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PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Recent Issues in Pediatric *Clostridium difficile* Infection

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Abstract
Purpose of Review We focus on two recent aspects of *Clostridium difficile* infection (CDI) in children, namely the emergence of community-associated CDI (CA-CDI) and the incidence and prevention of recurrent CDI.
Recent Findings Current surveys suggest that a large proportion of all pediatric CDI is acquired in the community. Risk factors and frequency estimates of pediatric CA-CDI, however, are confounded in babies and toddlers by a high rate of asymptomatic excretion, whose detection likely is exaggerated by the wide use of highly sensitive nucleic acid amplification tests. Recurrent diarrhea occurs in up to 25% of children with CDI. Preventative strategies for recurrent CDI in adults, namely pulse and taper antibiotic dosing, use of anti-CDI drugs with mild effect on the colonic microbiome, fecal microbiota transplantation, and passive immune therapy, currently are being tested in children.
Summary Future studies are required to better characterize community acquisition of CDI in children and to define the safety and effectiveness of preventative strategies for recurrent CDI.

Keywords *Clostridium difficile* · Pediatrics · Childhood diarrhea

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Introduction

Clostridium difficile is the most common cause of healthcare-associated diarrhea and it recently overtook MRSA as the leading nosocomial pathogen North America and Europe [1–4]. The organism can survive on inanimate surfaces for long periods of time through sporulation, which renders it resistant to desiccation and the action of most detergents. Once ingested, spores convert to the metabolically active vegetative form which elaborates two potent enterotoxins labeled toxin A and toxin B. These toxins characteristically produce an intense inflammatory response with pseudomembrane formation at the colonic mucosa. *C. difficile* usually cannot establish a stable existence in the colon in the presence of a healthy microbiome. The latter must be disturbed in some fashion, usually by exposure to antibiotics, for infection to occur. Hence, until recently, *C. difficile* infection was seen almost exclusively in hospitalized patients (where there was frequent contact with *C. difficile* spores) who recently had been treated with antimicrobials (opening the necessary ecological niche in the colonic microbial flora).

The incidence of *C. difficile* infection (CDI) nearly doubled during the early years of the new millennium, likely as a result of an increase in the use of broad-spectrum antibiotics, an aging population, and higher utilization of healthcare resources [5]. In addition, the severity of CDI also increased, at least partially related to the emergence of the hypervirulent strain labeled North American pulsed-field gel electrophoresis type 1 (NAP1) [6, 7]. In parallel to the rise of disease incidence and severity in adults, several pediatric studies have shown similar trends [5, 8, 9•, 10, 11••, 12–16]. The following will review recent aspects of CDI in children. Two topics will be discussed in particular, both of which also affect adult patients with CDI. First, we will examine the advent of community-associated CDI in children. We then will discuss

risk factors and preventative strategies for children afflicted with recurrent *C. difficile*-associated diarrhea.

Community-Associated *C. difficile* Infection

In the mid-2000s, the Centers for Disease Control and Prevention (CDC) reported the first cases of CDI in patients who either had not been recently hospitalized or had not been exposed to antibiotics, and in some instances, the disease was severe [17]. This evolving new epidemiology led to a new designation of CDI, namely "community-associated CDI (CA-CDI)." Shortly thereafter, several surveillance studies for CA-CDI in adults were undertaken which utilized similar but distinct case definitions. These subtle differences resulted in a wide range of disease prevalences. Depending on the definition used, one study reported a prevalence of CA-CDI that ranged from 10 to 37% of total cases [18]. A separate study found only 71% concordance between two definitions of CA-CDI [19]. This disparity in categorizations prompted the formation of a working group that proposed standardized definitions of hospital-associated CDI (HA-CDI) and CA-CDI [1, 20]. The proposed definition of CA-CDI was symptom onset occurring in the community or within 48 h of admission to a hospital, provided that there was no overnight hospitalization in the last 12 weeks. HA-CDI was defined as symptom onset after 48 h of admission to a hospital or within 4 weeks of discharge from a healthcare facility. A new "indeterminate" category was proposed, which defined symptom onset in the community between 4 and 12 weeks after discharge from a healthcare facility.

The population studied adds additional variation to the frequency of CA-CDI. In hospital-based surveillance among adult patients, the proportion of CDI defined as community-associated ranges from 10 to 30% [18, 21]. Population-based surveillance, on the other hand, suggest that the proportion of CA-CDI is 30 to 50% [11••, 22•, 23, 24]. A study conducted at Kaiser Permanente clinics indicated that only a small minority of adults with CA-CDI are ever hospitalized [25], suggesting the substantial majority of patients are treated as outpatients; hence, it is likely that hospital-based surveys underestimate the overall burden of CA-CDI.

