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Healthcare Provider Diagnostic Testing Practices for Identification of *Clostridioides* (*Clostridium*) *difficile* in Children: an Emerging Infections Network Survey

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Abstract

Objective: To characterize healthcare provider diagnostic testing practices for identifying *Clostridioides (Clostridium) difficile* infection (CDI) and asymptomatic carriage in children.

Design: Electronic survey

Methods: An eleven-question survey was sent by email or facsimile to all pediatric infectious diseases (PID) members of the Infectious Diseases Society of America's Emerging Infections Network (EIN).

Results: Among 345 eligible respondents who had ever responded to an EIN survey, 196 (57%) responded; 162 (83%) of them were aware of their institutional policies for CDI testing and management. 159 (98%) respondents knew their institution's *C. difficile* testing method; 99 (62%) utilize NAAT without toxin testing and 60 (38%) respondents utilize toxin testing, either as a single test or multi-step algorithm. 10/153 (7%) respondents reported that formed stools were tested for *C. difficile* at their institution, and 76/151 (50%) reported that their institution does not restrict *C. difficile* testing in infants and young children. The frequency of symptom- and age-based testing restrictions did not vary between institutions utilizing NAAT alone compared to those utilizing toxin testing for *C. difficile* diagnosis. 26/143 (16%) respondents permit testing of neonatal intensive care unit patients and 12/26 (46%) treat CDI with antibiotics in this patient population.

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Conclusions: These data suggest that there are opportunities to improve CDI diagnostic stewardship practices in children, including among hospitals using NAATs alone for CDI diagnosis in children.

Introduction

Clinical microbiologic diagnosis of *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) remains a significant challenge in both adults and children.[1] Frequent misuse of *C. difficile* diagnostic tests by healthcare providers leads to frequent misclassification of asymptomatic *C. difficile* carriers as having CDI.[2] This leads to unnecessary CDI antibiotic therapy and inaccurate CDI surveillance, making interfacility comparisons of CDI rates a major challenge.

Because CDI is caused by secreted *C. difficile* toxins in the gut, diagnostic tests that detect toxins A and/or B in stool are highly specific for CDI. However, because of reportedly suboptimal sensitivity of stool toxin enzyme immunoassays (EIAs), many clinical microbiology laboratories no longer use toxin EIA as the primary method for diagnosing CDI. Stool nucleic acid amplification tests (NAATs), such as PCR or loop-mediated isothermal amplification of the genes for toxins A and/or B (*tcdA, tcdB*), detect *C. difficile* strains that have the potential to produce toxins. However, because NAATs do not detect secreted toxin in stool, these tests do not differentiate asymptomatic carriage of *C. difficile* and CDI. Thus, compared to toxin EIAs, NAATs have poor diagnostic predictive value for CDI.[2] As such, NAATs have the potential to misdiagnose CDI in asymptomatic carriers, particularly when used in patients with low likelihood of CDI. This includes patients without diarrhea, patients with a more likely diarrheal etiology (e.g., viral etiologies, laxatives, etc.), and children with high probability of carriage (e.g., infants and young children).[2] For this reason, many hospitals have adopted strategies for minimizing NAAT testing of patients with low likelihood of CDI, such as rejection of formed stools and/or stools from infants and/or young children. The objective of this survey was to determine prevalence of CDI diagnostic practices in the United States as they relate to avoiding detection of asymptomatic carriage in children.

Methods

An eleven-question survey (Supplemental Materials) was developed to explore current CDI diagnostic practices for pediatric patients and whether any pediatric patient populations were tested for asymptomatic carriage of *C. difficile*. The survey was piloted among a group of Emerging Infections Network (EIN) members and pediatric infectious diseases (PID) providers. The EIN, a provider-based emerging infections sentinel network through the Infectious Diseases Society of America (IDSA), distributed the survey to all 362 PID physician members in the US and Canada via email or facsimile in January 2018. Two reminders were sent to non-respondents. A denominator of 345 active PID EIN members who had ever responded to an EIN survey was used to calculate response rate, a standard methodology that has been used in previous EIN surveys.[3] Members who were not aware of their institutional policies for testing and management of CDI were allowed to opt out of the survey either online or by email. Respondents were not required to answer every question;

thus, denominators for individual items vary. Proportions were compared by chi-square test using Stata v.12.1 (StataCorp, College Station, TX). Two-sided *P* values <0.05 were considered statistically significant.

