Clostridium difficile Infection in Children

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Clostridium difficile is the most common cause of health care–associated diarrhea among adults in the United States and is associated with significant morbidity and mortality. During the past decade, the epidemiology of *C difficile* infection (CDI) has changed, including a rise in the rate and severity of infection related to the emergence of a hypervirulent strain as well as an increase in disease among outpatients in community settings. Although less is known about CDI among pediatric patients, *C difficile* is increasingly recognized as an important pathogen among children. In this review, we discuss recent updates in the incidence and epidemiology of CDI among children, including risk factors for infection, and highlight the importance of CDI in special populations of children, particularly those with inflammatory bowel disease or cancer. In addition, we review current knowledge in the areas of diagnosis and management of CDI among children and highlight future areas for research.

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Clostridium difficile is the most common cause of health care–associated diarrhea in the United States and is associated with significant morbidity and mortality. During the past decade, the rate and severity of *C difficile* infection (CDI) have increased. Among adults, CDI rivals methicillin-resistant *Staphylococcus aureus* as the most common cause of health care–associated infections in the United States.[1] Much of this changing epidemiology is attributed to the emergence of a hypervirulent strain of *C difficile*, referred to as the North American pulsed-field gel electrophoresis type 1 strain (NAP1).[2,3] In particular, the incidence of CDI has grown among populations previously believed to be at low risk, including patients in ambulatory care, giving rise to the concept of community-associated (CA)–CDI.[2] Less is known about the epidemiology of CDI among children, although several studies have also shown a rise in CDI among children in both community and hospital settings.[4-8] In addition, whereas *C difficile* was formerly believed to cause milder disease in children than in adults, severe cases of CDI,[9,10] as well as infection with the NAP1 strain,[11] have been reported among children. Still, the significance and outcomes associated with CDI, as well as the optimal diagnosis and treatment, remain poorly defined among children.

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In this review, we discuss recent updates in the incidence and epidemiology of CDI among children, including risk factors for infection, as well as review current knowledge in the areas of diagnosis and management of CDI among children.

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OVERVIEW OF THE PATHOGEN AND CLINICAL MANIFESTATIONS

Clostridium difficile is a gram-positive, obligate anaerobic bacillus that produces 2

major toxins, toxin A and toxin B, important in disease pathogenesis. Nontoxigenic strains of *C difficile* also exist but do not cause CDI. The ability of *C difficile* to form spores enables the bacteria to remain in the physical environment for prolonged periods, facilitating transmission. The major inciting event for development of CDI involves perturbation of the lower intestinal microbiota, followed by acquisition of colonization with toxigenic strains, growth of *C difficile*, and elaboration of toxins. Transmission occurs via the fecal-oral route through contact with *C difficile* spores that transiently contaminate the hands of health care personnel or on environmental surfaces.

Still, many persons become only asymptomatically colonized after exposure to *C difficile* spores, which may be related to a more robust antibody response to toxin A in those individuals in addition to other host factors.[12] Asymptomatic carriage is particularly common in infants through the first year of life but diminishes with age as the lower intestinal microbiota becomes established, usually by age 2 years.[13] Intestinal carriage rates among healthy adults in the community are low, ranging from 1.6% to 4% for toxigenic strains in recent studies.[14,15] Among hospitalized adults, colonization rates vary between 5% and 26%[16] but may be as high as 52% among patients in long-term care facilities during epidemic settings.[17] Colonization rates among older children mirror those of adults. In a recent observational study evaluating hospitalized children with CDI at a tertiary care children's hospital, 25% of *C difficile*–positive stool samples were determined to represent asymptomatic colonization.[18] Risk factors for colonization with toxigenic strains among hospitalized children include underlying medical conditions, prior hospitalization, and exposure to 2 or more anti-infectives.[19]

