals are shown. All numbers are rounded to 2 significant digits. Data collected at the community level are used as proxy for determining total illnesses.)](image-url)
hospitalizations; and 960 deaths annually in the United States. These estimates are in line with a recent systematic review of older adults in HI/UMI countries, which reported 1.2 million to 4.8 million illnesses; 723,000 million to 2.2 million outpatient visits; 40,000 million to 763,000 inpatient visits; and 2000 to 13,000 norovirus-associated deaths annually in these countries. Putting these counts together with the overall population of 402 million older adults in HI/UMI countries, norovirus incidence rates can be calculated for these countries, which are similar to incidence rates previously reported from the United States (total cases: 12 vs 77 per 1000; outpatient visits: 5.5 vs 5.4–7.9 per 1000; inpatient visits: 190 vs 81 per 100,000; deaths: and 32 vs 20 per 1,000,000; rates are in HI/UMI vs United States, respectively). As the world population continues to grow and age, these numbers will correspondingly increase.

Studies from the United States, the United Kingdom, Canada, and Germany have reported age-specific norovirus incidence rates that have included adult populations (Table 2). Estimates vary by outcome, country, and estimation methods, but a U-shaped pattern of illness with the youngest and eldest most highly affected was evident among several studies that examined all age groups. For example, a study of patients submitting stool specimens for routine clinical diagnostics from a health maintenance organization in 2 regions of the United States reported highest incidence rates in children less than 5 years of age in the community (1521 per 10,000), followed by adults 46 years to 65 years of age (1012 per 10,000) and greater than 65 years of age (771 per 10,000); similarly, children less than 5 years of age had the highest outpatient incidence rate (256 per 10,000), followed by adults greater than 65 of age (79 per 10,000). Another US modeling study estimated norovirus associated hospitalization discharges that likewise followed the U-shaped distribution, with the oldest age groups most affected. When examining hospitalization, emergency department, and outpatient visit rates among adults only, higher incidence is observed among adults greater than 65 compared with adults less than or equal to 65 years old. Among adults greater than 65 years, the hospitalization rate appears to be even greater with increasing age, because the greater than 84-year-old group exhibited rates at least twice as high. Unlike the studies discussed previously, 2 studies reported rates in adults that were much lower than the others (0.61 per 10,000 in >59 year olds and 0.0041 per 10,000 in 65–85 year olds), but these were the only estimates that relied entirely on International Classification of Diseases, Ninth Revision, and International Classification of Diseases, Tenth Revision, codes, and the investigators noted that a substantial proportion of undiagnosed viral gastroenteritis cases were likely.

Adults greater than or equal to 65 years of age are at highest risk for death from norovirus; a study in the Netherlands reported a case fatality rate 21 times higher in this age group compared with adults 18 years old to 64 years old. Among studies estimating the incidence of norovirus-associated mortality, death rates were much higher in older adults compared with other age groups (see Table 2). In 2012, Hall and colleagues reported a death rate in adults greater than or equal to 65 that was 2 orders of magnitude higher than in children and adults 5 years to 64 years of age (0.2 vs 0.002 per 10,000, respectively) and in 2013 Werber and colleagues reported a similarly high rate in older adults greater than or equal to 70 compared with less than 70 years of age (0.32 vs <0.01 per 10,000).

Prevalence studies in patients with acute gastroenteritis have also demonstrated a high burden of norovirus disease. Globally, noroviruses account for 18% of all patients with acute gastroenteritis, with slightly lower rates in the inpatient (17%) compared with outpatient (20%) and community (24%) setting. Studies from Canada, China, the Netherlands, Portugal, Spain, Qatar, the United States, and the United Kingdom have demonstrated that norovirus accounted for 6% to 27% of acute gastroenteritis
Table 2
Studies estimating endemic norovirus incidence in adults greater than or equal to 18 y of age, by outcome

