

# Diagnosis and Management of *Clostridium difficile* Infection by Pediatric Infectious Diseases Physicians

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**Background.** The incidence of *C difficile* infection (CDI) has risen among children; however, optimal management of CDI within a diverse pediatric population remains unclear. Although adult guidelines recommend oral vancomycin for treatment of second recurrence or severe CDI, dedicated pediatric data to support pediatric specific management guidelines are lacking. Our objective was to describe current CDI management practices by pediatric infectious diseases (ID) physicians.

**Methods.** We surveyed pediatric members of the Emerging Infections Network, a network of infectious diseases (ID) physicians across North America, in October 2012. Clinical vignettes were used to determine how physicians modify CDI management based on clinical presentation or presence of comorbidities, including solid organ transplantation, inflammatory bowel disease, and neutropenia.

**Results.** Of the 285 physicians surveyed, 167 (59%) responded. There were no significant differences in geography, level of experience, or hospital type between respondents and non-respondents. All respondents (100%) used oral metronidazole for the initial occurrence of mild CDI in a normal host. Management varied substantially for mild CDI in patients with a variety of comorbidities, in whom metronidazole therapy was less frequently preferred (41–79%). For management of severe CDI, 65% preferred oral vancomycin alone or in combination with at least one other agent. For a second recurrence, oral vancomycin alone or in combination was preferred by 92%. Among 125 respondents who reported using alternative therapies for recurrent or severe CDI, 23 (18%) recommend fecal microbiota transplantation, while 20 (16%) reported using fidaxomicin.

**Conclusions.** Pediatric ID physicians prefer metronidazole for treatment of mild CDI in healthy children, but management strategies vary for patients with comorbidities or recurrent or severe disease. These findings highlight the need for pediatric comparative effectiveness studies aimed at determining the optimal treatment for pediatric CDI.

**Key words.** *C difficile*; health care-associated infection; pediatric; survey.

*Clostridium difficile* is the most common cause of healthcare-associated diarrhea in the United States and is increasingly recognized as an important pathogen in children [1, 2]. Over the past decade, the incidence of *C difficile* infection (CDI) has more than doubled among adults, and numerous studies have reported an increase in CDI among children in both the inpatient and ambulatory care settings [3–7]. In addition, CDI has been associated with increased risk of death, prolonged hospitalization,

and higher hospital costs among hospitalized children [8]. The diagnosis and management of CDI have also evolved over the past decade; nucleic acid amplification tests, such as polymerase chain reaction assays, have become more widespread in the detection of *C difficile*, and new therapies, such as fidaxomicin, have been approved for use in adults [9–11].

Although the incidence of CDI has increased among children, comparative effectiveness studies to determine

the optimal management of CDI are lacking, particularly within a diverse pediatric population that includes a wide spectrum of children, from neonates to immunocompromised patients. Although current evidence-based management guidelines from the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommend oral vancomycin for treatment of second recurrence or severe CDI based upon data from adult studies [12], dedicated pediatric data to support pediatric-specific management guidelines are lacking. Infectious diseases (ID) physicians are frequently consulted in the care of children with CDI and often guide local clinical practice. Our objective was to describe the current practices in the diagnosis and management of CDI in children by pediatric ID physicians.

## METHODS

We conducted a web-based survey of 285 pediatric members of the Emerging Infections Network (EIN), a network of ID physicians across North America, between September 26, 2012 and October 25, 2012. The pediatric membership of the EIN represents nearly one-quarter of all individuals who have received board certification in pediatric ID since 1994 [13]. Membership is drawn from the IDSA and the Pediatric Infectious Diseases Society.

The 10-item survey (Appendix) was partially adapted from a recent EIN survey of adult ID physicians on management of recurrent CDI and use of fecal microbiota transplantation; new survey items were developed with input from numerous individuals with content expertise in the diagnosis and management of CDI in children. The survey was then pilot-tested among a convenience sample of pediatric ID physicians and modified according to their feedback. For purposes of the survey, we defined recurrent CDI as an episode occurring 8 weeks or less after the onset of a previous episode, provided that symptoms from the previous episode resolved [14] and severe and/or complicated CDI by the presence of either serum white blood cell count  $>15\,000$  cells/ $\mu\text{L}$ , serum creatinine  $\geq 1.5$  times the patient's baseline, hypotension or shock, ileus, perforation or megacolon [12].