Compared to patients with HA-CDI, adult patients with CA-CDI are younger, have less antibiotic exposure, and have fewer comorbidities. That said, 60–80% of adults cataloged in series of CA-CDI have had recent exposure to antibiotics [11••, 18, 21, 22•, 23, 24], lower than the virtual 100% seen in HA-CDI but substantial nonetheless. Moreover, many adults with CA-CDI have some underlying chronic condition, not serious enough to require hospitalization but prompting frequent clinic visits. Indeed, approximately 80% of adults with CA-CDI reported recent outpatient healthcare contact, suggesting the outpatient setting as a potential reservoir for *C. difficile* [22•]. Patients with low-level healthcare exposure are more likely to have exposure to infants younger than 1 year of age, implying that infants may be a community source for CDI in adults as well [26].

Studies in children have shown an analogous increase in CDI without the risk factor of recent inpatient hospitalization [8, 11••, 27, 28••]. As with adults, the proportion of children with CA-CDI and the risk factors for its acquisition depends on the design of the study. In a hospital-based retrospective survey of pediatric CDI in children conducted at Johns Hopkins Hospital, for example, approximately 20% of their population had onset in the community, but as would be expected in a quaternary care children's facility, over 70% had comorbidities and 42% had recent antibiotic exposure [29]. Similar data regarding antecedent exposures were noted in a hospital-based case-control study conducted at the Texas Children's Hospital, including both inpatients and outpatients [30].

On the other hand, two recent population-based surveillance studies, one conducted in Minnesota and the other using a network of clinics throughout the USA, determined that 71 to 75% of total cases of pediatric CDI were community-acquired [11••, 28••]. While these proportions are striking, otherwise healthy children are frequently prescribed antibiotics for mild intercurrent infections and are regularly exposed to outpatient facilities, the two prominent risk factors for community-acquired disease in adults, adding credibility to these findings. Indeed, in both population-based studies the marked majority of children diagnosed with CA-CDI possessed one or both of these potential risk factors [11••, 28••].

Nevertheless, there are reasons to question the reported frequency of CA-CDI among otherwise healthy children. First, defining and elucidating risk factors for CDI in pediatrics has been confounded by the observation, first made in the early 1980s, that a high proportion of young children are asymptomatic carriers and shedders of *C. difficile* spores [31, 32]. While this phenomenon is most marked in children < 1 year of age, asymptomatic excretion of toxigenic *C. difficile* persists into the toddler years, albeit at a lower proportion [33]. This observation has prompted authorities to recommend against even testing for *C. difficile* in otherwise healthy infants with diarrhea [34]. Nevertheless, pediatricians persist in investigating young children for CDI. Kim et al., for example, trended the growing incidence of pediatric CDI through the first decade of the new millennium by using discharge diagnoses from 40 freestanding children's hospital and found that 26% of CDI diagnoses had been assigned to patients under a year of age [12]. Similarly, in both recent community-based surveys of pediatric CA-CDI, the highest incidence densities were recorded in the youngest age groups [11••, 28••].

The method of testing for CDI also may be contributing to an overestimation of CDI in children. The gold standard test for diagnosing CDI is toxigenic stool culture (Table 1), but this test is labor and resource intensive and requires 48 to 72 h of time for a

result. Thus, until recently, many laboratories used an enzyme immunoassay (EIA) to detect *C. difficile* toxins in the stool, which is easy to perform and has a rapid turnaround time. However, EIA has low sensitivity and a high rate of false-positive tests. In the setting of a population with low prevalence, these two factors negatively impact the positive predictive value of the test [35, 36]. Consequently, many laboratories now use nucleic acid amplification tests (NAAT) directed at the *C. difficile* gene for toxin B as a stand-alone diagnostic assay. Despite the increased sensitivity and specificity of NAAT, it cannot give details on the amount of toxin present in the sample, raising concerns that it is more prone to detect asymptomatic excretion at all ages, which is particularly problematic in young children [37]. (Table 1) Indeed, investigators at Long Island Jewish Hospital recently conducted a prospective study collecting stool specimens from pediatric inpatients and oncology patients with and without diarrhea. Nineteen percent of symptomatic patients, versus 24% of asymptomatic patients, were NAAT-positive for *C. difficile* [38•].