The clinical spectrum of CDI varies widely, ranging from asymptomatic carriage to clinical disease. Most commonly, CDI consists of mild or moderate diarrhea, rarely with blood or mucous.[20] Fever, cramping abdominal pain, and peripheral leukocytosis are also described.[16] Patients with severe colitis may develop a paralytic ileus or toxic megacolon, resulting in minimal or no diarrhea. Additional complications of severe colitis include dehydration, electrolyte disturbances, bowel perforation, hypotension, renal failure, sepsis, and death.[16] Although severe CDI is reported among children,[9,10] complications related to CDI are uncommon,[21] ranging from 0% to 12%.[10,18] Recurrent episodes of CDI can cause significant morbidity, occurring in up to 25% of adult patients, due either to relapsed infection with the original strain or reinfection with a new strain.[16] Reported rates of recurrence among children have been similar to those in adults.[10]

Extraintestinal manifestations of CDI are rare but include reports of bacteremia, peritonitis, perianal abscess, surgical site infections, and musculoskeletal infections, including septic arthritis, osteomyelitis, reactive arthritis, and acute flexor tenosynovitis.[22-25] Among adults, extraintestinal infections with *C difficile* are often polymicrobial and identified among patients with underlying comorbid conditions.[22] Rare presentations of CDI among children include rectal prolapse[26] and hemolytic uremic syndrome.[27]

INCIDENCE AND EPIDEMIOLOGY

Changing Epidemiology of CDI

Although CDI has been described since the 1970s, its epidemiology is changing. During the past decade, multiple reports documented a rise in both the number of outbreaks of CDI as well as the number of fulminant cases leading to colectomy or death.[3,28] In particular, the incidence of CDI has grown among populations previously believed to be at low risk, namely, previously healthy patients in the community.[2,28] These changes have occurred in parallel to the emergence of a hypervirulent strain of *C difficile* (NAP1), which is resistant to fluoroquinolones and capable of producing higher levels of toxin.[3] The first epidemic cases were reported between 2000 and 2002 from the United States and Quebec, Canada, where the NAP1 strain was associated with a dramatic rise in morbidity and mortality among affected patients.[29,30] Since then, NAP1 has spread throughout North America and has been associated with outbreaks in the United Kingdom, continental Europe, and Asia.[16] The NAP1 strain has also been identified among children.[10,11,31] Among consecutive *C difficile* toxin–positive stool samples at 2 tertiary care children's hospitals, 19.4% of samples were NAP1.[10,11]

Incidence and Epidemiology of CDI Among Children

Historically, health care–associated diarrhea among children was attributed to viral pathogens.[32] Because CDI is not a reportable disease, surveillance data are limited. However, *C difficile* is increasingly recognized as an important pathogen among children. Surveillance data from a tertiary care children's hospital in 2002 found that hospital-acquired diarrhea was the third most common nosocomial infection, of which *C difficile* was the single most common cause (32%).[32]

Several studies have noted a rise in CDI-related hospitalizations using large multicenter cohorts of patients.[4,7,8,33] The first, reported by Kim et al,[4] was a large retrospective cohort study among 4895 hospitalized children at 22 US children's hospitals, which showed that the incidence of CDI increased from 2.6 to 4 cases per 1000 admissions from 2001 to 2006. Of note, rates of *C difficile* testing remained stable during the study period. The median age at diagnosis was 4 years. Similar results were found using a time-series analysis within the Kids' Inpatient Database (KID), which reported a rise in pediatric CDI-related hospitalizations from 7.24 to 12.80 per 10 000 hospitalizations between 1997 and 2006.[8] The highest incidence of CDI-related hospitalizations occurred among children aged 1 to 4 years. Although rates of *C difficile* testing were not available in the database, the authors noted a concomitant increase in rotavirus-related hospitalizations during the study period, suggesting a potential reporting bias; however, rates of hospitalization for other enteritides remained stable.[8] Although administrative data are limited by a lack of clinical information, its use as an overall correlate for CDI in hospitalized children has been validated using multicenter pediatric data.[34]

