Published in final edited form as:

J Hosp Infect. 2009 June ; 72(2): 185–187. doi:10.1016/j.jhin.2009.03.010.

Noroviruses as a Cause of Sporadic Healthcare-Associated Diarrhea

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Keywords

norovirus; sporadic; diarrhea; healthcare-associated

Healthcare-associated diarrhea is an important nosocomial disease worldwide. The etiologic agent of healthcare-associated diarrhea is undefined in the majority of cases. *Clostridium difficile* (CD) is the only enteric pathogen regularly identified as a cause of healthcare-associated diarrhea, but is detected in only 15-20% of nosocomial diarrhea episodes.¹

Norovirus (NoV) gastroenteritis outbreaks in healthcare facilities have been well-documented.^{2, 3} However, the prevalence of sporadic NoV infections as a cause of healthcare-associated diarrhea in adults, in a non-epidemic setting, has not been established. With their environmental stability, resistance to most cleaning agents, and prolonged fecal excretion after clinical recovery,⁴ NoVs may play a role as a pathogen of healthcare-associated diarrhea. This study was designed to investigate the prevalence of sporadic NoV nosocomial diarrhea at a large tertiary university-based hospital in Houston, Texas.

Stool specimens from hospitalized patients with healthcare-associated diarrhea from January to December 2007 were collected at St. Luke's Episcopal Hospital (SLEH), a 627-bed tertiary university-based hospital. Stool samples were collected over one year to avoid possible overestimation biases related to isolated NoV outbreaks. No NoV outbreaks were noted at SLEH during this study period. Healthcare-associated diarrhea was defined as 3 unformed stools within a 24-hour period, with onset 72 hours after hospital admission or within 4 weeks after hospital discharge. Nosocomial diarrheal specimens testing negative for *C. difficile* by the direct cell culture cytotoxicity assay were included in this study. Patients who reported diarrhea < 72 hours after hospital admission or who were diagnosed with *C. difficile* infection (CDI) were excluded. This study was approved by the institutional review boards of the University of Texas Health Science Center at Houston and SLEH.

NoV detection was performed by using both conventional and real-time polymerase chain reactions (rtPCR) to enhance the sensitivity of the evaluation for NoVs.^{5, 6} Stool samples were tested by the SLEH microbiology laboratory for CD toxin B by tissue culture cell

cytotoxicity assay using a fibroblast cell line (Diagnostic Hybrids, Inc.) with antitoxin neutralization (Tech-Lab).⁷

Fecal specimens from 202 patients, who tested negative for CDI by cytotoxicity assay, were evaluated for this study. Ninety-three patients were excluded because they developed diarrhea < 72 hours after hospital admission or > 4 weeks after hospital discharge. Stool samples from 109 patients with healthcare-associated diarrhea were further investigated for the presence of NoV infection. A GI NoV strain was detected in 1 stool specimen from a patient suffering nosocomial diarrhea. GI NoV RNA in this patient's stool specimen was confirmed by repeated conventional and rtPCR assays. No GII NoV strains were detected. The NoV-positive patient was a 27 year-old man, with a history of end-stage renal disease, congestive heart failure, and past CDI, who was admitted for a methicillin-resistant *Staphylococcus aureus* thigh abscess. The patient was receiving intravenous vancomycin for the abscess. Seven days after admission, the patient developed bloody diarrhea with fever up to 101°C and an elevated white blood cell count of 13,500/μL. *C. difficile* cytotoxicity assays were negative twice. An indium-111-labeled leukocyte scan, performed to investigate for metastatic *S. aureus* foci, demonstrated ascending, transverse, and descending colonic inflammation. A colonoscopy did not reveal any abnormalities. The diarrhea resolved after 5 days with no specific therapy.

Healthcare-associated diarrhea is a significant cause of both morbidity and mortality and has been shown to prolong length of hospitalizations and increase medical costs.⁸ Despite advances in our understanding of CDI, little is known regarding the pathogenesis of nosocomial diarrhea, when *C. difficile* is excluded. This gastrointestinal disease likely represents a culmination of intestinal insults, leading to disruption of the normal intestinal microbiota. Factors contributing to the altered host intestinal microbiota include antibiotics, non-antimicrobial medications, chronic gastrointestinal disorders, medical procedures such as intra-abdominal surgeries, and other infectious processes.⁹ Other yet unidentified enteric pathogens may also contribute to the pathogenesis of healthcare-associated diarrhea.

NoV outbreaks are increasingly being reported in healthcare institutions. However, in this epidemiologic survey for NoVs as a cause of sporadic nosocomial diarrhea at a tertiary university-based hospital, NoVs were detected in only 1 patient with CD-negative healthcare-associated diarrhea. This patient's gastrointestinal illness developed in December 2007, during the peak season for NoV outbreaks in healthcare institutions,¹⁰ but the patient's dysentery and pancolitis were atypical for NoV gastroenteritis. NoVs characteristically cause pathologic changes in the small intestinal tract, rather than the colon.¹¹ This patient tested negative for CDI, but other undetected enteric pathogens such as *Klebsiella oxytoca* may have contributed to the hemorrhagic colitis. This patient may have been asymptotically infected with NoVs; up to 33% of NoV infections have no clinical sequelae.¹²

Limitations of this study include the relatively small sample size and the study of a single center. *C. difficile*-positive stools were not evaluated for NoVs. As a result, mixed *C. difficile* and NoV infections may have been missed. It is possible that other regions of the world, where NoVs are endemic and outbreaks are more frequently reported, have higher prevalence rates of sporadic NoV healthcare-associated diarrhea.

The pathogenesis of healthcare-associated diarrhea is poorly understood due to the complexity of interactions affecting the host intestinal microflora. NoVs are an important cause of healthcare-related epidemics, but appear to be an uncommon cause of sporadic healthcare-associated diarrhea at one tertiary university hospital in Houston, Texas. Further

studies are needed to clarify the etiology and pathogenesis of this important gastrointestinal disease, in which traditional infectious enteropathogens may play little role.

Acknowledgments

Financial Support: National Institutes of Health (P01-AI-057788 to RLA).

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