

Rotavirus and Norovirus in Pediatric Healthcare-Associated Gastroenteritis

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Rotavirus and norovirus are important etiologies of gastroenteritis among hospitalized children. During 2012–2013, we tested 207 residual stool specimens from children with healthcare-associated vomiting and/or diarrhea for rotavirus and norovirus. Twenty (10%) were rotavirus positive, and 3 (3%) were norovirus positive, stressing the importance of these pathogens in hospitalized children.

Keywords. gastroenteritis; healthcare-associated; norovirus; rotavirus.

Rotavirus and norovirus are associated with severe community-acquired diarrhea resulting in hospitalization. Prior to the introduction of rotavirus vaccine in 2006, 3%–27% of rotavirus infections in children were healthcare-associated [1, 2]. In the postvaccine era, healthcare-associated rotavirus decreased by 60%–74% [3, 4]. Norovirus is a common cause of gastroenteritis due to its low infectious dose, extended shedding (especially in immunocompromised hosts), sustained environmental persistence, emergence of pandemic strains every 2–3 years, and poor cross-protection between genotypes [5]. Norovirus is the most common cause of healthcare-related outbreaks in adults [5], and limited data suggest it is implicated in 5%–16% of pediatric healthcare-associated gastroenteritis [6, 7].

In this study, we sought to understand the epidemiology of rotavirus and norovirus infections among hospitalized children in metropolitan Atlanta, Georgia.

METHODS

This study was approved by the local institutional review board. From July 2012 to June 2013, residual stool was saved from

specimens submitted for standard of care (SOC) stool testing (eg, bacterial stool culture, *Clostridium difficile* toxin testing, rotavirus antigen testing) from children (≤ 18 years of age) at 2 tertiary care pediatric hospitals in Atlanta. Specimens obtained ≥ 48 hours after admission from children who had at least 1 episode of vomiting and/or diarrhea were considered healthcare-associated and included in this study. Specimens were de-identified and stored at -80°C until norovirus and rotavirus testing was performed.

Medical Information

Demographic information, clinical presentation, and outcomes were retrospectively abstracted from the electronic medical record. Children were considered immunocompromised if they received chemotherapy or other immunomodulators, received >20 mg/day or ≥ 2 mg/kg/day prednisone (or equivalent steroid) for >2 weeks duration within 3 months of stool collection, had ever undergone hematopoietic stem cell or solid organ transplant, were HIV infected, had asplenia, or had immunoglobulin deficiency. Rotavirus vaccination status was determined by review of an electronic state vaccination registry [8]. Children who were born after July 1, 2006 and were ≥ 8 months of age at the time of stool collection were considered eligible for rotavirus vaccination. SOC stool testing results were abstracted from the medical record.

Laboratory Testing

Stool suspensions for norovirus were tested by semi-quantitative TaqMan real-time reverse-transcriptase polymerase chain reaction (RT-PCR) as previously described [9]. Stool specimens were tested for rotavirus antigen with Premier Rotaclone EIA (Meridian Bioscience, Cincinnati, OH) as recommended by the manufacturer. Specimens with an $\text{OD}_{450\text{ nm}} \geq 0.150$ absorbance units were considered positive.

Statistical Analysis

Statistical analyses were performed using SAS v9.4 (Cary, NC), and statistical significance was assessed at the .05 level. Demographic information, clinical presentation, and laboratory outcomes were summarized using means and standard deviations for continuous variables and frequencies and percentages for discrete variables. Due to statistically low norovirus frequency and concern for heteroscedasticity in continuous variables, differences between norovirus and rotavirus were conservatively evaluated for significance using exact Kolmogorov-Smirnov tests for continuous variables and Fisher's exact test for categorical variables.

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Table 1. Healthcare-Associated Gastroenteritis in Children

	All Healthcare-Associated, (n = 207)	Rotavirus, (n = 20)	Norovirus, (n = 7)	P Value ^a
Demographics				
Female sex, No. (%)	112 (54)	13 (65)	4 (57)	1.000
Median age [IQR ^b], mo	71 [14–144]	57 [15–160]	27 [18–45]	.105
Race/ethnicity, No. (%)				
White	110 (53)	12 (60)	3 (43)	.278
Black	58 (28)	7 (35)	2 (29)	
Hispanic	25 (12)	1 (5)	1 (14)	
Asian	12 (6)	0 (0)	1 (14)	
Unknown	2 (1)	0 (0)	0 (0)	
Clinical factors				
Immunocompromised, ^c No. (%)	99 (48)	12 (60)	4 (57)	1.000
Median time to stool testing [IQR], h ^d	285 [142–823]	401 [210–1611]	106 [86–623]	.085
Median duration of hospitalization after stool testing [IQR], h ^e	277 [73–657]	328 [143–491]	64 [51–75]	.012
Rotavirus vaccine,^f No. (%)				
Vaccine eligible ^f	70 (34)	8 (40)	7 (100)	
Received all of series	24 (34)	2 (25)	4 (57)	.184
Received part of series	8 (11)	0 (0)	1 (14)	
No vaccine received	31 (44)	6 (75)	2 (29)	

^a Kolmogorov-Smirnov tests for continuous variables, Fisher's exact test for categorical variables.

^b Interquartile range.