Results

Among the 345 active PID EIN members to whom the survey was sent, 196 (57%) responded; 162 (83%) of them were aware of their institutional policies for CDI testing and management and completed the survey. Table 1 lists the respondent and non-respondent demographics. There were no statistically significant differences between respondents and non-respondents (*P* values ranged 0.38–0.83 for all demographics in Table 1).

Table 2 lists the *C. difficile* testing strategies (i.e., single test vs. multistep algorithm and specific assays used) reported by the 159/162 eligible respondents (98%) who knew their institution's CDI testing strategy. Irrespective of the specific strategy and assay used, 99/159 (62%) respondents utilize NAAT without toxin testing. While 60/159 (38%) respondents utilize toxin testing, 36 of these 60 (60%) respondents initially test stool with a combined glutamate dehydrogenase (GDH, *C. difficile* common antigen) and toxin EIA but follow-up with NAAT as an arbitrator of GDH-positive, toxin-negative stools. Thus, toxin EIA is utilized to rule-in CDI, but NAAT is used to rule-out CDI with this multistep algorithm. Among the 87 respondents providing information about their institution's use of a multiplex PCR panel for diarrheal pathogens, 39 (45%) report that they always suppress the *C. difficile* PCR result from this assay. Among the 48 respondents whose institution reports the *C. difficile* PCR result from the multiplex PCR panel, 13 (27%) require the healthcare provider to specifically request *C. difficile* PCR results, while 35 (73%) report the *C. difficile* PCR result even if *C. difficile* testing was not specifically requested.

Among the 153 respondents aware of symptom-based restrictions on *C. difficile* testing, 143 (93%) reported that only unformed stools were tested for *C. difficile* at their institution. Among the 151 respondents aware of age-based restrictions on *C. difficile* testing, 75 (50%) reported that their institution employed age-based restrictions; testing was limited to patients older than the following: 3 months (m; n=1, 1%), 12m (n=62, 83%), 24m (n=11, 14%), and 36m (n=1, 1%). Adoption of age-based restrictions was not associated with being a university-affiliated hospital (52% vs. 45%, $P = 0.43$), a freestanding children's hospital (53% vs. 45%, $P = 0.28$), or a hospital with more than 350 beds (52% vs. 49%, $P = 0.69$).

Testing restrictions and hospital characteristics (Table 3) were similar among respondents whose institution utilizes NAAT alone (either NAAT for only *C. difficile* or a multiplex PCR panel that includes *C. difficile*) compared to those whose institution uses toxin testing (either as a single test or part of a multi-step algorithm). Among the 143 respondents whose institution has a neonatal intensive care unit (NICU) and are aware of *C. difficile* testing policies for NICU patients, 26 (16%) permit testing of these infants. If patients in the NICU test positive, respondents reported that these patients are managed with contact isolation (n=17, 65%), single patient room or patient cohorting (n=5, 19%), and/or antibiotic therapy for CDI (n=12, 46%).

Only 1 (1%) respondent indicated that their institution routinely tests asymptomatic children to identify *C. difficile* carriage. This respondent reported that their institution tests for carriage in patients with a malignancy or bone marrow transplant. The only action that occurs when asymptomatic carriage *of C. difficile* is detected is enhanced environmental cleaning (e.g., frequency and/or type of disinfectant). If a known asymptomatic carrier subsequently develops diarrhea, that patient gets empiric CDI treatment without repeat testing. Asymptomatic carriers are not reported to the National Healthcare Safety Network (NHSN).

Discussion

Updated clinical practice guidelines for CDI were recently endorsed by the IDSA and the Society for Healthcare Epidemiology of America (SHEA).[4] Compared to the previous 2010 guideline, the updated document included clinical practice guidance for pediatric populations. While the guideline authors acknowledged the benefits and drawbacks of both toxin EIAs and NAATs, a single test was not wholly endorsed. NAATs (alone or as part of a multi-step algorithm) were recommended only if the hospital had preagreed criteria for submitting stool specimens for *C. difficile* testing. The purpose of these prearranged criteria are to limit *C. difficile* testing in patients with low likelihood of CDI and avoid detection of asymptomatic carriage. In institutions without preagreed criteria for submitting stool specimens for *C. difficile* testing, stool toxin testing as part of a multi-step algorithm was recommended. These survey data, gathered shortly before publication of the updated IDSA/SHEA-guidelines,[4] provide information about the prevalence of CDI diagnostic practices in the US as they relate to limiting detection of asymptomatic carriage in children. Thus, these data inform opportunities for improving *C. difficile* diagnostic stewardship, particularly among institutions utilizing NAATs for *C. difficile* diagnosis, in accordance with the recently updated guidelines. Because adoption of diagnostic stewardship practices is not associated with various hospital characteristics (e.g., freestanding children's hospital, hospital size or university affiliation), our data suggest that need for diagnostic stewardship practices is a relatively pervasive issue.

