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BRIEF REPORT

Pediatric Infectious Diseases Physicians' Preferences for Management of *Clostridioides difficile* Infection: An Emerging Infections Network Survey

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We queried pediatric infectious diseases physicians via the Emerging Infections Network regarding management preferences for *Clostridioides difficile* infection (CDI). We explored use of vancomycin, fidaxomicin, bezlotoxumab, and fecal microbiota transplantation and found that physicians are increasingly considering newer and adjunctive therapies for pediatric CDI, highlighting the need for updated guidelines.

Key words: management; *Clostridioides difficile*; fecal microbiota transplantation; fidaxomicin.

Lay summary

Pediatric infectious diseases physicians indicated a preference for oral vancomycin over metronidazole, increasing consideration of fidaxomicin and general accessibility of fecal microbiota transplant on an updated Emerging Infections Network survey about management of *Clostridioides difficile*.

BACKGROUND

The Infectious Diseases Society of America (IDSA) Emerging Infections Network (EIN) surveyed pediatric infectious diseases (PID) physicians about diagnostic and management preferences for pediatric *Clostridioides difficile* infection (CDI) in 2012.[1] In 2017, the IDSA and the Society for Healthcare Epidemiology of America published updated guidelines that included pediatric CDI recommendations.[2] Oral vancomycin and metronidazole were recommended as options for a first non-severe case of CDI in children and oral vancomycin was preferred for severe or fulminant cases.

Since then, multiple pediatric studies have explored oral vancomycin, fidaxomicin, bezlotoxumab, and fecal microbiota transplantation (FMT). In 2021, the IDSA released a focused guideline update recommending fidaxomicin over oral vancomycin for treatment of initial, non-fulminant disease in adults. Pediatric recommendations were not included.[3]

While pediatric CDI advances are promising, changes in management of CDI in children based on recent literature have yet to be explored. We aim to further characterize current PID physician preferences for CDI therapy.

METHODS

We conducted an electronic survey of PID physician management preferences for various presentations of CDI via the IDSA EIN, a provider-based sentinel network of infectious diseases clinicians who are IDSA and/or Pediatric Infectious Diseases Society members.[4]

Development of the EIN pediatric survey occurred simultaneously with an adult version; the survey differed from the prior EIN pediatric CDI survey in its focus on management strategies.[1,5] Additional questions were developed by PID providers with expertise in management of pediatric CDI. The 11-question survey was pilot tested by the research team for accuracy and functionality prior to distribution. The survey request was emailed to all pediatric EIN physician members ($n = 383$) on May 15, 2024 with 2 weekly reminders to non-responders. The full survey text is available in the Supplementary material. Denominators varied as respondents did not answer every question. Free text responses were included to highlight themes and are presented in their original form.

Data were analyzed using SAS v9.4 (SAS Institute Inc., Cary, NC). Frequencies and proportions were used to summarize results.

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RESULTS

Overall 43% (165/383) of EIN PID members responded to the survey and 36% (138/383) of those respondents had cared for a patient with CDI over the past year (Table S1). Among respondents who had seen patients with CDI within the past year, 67% (92/138) reported managing 1-10 children with CDI and 30% (42/138) of respondents reported managing between 10-30 cases. Most respondents were affiliated with university- (61%; 100/165) and non-university teaching hospitals (28%; 47/165).

Most respondents (75%; 104/138) treated an initial episode of mild or moderate CDI with oral vancomycin; 24% (33/138) preferred oral metronidazole (Table 1). Most respondents (94%; 130/138) treated an initial severe episode with oral vancomycin. The majority of institutional guidelines recommended oral vancomycin as first-line therapy for an initial episode of severe disease (64%; 86/135).

Most respondents (70%; 97/138) defined recurrent CDI as an episode occurring within 8 weeks after the initial episode. For first CDI recurrence, 79% (107/136) reported using a 10-day course of oral vancomycin. For a second recurrence, 78% (105/135) recommended a tapered-pulsed regimen of oral vancomycin and 65% (88/135) reported they would consider fidaxomicin (Table 1).