Participants responded to questions regarding diagnostic testing methods and treatment strategies for the management of recurrent or severe CDI in children. Clinical vignettes were used to determine how CDI management approaches were modified based on the following: (1) clinical presentation (eg, recurrent disease, severe disease, etc); (2) presence of underlying chronic conditions (eg, solid organ transplantation, inflammatory bowel disease [IBD], or neutropenia); and (3) patient age, particularly for infants.

Proportions from survey responses were compared using Pearson  $\chi^2$  or Fisher's exact tests, as appropriate, using SAS software version 9.3 (SAS Institute, Cary, NC). Two-sided  $P$  values  $<.05$  were considered statistically significant.

## RESULTS

Of the 285 physicians surveyed, 167 (59%) responded from 105 different institutions. There were no significant differences in geographic region, level of experience, employment, or hospital type between respondents and non-respondents. The majority of EIN pediatric ID physicians are employed by academic medical centers or nonuniversity teaching hospitals (90%), of which 60% have an academic appointment. Twenty-two respondents indicated that they have not consulted or managed patients with CDI during the past year and were excluded from further analysis. Of the remaining 145 physicians, 50% reported managing more than 5 patients with CDI per year and over 90% reported managing CDI recurrences. Recurrent episodes represented greater than 20% of all episodes managed for 59 (42%) respondents, and 50% of respondents perceived that the number of CDI recurrences has increased in the past 5 years. The majority (112; 79%) of respondents reported that fewer than 15% of CDI episodes managed were severe or complicated.

Nucleic acid amplification assays were used for diagnosis either alone or in combination with other laboratory methods by 97 (67%) respondents. Toxin enzyme immunoassay (EIA) was used by 32 (22%) respondents, of whom over one-third used toxin EIA alone. Nearly two-thirds of respondents reported no restrictions on *C difficile* testing by patient age. Of the 40 respondents who reported that infant testing was restricted or required approval, the majority (75%) indicated the restriction was present for infants less than 12 months of age. Seven respondents (5%) reported use of education or disclaimers on laboratory results to either discourage testing of infants or aid clinicians in interpreting positive results.

All respondents (100%) used oral metronidazole for the initial occurrence of mild CDI in an immunocompetent host. However, management of mild CDI varied substantially for patients with certain underlying comorbidities or immunosuppression, in whom metronidazole therapy was less frequently preferred (41%–79%) (Figure 1). In response to a positive *C difficile* test in a premature infant with multiple antibiotic exposures, frequent diarrhea, and no other source of infection identified, only 62 (43%) were in favor of recommending CDI-directed therapy.

For management of severe CDI, the majority (65%) of respondents preferred oral vancomycin either alone or in

