RESEARCH ARTICLE

Detection of Acute Gastroenteritis Etiology in Hospitalized Young Children: Associated Factors and Outcomes

Jamie M. Pinto, MD,[a] Anna Petrova, MD, PhD, MPH[a,b]

ABSTRACT

BACKGROUND: The decision to test for the etiology of diarrhea is a challenging question for practicing pediatricians.

METHODS: The main goal of this retrospective cohort study was to identify factors associated with testing for and diagnosis of rotavirus, *Clostridium difficile*, or other bacterial infections, as well as the length of stay (LOS) for children with acute gastroenteritis who were hospitalized at a single institution. Patients aged 6 to 60 months with acute diarrhea (<14 days) and no underlying gastrointestinal conditions were included. Data were analyzed by using multivariate logistic and linear regression models.

RESULTS: Stool testing was performed in 73.1% of the 331 patients studied. The majority were tested for multiple pathogens, including rotavirus (65.9%), *C difficile* (30.8%), and other bacteria (63.4%), with recovery rates of 33.0%, 9.8%, and 6.7%, respectively. Rotavirus was more often identified in older patients with dehydration and vomiting. Although testing for *C difficile* was more likely with prolonged diarrhea, no vomiting, and recent antibiotic use, no factors were associated with *C difficile* recovery. Patients who were diagnosed with *C difficile* were more likely to receive probiotics than those who received negative test results. LOS was not associated with stool testing or recovery of any tested pathogens.

CONCLUSIONS: Although children with acute gastroenteritis underwent frequent stool testing for diarrheal etiology, detection of a pathogen was uncommon and not associated with a change in LOS. Experimental research will be needed to make additional conclusions about the efficacy of testing for diarrheal etiology in the inpatient practice of acute pediatric diarrhea.

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Acute gastroenteritis (AGE) in young children is typically a mild illness of predominantly viral origin, with rotavirus traditionally playing a leading etiologic role.[1,2] Despite the recorded decline in rotaviral diarrhea associated with the implementation of rotavirus immunization programs,[3,4] AGE continues to contribute substantially to the overall rate of pediatric hospitalizations, with expenditures of >$2 billion annually.[5,6] The utility in performing stool testing to detect diarrheal etiology is a challenging question for practicing pediatricians because of the lack of compelling evidence regarding the value of microbiological studies in the clinical management of AGE. Although existing consensus-based guidelines do not endorse routine microbiological stool testing of children with AGE,[7–9] the detection of diarrheal etiology is recommended for surveillance and in children with severe AGE, bloody diarrhea, underlying chronic conditions, or a history of travel to at-risk areas.[8,10] The American Academy of Pediatrics accepted the Centers for Disease Control and Prevention's recommendations to perform stool cultures in children with suspected dysentery.[10] The American Academy of Pediatrics does not support the testing of *C difficile* in children during infancy without serious gastrointestinal pathology.[11] A recent European study classified the request for microbiological stool tests as the most common violation of recommendations for the management of pediatric patients with acute diarrhea.[12] Additionally, a few studies have reported substantial dissimilarities in the performance of stool testing,[12,13] the prevalence of positive results,[13–15] and factors associated with the recovery of bacterial or viral pathogens[14,16] in children who are admitted to the emergency department (ED) or hospital with AGE. To our knowledge, no study has explored the association between the diagnostic approach used for identifying diarrheal etiology and the medical care provided to hospitalized children with AGE.

The main goal of the present article is to identify the value of knowing the etiology of acute diarrhea in the management and outcomes for young children who are hospitalized with AGE. Specifically, this study describes factors that are associated (independent of other characteristics) with pediatricians' decisions to test for and the recovery of enteric pathogens, including rotavirus, *C difficile*, and other bacteria. Moreover, the present report explores the role of positive results from stool testing on the management and length of stay (LOS) of children who are hospitalized with AGE. The results of the current study will increase our knowledge about the clinical effect of the detection of diarrheal etiology in young children with AGE and, therefore, improve the management of the affected patients.