Respondents were more likely to recommend fidaxomicin for patients with recurrent CDI (76%; 104/136) and for those with a lack of clinical response to a prior course of therapy (76%; 104/136, Table 1). Insurance coverage for outpatients was the most frequently-identified barrier to prescribing fidaxomicin (60%; 82/137). Fidaxomicin's absence from professional guidelines as a preferred treatment for children was an additional barrier for 34% of respondents (47/137).

Bezlotoxumab was recommended for children <18 years by 22% (30/135) of respondents (Table 1). FMT was reported as available locally or regionally by 83% (111/134) of respondents and was most commonly used after 3 recurrences (Table 1). Selected free-text responses are included in Table 2.

DISCUSSION

We found that PID providers are moving away from the 2017 CDI guidelines and increasingly considering newer and adjunctive therapies for pediatric CDI that are more aligned with adult CDI guidelines.

In contrast to the 2012 EIN PID survey where all respondents reported use of oral metronidazole for an initial episode of CDI in an immunocompetent child, our study identified a preference for oral vancomycin.[1] Recently-published studies have also demonstrated this trend.[6] In 2019, a retrospective cohort study of 192 children found that oral vancomycin was associated with an increased likelihood of symptom resolution by day 5 compared with metronidazole in children with non-severe CDI.[7] Despite the preference for oral vancomycin, respondents expressed barriers to use including cost and the taste of the oral vancomycin suspension, a challenge unique to pediatrics.

While the 2021 update to adult CDI guidelines recommended fidaxomicin over oral vancomycin for treatment of an initial episode of CDI, real-world practice remains variable with many adult ID physicians continuing preferential vancomycin use.[8] In the current survey, few respondents endorsed using oral fidaxomicin for an initial non-severe episode in children but higher numbers reported they would consider fidaxomicin for a recurrent episode or in cases where there was no clinical response to metronidazole or vancomycin. Minimal data exist for use of fidaxomicin in pediatric patients outside of the 2020 SUNSHINE trial that demonstrated better sustained treatment response with fidaxomicin compared with vancomycin.[9,10]

Adult literature has also examined barriers to fidaxomicin prescribing.[5,11] Respondents to the current survey identified outpatient cost as the most common barrier, while most respondents did not consider lack of familiarity with fidaxomicin or absence from professional society guidelines to be barriers to use. Restricted inpatient availability, including absence from the institutional formulary, was not felt to be a major barrier, which may indicate that fidaxomicin is more widely available than anticipated. Although no pediatric guidelines include fidaxomicin as a recommended agent (as fidaxomicin was not yet approved for children at the time), this survey revealed that fidaxomicin is now being considered for specific cases and clinical scenarios. Additional research about appropriate indications for fidaxomicin is needed to help guide use in pediatrics.

Bezlotoxumab demonstrated promising results in adult patients, but its utility for pediatric CDI remains unclear. Despite limited efficacy data for pediatric CDI, some respondents reported recommending bezlotoxumab for their patients. Bezlotoxumab was taken off the market (after completion of the current survey) and future availability remains uncertain.[12]

FMT, a safe and effective therapy in children, has been a mainstay in treatment of recurrent CDI in adults with no changes in the updated adult guidelines. In the current survey, most participants recommend FMT for recurrent CDI, typically after 3 or more recurrences and very few recommend it for fulminant disease. Reassuringly, FMT appears to be more widely available than anticipated, with most respondents reporting it was available locally or regionally. After distribution of this survey, OpenBiome, one of the largest stool donor banks, announced plans to suspend operations which may affect future availability.[13]

In our survey, 16% of respondents had not seen a case of pediatric CDI in the past year and 22% of respondents noted a lack of institutional guidelines. These numbers highlight that there are PID providers with little or no experience with CDI as well as those with limited institutional guidance on best practices for managing these infections. We hope this survey of

Table 1. Survey Results.