These data suggest that many PID physicians have an opportunity to advocate for institutional changes to *C. difficile* diagnostic testing practices that may reduce misdiagnosis of CDI in asymptomatic carriers. Although routine testing for asymptomatic carriage is exceedingly uncommon, certain diagnostic stewardship practices, particularly IDSA/SHEA-endorsed age-based restrictions of testing, are only reportedly used at half of respondents' institutions, irrespective of whether or not toxin or NAAT testing is used. In addition, roughly one-third of respondents use a multiplex PCR to diagnose CDI at their institution, and nearly three-quarters of them report results even if not requested by the clinician. Thus, these data suggest that asymptomatic carriage is likely commonly detected, particularly in patients in whom toxin testing is not performed.

Because antibiotics are not generally indicated for asymptomatic carriage, misdiagnosis of carriage as CDI leads to unnecessary antibiotic exposure. The antibiotic stewardship implications of judicious use of *C. difficile* testing are highlighted in this survey by responses regarding management of NICU patients who are tested for *C. difficile*. Despite

strong evidence that *C. difficile* does not cause infection in neonates,[5] and American Academy of Pediatrics[6] (AAP) guidelines discouraging testing in this age group, roughly half of respondents who test NICU patients for *C. difficile* provide treatment for CDI. The AAP-endorsed age-based restrictions of *C. difficile* testing were adopted by the updated IDSA/SHEA guideline.[4] Age-based testing restrictions, the uptake of which may be improved with electronic order entry messaging,[7,8] may improve testing decisions and reduce unnecessary antibiotic therapy for *C. difficile* carriage, leading to reduced healthcare costs.[7,9] However, reducing unnecessary testing in older children may be more challenging. While the vast majority of respondents report that *C. difficile* testing is restricted for formed stools submitted to the laboratory, this does not prevent testing in children with clinically insignificant diarrhea (i.e., 2 or fewer unformed stools in 24 hours) or diarrhea in patients who are unlikely to have CDI. In these cases, pediatric healthcare provider education[7] and/or leveraging the electronic health record[9] to monitor frequency of diarrhea and recent laxative use may be effective. Of note, while this definition of clinically significant diarrhea has not been validated in children, this definition is recommended in the AAP CDI clinical care guidelines.[4]

In addition to the antibiotic stewardship implications of CDI misdiagnosis, there are also other consequences. For example, misattribution of diarrheal symptoms to *C. difficile* may delay identification of the true diarrheal etiology, potentially leading to worse outcomes. We have observed diarrheal symptoms caused by conditions such as typhlitis, ulcerative colitis, and toxic shock syndrome initially mistakenly attributed to CDI because of positive *tcdB* PCR in these patients. Furthermore, CDI misdiagnosis leads to overestimation of hospital CDI rates, impairing accurate institutional CDI surveillance and limiting reliable inter-facility comparisons of CDI rates. Healthcare-associated infection rates are an important hospital quality metric, and implementation and monitoring impact of CDI prevention initiatives require accurate surveillance. The impact of overestimation of CDI rates may be even higher in populations at high risk for *C. difficile* carriage, such as hospitalized children[10] and children with cancer.[11] Furthermore, with the potential for hospital non-reimbursement for healthcare-associated infections such as CDI, hospitals have a financial incentive for accurately measuring and avoiding overestimation of CDI rates.[12] These consequences highlight the importance of developing diagnostic testing methods that reliably distinguish carriage and CDI, which has been a difficult task.[2] Until that happens, diagnostic stewardship will remain an important strategy for optimizing utilization of *C. difficile* diagnostic testing.

Our study has some limitations. Although our 57% physician response rate was relatively high, and respondents are similar to non-respondents for all practice variables examined, a response bias may still exist. Testing practices may have differed between respondents and non-respondents. Physicians elect to join the EIN, and this convenience sample may not be generalizable to all pediatric infectious diseases physicians. In addition, although respondents reported the prevalence of policies, hospital and provider compliance with these strategies could not be determined.

