HHS Public Access

Author manuscript

Am J Infect Control. Author manuscript; available in PMC 2016 August 17.

Published in final edited form as:

Am J Infect Control. 2015 October 1; 43(10): 1066–1069. doi:10.1016/j.ajic.2015.05.032.

Control of norovirus outbreak on a pediatric oncology unit

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Abstract

Background—Patients undergoing treatment for cancer with chemotherapy and hematopoietic stem cell recipients are at risk for severe morbidity caused by norovirus (NV).

Methods—We describe a NV outbreak on the Memorial Sloan Kettering Cancer Center's pediatric oncology unit. Stool testing for diagnosis of NV was performed by real-time polymerase chain reaction (PCR).

Results—Twelve NV cases occurred; 7 were hospital acquired. Twenty-five health care workers reported NV compatible illness. Patient-to-patient transmission occurred once. The practices of the Centers for Disease Control and Prevention were supplemented with electronic surveillance, surrogate screening for NV, and heightened cleaning. Two additional cases occurred after implementation of interventions. Long-term shedding was detected in 2 patients.

Conclusion—We describe interventions for controlling NV on a pediatric oncology unit. High-risk chronic shedders pose ongoing transmission risks. PCR is a valuable diagnostic tool but may be overly sensitive. Surrogate markers to assess NV burden in stool and studies on NV screening are needed to develop guidelines for high-risk chronic shedders.

Keywords

Norovirus; Outbreak; Pediatric; Molecular diagnostics; Immunocompromised

Norovirus (NV) is the most common cause of gastroenteritis in the United States.[1] Three NV genogroups are known to cause disease in humans; among these, genogroup 2 genotype

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Conflicts of interest: None to report.

4 is associated with a high rate of hospitalization and occasional mortality.[2] For all genogroups, the incubation period is short (15-50 hours), and time to symptoms appears to correlate with the viral inoculum. In otherwise healthy individuals, illness is sudden with short, self-limiting symptoms of gastroenteritis, including nausea, vomiting, diarrhea, and abdominal pain.[3] NV has been identified as a cause of prolonged and severe gastroenteritis in immunocompromised hosts, especially solid organ and hematopoietic stem cell transplant (HSCT) recipients.[4,5]

The infectious dose (50%) of NV is low (approximately 1,320 genomic equivalents) with transmission occurring via the fecal-oral route, contact with secretions during vomiting, contaminated food with improper handling, and fomites.[6] The virus can survive in the environment for up to 12 days on certain surfaces but is generally susceptible to sodium hypochlorite (concentration ≤ 1000 ppm).[7,8]

NV cannot be isolated using traditional cell culture. Antigen tests have limited sensitivity and negative predictive value and therefore are not ideal for clinical diagnostics.[9] The current gold standard for diagnosis of NV is genetic detection by reverse transcriptase real-time polymerase chain reaction (PCR).[10] Hospital outbreaks caused by NV are usually associated with >50% attack rate and often require ward closures.[11]

We describe an outbreak of NV infection on the pediatric oncology unit at Memorial Sloan Kettering Cancer Center (MSKCC) in January-February 2014. We discuss the infection control interventions and novel surveillance strategies that helped successfully contain the outbreak. We also discuss unresolved infection control issues surrounding the isolation and management of NV cases in the outbreak and nonoutbreak oncology-transplant setting, especially in the context of highly sensitive and rapid newer nucleic acid amplificatio–based detection methods that are now the most widely used tests for routine diagnosis of NV.[12]

MATERIALS AND METHODS

MSKCC is a 470-bed tertiary care hospital in New York City with a 33-bed inpatient pediatric unit. Each year there are approximately 1,500 pediatric admissions and 11,000 pediatric patient days. The average length of stay for pediatric patients is 7.4 days. The pediatric day hospital is a 36-bed facility for outpatient chemotherapy administration and outpatient evaluation and management with 110-150 visits per day. The pediatric day hospital is located adjacent to the inpatient pediatric unit and incorporates a 9-bed pediatric urgent care center.

A case was defined as a patient with symptoms and a positive PCR test. For staff, a case was defined as sudden onset gastrointestinal illness (nausea, vomiting, or diarrhea) that resolved in <72 hours. Hospital-acquired cases were defined by onset of illness 24 hours after hospital admission. For the purpose of this article, special contact precautions refer to use of gowns, gloves, hand hygiene (alcohol based gel or handwashing with soap and water) before entry into patient room, and handwashing after patient encounter. All special contact isolation rooms are cleaned daily with bleach.