Survey items and response options	No. (%)
Reported agent in usual practice for initial episode of mild or moderate, non-fulminant pediatric CDI ($n = 138$)	33 (24)
Metronidazole (PO)	104 (75)
Vancomycin (PO)	1 (0.7)
Fidaxomicin	
Recommended agent per respondent's institutional guidelines for initial episode of mild or moderate, non-fulminant pediatric CDI ($n = 138$)	17 (12)
	44 (32)
Metronidazole (PO)	1 (0.7)
Vancomycin (PO)	45 (33)
Fidaxomicin	31 (22)
Oral metronidazole or vancomycin are both considered appropriate	
No institutional guidelines	
Reported agent in usual practice for initial episode of severe, non-fulminant pediatric CDI ($n = 138$)	2 (1)
Metronidazole (PO)	130 (94)
Vancomycin (PO)	6 (4)
Fidaxomicin	
Recommended agent per respondent's institutional guidelines for initial episode of severe, non-fulminant pediatric CDI ($n = 135$)	1 (0.7)
Metronidazole (PO)	86 (64)
Vancomycin (PO)	5 (4)
Fidaxomicin	9 (7)
Oral metronidazole or vancomycin are both considered appropriate options	34 (25)
No institutional guidelines	
Respondents' definition of recurrent CDI when deciding on treatment ($n = 134$)	97 (72)
CDI episode occurring within 8 weeks after the initial episode	34 (25)
CDI episode occurring within 6 months after the initial episode	2 (2)
CDI episode occurring within 1 year after the initial episode	1 (0.7)
CDI episode occurring more than a year after the initial episode	
Reported agent in usual practice for 1st CDI recurrence ($n = 136$)[a]	10 (7)
Metronidazole (PO)	107 (79)
Vancomycin (PO), 10-day course	22 (16)
Fidaxomicin	34 (25)
Oral vancomycin, tapered-pulsed regimen	1 (0.7)
Fidaxomicin, extended-pulsed regimen	1 (0.7)
CDI therapy, followed by a rifaximin chaser	
Reported agent in usual practice for 2nd CDI recurrence ($n = 135$)[a]	3 (2)
Metronidazole (PO)	27 (20)
Vancomycin (PO), 10-day course	69 (51)
Fidaxomicin	105 (78)
Oral vancomycin, tapered-pulsed regimen	19 (14)
Fidaxomicin, extended-pulsed regimen	6 (4)
CDI therapy, followed by a rifaximin chaser	
Patient factors that would influence respondents to use fidaxomicin rather than other agents for non-fulminant CDI ($n = 136$)[a]	104 (76)
Recurrent CDI	60 (44)
Immunocompromised patient	41 (30)
Severe CDI	16 (12)
Ongoing concomitant systemic antibiotics	20 (15)
Inflammatory bowel disease	104 (76)
Lack of clinical response to prior course of metronidazole and/or vancomycin	5 (4)
Would not use/recommend fidaxomicin	
Barriers that prevent respondents from prescribing/recommending fidaxomicin rather than other agents for non-fulminant CDI ($n = 137$)[a]	31 (23)
	82 (60)
N/A, no barriers to use	35 (26)
Challenges with outpatient insurance coverage (eg, prior authorization, copays)	47 (34)
Restricted inpatient availability (eg, non-formulary or high inpatient costs)	20 (15)
Not yet listed in professional society guidelines as preferred agent in children	
Lack of familiarity with fidaxomicin	
Reported use/recommendation of bezlotoxumab for children <18 years of age with recurrent CDI ($n = 135$)	105 (76)
No	30 (22)
Yes	

(*Continued*)

Table 1. Continued.

Survey items and response options	No. (%)
Reported recommendation of FMT for treatment of recurrent CDI ($n = 129$)[a]	49 (38)
No, not available	1 (0.7)
No, would not recommend	4 (3)
Yes, for acute fulminant disease	82 (64)
Yes, for recurrent infection	2/80 (2)
After one recurrence	23/80 (29)
After two recurrences	55/80 (69)
After at least three recurrences	
Reported availability of FMT for children with recurrent CDI ($n = 134$)	61 (46)
Available at my institution	50 (37)
Not available at my institution but is available elsewhere in my region	23 (17)
Not available at my institution nor elsewhere in my region	

Abbreviations: CDI = *Clostridioides difficile* infection; PO = per os; FMT = fecal microbiota transplant. [a]Respondents instructed to select all that apply; numbers add to >100%.

