HHS Public Access

Author manuscript

J Hosp Infect. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

J Hosp Infect. 2015 April ; 89(4): 296–301. doi:10.1016/j.jhin.2015.01.011.

Burden of norovirus in healthcare facilities and strategies for outbreak control

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SUMMARY

Norovirus is the most frequently occurring cause of community-acquired acute gastroenteritis in people of all ages. It is also one of the most frequent causes of outbreaks in healthcare settings, affecting both long-term care facilities and acute care hospitals. Whereas norovirus gastroenteritis is typically mild and resolves without medical attention, healthcare-associated infections often affect vulnerable populations, resulting in severe infections and disruption of healthcare services. Globally, most norovirus outbreaks in hospitals and residential care institutions are associated with genogroup II type 4 (GII.4) strains. Recent data demonstrate that excess mortality occurs during outbreak periods in healthcare facilities. Nosocomial outbreaks can result in large economic and societal costs. Current control measures for norovirus are largely based on general infection control principles, and treatment is mainly supportive and non-specific. While neither vaccines nor antiviral agents are currently available, both are being developed with encouraging results.

Keywords

Antiviral agents; Gastroenteritis; Genogroup II type 4; Infection control; Norovirus

Introduction

Norovirus is the leading cause of community-acquired gastroenteritis in all age groups, being associated with 18% of all acute gastroenteritis cases globally.[1] An estimated 19–21 million cases of norovirus and nearly 800 resulting deaths occur in the USA each year.[2] The high prevalence of norovirus in the community makes it difficult to prevent introduction into healthcare settings, including long-term care facilities and acute care hospitals, where infection can spread and result in severe illness. Surveillance data from high-income countries around the world consistently indicate that most norovirus outbreaks occur in healthcare facilities.[3] Both acute care hospitals and long-term care facilities are affected.

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Conflict of interest statement

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

From 1992 to 2000, ~40% of 1877 reported norovirus outbreaks in England andWales occurred in hospitals, with another 39% in residential care facilities.[4] Similar findings have been reported elsewhere in Europe and in other high-income countries, where outbreaks in acute care and long-term care facilities are roughly equal in frequency.[5–7] Reports of acute care outbreaks in the USA, however, are relatively infrequent, and >60% of all reported norovirus outbreaks in the USA occur in long-term care facilities such as nursing homes.[8] Though this discrepancy in rates of acute care norovirus outbreaks between the USA and other high-income countries may be the result of a lower incidence of acute care outbreaks in the USA, it may also signify substantial underreporting of such outbreaks. A recent survey of infection prevention personnel in US hospitals provides evidence for underreporting; norovirus was reported as the most frequent cause of outbreaks of hospital-acquired infection, accounting for 18% of outbreaks and >65% of hospital unit closures.[9] Studies in Europe also have found evidence for significant underreporting of norovirus illness, including nosocomial infection.[10,11]

Biology and transmission characteristics

Noroviruses are positive-sense single-stranded RNA viruses that are both genetically and antigenically diverse.[12] Human illness is predominantly caused by two genogroups (G) of norovirus, GI and GII, which consist of nine and 22 genotypes, respectively.[13] Noroviruses have evolved several characteristics that facilitate transmission through human populations. The virus is transmitted primarily through the fecal-oral pathway; ingestion of as little as 18–1000 viral particles can lead to infection.[14,15] Recent analysis of volunteer studies suggests a higher ID^{50}, but still supports the notion of a low infectious dose. In addition to direct person-to-person transmission, people may come into contact with norovirus through contaminated food, water, or aerosolized particles.[16–18] Aerosolization of norovirus following vomiting can be particularly problematic, as norovirus particles can settle on surfaces and fomites and survive for long periods of time, and have been shown to withstand low levels of chlorine disinfection and temperatures ranging from freezing to 60°C.[16,19–22] A study of environmental samples from outbreak-affected hospital wards found GII norovirus on almost half of the swabs, including in dust and on surfaces.[23] Once the virus is ingested, there is an incubation period of between 12 and 48 h, after which infected persons generally experience acute onset of symptoms of gastroenteritis, such as vomiting, diarrhoea, abdominal cramps, as well as systemic symptoms, including fever. However, 20–30% of infected individuals may remain asymptomatic. [24] The dynamics of viral shedding can also facilitate norovirus transmission. Shedding can precede symptom onset in up to 30% of those exposed to the virus, peaks around four days after exposure, and can continue for up to eight weeks.[14,25] Viral particles are shed profusely in faeces, with between 10^5 and 10^{10} viral copies per gram of stool, but can also be found in vomitus.[25] Asymptomatic individuals may also shed norovirus, though the infectivity of shed particles is unknown. [14,25,26] Together, the long shedding period and large amount of virus shed per infected person contribute to environmental persistence of the virus and secondary attack rates of ≥30% among contacts of infected individuals.[20]