Stool specimens were tested for NV by a reference laboratory (ViraCor-IBT Laboratories, Lee's Summit, MO) using qualitative real-time reverse transcription PCR assay detection and differentiation of NV genogroups I and II.[10] Additional testing (surveillance) was performed in-house on a limited number of specimens using the Luminex xTAG Gastrointestinal Pathogen Panel Assay (Luminex, Austin, TX).[10] The xTAG Gastrointestinal Pathogen Panel (GPP; Luminex, Austin, TX) is a multiplexed nucleic acid test which was developed and received clearance from the United States Food and Drug Administration in 2013. The current version of the GPP assay detects the following targets: *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Clostridium difficile* (toxins A and B), shiga toxi–producing *Escherichia coli*, enterotoxigenic *E coli*, vibrio cholera, NVs (group GI and GII), rotavirus, adenovirus (40/41), *Entamoeba histolytica*, *Giardia lambia*, and *Cryptosporidium* spp. Detection of pathogens by the GPP assay is accomplished using 4 steps: nucleic acids extraction from stool samples, amplification of targets DNA-RNA by PCR or real-time PCR, hybridization of amplified DNA to Luminex beads, and detection of the beads by the Luminex 200 platform. All steps are performed in a single reaction with a turnaround time of 5-6 hours. The rapid turnaround time of the GPP (within 24 hours) and its inclusion of NV allows for almost real-time detection of NV outbreak because the number of stool samples positive for NV can be monitored and tracked daily, and any increase over baseline can readily be identified.

The MSKCC Institutional Review Board granted a Health Insurance Portability and Accountability Act waiver of authorization to conduct the study.

RESULTS

Outbreak

The timeline of cases, including patients and health care workers (HCWs), is shown in Figure 1. Fourteen cases of NV were identified at MSKCC between January 31, 2014, and February 22, 2014. Twelve occurred in pediatric patients, and 2 occurred among adult patients admitted on separate floors. Their demographic and clinical profile is shown in Table 1. Seven cases were hospital acquired, occurring on days 2, 2, 5, 12, 19, 45, and 115 of hospitalization. The index case (case 1) was diagnosed on a specimen sent January 30, 2014. The patient was a 21-month-old boy with severe combined immunodeficiency who had undergone allogenic HSCT complicated by gastrointestinal graft versus host disease. Only 2 cases shared a room and appeared linked epidemiologically; these were the second and third cases who were roommates for 19 hours at the time that case 2 developed symptoms of vomiting and diarrhea. Case 3 developed symptoms 24 hours later.

Twenty-five HCWs reported NV compatible illness between February 1 and February 15; only 1 among these was tested and was positive. With the exception of 1 nurse, all HCWs with NV compatible illness on the ward had direct contact with patients infected with NV.

Infection control interventions

Several interventions were initiated to address the outbreak (Fig 2). All patients on the pediatric floor were placed on special contact precautions. In addition, all HCWs wore

masks when caring for patients with active vomiting. Bleach was used on all items in contact with patients, including soiled linen and other items. The inpatient playroom was closed, and all toys were cleaned with bleach. Environmental cleaning with bleach was increased to twice daily for the rooms and 3 times daily for high traffic areas, including the pantry and pediatric day hospital. All necessary medical testing, such as radiographs and ultrasound, was performed on the floor for symptomatic patients, and nonurgent testing was postponed.

In addition, clinical and laboratory-based surveillance were implemented. For clinical surveillance, daily reports of patients and staff with gastrointestinal symptoms were prepared by infection control staff and the nursing supervisor for the pediatric floor. All symptomatic patients were placed in private rooms until testing results were available and negative. Staff with gastrointestinal symptoms were furloughed until no longer symptomatic for 24 hours. Laboratory surveillance was performed by generating an automated hourly electronic report for all stool testing performed for NV throughout the hospital, including tests done in pediatric patients. The number of tests sent for *C difficile* infection was monitored as well. This was considered as a surrogate marker for symptom surveillance.

To ascertain the completeness and appropriateness of testing, 12 specimens routinely submitted from the pediatric floor for *C difficile* testing during the outbreak were recovered from storage and tested for NV. All 12 specimens were negative. Other strategies implemented included restriction of visitors and ancillary staff and communication to all visitors and all ancillary departments (eg, dietary, radiology, physical therapy) throughout the hospital.

Overall, 4 hospital-acquired cases occurred after implementation of infection control precautions; however, the first 2 were within 48 hours of the interventions and likely represented transmission events that occurred before the interventions were implemented. Repeat testing was performed in 8 patients; 7 were still shedding NV when tested 5, 10, 13, 14, 19, 95, and 123 days after the first test. A single patient tested negative when retested 48 days later. The index case shed NV for 123 days, and secondary transmission from the index case to 3 HCWs was suspected 59 days after NV was first detected. This patient's post-HSCT course was complicated by gastrointestinal graft versus host disease and recurrence of gastrointestinal symptoms correlated with suspected NV transmission to HCWs.