<table>
<thead>
<tr>
<th>Country</th>
<th>Data Period Studied</th>
<th>Study Design</th>
<th>Population</th>
<th>Reported Incidence by Age Group (per 10,000 Population)</th>
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<td>Werber et al,105 2013 Germany 2004–2008 Retrospective analysis surveillance National surveillance system for notifiable diseases, Federal Statistical Office ≥70 y: 0.32 &lt;70 y: &lt;0.01</td>
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<td>Hall et al,35 2012 US 1999–2007 Retrospective analysis using time-series regression models Gastroenteritis-associated deaths from National Center for Health Statistics multiple cause-of-death mortality data ≥65 y: 0.20 5–64 y: 0.0022</td>
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<td>Hospitalizations</td>
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<th>Study Design</th>
<th>Population</th>
<th>Reported Incidence by Age Group (per 10,000 Population)</th>
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</table>
| Lopman et al,  2011 | US                  | Retrospective analysis using time-series regression models | Gastroenteritis-associated hospital discharges from National Inpatient Sample                      | <5 y: 9.4  
5–17 y: 1.1  
18–64 y: 1.0  
65–74 y: 4.7  
75–84 y: 9.2  
85+ y: 18.5 |
| Grytdal et al, 2015 | US                  | Prospective passive surveillance           | AGE cases at 4 Veterans Affairs hospitals                                                            | <65 y: 0.8 community-acquired inpatient;  
4.5 for hospital-acquired inpatient  
≥65 y: 1.4 for community-acquired inpatient; 6.6 per 10,000 for hospital-acquired inpatient |
| Haustein et al, 2009 | UK                  | Retrospective analysis using linear regression models | Gastroenteritis-associated hospital discharges from national statistical data warehouse and national laboratory database | 18–64 y: 0.23–0.48  
≥65 y: 1.0–4.3 (range, low to high season) |
| Chui et al,  2011 | US                  | Retrospective database review              | Norwalk virus hospital discharge codes and US Census                                                | 65–85 y: 0.0041  |
| Ruzante et al, 2011 | Canada              | Retrospective database review              | Norovirus hospital discharge codes and Canadian Institute for Health Information, Vital Statistics Registry, National Notifiable Diseases database | <1 y: 0.59  
1–59 y: range 0.06–0.2  
>59 y: 0.61 |
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<td>Year</td>
<td>Study Design</td>
<td>Surveillance System</td>
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**Abbreviations:** AGE, acute gastroenteritis; IID, infectious intestinal disease.

<sup>a</sup> In Germany, norovirus is nationally notifiable, and many cases are captured through the acute gastroenteritis surveillance system when patients present to providers, which may include laboratory testing. Thus, these estimates include medically-attended cases and, therefore, likely extend beyond the outpatient setting.

<sup>b</sup> If point estimate was not reported in text or table, data points were extracted by digitizing plots.
cases in adults of all ages, and 8% to 41% of acute gastroenteritis in adults greater than or equal to 65 years old (Table 3).

OUTBREAKS

Globally, norovirus is the predominant cause of gastroenteritis outbreaks and accounts for approximately half of all outbreaks in developed countries. In the United States, norovirus is also the leading cause of foodborne disease outbreaks and a frequent cause of outbreaks in institutional settings, such as LTCFs and child care centers. Other common norovirus outbreak settings include restaurants, catered events, cruise ships, schools, prisons, and military encampments.

These outbreaks occur year-round but are more frequent during the winter, with more than half occurring in the December-February timeframe. Although multiple routes of transmission can occur within a single outbreak, norovirus is the most frequently reported cause of acute gastroenteritis outbreaks transmitted through person-to-person contact, environmental contamination, and unknown mode of transmission. Most norovirus outbreaks globally and in the United States are caused by GII noroviruses, and GII.4 is the most common genotype identified in norovirus outbreaks in the United States.

Long-term Care Facility Outbreaks

Older adults living in LTCFs might be at additional risk for norovirus infection and complications. In the United States, LTCFs, which generally refer to facilities that provide prolonged care for individuals who require daily living and/or nursing care support, are the most commonly reported setting for norovirus outbreaks. In the United States and Australia, 6 to 17 norovirus outbreaks per 100 LTCFs are estimated annually.