^c Immunocompromised was defined as having received chemotherapy or other immunomodulators, received >20 mg/day or ≥2 mg/kg/day prednisone (or equivalent steroid), having undergone hematopoietic stem cell or solid organ transplant, HIV infected, asplenia, or immunoglobulin deficiency.

^d Time of the admission order to the time of the stool testing order.

^e Time of the stool test order to the time of the discharge order.

^f Includes those who were >8 months of age and born after July 1, 2006.

RESULTS

From July 2012 to June 2013, 207 specimens from children with healthcare-associated illness were analyzed. Rotavirus was detected in 20 (10%) children, and norovirus was detected in 7 (3%). There was 1 co-detection of norovirus and rotavirus. (Table 1). All children had at least 1 underlying medical problem, and there were no differences in sex, race/ethnicity, or immunocompromising conditions between children who were norovirus and rotavirus positive. Children who were rotavirus positive tended to be older (median, 57 months [interquartile range (IQR), 15–160]) compared with those who were norovirus positive (median, 27 months of age [IQR, 18–45]), but this did not achieve statistical significance ($P = .105$). Children with rotavirus tended to have stool submitted for testing later in their hospitalization (median, 401 [IQR, 210–1611] vs 106 [IQR, 86–623] hours; $P = .085$). Children with rotavirus had a longer duration of hospitalization after the stool test was submitted than those with norovirus (median, 328 [IQR, 143–491] vs 64 [IQR, 51–75] hours; $P = .012$).

Only 31% (65/207) of all children and 40% (8/20) of children who had rotavirus detected had specimens submitted for rotavirus SOC testing. Pathogenic bacteria were not isolated from culture from any of the 97 (47%) stools submitted for SOC bacterial culture. *C. difficile* toxin A/B was detected in 21 of 184 (11%) of stools in which SOC testing was ordered, and 6 (29%) of these were from children <3 years of age. There were

5 (25%) *C. difficile* and rotavirus co-detections, and 3 (60%) of these were among stools collected from children <3 years of age. There were no *C. difficile* and norovirus co-detections.

Seventy (34%) children were eligible for rotavirus vaccination; 31 (44%) had not received any dose of a rotavirus vaccine. Rotavirus was detected in 2 children who were fully rotavirus vaccinated: a 45-month-old child who had a hematopoietic stem cell transplant (fully rotavirus vaccinated at 4 months of age), and a 14-month-old child who had a solid organ transplant (fully vaccinated at 6 months of age).

DISCUSSION

In this peak year for community-acquired rotavirus and norovirus (July 2012–June 2013), rotavirus and norovirus were detected among 10% and 3% of children, respectively, with healthcare-associated gastroenteritis [10, 11]. Rotavirus tended to be detected in older children compared with norovirus, possibly due to vaccine-induced protection of younger vaccinated children. Children with rotavirus had an increased duration of hospitalization after detection in comparison with those with norovirus, but the role of rotavirus vs the role of underlying comorbidities in prolonging hospitalization remains uncertain. All children with healthcare-associated illness had underlying medical conditions, and about 50% had an immunocompromising condition. This observation is similar to another study that we conducted from December 2009 to

December 2010 in which we identified that immunocompromised children comprised one-third of all healthcare-associated gastroenteritis. In that study, norovirus was identified in 9% and rotavirus in 4% of children with healthcare-associated diarrhea [12]. After rotavirus vaccine introduction, healthcare-associated rotavirus declined by 60%–74% [3, 4]. Because community-acquired rotavirus in the postvaccine era is known to have biennial peaks [13], and because healthcare-associated rotavirus appears linked to community-acquired rotavirus [3, 14], it should not be surprising that rotavirus was more commonly identified as a cause of healthcare-associated gastroenteritis in this study, which was conducted during a peak rotavirus season [10, 15].

A large number of children had SOC *C. difficile* testing (89%) and stool culture (47%) performed, but only 31% had SOC rotavirus testing. Of those that were positive for *C. difficile*, nearly 33% were <3 years of age. Detection in this age group may reflect colonization [16]. Because rotavirus had a similar prevalence as *C. difficile*, clinicians should consider rotavirus testing in patients with healthcare-associated diarrhea during peak rotavirus seasons in the postvaccine era. No bacterial pathogens were identified from any children that had an SOC stool culture, which supports current recommendations against performing stool cultures in patients with healthcare-associated diarrhea [17].

Many children did not receive rotavirus vaccine, and some of these missed opportunities may have been due to their underlying medical condition (eg, immunocompromising condition or a prolonged neonatal intensive care unit stay). Two rotavirus vaccine failures were observed, both among severely immunocompromised children. These findings stress the importance of vaccinating eligible children for rotavirus, not only to provide direct protection but also to indirectly protect those who are unable to be vaccinated and those who are severely immunocompromised.

Limitations of this study include the retrospective nature of stool specimen and data collection. We had small numbers of children in whom rotavirus and norovirus were detected over a single year from 2 hospitals in Atlanta, Georgia. We were also not able to evaluate for outbreaks. Thus, these results may not be generalizable.

Additional data are needed about healthcare-associated rotavirus and norovirus. Clinicians should consider rotavirus and norovirus as causes of healthcare-associated gastroenteritis, particularly during peak years of community-acquired disease.

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