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Clostridium difficile Infection in Children

Ana M. Alvarez, MD, FPIDS[a,b],
Mobeen H. Rathore, MD, CPE, FPIDS[a,b,*]

[a]Pediatric Infectious Diseases and Immunology, University of Florida Center for HIV/AIDS Research, Education and Service (UF CARES), 910 North Jefferson Street, Jacksonville, FL 32209, USA; [b]Wolfson Children's Hospital, 800 Prudential Drive, Jacksonville, FL 32207, USA

Keywords

• *Clostridium difficile* • Infection • Children • Antibiotics

Key points

- The incidence of *Clostridium difficile* infection (CDI) in children has increased remarkably in the past decade. Unlike cases in adults, most pediatric cases are community associated.
- Certain precautions when ordering CDI testing are recommended because of the inability of the currently available tests to differentiate disease from asymptomatic colonization.
- The management of CDI is complicated by an increasing incidence of severe disease and a high rate of recurrences.
- New therapies and strategies for the treatment and prevention of CDI seem promising, but more studies in children are needed.
- Strong infection prevention and control programs, including antibiotic stewardship, are essential to control *C difficile* transmission.

INTRODUCTION

Clostridium difficile infection (CDI) is the leading cause of health care–associated diarrhea in the United States [1], and it is one of the most common health care–associated infections, surpassing methicillin-resistant *Staphylococcus aureus* (MRSA) in some areas of the country [2]. Once thought of as only a

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*Corresponding author. Pediatric Infectious Diseases and Immunology, University of Florida Center for HIV/AIDS Research, Education and Service (UF CARES), 910 North Jefferson Street, Jacksonville, FL 32209, USA. *E-mail address:* mobeen.rathore@jax.ufl.edu

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hospital-acquired infection mostly affecting adults, CDI has emerged as an important community-associated infection in adults and children over the last decade [3]. In 2013, the Centers for Disease Control and Prevention (CDC) categorized *C difficile* as one of 3 urgent threats among 18 drug-resistant threats in the United States, requiring urgent public health attention [4]. This article summarizes epidemiologic trends and updated recommendations for the diagnosis, treatment, and prevention of CDI in children. It also discusses emerging treatment and prevention strategies.

PATHOGENESIS

C difficile is an anaerobic, spore-forming, gram-positive bacillus. The spores are dormant in the environment, including health care facilities. They can also be found in low levels in the food supply [5]. They are resistant to acid, heat, antibiotics, and most disinfectants. The spores germinate after they reach the intestine, where *C difficile* can overgrow if there are alterations of the intestinal microbiota (intestinal dysbiosis). Not all strains of *C difficile* are pathogenic. In the intestine, the pathogenic strains are able to produce toxins A and B, which are responsible for the clinical manifestations by disrupting the cytoskeletal structure of the epithelial cells [6]. Toxin B is the most important virulent factor and it is more potent than toxin A in causing mucosal damage. Strains not producing toxin A can be as virulent as strains producing both toxins [7]. Infections outside the intestine are rare. Other factors affecting the pathogenesis include colonization with nontoxigenic strains, production of antibodies against toxins, and variable expression of toxin receptors in the intestine [5].

The transmission of *C difficile* spores can be the result of person-to-person spread through the fecal-oral route or direct exposure to contaminated surfaces, including hands. Transmission from asymptomatic carriers and health care personnel is well known [8]. The incubation period from colonization to infection has not been clearly established but it has been estimated to vary from 2 days to more than a week [2].

Risk factors

Several risk factors have been associated with CDI. However, antibiotic exposure is the most important for both community-associated and health care–associated CDI (HA-CDI) [8,9]. Disease usually occurs 5 to 10 days after starting antibiotics but has been described on the first day of treatment and up to 10 weeks after antibiotic cessation [10]. Certain antibiotic classes, such as cephalosporins, fluoroquinolones, and lincosamides, have been more frequently associated with CDI, but any antibiotic can be responsible for CDI. *C difficile* infection can also occur without antibiotic exposure [9]; antibiotic exposure was not identified as a risk factor in more than 40% of children with CDI [9]. Other identified risk factors in children include acid suppression medications (ie, proton pump inhibitors [PPIs] and histamine-2 receptor antagonists) [11] and gastrointestinal feeding devices [12].

Use of PPIs or narcotics, leukocytosis greater than 15×10^9/L, increased serum creatinine level greater than 1.5-fold from baseline, and older age

have been identified as risk factors for severe disease in adults [13]. Risk factors for severe disease reported in children include exposure to multiple classes of antibiotics in the 30 days before infection [14] and the presence of a gastrostomy tube [15].