The unique setting of LTCFs can promote norovirus transmission, such as in shared rooms and common areas, where norovirus can spread through many routes, including person-to-person contact, contact with contaminated surfaces, and airborne dissemination of vomitus. Most norovirus outbreaks in LTCF settings have high levels of person-to-person transmission, likely due to the caregiving and close contact required between staff and residents with limited mobility. Shared dining facilities in some LTCFs might also increase the risk for foodborne exposures and transmission.

Attack rates and deaths are also higher in norovirus outbreaks in LTCF compared with other causes of acute gastroenteritis outbreaks. A systematic review of norovirus disease risk among older adults in HI/UMI countries found that attack rates ranged from 3% to 45%, case hospitalization rates 0.5% to 4.3%, and case fatality rates 0.3% to 1.6% in norovirus-associated LTCF outbreaks. Once infected, LTCF residents are more likely to suffer severe outcomes due to nutritional status, immunosenescence, chronic inflammation, microbiome alterations, and use of certain medications. Outbreaks in LTCFs have been reported to recur within the same facility despite implementation of control measures; can last for prolonged periods, up to months in some cases; and result in increased hospitalizations and mortality rates for residents.

Hospital Outbreaks

Norovirus outbreaks are common in hospitals, with attack rates ranging from 5% to 60%. These outbreaks tend to occur seasonally, more commonly occurring in the 6 months from November to April and peaking in January, February,
Table 3
Studies of endemic norovirus disease in adult populations estimating prevalence of norovirus among cases with gastroenteritis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Data Period Studied</th>
<th>Study Design</th>
<th>Population</th>
<th>Prevalence of Norovirus Among Gastroenteritis Cases (n/N), Unless Otherwise Specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td></td>
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</table>
| Hall et al, 2012 | US      | 1999–2007           | Retrospective analysis using time-series regression models                 | Gastroenteritis-associated deaths from National Center for Health Statistics multiple cause-of-death mortality data | 0–4 y: 4.5% (27/599)  
5–64 y: 3.9% (52/1347)  
≥65 y: 7.7% (718/9310) |
| Harris et al, 2008 | UK    | 2001–2006           | Retrospective regression analysis                                            | Mortality statistics of gastrointestinal pathogens from Health Protection Agency, Office of National Statistics/England and Wales | ≥65 y: 20% of deaths caused by IID other than C difficile were associated with norovirus infection; 13% of deaths from noninfectious IID were associated with norovirus |
| Hospitalizations |         |                     |                                     |                                                                             |                                                                                   |
| Grytdal et al, 2015 | US  | 2011–2012           | Prospective laboratory-based passive surveillance                           | AGE cases presenting to 4 Veterans Affairs hospitals                          | <65 y: 4.6% (10/217)  
≥65 y: 8.2% (13/158) |
| Rovida et al, 2013 | Italy | 2011–2012           | Retrospective laboratory based                                                | GE inpatients at 1 hospital                                                   | >65 y: 13.6% (20/147) |
| Verhoef et al, 2013 | Netherlands | 2008–2009           | Retrospective regression analysis                                            | AGE patients admitted to 6 hospitals                                          | ≥18 y: 6.7% (905/13,598)  
noroviruses cases/AGE hospitalizations; 4/41 samples = 9.8% |
| Fernandez et al, 2011 | Spain  | 2000–2007           | Retrospective laboratory based                                                | GE specimens submitted from inpatients at 1 hospital                         | 6–16 y: 7.2%  
16–64 y: 8.6%  
≥65 y: 11.1% |