METHODS

A retrospective-cohort study design was employed to answer our research questions. We used an administrative database to identify children with AGE who were admitted to a single institution between June 2010 and September 2015. The *International Classification of Diseases Ninth Revision* diagnostic codes for acute unspecified or infectious diarrhea or gastroenteritis (008.61–008.63, 008.8, 009.0–009.3, 558.9, 787.03, and 787.91) were used to select the study population. The Meridian Health Institutional Review Board approved the study of children who were hospitalized with AGE. Of the 627 medical records identified, 331 subjects met the inclusion criteria: age between 6 and 60 months, acute diarrhea of <14 days duration, and no underlying gastrointestinal condition or immunodeficiency. Patients were excluded from analysis if they had diarrhea and/or vomiting associated with respiratory illnesses, neurologic illnesses, surgical conditions, bacterial infections of a nongastrointestinal site, or other noninfectious diarrheal conditions. A standardized data extraction tool was used to collect information documented in the medical records, including demographics (age, sex, race and/or ethnicity [defined as non-Hispanic white, non-Hispanic black, Hispanic, and other]), history of current illness (duration of diarrhea, recent use of antibiotics and/or probiotics before admission, and recent travel), month of admission, and clinical and laboratory data. No information was available in the medical records regarding vaccine status for rotavirus. Patients with decreased intake but normal physical examination findings were considered to be <3% dehydrated (mild or no dehydration), whereas those with mild tachycardia, irritability, dry mucous membranes, sunken eyes, reduced tear production, decreased urine output, and/or cool extremities were considered to be 3% to 9% dehydrated (mild to moderate dehydration). Children with >9% (severe) dehydration had tachycardia and depressed mental status in addition to other findings associated with hypovolemia.[17,18] Hospitalization of patients from December to April was considered to be admission during rotavirus season.[19]

The investigation for infectious etiologies of diarrhea was restricted by the microbiology testing available at our institution's laboratory, which does not include an enteric pathogen panel. Single or simultaneous testing of stool for rotavirus antigens, *C difficile* toxins, and/or bacterial cultures was requested from samples provided to the hospital-based laboratory during routine clinical care at the discretion of the attending physician. The hospital laboratory used enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), and stool cultures for the detection of rotavirus antigens, *C difficile* toxins, and other bacterial pathogens. In general, reports from ELISA, PCR, and bacterial cultures were released within 2 hours, 3 times a day, and after 48 hours, respectively. We estimated intervals (in hours) to classify a time frame for the initiation of stool testing as follows: (1) at admission if the stool sample was sent to the microbiology laboratory from the ED, (2) within 6 hours, (3) from 6 to 12 hours, and (4) after 12 hours of admission. We collected data on the treatments provided during hospitalization, including probiotics and intravenous fluids (IVF). Duration of IVF administration was defined as the time (in hours) from the initiation of IVF in the ED (if applicable) to discontinuation before discharge. LOS was calculated as time (in hours) between admission to the pediatric floor and the placement of a discharge order.

Data Presentation and Statistical Analysis

Univariate data were compared with explored differences between variables (demographic and clinical) on the basis of the type of stool testing performed and recorded results by using χ^2 and analysis of variance followed by the Tukey test. The factors that showed a bivariate association with the dependent variable at a level of $P < .1$ were entered into multivariate logistic regression models. Duration of illness (in days), the use of antibiotics before admission (yes versus no), the presence of vomiting (yes versus no), and dehydration (<3% vs >3%) were selected for inclusion in the logistic regression models to identify the association of each of these factors with both stool testing and the detection of a diarrheal etiology. All models were adjusted for age, sex, race and/or ethnicity, and season (rotavirus vs nonrotavirus season) regardless of *P* values. We grouped race and/or ethnicity as non-Hispanic white versus other because of a high prevalence of non-Hispanic white patients (70%). In addition, multivariate linear regression models were constructed to identify the independent role of different factors, including age, dehydration, duration of IVF, the use of probiotics, requests for stool studies, requests for stool studies after 12 hours of admission, and the detection of any pathogen over the duration of hospitalization.

Categorical data are presented as a proportion (in percent) and continuous data as a mean with a 95% confidence interval (CI). Associations that were identified in linear regression analysis are expressed as a regression coefficient (β) $\pm$ SE and in logistic regression as odds ratios and 95% CIs. All statistical tests were 2-sided with the significance level set at a *P* value of <.05.