Transmission and control in healthcare settings

Many of the same characteristics that promote community transmission are magnified in the healthcare setting. Whereas most community cases of norovirus resolve within 12–60 h and without medical attention, nosocomial outbreaks of norovirus largely affect vulnerable populations, including the institutionalized elderly and the immunocompromised.[27] In such populations, typically mild infections may progress to more severe or prolonged illness.[27–31] Among vulnerable populations, symptoms of norovirus may last for between four and six days.[32] However, chronic norovirus symptoms and shedding lasting for 15 months were described in an HIV-affected patient. [31] In addition to longer symptomatic periods, individuals in healthcare settings may shed for extended periods of time, acting as reservoirs for spread of the virus to other susceptible persons.[32–34] Reports have detailed shedding periods ranging from 22 to 433 days in paediatric cancer patients.[35]

Nosocomial outbreaks of norovirus may result in severe patient outcomes. Whereas deaths caused by norovirus are rare in the community, individuals in healthcare facilities, particularly the elderly, are more likely to be hospitalized or die.[36–40] Estimates from England, Wales, The Netherlands, and the USA suggest that norovirus constitutes a leading cause of gastroenteritis-associated deaths in those aged >65 years of age.[36,37,41,42] Increases in the annual numbers of deaths have been observed in years in which novel GII.4 viruses emerged, and were recognized to cause global increases in cases. The widely circulating GII.4 noroviruses undergo antigenic changes to escape from population immunity, resulting in emergence of a new strain every two to four years.[43–47] These novel strains have been associated with pandemics as well as with increased morbidity and mortality.[40,45,46,48,49] GII.4 noroviruses are particularly predominant in healthcare settings.[5,7,21] Some of the strongest evidence that norovirus plays a causal role in deaths comes from a study of >400 US nursing home outbreaks, where an 11% (95% CI: 5–18%) increase in all-cause mortality was observed during periods in which these institutions were experiencing outbreaks.[50] A detailed outbreak investigation suggested that some excess mortality may be associated with drugs used frequently in the elderly.[51]

In addition to causing severe illness in hospitalized individuals, norovirus may also spread rapidly throughout facilities, leading to high attack rates. A recent study demonstrated that the average interval of time from the infection of one patient to another (i.e. the serial interval) was 1.86 days.[52] This study also provided evidence that proximity (i.e. occupying a bed in the same bay as an infected patient) was a risk factor for infection in patients. Since nurses and other healthcare staff also work in close proximity to patients, the virus commonly affects staff working in outbreak wards. In one outbreak in a US tertiary care hospital, 105 healthcare workers in two separate units became ill, of whom 13 visited the emergency department or were hospitalized for their condition. [53] Given the high levels of contact in healthcare settings, defining the relative role of staff and patients, both symptomatic and asymptomatic, is a critical question for norovirus transmission. A modelling study of a series of outbreaks in Dutch hospitals suggests that symptomatic patients, rather than asymptomatic healthcare workers, are the main drivers of transmission.[54]

Current prevention and control measures for norovirus aim to minimize the risk of introduction and transmission of the virus in healthcare settings.[55,56] The recommendations for prevention and control are summarized in Box 1.[57] One particularly controversial control measure is the closure of hospital wards or units to new admissions. This is a costly measure from an economic perspective and disruptive to the provision of healthcare services. The efficacy and costeffectiveness of ward closure remain a subject of debate, although there is some evidence suggesting that rapid implementation of control measures reduces the overall duration and final outbreak size.[58]

Box 1

Key infection control recommendations for the control of norovirus outbreaks in healthcare settings[a]