Table 2. Selected Free Text Comments.

Management of CDI, initial episode, non-severe:
"I think metronidazole should be removed as a recommended first line agent for CDI in children."
"Recommendation depends on patient's underlying conditions (e.g., IBD, multivisceral transplant)"
"We provide some guidance for when oral metronidazole can be considered (mild diarrhea, no comorbidities, cost implications/access, etc) but vancomycin used in most situations for our patient population."
"Based on adult data showing the inferiority of metronidazole to oral vancomycin, I recommend oral vancomycin as first line for all CDI. The cost of oral vancomycin pills limits their use inpatient - most patients have to drink liquid vancomycin which can be limiting in the kids that do not take bad tasting liquid medications well. Fidaxomicin is not on formulary at my institution so is rarely used."
Use of fidaxomicin:
"Cost, insurance, availability are all major issues. Adoption of PO vancomycin is very recent and hesitance to change again so soon."
"I haven't used fidaxomicin due to difficulty getting it covered by insurance and families not wanting to wait to start treatment"
"It would be my preference to use fidaxomicin first line, but to date, the associated insurance companies to those patients have refused all PAs and appeals for fidaxomicin."
"Would need multiple recurrences for me to consider using"
"Adult data when compared to vancomycin is not completely convincing. We do not have a high recurrence within 8 weeks or high 30d readmission rate. We do not have this medication on formulary."
Scenarios when respondents used bezlotoxumab in pediatric patients:
"Child with recurrent CDI and Crohn's disease with family very resistant to fecal transplant"
"Would use this for immunocompromised or IBD patients who have had >2 recurrences and are able to discharge to the infusion clinic for administration."
"I have used this in IBD patients with a first recurrence and in oncology patients that have not completed intensive chemo"
"Recurrent C diff in IBD kids (GI frequently requesting it)"
Use and availability of FMT:
"We would like to be able to offer FMT at our institution but have not gotten buy in from our GI colleagues to administer during a scope. We are also hindered by the lack of easily accessible commercially available products for the pediatric age group."
"I would like to do more FMT for acute fulminant CDI and recurrent CDI but every time I try to recommend it, the response from the primary teams are that they are not sick enough to warrant this (for recurrent disease) or that they are too sick to tolerate it (for acute fulminant CDI). Wishing we had more pediatric data and stronger recommendations around FMT."
"FMT: challenges with children swallowing capsules OR need for sedated procedure = $$$"
Additional commentary:
"We have aligned our guidelines more with the adult guidelines since there is evidence for use of fidaxomicin and bezlotoxumab in children, but not yet in national guidelines."
"CDI at my current institution is very fraught such that we're going to create an institutional level guideline with stakeholders from ID, GI, HONC/BMT and Liver transplant."

Abbreviations: C diff = *Clostridioides difficile* infection; CDI = *Clostridioides difficile* infection; chemo = chemotherapy; d = day; FMT = fecal microbiota transplant; GI = gastroenterology; HONC/BMT = hematology oncology/bone marrow transplant; IBD = inflammatory bowel disease; ID = infectious diseases; PA = prior authorization; PO = per os.

current management practices of PID providers can serve as an additional resource for these providers.

The current study has several limitations. The response rate of respondents who had cared for patients with CDI in the past year was 36%, which is consistent with similar surveys but produces potential for non-response bias. While EIN membership includes several hundred PID-trained physicians from diverse institutions and practices, diagnosis and management practices of EIN members may not be generalizable to all PID physicians. Responses to some questions may be subject to recall bias. Finally, the availability of both bezlotoxumab and FMT has changed since the distribution of our survey.

Additional research on PID provider use of alternative agents that may become more available, such as live biotherapeutics, would be helpful.

We found that practice patterns of PID physicians have shifted since publication of the existing pediatric CDI guidelines. Additional pediatric research about use of fidaxomicin and FMT would be valuable. PID physicians desire more detailed guidance on use of these therapies and updated guidelines for management of CDI in children.

Supplementary material

Supplementary material is available at *Journal of the Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

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Conflicts of interest

None declared.

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