Similar to findings in adults, several studies have reported a rise in CA-CDI among children.[2,6,35] A prospective cohort study evaluating children with diarrhea presenting to a pediatric emergency department found that 47% of stool samples yielded a bacterial pathogen; of these, *C difficile* was identified most often (12%).[5] A rise in CA-CDI rates has also been supported by recent data documenting an increased proportion of cases of CDI presenting to the emergency department[6] as well as increased identification of *C difficile* during outpatient colonoscopy for previously undiagnosed gastrointestinal complaints.[35] In a cohort of 181 hospitalized children with CDI, 25% of cases were CA.[18]

RISK FACTORS FOR CDI IN CHILDREN

Major risk factors for the development of CDI in adults include factors that decrease host defenses, including advanced age, impaired immune status, and alterations in the lower intestinal microbiota, as well as increased exposure to *C difficile* spores.[16,20] Previous antibiotic exposure is recognized as the single most important risk factor for CDI in adults and children, and nearly all antimicrobials have been associated with *C difficile* disease.[36] Still, dedicated epidemiologic studies evaluating risk factors for CDI among children are limited, are typically single center, and often have conflicting results.

Among hospitalized children, the majority of studies have reported an association between both antibiotic exposure and previous hospitalization and CDI. An evaluation of hospital records of all children with *C difficile* toxin–positive stools at a university-affiliated pediatric hospital in Canada between 2000 and 2003 found that among 200 children with CDI, 75% had record of antibiotic use in the previous 2 months and 56% had been hospitalized in the preceding month.[37] More recently, a large case-control study among hospitalized children tested for *C difficile* at a tertiary care children's hospital identified risk factors for CDI in addition to previous antibiotic exposure, including solid organ transplantation and presence of a gastrostomy or jejunostomy tube.[18] Receipt of *C difficile*–active antibiotics within 24 hours before testing was protective in this study, suggesting that *C difficile* testing may be low yield in patients receiving *C difficile*–active therapies. Of note, some pediatric observational studies have shown that lack of prior hospitalization is associated with CDI after multivariable analysis, perhaps reflective of acquisition of *C difficile* colonization and infection during hospitalization.[18,38]

As the epidemiology of CDI has shifted to include outpatients in the community, several adult studies have explored risk factors for CA-CDI. Although definitions for CA-CDI differ between authors, a common finding between studies is the lack of previous antibiotic exposure in a large proportion of patients, suggesting there may be additional factors at play.[39,40] Among pediatric studies describing the features of patients presenting with CDI in the community, the presence of prior antibiotic exposure is variable; however, cautious interpretation of these findings is warranted, given incomplete capture of patients with *C difficile* and poor documentation of prior antibiotic use in the emergency department record.[5,6] Additional dedicated pediatric studies evaluating risk factors for CA-CDI are needed.

The use of gastric acid–suppressing agents, particularly proton pump inhibitors (PPIs), was associated with a higher risk of CDI among adults in recent meta-analyses[41-43] and was the subject of a recent Food and Drug Administration Drug Safety Alert. Although the mechanism of association between PPIs and the development of CDI is unclear, gastric acid production is a critical part of host defense mechanisms against ingested pathogens, and it has been shown that the vegetative forms of *C difficile* can survive in gastric contents with an elevated pH.[44] In addition, concomitant use of antibiotics and PPIs has been shown to confer a greater risk of CDI than use of PPIs alone, suggesting a common pathway to risk.[42] Among children, existing data on the link between PPIs and development of CDI are limited; few pediatric studies were included in the recent meta-analyses. In a dedicated pediatric study evaluating the risk of CDI among children with abdominal pain and diarrhea who had undergone *C difficile* testing, the use of PPIs was significantly associated with CDI after multivariable analysis.[38] Other pediatric studies have failed to show an association,[19] including the largest pediatric risk factor study to date.[18] Still, the recent findings in adults support more judicious use of these drugs in children.