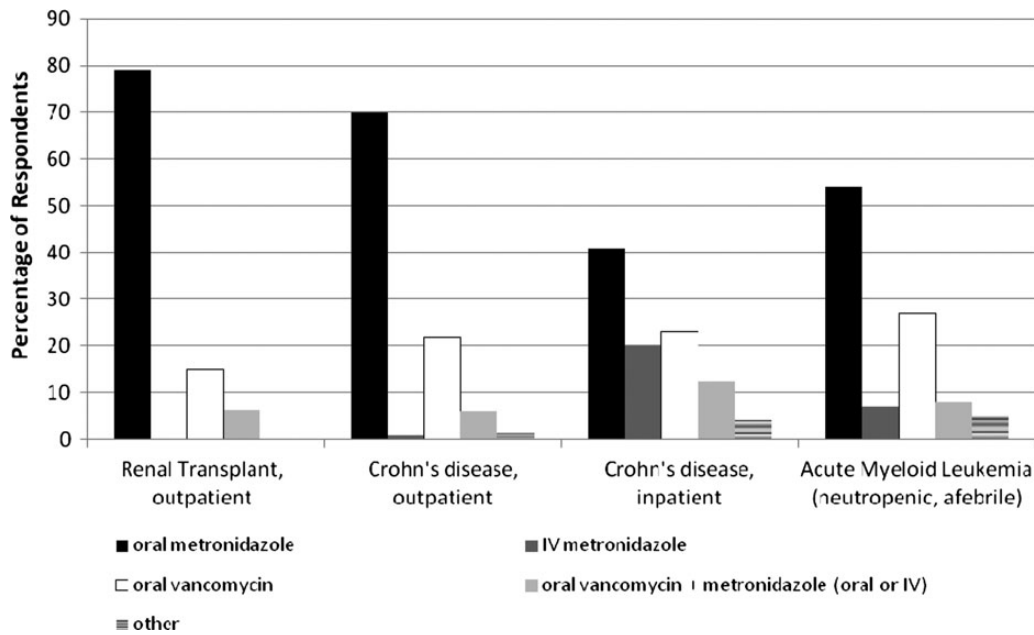


Figure 1. Management of initial, mild *Clostridium difficile* infection by patient type. Abbreviation: IV, intravenous.

combination with at least one other agent; however, over 30% used metronidazole alone for severe disease (Figure 2). For management of a second recurrence, 92% (131) would recommend oral vancomycin either alone or in combination with another agent; 16% of these respondents would use a vancomycin taper. The management of subsequent recurrences (third or more) varied (Table 1). Among 125 respondents who reported ever using or recommending alternative therapies for recurrent or severe CDI, 23 (18%) reported recommending fecal microbiota

transplantation, most commonly for treatment of a third or later recurrence, whereas 20 (16%) reported ever using fidaxomicin (Table 2).

DISCUSSION

Our study demonstrates that there is considerable variability in the management of CDI in children by pediatric ID physicians, particularly in cases of recurrent or severe disease. Although existing data suggest that the incidence

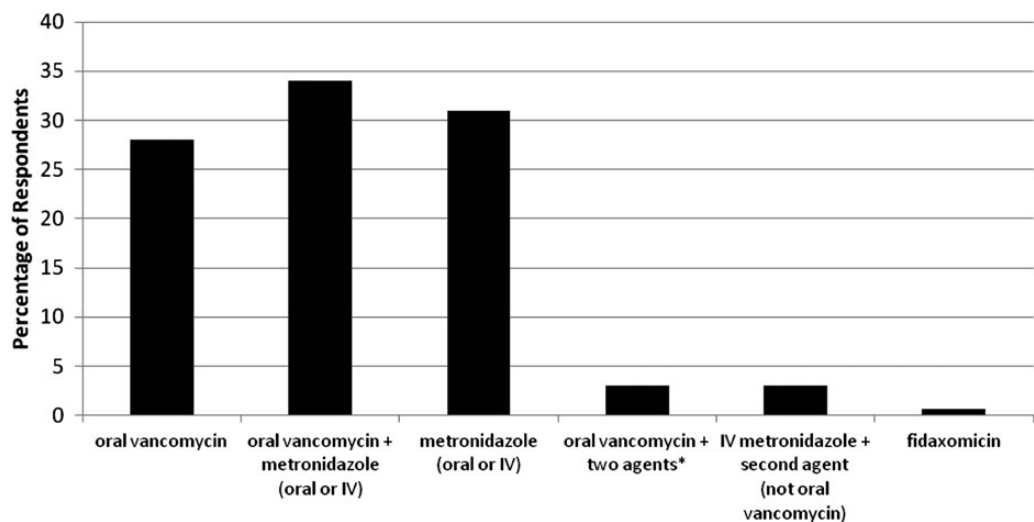


Figure 2. Therapeutic preference for management of severe *Clostridium difficile* infection. \*Two additional agents included by 4 respondents as follows: 1) intravenous (IV) metronidazole, oral metronidazole; 2) IV metronidazole, intravenous immunoglobulin; 3) IV metronidazole, vancomycin per rectum; 4) IV metronidazole, fecal microbiota transplant. Abbreviation: IV, intravenous.