DISCUSSION

We describe an outbreak of NV among hospitalized children on a pediatric oncology unit. At least 2 of the affected children have become long-term shedders and may represent a risk for future outbreaks. The impact of NV infection on immunocompromised patients, especially HSCT recipients, can be profound and long lasting. NV can lead to chronic debilitating wasting syndrome, often requiring nutritional support and prolonged hospitalization for management.[4] Early recognition of an outbreak and timely intervention are crucial to minimize spread of NV in high-risk patients. Recommendations from the Centers for Disease Control and Prevention on outbreaks in health care settings are a useful resource for the management of outbreak; however, gaps persist in best practices for long-term shedders and the role of active surveillance.[13]

In addition to implementing Centers for Disease Control and Prevention's recommendations for outbreak control, we used several additional novel strategies to mitigate transmission risk to patients. First, we generated automated hourly NV diagnostic testing reports (requested and sent). Infection control staff used these reports for surveillance purposes to ensure all symptomatic patients were promptly placed in isolation and to prioritize reporting of test results. Second, we performed in-house screening (using xTAG GPP) on stool samples submitted for a different diagnostic test (Xpert *C. difficile* PCR; Cepheid, Sunnyvale, CA) to understand the magnitude of the outbreak. This strategy was used to determine if unit-wide screening for NV should be implemented. All results were negative, and further screening or ward closure was not pursued. Third, high traffic areas on the unit were identified, and heightened cleaning with bleach was performed in these areas. In addition to these, NV-specific information was provided for education of patients and families and staff members. Finally, restriction of all patient visits by volunteers, teachers, and ancillary staff was implemented through the period of the outbreak along with daily communication with Ronald McDonald house.

There was widespread NV activity in the community at the time of the outbreak. Although several HCWs became ill in the post-intervention period, the steps taken were successful in limiting the spread of NV to patients, with only 2 additional cases detected >48 hours after the infection control interventions were put into place. It is possible that there was ongoing shedding occurring from the HCWs and patients, which would only be detected through ongoing systematic retesting of all cases, which was not feasible in this setting.

Our study has several limitations. The case definitions for patients (laboratory testing based) and staff (clinical) were different. This might have led to an overestimation of cases among staff; however, the symptoms and timing were very suggestive. Second, we did not perform sequence-based analysis to confirm genetic identity of NV cases; however, all belonged to genogroup GII. Because of this, we are unable to determine how many cases among patients and staff might have arisen from community-based exposures.

Although peak NV activity is observed during winter months, transmission can occur year-round. Horizontal spread of NV has mainly been reported from symptomatic patients.[14] The risk of secondary transmission of NV from chronic shedders is not completely understood, but it has been reported in a single retrospective study.[15] No reported outbreaks among high-risk patients have been linked to an asymptomatic shedder.[16,17] The duration of shedding that we noted in our patients is consistent with the longer duration of symptoms and shedding that has been noted in other studies of immunocompromised patients, including immunocom-promised pediatric patients, as compared with immunocompetent patients.[18-22] Diagnostic testing with PCR allows for rapid testing of samples and early institution of infection control precautions; however, the higher sensitivity of the test results in frequent detection of prolonged NV shedding.[18] Because of the possibility of long-term shedding and the increased likelihood of detecting it, development of surrogate markers of viral burden in stool and studies on utility of seasonal screening for NV in certain high-risk population may be necessary to distinguish between detection of chronic shedding and new acquisition of NV in the context of PCR-based testing.

In an outbreak setting among high-risk patients, we now extend isolation precautions through the duration of hospitalization. For transplant recipients with chronic NV shedding in the early post-transplant period or with coexistent gastrointestinal graft versus host disease, we continue special contact precautions while patients are hospitalized and recommend strict hand hygiene with soap and water during ambulatory visits. In this situation, complex host issues, including treatment-related impairment in cell-mediated immunity, influence the amount of virus shed in stool and associated symptoms, which affects the likelihood of transmission. For other oncology settings, lack of occurrence of secondary cases in conjunction with absence of gastrointestinal symptoms and stable immunosuppression (lack of use of T-cell suppressive regimen) can help determine when contact precautions can be terminated for long-term shedders, an approach similar to what is currently recommended for individuals asymptomatically colonized with *C difficile*.