CDI IN SPECIAL POPULATIONS OF CHILDREN

The presence of underlying comorbid conditions is a common feature among children with CDI, likely reflective of the unique combinations of increased health care exposure, as well as exposures to antibiotics, immunosuppression, and other factors that alter the intestinal microbiota in these children. In the large retrospective cohort study in pediatric inpatients by Kim et al,[4] 67% of patients had at least 1 underlying comorbid condition; however, these conditions varied significantly across age groups. Underlying cardiovascular disease was most common among the youngest children (newborns), whereas cancer was most common among older children (aged 5-17 years).

Several studies have reported increased incidence of CDI among children with inflammatory bowel disease (IBD). An evaluation of trends in cases of CDI within KID between 1997 and 2006 revealed that children with CDI had a higher mean number of diagnoses than those without CDI, but of the comorbid conditions analyzed, IBD was most highly associated with CDI.[33] Among a cohort of children with IBD at a tertiary care children's hospital, the annual rate of CDI was 7.4%.[45] Hospitalized children with CDI and IBD have been shown to have higher rates of CDI recurrence[46] and treatment failure[45] than patients with CDI but no IBD. In addition, the presence of CDI has been shown to affect IBD disease severity and has been associated with higher rates of hospitalization and escalation of IBD-directed therapy after infection.[46]

Clostridium difficile infection can be particularly problematic for children with cancer or those receiving immunosuppressant therapies.[47,48] In a recent study evaluating risk factors for severe CDI among hospitalized children at 2 children's hospitals, all children with can-

cer and CDI had severe disease.[10] Among children with cancer identified using KID, the rate of CDI was 15 times greater among children with cancer compared with those without.[49] Furthermore, children with cancer accounted for 21% of all pediatric CDI cases.

INFANTS AND *C DIFFICILE*

Among infants, the significance of *C difficile* remains controversial. Numerous studies have reported rates of asymptomatic colonization up to 70% among healthy infants, with an early peak in colonization within the first month of life.[13,50-54] More recently, prospective screening for *C difficile* in children younger than 2 years revealed colonization rates of 33% overall.[55] Neonates are uniquely susceptible to *C difficile* colonization because of the immaturity of the neonatal intestine and lack of protective intestinal microbiota. Lack of disease may also be related to immature or diminished receptor sites for toxin A along the intestinal epithelium.[56] The source of colonization seems to be exposure to *C difficile* spores within the nursery or health care environment rather than the mother.[50,52,53] Higher colonization rates have been reported among bottle-fed than among breastfed infants[54,57] and among those with longer nursery stays.[53] Of note, CDI may be more likely to manifest in certain populations of infants, namely those with Hirschsprung disease.[58]

Still, *C difficile* testing among infants is common.[10,18] Zilberberg et al[7] demonstrated that CDI-related hospitalizations nearly doubled among infants younger than 12 months from 2000 through 2005, corresponding to an 18% increase annually, whereas hospitalizations related to other enteritides remained stable. In addition, Benson et al[6] found that 61% of stool specimens positive for *C difficile* at a tertiary care children's hospital were obtained from children younger than 2 years, of whom 50% had suspected or confirmed necrotizing enterocolitis and 18% underwent colostomy or colectomy. Limited data from single-center studies have suggested that *C difficile* among infants may be associated with longer hospital stays in the neonatal intensive care unit as well as more frequent diarrheal symptoms,[54,59] whereas others have shown opposite results.[60] Thus, the significance of positive *C difficile* results among infants remains unclear, and such findings should be interpreted with caution.

DIAGNOSIS

The diagnosis of CDI should be made using a combination of clinical judgment and laboratory results; stool testing should only be performed on unformed specimens and should not be repeated for "test of cure." Enzyme immunoassay (EIA) for toxins A and B had largely replaced the conventional reference standard of cell culture cytotoxicity neutralization assays (CCNAs) because CCNA was labor intensive with a slow turnaround time. Although EIA testing is rapid and relatively inexpensive, its use has been criticized owing to the suboptimal sensitivity and specificity of many commercial assays, such that recent clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) now discourage their use.[16] Enzyme immunoassay testing for *C difficile* glutamate dehydrogenase (GDH) is both rapid and sensitive. However, GDH testing is not specific for toxigenic strains of *C difficile* and so requires confirmatory testing with toxigenic culture or cytotoxicity assay.