In summary, these data suggest that there are pervasive opportunities to improve CDI diagnostic stewardship practices in children and develop institutional policies to align with

recently updated IDSA/SHEA guidance, particularly in hospitals using NAATs alone for CDI diagnosis in children. However, even with implementation of these IDSA/SHEA-endorsed practices, provider education remains an essential component of diagnostic stewardship to assist providers in appropriately selecting patients for *C. difficile* testing. Future work should identify cost-effective, scalable, and sustainable strategies for CDI diagnostic stewardship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Survey Demographics of 196 Respondents and 149 Non-respondents

Demographic	Respondents (n=196) n (%)	Non-respondents (n=149) n (%)
Practice Location *		
US (per Census Bureau Division)		
New England	7 (4)	10 (7)
Mid Atlantic	29 (15)	18 (12)
East North Central	35 (18)	16 (11)
West North Central	17 (9)	11 (7)
South Atlantic	31 (16)	26 (17)
East South Central	12 (6)	12 (8)
West South Central	11 (6)	11 (7)
Mountain	15 (8)	6 (4)
Pacific	36 (18)	36 (24)
Canada	3 (2)	3 (2)
Years since completing fellowship training #		
<5 years	50 (26)	35 (23)
5–14	64 (33)	56 (38)
15–24	43 (22)	25 (17)
≥25	39 (20)	33 (22)
Employment ^		
Hospital/clinic	59 (30)	42 (28)
Private group or practice	17 (9)	11 (7)
University	117 (60)	92 (62)
Federal/state government or military	3 (2)	4 (3)
Primary hospital type *		
University hospital	122 (62)	94 (63)
Non-university teaching hospital	54 (28)	38 (26)
Community hospital	15 (8)	8 (5)
City/county hospital	2 (1)	6 (4)
Department of Defense or Other hospital	3 (2)	3 (2)
Children's hospital type *		
Freestanding children's hospital	111 (57)	72 (48)
Children's hospital within an adult hospital	62 (32)	52 (35)
Pediatric ward within an adult hospital	21 (11)	23 (15)
None of the above	2 (1)	2 (1)
Hospital bed number #		
<200	49 (25)	39 (26)
200–350	76 (39)	47 (32)
351–450	14 (7)	15 (10)

Demographic	Respondents (n=196) n (%)	Non-respondents (n=149) n (%)
451–600	38 (19)	28 (19)
>600	19 (10)	20 (13)

[*] $0.3 < P < 0.4$;

[#] $0.5 < P < 0.6$;

[^] $0.8 < P < 0.9$

Table 2:

C. difficile Testing Strategies at the Institutions of 159 Survey Respondents

Testing Strategy	n (%)
Single test	
Nucleic acid amplification test (NAAT)-detects only *C. difficile*	63 (40)
Multiplex PCR panel of multiple gastrointestinal pathogens	3 (2)
Enzyme immunoassay (EIA) for toxin only	4 (3)
Combined EIA for glutamate dehydrogenase (GDH) and toxin	8 (5)
Toxigenic culture (*C. difficile* culture followed by detection of toxins)	0
Multi-step algorithm	
GDH EIA followed by cell cytotoxicity neutralization assay or toxin EIA (if GDH positive)	1 (1)
GDH EIA followed by NAAT (if GDH positive)	8 (5)
NAAT followed by toxin EIA (if NAAT positive)	5 (3)
Combined GDH/toxin EIA followed by NAAT for discordant results (GDH-positive, toxin-negative stools)	27 (17)
Combinations of the above single test or multi-step algorithms	
Multiplex PCR panel plus NAAT	21 (13)
Multiplex PCR panel plus GDH/toxin EIA followed by NAAT for discordant results	6 (4)
11 other combinations of testing were each selected by 1 or 2 respondents	13 (8)

Table 3:

Utilization of *C. difficile* Testing Restrictions and Hospital Characteristics Relative to Hospital *C. difficile* Testing Strategy

Hospital Characteristic	Toxin Testing*	NAAT Alone#	*P*
Restrict *C. difficile* testing to unformed stools	53/56 (95%)	88/95 (93%)	0.63
Age-based *C. difficile* testing restrictions	28/56 (50%)	47/93 (51%)	0.95
University hospital	37/60 (62%)	62/99 (63%)	0.90
Freestanding children's hospital	35/60 (58%)	53/99 (54%)	0.56
Fewer than 350 hospital beds	39/60 (65%)	64/99 (65%)	0.97

*Toxin Testing: Toxin test used either as a single test or part of a multi-step algorithm

#NAAT Alone: Used either an NAAT assay that only detects *C. difficile*, or a multiplex PCR panel that includes *C. difficile*, without initial or confirmatory toxin testing