RESULTS

Frequency and Type of Stool Testing

Of the 331 children who were hospitalized with AGE, ELISA for rotavirus antigens was requested in 218 (65.9%), PCR for *C difficile* toxins in 102 (30.8%), and bacterial cultures in 210 (63.4%) stool specimens. The majority of patients ($n = 242$) had at least 1 stool microbiological test performed, and no testing was requested in only 89 (26.9%) of the studied patients. In tested children, a single study was ordered for 41 (16.9%), 2 studies for 117 (48.4%), and 3 studies for 84 (34.7%) patients. Stool microbiology testing was initiated in the ED (14.5%, $n = 35$), within 6 hours of admission (17.3%, $n = 42$), 6 to 12 hours from admission (17.8%, $n = 43$), and after 12 hours of admission (50.4%, $n = 122$) to the pediatric floor. Rotavirus and other bacterial pathogens were more likely to be tested for 12 hours post-admission when compared with *C difficile* (49.8% vs 35%; $P < .02$).

Factors Associated With Request for Stool Testing

Patients' characteristics were comparable between those who were tested and those who were not tested for rotavirus or with bacterial cultures (Table 1). Patients who were tested for *C difficile* were characterized as having a prolonged duration of illness, an increased use of antibiotics, and decreased rates of vomiting when compared with patients who were not tested for *C difficile* and patients in the reference group (no stool testing). No single factor included in the multivariate logistic regression model was associated with requests of rotavirus antigens. Bacterial cultures were more likely to be ordered for patients who were admitted outside of rotavirus season (1.27, 95% CI 1.0–1.62). *C difficile* toxins were more likely tested for in patients with a longer duration of illness (1.22, 95% CI 1.1–1.37) and a recent use of antibiotics (1.69, 95% CI 1.18–2.46), and they were less likely in patients with vomiting (0.88, 95% CI 0.56–0.98) and in patients who were not non-Hispanic white (0.71, 95% CI 0.54–0.94).

Rate of Positive Stool Microbiology

Rotavirus, *C difficile*, and other bacterial infections were detected in 33.0% ($n = 72$ of 218), 9.8% ($n = 10$ of 102), and 6.7% ($n = 14$ of 210) of the tested patients, respectively. Among 14 patients with detected bacterial pathogens, nontyphoid strains of *Salmonella* were recorded in 9, *Shigella* spp. in 2, *Campylobacter jejuni* in 2, and *Aeromonas hydrophilia* in 1. In 2 patients, bacteria and a *C difficile* toxin were detected simultaneously. Only a few patients with *Salmonella* had blood in their stool samples.

Factors Associated With Recovery of Pathogens

As shown in Table 2, patients with rotavirus-associated AGE were older, had a shorter duration of illness, and symptoms of vomiting and moderate dehydration more often when compared with those without a rotavirus infection. Children with bacterial cultures that were positive for gastroenteritis were less likely to be admitted during rotavirus season and had less vomiting than those whose culture results were negative. No difference in history or clinical presentation between patients with and without *C difficile* has been identified. By using multivariate logistic regression models, we found an increased likelihood for a diagnosis of rotavirus diarrhea with increased age (1.03, 95% CI 1.01–1.12), symptoms of vomiting (1.19, 95% CI 1.1–2.33), and dehydration (2.01, 95% CI 1.41–2.85) and a decreased likelihood in patients who were not non-Hispanic white (0.66, 95% CI 0.47–0.93), with a longer duration of illness (0.79, 95% CI 0.67–0.93), and admission outside of rotavirus season (0.53, 95% CI 0.38–0.75). A bacterial culture with a positive result was less likely to be recorded in patients who were admitted during rotavirus season (0.49, 95% CI 0.27–0.89) and with symptoms of vomiting (0.47, 95% CI 0.26–0.84). None of the factors included in the regression model was associated with the detection of *C difficile*.

Comparison of treatments and LOS with respect to the detection of diarrheal etiology only recorded a higher frequency of probiotic use (a *Lactobacillus acidophilus* mixture or *Lactobacillus rhamnosus*) among patients who were diagnosed with *C difficile* when compared with those without this infection (80% vs 29.4%, $P < .002$).