Prior research reported that nearly one-third of EIA tests used to evaluate pediatric inpatients for CDI had false-positive results.[10,61] This finding was likely due to the low prevalence of CDI in pediatric hospitals, which was approximately 5% across the 2 centers evaluated. Even with relatively high test specificity, positive predictive value diminishes as the prevalence of disease in the tested population decreases. In addition, a recent study evaluating stool samples from hospitalized children with suspected CDI reported the sensitivity of stool EIA testing at 35% compared with stool culture.[62] These findings raise serious concerns about the widespread use of EIA assays to diagnose CDI in children and are in keeping with recommendations from SHEA and IDSA that discourage use of toxin testing alone.

Nucleic acid amplification tests (NAATs), including polymerase chain reaction techniques, have emerged as rapid, sensitive, and specific alternatives in *C difficile* detection, with sensitivities equal to or exceeding CCNA. However, owing to the higher costs associated with NAAT methods, 2-step algorithmic approaches consisting of GDH and EIA testing for *C difficile* toxin followed by confirmatory testing with NAAT methods for those specimens with discrepant findings have gained broader use.[63] Two-step algorithmic approaches have been evaluated in children with promising results.[64,65] Evaluation of a 2-step algorithm in a tertiary care children's hospital that included initial EIA testing for GDH and toxins A and B followed by NAAT revealed a sensitivity, specificity, positive predictive value, and negative predictive value of 81%, 100%, 100%, and 96%, respectively, and facilitated immediate reporting of 50% of all true-positive findings.[65]

TREATMENT AND OUTCOMES

To date, there are limited data on the outcomes associated with CDI in hospitalized children. Recently, length of stay, in-hospital mortality, and total hospital charges were compared between hospitalized children with or without CDI in KID.[33] Patients with CDI were matched to those without CDI by propensity score and found to have worse outcomes, including longer stay, higher in-hospital mortality rates, and increased hospital charges. However, this study was limited by the lack of availability of any treatment data within the database, which is important in determining outcomes.

SEVERE CDI IN CHILDREN

Complications related to CDI, including toxic megacolon, colectomy, sepsis, and death, although relatively rare in children, have been reported.[9,66] In the multicenter study by Kim et al[4] evaluating CDI among hospitalized children, 1.25% underwent colectomy; the all-cause mortality rate among children with CDI was 4%. To further

investigate the epidemiology of severe CDI among children, our group recently evaluated the risk factors and outcomes associated with severe CDI among a cohort of hospitalized children at 2 centers.[10] Severe CDI was defined as CDI and at least 1 complication or more than 2 laboratory or clinical indicators consistent with severe disease. The majority of patients met criteria for severe disease (59%); among children with CDI, the most frequent complication was admission to the intensive care unit on the day of or within 2 days of diagnosis (17%); toxic megacolon, gastrointestinal perforation, and surgical intervention due to CDI were rare, each occurring in less than 2% of the cohort.

MANAGEMENT OF PEDIATRIC CDI

Despite the increasing incidence of CDI among children, the optimal management of pediatric CDI remains unclear. Due to concerns about the increased risk of resistant bacteria and excess costs associated with vancomycin use, groups such as the American Academy of Pediatrics recommend metronidazole as first-line therapy for children with CDI. However, evidence in support of the expanded use of oral vancomycin in adult CDI patients is growing, particularly in those with severe disease.[67] Based on these findings, current guidelines by IDSA and SHEA recommend oral vancomycin as first-line therapy for severe CDI in adults, or when metronidazole fails or is contraindicated.[16] Comparative effectiveness studies among children with CDI are lacking.