Patient cohorting and isolation precautions

- Place patients with norovirus gastroenteritis on contact precautions for a minimum of 48 h after the resolution of symptoms.
- When symptomatic patients cannot be accommodated in single occupancy rooms, efforts should be made to cohort patients into separate groups (e.g. grouped among those who are symptomatic, exposed but asymptomatic, and unexposed).
- Minimize patient movements within a ward or unit during norovirus outbreaks.
- Symptomatic and recovering patients should not leave the patient care area unless it is for essential care or treatment.
- Consider suspending group activities.
- Healthcare personnel who have recovered from recent suspected norovirus infection associated with this outbreak may be best suited to care for exposed or symptomatic patients.

Hand hygiene

- Actively promote adherence to hand hygiene among healthcare personnel, patients, and visitors in patient care areas affected by outbreaks of norovirus gastroenteritis.
- During outbreaks, prioritize hand hygiene with soap and water after providing care or having contact with patients suspected or confirmed with norovirus gastroenteritis.

Personal protective equipment (PPE)

- If norovirus infection is suspected, individuals entering the patient care area should wear PPE according to contact and standard precautions (i.e. gowns and gloves, and among vomiting patients, face masks).

Environmental cleaning

- Perform routine cleaning and disinfection of frequently touched environmental surfaces.
- Increase the frequency of cleaning and disinfection of patient care areas and frequently touched surfaces during outbreaks of norovirus gastroenteritis.
- Clean and disinfect surfaces, starting from the areas with a lower likelihood of norovirus contamination, then to areas with greater likelihood.
- Use standard precautions for handling soiled patient-service items or linens, which includes the appropriate use of PPE.
- Consider changing privacy curtains routinely and upon patient discharge or transfer.

Patient transfer and ward closure

- Closure of wards to new admissions or transfers may be a measure to attenuate the magnitude of a norovirus outbreak.

- Consider patient transfers only if receiving facilities are able to maintain contact precautions. During outbreaks, medically suitable individuals recovering from norovirus gastroenteritis can be discharged to their place of residence.

Personnel leave

- Exclude ill personnel from work for a minimum of 48 h after the resolution of symptoms. Once personnel return to work, strict adherence to hand hygiene must be maintained.
- Establish protocols for staff cohorting in the event of a norovirus outbreak.
- Exclude non-essential healthcare providers, students, and volunteers from working in areas experiencing outbreaks of norovirus.

Visitors

- Restrict non-essential visitors from affected areas during outbreaks.
- For those facilities where it is necessary to have continued visitation privileges, screen and exclude visitors with symptoms consistent with norovirus infection.

Diagnostics

- Submit stool specimens as early as possible during a suspected norovirus gastroenteritis outbreak and ideally from individuals during the acute phase of illness.
- In the absence of clinical laboratory diagnostics for norovirus, or in the case of delay in obtaining laboratory results, use Kaplan's clinical and epidemiologic criteria to identify a norovirus gastroenteritis outbreak.

[a] Adapted from MacCannell *et al.*[57]

Economic burden

Control measures such as exclusion of infected healthcare workers, patient isolation, and ward closures are intended to reduce viral transmission, but they may also lead to disruption of health services and contribute to the economic losses. The large number of affected healthcare workers in the previously described US tertiary care hospital outbreak led to staffing shortages and a restriction on new patient admissions. This single large outbreak was estimated to have resulted in more than $650,000 in lost revenue, staff wages, and cleaning expenses. [53] Hospitals in other countries have also experienced similarly substantial losses. An outbreak in a Swiss hospital cost $40,675 in additional diagnostic materials, increased need for healthcare, revenue loss, and sick leave.[59] In this outbreak, patient bed closures were found to have contributed the most to incurred losses, costing roughly three times more than lost productivity costs from infected healthcare staff.[59] Nosocomial outbreaks of acute gastroenteritis have been estimated to cost the English National Health Service roughly $184 million annually.[3]

Progress in antiviral treatment and vaccine development

In recent years, improved understanding of the public health burden of norovirus infection and the accompanying costs have given impetus to the development of antiviral treatments and vaccines. There is currently no specific treatment for norovirus gastroenteritis; cases are managed with supportive therapy such as rehydration. Effective treatment is especially important for those who are immunocompromised, since they may have one or more comorbidities or may be recovering from a major procedure such as an organ transplant. [29]

In these individuals, large volumes of fluid loss and the inability to digest food may necessitate intravenously administered nutritional formulae.[29] Antivirals such as favipiravir and ribavirin, which work by inhibiting viral entry and replication, have demonstrated activity against other RNA viruses as well as norovirus replicons.[29,60] These treatment options have not been tested in humans. Moreover, the rapid kinetics of norovirus infection may limit the clinical utility of antivirals.