Factors Associated With Duration of Hospitalization

We performed multivariate linear regression analysis to identify factors

TABLE 1 Comparison of Patients' Characteristics With Respect to Requested Pathogen-Specific Stool Examinations

Variables	Requested Pathogen-Specific Stool Microbiology						
	Rotavirus		*C difficile*		Other Bacteria		None Requested (n = 89)
	Yes (n = 218)	No (n = 113)	Yes (n = 102)	No (n = 229)	Yes (n = 210)	No (n = 121)	
Mean age, mo	23.3	25.2	24.1	23.9	24.1	23.7	24.1
95% CI	21.4–25.1	22.7–27.7	21.3–27.0	22.1–25.6	22.1–26.0	21.4–26.0	21.5–26.7
Boy, %	53.1	52.7	56.4	51.5	53.1	52.9	55.1
Non-Hispanic white, %	71.6	67.0	79.2**	66.0	73.2	64.5	66.3
Recent travel, %	6.6 (n = 198)	7.7	6.5 (n = 93)	7.2 (n = 209)	6.8 (n = 190)	7.1 (n = 113)	8.4 (n = 83)
Rotavirus season, %	55.3	58.9	50.5	59.1	53.3	62.0	58.4
Mean duration of illness, d	3.5	3.3	4.1	3.1	3.6	3.3	3.2
95% CI	3.2–3.8	2.9–3.6	3.6–4.7* $^{\gamma\gamma\gamma}$	2.9–3.4	3.2–3.9	3.0–3.6	2.8–3.5
Use of antibiotic, %	33.9	26.8	41.6** $^{\gamma}$	27.1	33.5	28.1	28.1
Vomiting, %	88.5	93.8	83.2** $^{\gamma\gamma}$	93.5	88.0	94.2	96.6
Dehydration, %							
<3	45.4	50.9	53.4	44.5	48.2	43.8	47.2
3–9	51.8	46.4	44.6	52.4	47.9	53.7	49.4
>9	2.8	2.7	2.0	3.1	2.9	2.5	3.4

* $P < .02$; ** $P < .01$: comparison between patients with and without stool testing on a specified pathogen.
$^{\gamma}$ $P < .05$; $^{\gamma\gamma}$ $P < .02$; $^{\gamma\gamma\gamma}$ $P < .01$: comparison between patients who were tested for each pathogen with the patients who were in the reference group (no stool study for rotavirus, *C difficile*, or bacterial culture was requested).

associated with LOS for studied patients (Table 3). We did find a significant association between LOS with the duration of IVF and requests for stool testing after 12 hours of admission. No association between LOS with the use of probiotics and requests for stool testing was found in the adjusted model.

DISCUSSION

In the present article, stool studies were performed in approximately three-quarters of young children with AGE. Of these young children, ≤85% were simultaneously tested for multiple diarrheal etiologies, with rotavirus recovered in one-third and *C difficile* and other bacterial infections in <10% of the tested cases. We found that factors associated with requests for pathogen-specific stool testing were not able to precisely predict the diagnosis of an enteral infection except for other bacterial enteritis, which was more likely to be tested for and detected outside of the rotavirus season. Antibiotic therapy, a known risk factor for *C difficile* infection,[20] was associated with an increased likelihood of

TABLE 2 Comparison of Patients' Characteristics With Respect to the Detection of Enteric Pathogens

Variables	Rotavirus Tested (n = 218)		*C difficile* Tested (n = 102)		Bacterial Culture Tested (n = 210)	
	Positive (n = 72)	Negative (n = 146)	Positive (n = 10)	Negative (n = 92)	Positive (n = 14)	Negative (n = 196)
Mean age, mo	27.2**	21.4	23.9	24.0	28.1	23.8
95% CI	23.6–30.7	19.2–23.5	11–36	21.1–27	20.1–36.1	21.8–25.8
Boy, %	51.4	54.1	42.9	53.3	50.0	56.5
Non-Hispanic white, %	81.9**	66.4	90.0	78.3	71.4	72.8
Rotavirus season, %	59.7	53.1	50.0	50.0	28.6*	57.8
Duration of illness, d	2.9**	3.8	5.1	4.0	3.5	3.5
95% CI	2.6–3.2	3.3–4.3	2.2–8.0	3.4–4.6	2–5	3.2–3.9
Use of antibiotic, %	36.1	32.9	50	40.2	14.3	35.4
Vomiting, %	98.6**	83.6	90.0	82.6	64.3***	89.2
Dehydration, %	***	–	–	–	–	–
<3	25.0	55.5	60.0	53.3	48.7	50.0
3–9	70.8	42.5	40	40.0	48.7	42.9
>9	4.2	2.0	0	2.2	2.6	7.1

* $P < .05$; ** $P < .02$; *** $P < .01$.