**Table 1.** Therapeutic Preference<sup>a</sup> for Management of Recurrent *Clostridium difficile* Infection, Beyond a Third Recurrence

Choice of Therapy	Number Reporting (%) N = 144 Respondents
Oral vancomycin taper	65 (47)
Oral vancomycin	19 (14)
Oral vancomycin plus 1 or more agents	28 (19)
Nitazoxanide	8 (6)
Rifaximin	6 (4)
Nitazoxanide plus rifaximin	1 (0.7)
Fidaxomicin	5 (3)
Oral metronidazole	2 (1)
Add intravenous immunoglobulin	4 (3)
Add fecal microbiota transplantation	14 (10)

<sup>a</sup> Respondents were asked to select 1 or more treatment choices by indication for the following case scenario: A 5-year-old male with no underlying medical conditions was recently hospitalized and has completed a course of antibiotic therapy. He now has foul-smelling diarrhea, mild abdominal discomfort and his stool is *C. difficile* toxin B positive. He is otherwise well-appearing; other labs are normal.

of CDI has increased dramatically amongst children over the past decade [3, 4, 6], there are limited pediatric data to guide treatment choices for children with CDI [2, 15, 16]. Our study addresses an important knowledge gap by providing data on current CDI management strategies by practicing pediatric ID physicians.

There is consensus among pediatric ID physicians surveyed in the EIN regarding the initial management of mild CDI in an immunocompetent host. However, management of mild CDI among children with underlying comorbidities was more variable, particularly for patients with neutropenia or IBD, where the use of oral metronidazole was less frequently preferred. This finding is consistent with current data showing that children with malignancy constitute a substantial portion of hospitalized children with CDI and experience worse outcomes, including longer lengths of stay and higher rates of in-hospital mortality, compared with hospitalized children with

malignancy and no CDI [17, 18]. Likewise, children with CDI and IBD have been shown to have higher rates of CDI recurrence and treatment failure compared with children with CDI without IBD [19, 20]. Current guidance from the American Academy of Pediatrics' (AAP) Red Book recommend oral vancomycin as initial therapy for patients with underlying intestinal tract disease [21], but there are limited pediatric data on the optimal treatment strategies for children with underlying chronic conditions who may be at higher risk for CDI and its complications. Our findings signal a need for additional guidance around management of CDI in special populations of children.

A majority of pediatric ID physicians surveyed in the EIN consulted on or managed recurrent episodes of CDI, with significant variability in management approaches between providers. Although the majority of respondents preferred a regimen containing oral vancomycin for management of a second recurrence, the management of third or more recurrences varied substantially, which is consistent with current adult guidelines [12]. The use of alternative therapies, such as fecal microbiota transplantation, was not uncommon, especially for management of CDI beyond the third recurrence. Of particular interest was the finding that many respondents reported using or recommending fidaxomicin therapy. Although fidaxomicin has been approved by the US Food and Drug Administration for management of CDI in adults, pediatric data are not yet available. In adults with CDI, fidaxomicin has been shown to be noninferior to oral vancomycin in achieving clinical cure, but it is associated with a significantly lower recurrence rate [9, 10]. In addition, fidaxomicin may be more effective than vancomycin in the face of concomitant antibacterial therapy [22]. Given that the majority of respondents reporting use of fidaxomicin preferred this agent for the management of CDI beyond the third recurrence, these findings underscore the need for additional pediatric data to guide management in challenging cases.