EPIDEMIOLOGY

Since 2002, there has been a remarkable increase in the rates of CDI, as well as in the severity of the illness. The increase in incidence rates has also been observed in children [16,17]. For example, CDI incidence increased from 2.6 to 32.6 per 100,000 population from 1991 through 2009 in children residing in Minnesota. Most of the cases were acquired in the community [8]. The overall CDI incidence increase has been attributed at least in part to the emergence of a hypervirulent strain of *C difficile* known as the North American pulse-field gel electrophoresis type 1 ribotype 027 (NAP1), identified in the mid-2000s [2]. However, in the pediatric population this NAP1 strain is only present in 10% to 20% of cases, which suggests that there are other factors driving the increased incidence and severity of CDI in children [14,18].

Another phenomenon observed in the mid-2000s was the increased incidence of CDI cases in the community, in people without the classic high-risk factors [19]. For surveillance purposes, CDI case definitions have been standardized as shown in Box 1 [2].

Based on CDC surveillance data from 2009 to 2011, out of 984 cases of community-associated CDI (CA-CDI), 82% were associated with exposure to ambulatory health care facilities and 36% were not exposed to antibiotics within 12 weeks of diagnosis. However, 31% of cases without antibiotic exposure had received PPIs [3].

In the largest active population-based surveillance of pediatric CDI in the United States, 71% were CA-CDI. There were no significant differences regarding demographics, exposures, and clinical characteristics among different age groups. However, the group with the highest burden was children 1 to 3 years old, suggesting true disease and not asymptomatic colonization in this group. Children less than 12 months of age were excluded [20].

Box 1: Epidemiologic definitions

Health care facility-onset CDI: cases occurring more than 3 days after admission to the facility (ie, on or after day 4 of hospitalization)

Community-onset, health care facility-associated CDI: cases occurring within 28 days after discharge from a health care facility (ie, postdischarge cases)

Community-associated CDI: cases occurring in patients with no inpatient stay in the previous 12 weeks.

Data from McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66:e1–48.

A few studies have found differences among children with CA-CDI compared with children with HA-CDI, such as lower rates of exposure to antibiotics, immunosuppressants, acid suppressants, and narcotics [21,22], and fewer comorbid conditions, fewer prior surgical procedures, and a trend toward more complicated courses and a higher proportion of recurrences in children with CA-CDI [22].

In general, special populations at increased risk of CDI include patients with inflammatory bowel disease (IBD), patients with chronic renal disease, solid organ transplant recipients, and hematopoietic stem cell transplant (HSCT) recipients. In addition, these patients have higher CDI-associated morbidity and mortality as well as increased risk of recurrences [2]. In children in particular, the conditions associated with increased risk for CDI include cancer [23,24], transplant [25], IBD [26], cystic fibrosis [27], Hirschsprung disease (HD), and structural or postoperative intestinal disorders [28].

The incidence of CDI in children with cancer has been reported as more than 15 times greater than in children without cancer. Their increased susceptibility to CDI is caused by factors such as increased health care contact, immunosuppression caused by chemotherapy, and repeated and/or prolonged exposure to broad-spectrum antibiotics [24]. Variations in the risk of HA-CDI among different antipseudomonas β-lactam antibiotics has been reported in children with leukemia [29]. Specifically, cefepime and ceftazidime were independently associated with CDI. In the same study, the investigators found that even 1 additional day of exposure to antipseudomonas β-lactam antibiotics in the last 30 days increased the risk for CDI [29]. A prospective study of *C difficile* colonization in this population reported that approximately one-third of their pediatric oncology patients were colonized on admission, and more than half of their patients with history of CDI remained persistently or intermittently colonized during a follow-up period of up to 20 weeks after diagnosis and treatment. Many of their patients were colonized with different strains, which suggests either carrying multiple strains or acquisition of new strains. They also showed a high acquisition rate in newly diagnosed oncology patients [23]. The acquisition can occur during hospitalization or ambulatory visits, or in the community. These patients probably represent a large reservoir for HA-CDI [24].

Data on the risk of CDI in pediatric transplant recipients are lacking. However, based on data in the adult population, it is predicted that these patients have very high risk for CDI. Several risk factors for the development of CDI in adult transplant patients have been reported retrospectively. These risk factors include acute graft-versus-host disease, chemotherapy before conditioning for HSCT, broad-spectrum antibiotic use, colonization with vancomycin-resistant enterococci, cord blood as the source for stem cells, and total body irradiation of at least 12 Gy [25].

The prevalence of CDI in pediatric patients with IBD seems to vary significantly from one center to another, ranging from 3.5% to 69% [30]. These children do not seem to share the same risk factors for CDI as the general

population or other pediatric subgroups. For example, antibiotic exposure does not seem to play a role. However, most experts believe that IBD plays an important role, in addition to the frequent use of immunosuppressive therapies and health care–based services [26]. In a recent prospective, multicenter study of the occurrence and course of CDI among 211 European children with IBD, the investigators found an overall 1-year occurrence of 11.5%, and an asymptomatic colonization rate of 28.5%. CDI was associated with a more severe IBD course (ie, more active disease, higher number of hospitalizations, and more intensification of immunosuppressive or biologic therapy). Antibiotics, immunosuppressive therapy, and PPIs were not predisposing factors [26].