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<tr>
<th>Study</th>
<th>Country</th>
<th>Data Period Studied</th>
<th>Study Design</th>
<th>Population</th>
<th>Prevalence of Norovirus Among Gastroenteritis Cases (n/N), Unless Otherwise Specified</th>
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<tbody>
<tr>
<td>Hospital and emergency department</td>
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<tr>
<td>Yi et al,32,2016</td>
<td>US</td>
<td>2013</td>
<td>Retrospective laboratory based</td>
<td>Residual specimens sent for culture from emergency department or inpatients at 2 hospitals</td>
<td>≥65 y: 11%</td>
</tr>
<tr>
<td>Tang et al,111,2013</td>
<td>Taiwan</td>
<td>2011–12</td>
<td>Prospective cohort</td>
<td>AGE patients at 1 hospital (53 outpatients, 6 emergency unit, 19 inpatients)</td>
<td>&lt;10 y: 28.1% (9/32) 10–40 y: 9.6% (3/31) &gt;40 y: 5.4% (5/92)</td>
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<tr>
<td>Emergency department</td>
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<tr>
<td>Al-Thani,155,2013</td>
<td>Qatar</td>
<td>2009</td>
<td>Prospective cohort</td>
<td>AGE patients presenting to emergency department in 1 hospital</td>
<td>&lt;1 y: 26.3% (10/38) 1–10 y: 20.5% (17/83) 11–20 y: 31.0% (9/29) 21–50 y: 38.7% (29/75) 51–60 y: 29.1% (7/24) &gt;60 y: 34.5% (10/29)</td>
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<td>Outpatient</td>
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<tr>
<td>Yu et al,112,2017</td>
<td>China</td>
<td>2012–2013</td>
<td>Prospective cohort surveillance</td>
<td>AGE cases presenting to 10 outpatient clinics at sentinel hospitals</td>
<td>5–24 y: 18% 25–44 y: 21% 45–64 y: 24% ≥65 y: 20%</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Year</td>
<td>Study Design</td>
<td>Setting</td>
<td>Age Distribution</td>
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<tr>
<td>Leblanc et al, 2017</td>
<td>Canada</td>
<td>2008–2009</td>
<td>Prospective laboratory based</td>
<td>Diarrheic and nondiarrheic cases receiving medical care</td>
<td>&lt;1 y: 11%&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
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<td>2–5 y: 54%</td>
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<td>6–10 y: 3%</td>
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<td>10–20 y: 18%</td>
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<td>20–30 y: 20%</td>
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<td>30–40 y: 25%</td>
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<td>40–50 y: 21%</td>
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<td>50–60 y: 16%</td>
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<td>60–70 y: 12%</td>
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<td>&gt;70 y: 19%</td>
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<tr>
<td>Costa et al, 2015</td>
<td>Portugal</td>
<td>2011–2013</td>
<td>Prospective cohort surveillance</td>
<td>National surveillance of hospitalized acute diarrhea cases</td>
<td>≥19 y: 6.4% (16/250)</td>
</tr>
<tr>
<td>Wu et al, 2015</td>
<td>China</td>
<td>2013–2014</td>
<td>Prospective laboratory based</td>
<td>AGE patients presenting as outpatients at 1 hospital</td>
<td>≥16 y: 26.5% (211/796)</td>
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<td>&gt;60 y: 15.2% (32/211)</td>
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<tr>
<td>Gao et al, 2015</td>
<td>China</td>
<td>2011–2013</td>
<td>Prospective laboratory based</td>
<td>AGE patients presenting as outpatients to 17 hospitals</td>
<td>≥18 y: 17.9% detection of Human</td>
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<td>Calicivirus (overall of 287 HuCV-</td>
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<td>positive samples, including from</td>
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<td>kids, 8% were sapovirus, 83%</td>
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<td>norovirus GII, and 7.3% norovirus</td>
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<td>G1)</td>
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<td>18–29 y: 16.2% (191/1179)</td>
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<td>30–39 y: 19.2% (129/672)</td>
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<td>40–49 y: 19.7% (92/467)</td>
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<td>50–59 y: 19.0% (96/504)</td>
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<td>60–69 y: 18.8% (53/282)</td>
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<td>70–79 y: 15.5% (42/271)</td>
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</table>