Even before the introduction of NAATs, however, investigators were unable to demonstrate that *C. difficile* is a significant pathogen in community-associated diarrhea in children. Three studies completed in the early 1980s in children admitted with diarrhea to the emergency room or hospital, for example, consistently found that children without diarrhea were actually more likely to be positive for *C. difficile* than those with gastrointestinal symptoms [39–41]. Similarly, a study of a cohort of American children followed prospectively to identify the etiology of diarrhea detected *C. difficile* in 3.5% of enrollees at their asymptomatic baseline, but only 1.9% of specimens when the children were beset with diarrhea [42]. Moreover, investigators in the emergency department at Seattle Children's Hospital aimed to establish the causes of childhood diarrhea by testing the stools of symptomatic children for a host of potential pathogens and then comparing those results to those found in stool specimens from age-matched asymptomatic controls. No association between diarrhea and isolation of *C. difficile* could be established [9•].

What, then, is one to make of the epidemiological studies suggesting a dramatic increase in the occurrence of CA-CDI? It is likely that in adult patients, *C. difficile* has jumped the boundaries of the hospital and is occurring with regularity in the ambulatory population. The picture in pediatrics is less clear. While it is plausible that children with significant underlying illnesses requiring intense exposure to medical interventions are contracting *C. difficile*-associated diarrhea in the community, the importance of this organism among healthy ambulatory children is obscured by the substantial occurrence of colonization, and one should exercise caution in attributing diarrhea in such patients to *C. difficile* unless a thorough investigation for alternative causes has been completed.

Recurrent *C. difficile* Infection in Children

While several antimicrobial regimens have proved effective in treating primary CDI (Table 2), approximately 15–35% of adults experience a recurrence of *C. difficile*-associated colitis after initial resolution of symptoms [43]. The proportion of children experiencing recurrent CDI after their primary episode is slightly lower, approximately 10–25% [44–47]. Over half of those afflicted by a second bout of CDI will be struck by additional recurrences thereafter, resulting in prolonged, debilitating illness [48]. The two principal antibiotics utilized for primary CDI, oral metronidazole and oral vancomycin, prolong the perturbation of the colonic microbiome [49] and thus potentiate recurrent disease. In some patients, the mechanism of recurrence is *relapse*; that is, spores retained in the gastrointestinal tract convert to the

Table 1 *C. difficile* diagnostic tests

Test	Sensitivity	Specificity	PPV	Comment
Toxigenic culture (TC)	N/A	N/A	N/A	Gold standard test
Cytotoxin neutralization assay (CCNA)	N/A	N/A	N/A	Gold standard test
Glutamate dehydrogenase antigen (GDH)	80–100%[a]	83–100%[a]	49–100%[a]	Only used as the initial screening test in a multi-step testing algorithm. Does not detect toxigenic strains
Toxin A + B enzyme immunoassay (EIA)	75–95%[b]	83–98%[b]	51–97%[b]	Not recommended as a stand-alone test. Can be used as a confirmatory test after a positive GDH
Toxin gene nucleic acid amplification test (NAAT)	72–100%[c]	88–100%[c]	71–93%[c]	Risk for false-positive tests. Used as the primary test in acute CDI or as a confirmatory test after a positive GDH

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Table 2 Therapeutic options for primary *C. difficile* infection

Therapeutic modality	Strengths	Weakness
Discontinue the offending antibiotic	• May help to restore the gut flora	• Stopping the offending antibiotic may not be possible, given the individual's medical condition
Oral metronidazole	• First-line treatment • Relatively inexpensive	• In severe CDI, lower rates of cure when compared with oral vancomycin • More side effects with repeated dosing
Oral vancomycin	• Preferred first-line in severe CDI • Poor intestinal absorption, therefore fewer systemic side effects • Able to administer as an enema	• Theoretical concern for vancomycin-resistant enterococci • Higher costs when compared to oral metronidazole (~ 40 × metronidazole)
Fidaxomicin	• Narrow spectrum agent. Effective against Gram-positive aerobic and anaerobic bacteria • Lower recurrence rates compared with vancomycin	• Extremely higher costs (~ 180 × metronidazole, ~ 4 × vancomycin)
Rifaxamin	• Good activity against vegetative *C. difficile* • Mild activity against the colonic microbiome	• Emergence of rifamycin-resistant *C. difficile*
Nitazoxanide	• May be as effective as vancomycin and metronidazole	• Lack of comparative effectiveness studies • Lack of long-term safety and efficacy data
Immunotherapy (IVIG, neutralizing antibody)	• Neutralizing antibody may reduce disease recurrence	• No RCTs showing a benefit of IVIG in primary CDI
Probiotics		• No strong data to support the effectiveness of probiotics in improving outcomes in primary CDI

toxin-producing vegetative form after cessation of therapy, resulting in the return of symptoms. In others, the mechanism is *reinfection*; that is, patients requiring continued need for medical care are re-exposed to a new strain of *C. difficile* which is enabled by the residual colonic dysbiosis. Molecular comparisons of the first and subsequent isolates have indicated that relapse is the most prominent mechanism, even if symptoms recur after many weeks [50, 51••].