**Table 2.** Alternative Therapies Ever Used or Recommended<sup>a</sup> for Management of *Clostridium difficile* Infection by Indication

	Number Reporting (%) N = 125 Respondents	Severe Disease	First Recurrence	Second Recurrence	≥Third Recurrence
Probiotics for <i>prevention</i> of CDI recurrence	83 (66)	26 (38)	54 (78)	30 (43)	21 (30)
Probiotics for <i>management</i> of active CDI	73 (58)	25 (37)	55 (82)	33 (49)	29 (43)
Nitazoxanide	73 (58)	7 (10)	9 (13)	24 (35)	40 (58)
Rifaximin	52 (42)	7 (13)	4 (8)	18 (35)	35 (67)
IVIG	36 (29)	19 (54)	1 (3)	4 (11)	17 (49)
Vancomycin per rectum	36 (29)	31 (91)	2 (6)	2 (6)	3 (9)
Fecal microbiota transplant	23 (18)	4 (17)	0	0	20 (87)
Fidaxomicin	20 (16)	4 (20)	3 (15)	5 (25)	16 (80)

<sup>a</sup> Respondents were asked to select all treatments for *C. difficile* infection that they had "ever used or recommended" for each indication.

For management of severe CDI, nearly one-third of respondents recommend oral metronidazole, in contrast to adult guidelines recommending oral vancomycin therapy [12]. Although dedicated pediatric data are limited, adult studies have shown that oral vancomycin is superior to metronidazole in the management of patients with severe disease [23], and the use of oral vancomycin for cases of severe CDI is now a clear recommendation from the AAP [21]. Although severe or complicated cases of CDI represented only a minority of episodes managed by pediatric ID physicians, this finding reveals an area where pediatric practice might be improved.

Our study also provides important data on the diagnostic strategies used by pediatric ID physicians. Although the majority of respondents reported the use of nucleic acid amplification assays for diagnosis of CDI in their institution, nearly 10% reported the use of toxin EIA alone. Relative to adult patients, toxin EIA results in children are often falsely positive, likely due to the relatively low prevalence of CDI in pediatric hospitals [24]. The use of toxin EIA alone is also discouraged in current practice guidelines, which recommend that toxin EIA be used only in the context of a 2-step algorithm due to its poor sensitivity [12].

Infants pose a unique challenge in the management of CDI. Colonization with *C difficile* is common among infants [25–27], yet infant testing was not restricted in a majority of institutions, suggesting that infant testing may be common. In keeping with the variability in access to infant *C difficile* testing, physicians also differed in their approach to a positive *C difficile* test result in an infant, indicating that a significant proportion of practitioners consider CDI a viable diagnosis in infants given the right circumstances. This finding is supported by recent epidemiologic studies showing that many infants are diagnosed and treated for CDI [5, 7] and that CDI-related hospitalizations have increased among infants over the past decade [28]. Although it is rare, fulminant cases of CDI, including demonstration of pseudomembranous colitis on autopsy, have been identified among infants [29, 30]. In addition, a few small studies have suggested that *C difficile* among infants may be associated with longer hospital stays and more frequent diarrheal symptoms [27, 31], although inconsistently [32]. Thus, our findings suggest that CDI in infants remains a controversial topic in need of further study.

Our study has potential limitations. Responses to clinical vignettes regarding CDI diagnosis and management may not represent actual practice. In addition, responses may be subject to recall bias. It is also unclear whether the diagnosis and management practices of EIN members are generalizable to all pediatric ID physicians. The EIN

membership comprises approximately one-quarter of all board-certified pediatric ID physicians in North America; thus, our respondents comprise approximately one-sixth of that total. Still, the EIN comprises a geographically diverse group of physicians from both academic and nonuniversity teaching hospitals. Lastly, given that the 167 respondents were identified from 105 unique institutions, some institutions may have had a designated respondent while others may have had multiple respondents to the survey.

## CONCLUSIONS

In conclusion, our study shows that pediatric ID physicians prefer oral metronidazole for the treatment of mild CDI in an immunocompetent host, but practice varies significantly for management of mild CDI in subpopulations of children with underlying gastrointestinal or immunocompromising conditions as well as for recurrent or severe disease. Given that CDI has increased dramatically in pediatric patients over the past decade [3, 4, 6], and it has been associated with worse outcomes, including prolonged hospitalization and increased mortality [6, 8], these findings underscore the need for comparative effectiveness studies aimed at determining the optimal treatment for children with CDI.

## Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online (<http://jpid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that published to benefit the 270 reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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