*(continued on next page)*
## Table 3 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Data Period Studied</th>
<th>Study Design</th>
<th>Population</th>
<th>Prevalence of Norovirus Among Gastroenteritis Cases (n/N), Unless Otherwise Specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grytdal et al, 2015</td>
<td>US</td>
<td>2011–2012</td>
<td>Prospective laboratory based passive surveillance</td>
<td>AGE cases using at 4 Veterans Affairs hospitals</td>
<td>≥65 y: 9.2% &lt;65 y: 5.5%</td>
</tr>
<tr>
<td>Tian et al, 2014</td>
<td>China</td>
<td>2008–2009</td>
<td>Prospective cohort</td>
<td>AGE patients presenting to gastroenterology department of 1 hospital</td>
<td>14–19 y: 23% (9/40) 20–29 y: 25% (43/174) 30–39 y: 26% (24/90) 40–49 y: 25% (16/65) 50–59 y: 22% (15/69) ≥14 y: 26.2% (136/519) ≥60 y: 36.7% (28/36)</td>
</tr>
<tr>
<td>Manso et al, 2013</td>
<td>Spain</td>
<td>2010–2011</td>
<td>Prospective laboratory based</td>
<td>GE cases presenting as outpatients (90%) or inpatients (10%) at 1 hospital</td>
<td>0–2 y: 31.4% (281/895) 3–5 y: 20.7% (41/198) 6–12 y: 31.3% (76/243) 13–18 y: 28.6% (20/70) 19–59 y: 28.2% (180/637) ≥60 y: 24.6% (146/593)</td>
</tr>
<tr>
<td>Gao et al, 2011</td>
<td>China</td>
<td>2007–2008</td>
<td>Prospective laboratory based</td>
<td>AGE patients presenting as outpatients at 1 hospital</td>
<td>18–83 y: 11.9% (48/403)</td>
</tr>
<tr>
<td>Gastañaduy et al, 2013</td>
<td>US</td>
<td>2001–2009</td>
<td>Retrospective analysis using time-series regression models</td>
<td>Gastroenteritis-associated health care encounters from MarketScan Commercial Claims and Encounters database</td>
<td>18–64 y: 8% (43,709/533,224) ≥65 y: 8% (10,744/133,007)</td>
</tr>
</tbody>
</table>
| Lau, 2004 | China | 2001–2002 | Retrospective laboratory based | 1. Patients at outpatient clinics in the Acute Diarrheal Disease Surveillance Program  
2. Patients with AGE at public hospitals |
|---|---|---|---|---|
|   |   |   |   | 1. 14-24 y: 4.7% (4/85)  
25–59 y: 7.6% (38/497)  
>60 y: 10.3% (26/252)  
2. 14–24 y: 9.7% (3/31)  
25–59 y: 8.9% (5/56)  
>60 y: 7.7% (2/26) |

<table>
<thead>
<tr>
<th>Huhulescu et al, 2009</th>
<th>Austria</th>
<th>2007</th>
<th>Prospective cohort</th>
<th>AGE cases to 3 general practitioners</th>
</tr>
</thead>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>&gt;60 y: 2/59 = 4.1%</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Community</th>
<th>deWit, 2001</th>
<th>Netherlands</th>
<th>1998–1999</th>
<th>Prospective cohort study (Sensor)</th>
<th>AGE in community cases</th>
</tr>
</thead>
</table>
|   |   |   |   | 18–64 y: 7.0%  
≥65 y: 12.9% |

<table>
<thead>
<tr>
<th>Amar et al, 2007</th>
<th>UK</th>
<th>1993–1996</th>
<th>Retrospective analysis of prospective cohort (IID study)</th>
<th>AGE in community cases initially drawn from the catchment of 70 general practices and followed over time</th>
</tr>
</thead>
</table>
|   |   |   |   | 10–19 y: 26% (30/117)  
20–29 y: 33% (100/303)  
30–39 y: 36% (137/382)  
40–49 y: 24% (70/295)  
50–59 y: 22% (47/209)  
60–69 y: 25% (48/194)  
≥70 y: 41% (57/138) |

*Abbreviations: AGE, acute gastroenteritis; GE, gastroenteritis; HuCV, human calicivirus; IID, infectious intestinal disease.  
* If point estimate was not reported in text or table, data points were extracted by digitizing plots.*
and March. Transmission is most likely to be person to person, and the outbreak length can range from 1 day to months. Hospital outbreaks are more commonly reported from several developed countries, at times leading to closure of wards or hospitals compared with the United States, where outbreaks in LTCFs predominate. The reason for these differences in norovirus hospital outbreak setting and control measures by country is not well understood but could be due to differences in reporting, testing, infection control, or epidemiology.