Given the debilitating nature of recurrent CDI, investigators have sought to identify factors that predispose a given patient to repeated episodes. Most of these studies have been conducted in adult subjects. The factor that has been most frequently identified has been exposure to non-CDI related antibiotics during or after the episode of diarrhea [43, 52, 53]. Other factors that have been less consistently established include older age [48, 54], severity of the initial episode [55], gastrointestinal surgery [54], and exposure to proton-pump inhibitors [56]. Additionally, the NAP1 strain may be associated with more recurrences than non-NAP1 strains [57, 58]. A meta-analysis of 12 primary observational studies and randomized clinical trials in adults identified exposure to non-*C. difficile* antibiotics (odds ratio, (OR) 4.23 (95% CI, 2.10–8.55)); use of antacid medications ((OR) 2.15 (1.13–4.08)); and older age (OR 1.62 (1.11–2.36)) as the factors most strongly associated with recurrent CDI [59].

Fewer risk-factor studies have been performed in pediatric patients with recurrent infection. Similar to adult studies, the series reported by Tschudin-Sutter et al. [47] identified exposure to non-CDI antibiotics as a risk factor for recurrence. Three studies conducted at separate large university pediatric centers among populations composed of both inpatients and outpatients identified underlying malignancy as a principal predisposing factor for recurrent CDI in children [44–46].

The first recurrent episode of CDI can be treated with the same antibiotic as the initial bout, as emergence of resistance to metronidazole or vancomycin is rare [1]. Metronidazole is avoided for recurrences beyond the first, since repeated exposures to the drug can result in neurotoxicity [1]. It is greatly preferred, however, that symptoms do not recur in the first place, and in that spirit, multiple strategies have been explored to prevent recurrent CDI, as discussed below.

(1) Pulse and taper therapy. Authorities have proposed pulse- and taper-dosing in the patient with recurrent disease to reduce the likelihood of subsequence recurrences. In this strategy, a conventional course of oral vancomycin is followed by a gradual reduction in dose interspersed with 2–3 days in which there is no exposure to antibiotic at all. The theoretical underpinning of this strategy is to allow reconstitution of the colonic microbiome through tapering and eradication of retained spores that have newly converted to the vegetative form through repeated pulse dosing. Despite practice guideline recommendations for this strategy [1], there are few data supporting its use. A recent observational series of 100 adult patients with recurrent CDI documented that approximately 60–81% of those treated with taper/pulse dosing were free of subsequent recurrences, depending on how the regimen was scheduled

[60]. Further validation of this approach awaits the result of a current randomized clinical trial [60]. To the best of our knowledge, there is no published experience testing this strategy in children.

(2) Use of antibiotics with gentle effects on the microbiome. Selected antibiotics have activity against *C. difficile* but result in relatively mild perturbations of the colonic microbial ecology and thus reduce the likelihood of recurrence. Fidaxomicin is a first-in-class macrocyclical molecule with such properties; it has selective in vitro activity against Clostridia species but poor activity against anaerobic and facultative Gram-negative bacteria [61, 62]. Large multicenter trials in adults with CDI, including subjects with both first-episode and recurrent disease, indicated that patients treated with fidaxomicin have a similar clinical cure rate compared with oral vancomycin but approximately half the incidence of further recurrences [63, 64]. To date, the drug remains very expensive, with an average wholesale price of an adult 10-day course exceeding $4000. The drug is not yet licensed for pediatric use but trials in children are ongoing. Rifaximin, a non-absorbable rifamycin, similarly possesses activity against vegetative *C. difficile* but mild activity against the colonic microbiome. A small trial of the drug in adults with recurrent diarrhea indicated effectiveness when given after a conventional course of vancomycin, but emergence of rifamycin-resistant *C. difficile* was recorded [65].