TABLE 3 Factors Associated With LOS for Patients With AGE ($\beta \pm$ SE): Multivariate Linear Regression Analysis

Characteristics	Unadjusted	Adjusted
Age, mo	−0.111 ± 0.064	−0.019 ± 0.026
Degree of dehydration	0.056 ± 0.058	0.013 ± 0.027
Duration of IVF, h	0.864 ± 0.033****	0.919 ± 0.027****
Use of probiotics	0.158 ± 0.064***	0.030 ± 0.026
Request for stool study	0.202 ± 0.54***	0.006 ± 0.026
Request for stool study after 12 h of admission	0.176 ± 0.06**	0.052 ± 0.026*
Detection of any pathogen	0.061 ± 0.064	−0.040 ± 0.027

The degree of dehydration was coded as 1 if the degree of dehydration was classified as >3% and 0 if it was <3%. Categorical data were coded as dichotomous variables: yes (1) and no (0).
* $P < .05$; ** $P < .02$; *** $P < .01$; **** $P < .002$.

testing for, but not detection of, a *C difficile* toxin. Whereas probiotic use was more likely with the identification of a *C difficile* infection, recovery of any enteric pathogen had no association with LOS.

To our knowledge, no retrospective or prospective studies (including our study) could provide a complete analysis for the infectious etiology of AGE because of the restrictive stool panels available at different healthcare facilities. Moreover, comparison of our results with other reports is limited by the substantial differences in participants' ages, the stool microbiology testing used, the types of collected clinical data, and the reported outcomes. Overall testing of stool microbiology in 35.8% of children who were hospitalized for acute diarrhea without specification of tested pathogens has been recently reported in Italy.[12] Data from Klein et al's prospective cohort study revealed a detection of rotavirus in 33.5%, *C difficile* in 6.7%, and bacteria in 7.3% of children presenting to the ED with diarrhea.[14] These results are not dissimilar to our own. Perhaps, our higher detection of rotavirus in older patients is related to increasing rates of immunization in young infants after widespread introduction of the rotavirus vaccine in 2006.[21] Vaccination coverage among children aged 19 to 35 months in New Jersey increased from 56.3% in 2011 to 75.2% in 2015.[22,23] The absence of vomiting was correlated with other bacterial causes of AGE in the current study. Klein et al[14] reported an increased risk for positive results from stool cultures in patients who presented to the ED and were of older age, had travelled recently, had a fever, and had passed >10 stools in the previous 24 hours. The detection of viral pathogens in the same study was related to the use of antibiotics, vomiting, and the presence of fever. A Canadian study by Deorari et al[16] revealed an association between the season of admission and older age and bacterial versus nonbacterial diarrhea in children hospitalized with community-acquired diarrhea.

This study has several limitations. Firstly, retrospective collection of existing clinical and laboratory data increases the risk for missing relevant factors and of not detecting other gastrointestinal viruses. Secondly, the low prevalence of *C difficile* and other bacterial infections increases the risk for missing meaningful covariances for controlling in the regression models, although the cutoff point for *P* values of .1 was applied for the selection of variables from a univariate analysis. Thirdly, there is a risk for decreased external validity associated with the analysis of clinical data of patients who are hospitalized to a single pediatric setting. Possibly, studies from other settings would find different risk factors because of the variability in population and clinical care provided. A multicenter study would be needed to extend our knowledge of the impact of testing for diarrheal etiology in young children who are hospitalized with AGE.

CONCLUSIONS

The present observational study revealed an association between a high frequency of simultaneous testing for various enteric pathogens with relatively low detection rates and a minimal effect of known diarrheal causes on the management and duration of hospitalization of young children with AGE. Although no routine testing for diarrheal etiology is a reasonable approach in the management of pediatric AGE, an experimental study design will be needed to complete recommendations for testing strategies for young children who are admitted to the general pediatric floor.

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