Few studies have examined norovirus genotypes affecting older adults, but available evidence suggests that GII.4 viruses predominate as a cause of norovirus disease in both LTCFs and health care–associated outbreaks as well as among older adults hospitalized for acute gastroenteritis. GII.4 outbreaks have been associated with more severe illness, hospitalizations, and deaths.

PREVENTION AND CONTROL OF NOROVIRUS OUTBREAKS IN HEALTH CARE SETTINGS

Health care facilities, including LTCFs and hospitals, are the most commonly reported settings for norovirus outbreaks in the United States and other industrialized countries. These outbreaks pose risks to patients, health care personnel, facility staff, and visitors and can affect the provision of care extending beyond an affected ward or unit.

Patient Cohorting and Isolation Precautions

In health care settings where the risk of transmission is high, transmission-based precautions can be the most effective means of interrupting transmission. Patients with symptoms of norovirus gastroenteritis should be separated from asymptomatic patients, and placed in a single occupancy room whenever possible. In absence of available private rooms, facilities should cohort symptomatic patients to reduce ongoing transmission. The patients should be managed with standard and contact precautions. Contact precautions should be maintained until at least 48 hours after resolution of symptoms; longer periods of time can be considered for those with complex medical problems who may experience prolonged diarrhea, viral shedding, and symptom relapse. Patient movement within a ward or unit should be minimized, and symptomatic and recovering patients should not leave the patient care area unless it is medically necessary. Nonessential visitors should be restricted from affected areas.

Staff Precautions, Hand Hygiene, and Personal Protective Equipment

Ill staff members should be excluded during their illness and for 48 hours to 72 hours after symptom resolution. To minimize the spread of infection, staff who have worked on affected areas should not be transferred to or work on unaffected areas for 48 hours after exposure. Nonessential staff should be excluded from working in areas experiencing a norovirus outbreak.

During outbreaks, washing hands with plain or antiseptic soap and running water for 20 seconds is paramount before and after providing care for patients with suspected or confirmed norovirus gastroenteritis. The use of alcohol-based hand sanitizers might additionally provide protection in between handwashing; however, studies have shown mixed effectiveness of alcohol-based hand sanitizers against norovirus and their use for norovirus remains controversial.

Personal protective equipment with contact and standard precautions (ie, gown and gloves) is recommended for persons entering the patient care area. If there are anticipated risks of splashing to the face, such as with patients who are vomiting, use of a surgical or procedure mask and eye protection or a full face shield can be considered.
Patient Transfer and Ward Closure

Consideration to the closure of wards to new admissions or transfers should be given to help reduce the size of the outbreak. Individuals recovering from symptoms can be discharged to their residence. Ward closure can be a costly measure and disruptive to the provision of care; the threshold for ward closure depends on the size of the outbreak and risk assessments by infection control personnel and facility leadership.2,77

Environmental Cleaning

Routine cleaning and disinfection of frequently touched environmental surfaces are key to interrupting norovirus spread; high-contact areas include toilets, faucets, hand/bed railings, phones, door handles, computer equipment, and kitchen preparation surfaces. In health care settings, Environmental and Protection Agency–registered products with label claims for use in health care settings should be used according to manufacturer’s recommendations (https://www.epa.gov/pesticide-registration/list-g-epa-registered-hospital-disinfectants-effective-against-norovirus). Sodium hypochlorite (chlorine bleach) is the preferred agent to disinfect human norovirus from surfaces and should be applied at a concentration of 1000 ppm to 5000 ppm (5–25 tablespoons household bleach per gallon of water).9

VACCINE PROSPECTS

A norovirus vaccine has the potential to reap enormous benefits to society, through reduction in morbidity and mortality as well as cost savings. In the United States, vaccination could avert 1.0 million to 2.2 million cases annually, assuming 50% efficacy and 12 months of protection; a vaccine with longer duration of protection up to 48 months and 75% efficacy at a cost of $50 could prevent 21,000 to 47,000 hospitalizations and 240 to 550 deaths and save $100 million to $2.1 billion dollars annually.145 Norovirus vaccines in development have been based on virus-like particles (VLPs), which contain the major capsid antigen but lack genetic material for viral replication.146 VLPs have been shown to be morphologically and antigenically similar to native viruses and cause humoral, mucosal, and cellular immune responses after oral and intranasal administration.147–149