(3) Fecal microbiota transplantation. A third strategy to reduce the frequency of recurrent *C. difficile* disease is through fecal microbiota transplantation (FMT), a process aimed to reconstitute the aberrant colonic microbiome and thus render it resistant to *C. difficile* colonization. The approach involves the harvesting of stool from a healthy, non-antibiotic exposed donor, screening the sample for a host of pathogenic microorganisms and then transplanting the preparation into the patient after resolution of the *C. difficile*-associated diarrhea. The transplantation itself is accomplished through installation of the donor stool via a nasogastric or nasojejunal tube, enema, or colonoscopy [66•]. Anecdotal experience through the 1990s using FMT to treat adults with multiple recurrences of CDI suggested a very high success rate in preventing further recurrences [67]. Its effectiveness subsequently has been demonstrated in small randomized clinical trials, demonstrating an efficacy of approximately 75% in patients who had suffered many recurrences despite repeated treatments with conventional therapy [66•, 68, 69]. Some subjects who failed the initial administration of FMT responded to a repeated dose. Microbiome analysis of the stool of FMT recipients confirms resolution of the dysbiosis found during the period of the patient's diarrhea, with the complexity and diversity of microbial populations seen in healthy persons, indeed, reflecting those seen in the donor. FMT has been reported in small numbers of children with recurrent CDI and appears similarly effective [70–72]. Protocols for donor stool preparations have been published in pediatric journals [70], and studies in children who have received FMT have indicated that it results in a reconstituted, healthy microbiome [72].

Although to date, FMT appears safe even with widening use, some investigators have preached caution. The strategy, by definition, involves the deliberate transfer of an enormous burden and array of microorganisms from one person to another, and the potential for inadvertently transmitting a known or yet-unknown pathogen remains. Moreover, a recent small trial in adults comparing the effectiveness of FMT (given by enema) to oral vancomycin taper therapy in reducing recurrent CDI did not show a significant difference between the two strategies [73]. If these results are borne out in large, randomized trials, they may recommend safer and easier approaches to recurrent CDI than FMT. Recently, investigators have attempted to develop FMT capsules composed of frozen flora from thoroughly screened donors, and if effective, the availability of such preparations may address some of the FMT-related safety issues [74]. Use of FMT in the pediatric patient raises additional concerns. In children, the colonic microbiome evolves over time and is critical in establishing local and systemic immune competence. FMT donors for children with recurrent CDI usually are adult relatives, and the long-term effect of establishing an adult flora in the colon of a young child is not known [75].

(4) Immunotherapy. Serum neutralizing antibody against *C. difficile* enterotoxin appears to be protective against recurrence in animals. Although data regarding this phenomenon in humans are limited [57, 76], antitoxin antibody is effective in a range of other toxigenic human diseases. Based on these observations, a multicenter American trial tested the efficacy of passive immunization of adults being treated for both primary and recurrent CDI against further recurrences, employing humanized monoclonal antibodies against toxin A and toxin B. At 3-month follow up, significantly fewer antibody recipients experienced laboratory-confirmed *C. difficile* recurrence (7%) compared with those who had received placebo (25%). Subsequent studies performed in over 300 international sites in adults with CDI measured the efficacy of monoclonal antibodies to toxin A and toxin B separately and in combination versus placebo, in reducing the incidence of recurrence. These trials demonstrated the primacy of anti-toxin B in preventing recurrent CDI in humans, as the addition of anti-toxin A to the preparation did not improve protection. Pediatric trials testing immunotherapy to reduce recurrent CDI in children are planned in the near future.

Conclusion

The evolving epidemiology of CDI has led to new categorizations and definitions of disease. It is clear that the burden of CA-CDI is increasing in the adult population. The diagnosis of CA-CDI in children is complicated by many factors, not the least of which is a high rate of asymptomatic carriage. This is compounded by the highly sensitive and specific diagnostic NAAT that, while able to accurately detect the toxin gene, cannot reveal information on the toxin load that is responsible for causing symptomatic diarrhea. Further pediatric studies are required to define the risk factors for CA-CDI, taking into consideration the unique characteristic of asymptomatic carriage in children. Recurrent CDI is not an uncommon affliction in pediatrics. Exposure to non-CDI antibiotics and malignancy appear to be associated with recurrent CDI in children. More studies are needed to further refine risk factors for this debilitating disease. While prevention strategies for recurrent CDI have been studied in adults, reports in children are sparse. We look forward to the results of pharmacological trials with the goal of preventing pediatric recurrent CDI.

Compliance with Ethical Standards

Conflict of Interest Drs Clayton and Toltzis declare no conflicts of interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards.

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