In our experience, symptom-based assessment for discontinuation of precautions among pediatric oncology patients may not be reliable because of the presence of chronic symptoms associated with NV infection or coexistent conditions, such as gastrointestinal graft versus host disease and chemotherapy or antibiotic-related diarrhea. An indirect estimate of NV viral burden based on signal intensity or threshold cycle value for PCR-based diagnostic tests may help establish reliable cutoffs and how these results are reported to clinicians.

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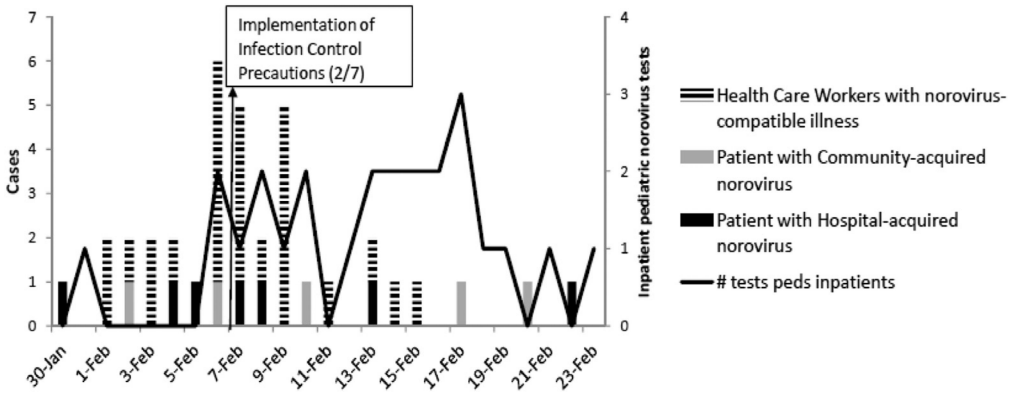

Fig 1.

Timeline of onset of the norovirus cases among 25 health care workers (clinical) and 12 patients (laboratory confirmed). *peds*, pediatric.

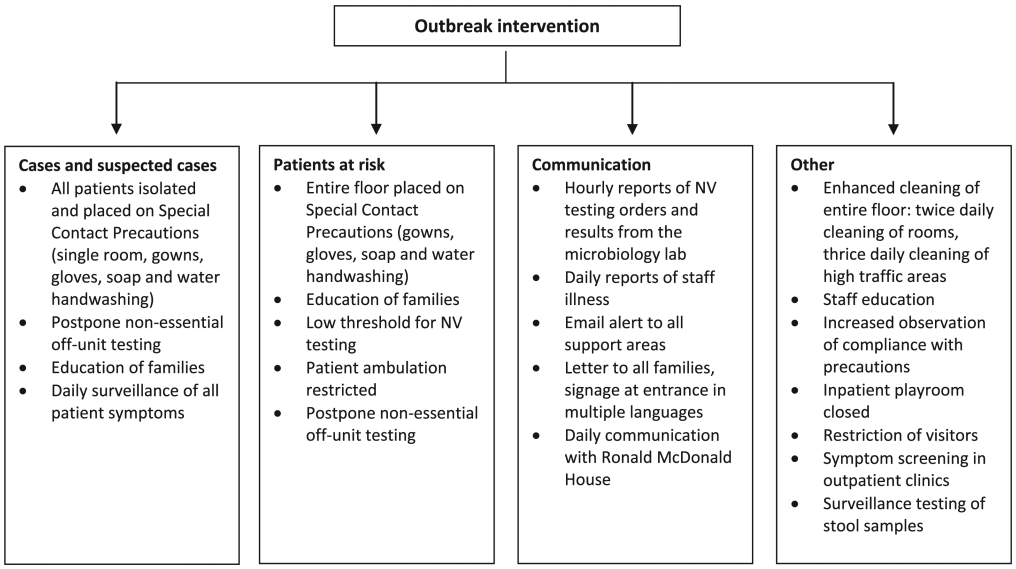

Fig 2.

Outbreak interventions implemented to contain NV transmission on a pediatric oncology unit. *NV*, norovirus.

Table 1

Demographic and clinical characteristics of patients with community-onset and hospital-acquired norovirus infection

Characteristic	Value
Sex	
Male	6 (50)
Female	6 (50)
Mean age (y)	5.5
Underlying disease	
Acute lymphoblastic leukemia	3 (25)
Chronic granulomatous disease	1 (8)
Ewing sarcoma	1 (8)
Neuroblastoma	4 (33)
Non-Hodgkin lymphoma	1 (8)
Severe combined immunodeficiency	2 (17)
Hematopoietic stem cell transplant recipient	3 (25)
Hospital day of onset (mean)	29
Origin of infection	
Hospital acquired	7 (58)
Community acquired	5 (42)

NOTE. Values are n (%) or as otherwise indicated.