There are several norovirus vaccines that are under development in preclinical and clinical trials using VLPs and involving intranasal, oral, and intramuscular routes of administration. One of the earlier candidates was a monovalent intranasal GI.1 VLP vaccine that demonstrated a serologic response in 70% of healthy adults who received 2 doses of the vaccine.150 This candidate vaccine was also efficacious against homologous challenge, and reduced the risk of gastroenteritis by 47% (95% CI, 15%-67%) and infection by 26% (95% CI, 1%-45%) and was well tolerated and immunogenic.150 The vaccine was subsequently modified from an intranasal to an intramuscular route of administration and from a monovalent to a bivalent formulation. It is currently in phase II clinical trials, contains GI.1 and GII.4 VLPs, and is the vaccine furthest along in clinical development.151 Serologic responses were demonstrated for both GI.1 and GII.4 as well as protection against severe clinical symptoms; however, vaccine efficacy was only 13.6% (95% CI, −21.0%-38.3%) for human norovirus infection. The only other vaccine in clinical trials is an adenoviral-vector based vaccine in a tablet formulation that encodes for a full length VP1 gene from GI.1; this vaccine recently met primary and secondary endpoints for safety and immunogenicity in an adult population in a phase I trial.152

Because norovirus affects multiple age groups, and unique populations have specific risk factors, including travelers, health care workers, individuals in LTCFs, and food handlers, developing a research agenda and clinical development plan has
been challenging. The vaccine candidates discussed previously have been studied in healthy adults, but the greatest burden of disease is in young children and older adults, and a vaccine is likely to yield greatest impact in these age groups. Ongoing clinical trials in these groups include the intramuscular GI.1/GII.4 vaccine candidate with aluminum hydroxide adjuvant in the pediatric population as well as safety and immunogenicity studies of the bivalent formulation in adult and elderly participants.

Several considerations remain for the development of a norovirus vaccine. First, due to limited duration of immunity after natural infection and challenge studies, as well as the continual emergence of new strains, any vaccine candidate will warrant close attention to the duration of protection, need for booster doses, and reformulation. Second, the diversity between and within genogroups will necessitate development of a vaccine that affords broad heterotypic protection; a multivalent vaccine could offer such protection. Third, given prior exposure and underlying conditions, the immune response is likely to differ in children, adults, the elderly, and the immunocompromised; consideration of different vaccines for these populations might be explored. Fourth, uptake of vaccines in the elderly has proved challenging. Incorporation into the childhood immunization schedule might be more feasible and could have important indirect benefits by limiting transmission in the general population, but the complexity of the pediatric schedule necessitates careful consideration of many factors, including acceptability and level of vaccine effectiveness. Combination vaccines could improve acceptability across different age groups; products in the preclinical phase include a trivalent norovirus/rotavirus combination vaccine, and a norovirus P particle dual vaccine that includes norovirus with influenza, hepatitis E, and rotavirus. Additionally, targeting high-risk groups for vaccine receipt, such as vaccination of older adults who are living in LTCFs as well as staff and employees who work there, could be an attractive option for this particularly vulnerable population.

SUMMARY

The burden of norovirus disease is vast, and older adults are particularly at risk for severe outcomes, including prolonged symptoms and death. LTCFs and hospitals are the most commonly reported settings for norovirus outbreaks in developed countries, and older adults in these settings are more likely to experience health care–associated infection with more severe infections and poor outcomes. Although the current treatment of norovirus infection is primarily supportive, with the recent description of a human enteroid culture system, renewed interest in development of antivirals is anticipated. In addition, the future holds promise for prevention of disease, because several norovirus vaccines in clinical trials have the potential to reap enormous benefits for multiple age groups and populations.

REFERENCES