Based on current observational data, the majority of children with CDI are treated with a single agent, typically metronidazole (53%-63%).[4,10,18] Use of oral vancomycin among children varies by hospital, ranging from 3.5% to 30% in recent studies.[4,10,18] In the analysis by Kim et al[4] of treatment chosen by providers for patients with CDI in US children's hospitals, oral vancomycin use was limited to 5 of the 22 hospitals evaluated.

Although metronidazole and oral vancomycin are used most commonly, there are a number of agents used in the management of CDI, particularly in cases of recurrent or refractory disease; however, pediatric data are limited for most of these therapies. Rifaximin has been shown to have cure rates comparable to those of vancomycin in a small study in adults (20 patients) and was used successfully in adult patients with multiple CDI recurrences; however, one caution in using rifaximin is the recognition of the development of high-level resistance by clinical *C difficile* isolates during therapy.[68,69] Nitazoxanide has also been compared with both metronidazole and oral vancomycin in adults; it was shown to have cure and recurrence rates similar to those of metronidazole in adult patients with CDI, but noninferiority compared with vancomycin could not be established owing to small sample size.[68] Other antibacterial agents used in adults include intravenous tigecycline, teicoplanin (not available in the United States), bacitracin, and fusidic acid.[68]

Among the newer antibacterial therapies for CDI, fidaxomicin has been approved by the Food and Drug Administration for use in adults. Fidaxomicin is a macrocyclic antibiotic that has a selective spectrum and may be less active against elements of the normal microbiota of the gut.[70] Interim analyses from phase 3, randomized, placebo-controlled, double-blinded trials comparing fidaxomicin with vancomycin in adults have shown that fidaxomicin is not inferior to vancomycin in achieving clinical cure and has a significantly lower recurrence rate.[71] In addition, a recent study using data from phase 3 trials showed that fidaxomicin was more effective than vancomycin in achieving clinical cure in the presence of concomitant antibacterial therapy.[72] Fidaxomicin may have potential applications for use in children once safety studies are performed, but it is not yet approved for use in children.

An evaluation of nonantimicrobial therapies for CDI is beyond the scope of this review, but these therapies include intraluminal toxin-binding agents, biotherapeutics (including use of probiotics [*Saccharomyces boulardii* and *Lactobacillus* species] and fecal transplants), and intravenous immunoglobulin. Use of probiotics has theoretic benefit in restoring the normally protective function of intact lower intestinal microbiota after disruption by antimicrobial therapy[68]; however, results from clinical studies are largely inconclusive.[73] The use of fecal transplants has resulted in cure of recurrent CDI in uncontrolled case series, including a case in a child[74]; however, results of larger, clinical trials are still pending at the time of this writing.[68]

PREVENTION

Clostridium difficile infection can be prevented by minimizing the frequency, duration, and number of antimicrobial agents used. This objective can be supported through the implementation of antibiotic stewardship programs and is recommended by SHEA and IDSA in their current clinical practice guidelines.[16] A detailed review of the preventive measures for CDI is beyond the scope of this review; however, the transmission of *C difficile* can be mitigated in hospital settings through the proper use of hand hygiene as well as the implementation of contact precautions. Of these measures, the use of gloves has been shown to be the most effective in interrupting the transmission of *C difficile*.[75] In addition, environmental surfaces should be cleaned with chlorine-containing or other sporicidal agents.

SUMMARY AND FUTURE DIRECTIONS

The epidemiology of CDI has changed dramatically in recent years, such that CDI is now a growing problem among children. Although several studies have documented a rise in incidence of CDI among children, additional studies are needed to better evaluate the epidemiology of CDI among children in the community. In addition, whereas asymptomatic colonization among infants is well known, testing for CDI in this population is common and warrants further study to understand the significance of positive tests in this group. Likewise, the diagnosis of CDI should be made only in the context of appropriate clinical findings with the use of sensitive and specific diagnostic testing algorithms; toxin EIA should not be used alone. Finally, comparative effectiveness stud-

ies evaluating different treatment strategies for CDI in children are lacking, especially for those special populations of children at highest risk for poor outcomes related to CDI.

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