Though evidence suggests that there may be numerous potential benefits from norovirus vaccines, development has been impeded by technical limitations, most notably by the lack of a cell culture system. A norovirus vaccine could potentially decrease societal costs each year by up to $2.1 billion and prevent nearly 48,000 hospital admissions.[61] However, there has been little success in culturing norovirus *in vitro*, so attenuated and inactivated vaccines cannot be created.[62] Since the virus is only known to infect humans, there are no appropriate animal models available to evaluate immune response. Recently, however, one study reported a successful culture system for human norovirus. Researchers demonstrated that the GII.4 Sydney strain of norovirus infected human B cells *in vitro* in the presence of histo-blood group antigens (HBGA) or HBGA-expressing bacteria.[63] Although this recent achievement has not yet been replicated, the ability to grow norovirus in the laboratory would lead to critical developments including infectivity and neutralizing antibody assays. To date, norovirus vaccine development has largely been predicated on the ability to produce virus-like particles (VLPs), viral capsid structures made of self-assembling proteins.[64–66] Although they lack a viral genome, VLPs mimic the native virus, and have successfully been used in vaccines for hepatitis B and human papillomavirus.[67] Results from a multicentre trial of a monovalent VLP intranasal vaccine found that the vaccine reduced the frequency of norovirus gastroenteritis from 69% in recipients of the placebo to 37% in volunteers who received the vaccine.[68] The success of the monovalent vaccine prompted the development of a bivalent injectable vaccine containing both GI.1 and GII.4 virus-like particles. The vaccine was found to be immunogenic and well tolerated by volunteers, and reduced the severity of illness in those who received the vaccine. [69,70] This vaccine is yet to be evaluated for safety or efficacy in a large Phase III trial. Other VLP-based vaccinations are also in development, including a trivalent GII.4/GI.3/ rotavirus VP6 product and a dry powder intranasal formulation. [71,72] An alternative vaccine, based on norovirus P particles expressed in an *Escherichia coli* system, contains only the protruding outer portion of the norovirus protein.[73,74] When administered to mice, this vaccine candidate elicited effective humoral and cellular immune responses, and may elicit a stronger T-cell response in comparison to the two-dose intranasal VLP vaccine.[74,75]

There are several challenges in developing and licensing a norovirus vaccine, as well as in establishing recommendations for them. Noroviruses are genetically diverse, and frequently undergo antigenic drift, giving rise to new strains.[76] Immunity to norovirus is of limited duration. Data from early human challenge studies suggested that immunity could last from two months to two years; subsequent studies demonstrated immunity of at least six months.[77,78] Moreover, protection against one strain of norovirus may not preclude infection with another strain. In a study of volunteers who were challenged with three different strains, individuals were susceptible to antigenically distinct strains earlier than they were to

more closely related strains.[79] Vaccines should aim to elicit some type of cross-reactive protection, and include consideration of potential novel strains during formulation.

Conclusions

While norovirus affects people of all ages and is exceedingly widespread in the community, much of the considerable health and economic burden is concentrated in healthcare-associated outbreaks. It may be impossible to prevent every introduction of norovirus into healthcare facilities. Controlling transmission is also challenging, owing to the multiple routes of transmission, high infectiousness, and environmental stability of noroviruses. Current guidelines for prevention and control are largely based on sound infection control principles, but an evidence base for the efficacy of specific measures is lacking. Both observational and intervention studies should be undertaken to address this knowledge gap. In the future, a norovirus vaccine may become an important tool for control of disease in healthcare settings, but several challenges remain.

Acknowledgments

Funding sources

This research was supported in part by an appointment to the Research Participation Program at the Centers for Disease Control and Prevention administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and CDC.

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