Children with HD are particularly susceptible to CDI because of colonic stasis and altered intestinal microbiota. The role of CDI in Hirschsprung-associated enterocolitis (HAEC), a condition that frequently complicates the HD course, has been investigated with conflicting conclusions. Many investigators have found high rates of *C difficile* isolation in patients with HD and HAEC. In addition, severe pseudomembranous colitis in patients with HD has been reported with and without *C difficile* isolation. However, a causal association has not been established, partly because of the high rate of asymptomatic colonization in young children [28].

CLINICAL PRESENTATION

The clinical spectrum of CDI is wide, from asymptomatic colonization to severe, sometimes fatal disease.

Colonization

Colonization with *C difficile* seems to occur soon after birth. However, the reported colonization rates in neonates have a wide variation from 2.5% to 90%. It seems to be more common in premature babies than in full-term babies. These rates increase with age to peak at 1 year [31], probably because of low resistance to colonization caused by immature intestinal flora. Formula-fed infants have higher colonization rates of *C difficile* than breast-fed infants [32]. Disease can occur in this age group, but it is rare, possibly because of the lack of intestinal toxin receptors in infants [31].

Colonization is transient and can be caused by different strains in the same patient [2]. After the first year of life, colonization rates decrease with increasing age and in children more than 2 years of age the rates are similar to adults' rates (1%–3%) [32]. However, rates of colonization in hospitalized children seem to be higher, with one center reporting colonization in up to 24% using polymerase chain reaction among pediatric patients aged 1 to 18 years. The prevalence did not vary markedly with age [33]. Pediatric oncology patients in particular seem to have higher rates of colonization, up to 33% [23].

Disease

By far, the most common clinical manifestations of *C difficile* involve the gastrointestinal tract. However, extracolonic manifestations have been reported.

Gastrointestinal manifestations: an acute diarrheal illness is the classic presentation, which can be mild to severe. The clinical features include profuse watery diarrhea with more than 6 stools per day, fever, and abdominal cramping or pain. Vomiting is not common but can present in one-third of the patients. Approximately one-quarter of the patients have bloody stools, but grossly bloody stools are seen in less than 15% of patients [21]. Children with severe CDI can present with severe abdominal pain and distension, hemodynamic instability, hypoalbuminemia, increased age-adjusted creatinine level, leukocytosis, and lactic acidosis. Some of these patients do not present with diarrhea because of prolonged paralytic ileus [10,21].

Complications associated with CDI include pseudomembranous colitis, pneumatosis intestinalis, toxic megacolon, intussusception, rectal prolapse, gastrointestinal perforation, sepsis, and death. In population-based studies, 8% to 9% of children with CDI experienced severe disease, and 0.7% to 3% had CDI-associated complications [14,21]. However, these numbers were higher in a cohort of hospitalized children with CDI, with 59% of them having severe disease and 17% to 31% having CDI-associated complications, depending on the definition used [34].

Extracolonic manifestations include bacteremia, skin and soft tissue infections, osteomyelitis, and reactive arthritis [35]. These manifestations are rare, especially in children.

A recurrent CDI case is defined as an episode of symptom onset and positive assay result following an episode with positive assay result in the previous 2 to 8 weeks for epidemiologic purposes [2]. Recurrences typically occur 1 to 3 weeks after the initial episode. The recurrence rates are similar in children and adults (20%–30%). A few studies have identified certain risk factors predisposing children to have recurrent CDI: malignancy, antibiotic exposure, recent surgery, presence of tracheostomy tube, receipt of concomitant antibiotics during the first episode, and CA-CDI [36–38]. The risk of further recurrences increases with each successive recurrence [2]. In addition, the mortality risk is 33% higher in patients with recurrent CDI compared with those without recurrence [39].

DIAGNOSIS

Challenges in the diagnosis of CDI in children are underscored by the difficulty in distinguishing colonization from symptomatic infection. Available laboratory tests, including molecular assays, do not help to make that distinction, which highlights the importance of a thorough clinical evaluation, including looking for other causes of diarrhea and careful assessment of response to therapy. However, validated clinical criteria are lacking.

Testing all children with diarrhea for CDI may lead to misdiagnosis and inappropriate and unnecessary treatment, therefore it is not recommended [40,41]. Indications for testing should incorporate factors such as clinical presentation, age, exposure to antibiotics or gastric acid suppressants, and the predisposing conditions described earlier (eg, having a gastrointestinal feeding device, malignancy, transplantation, IBD).

Based on clinical presentation, CDI testing is indicated for patients with new-onset diarrhea (3 or more unformed stools in 24 hours) with no other clearly attributable cause (eg, IBD exacerbation, laxatives, intensive chemotherapy, enteral tube feeding) [2,10]. In particular, diarrheal illnesses are frequent and more commonly caused by viral agents in children. It is difficult to distinguish CDI from the other viral causes of diarrhea in children. However, symptoms like fever, nausea, and vomiting are more prominent with viral infections than with CDI.

Recommended restrictions/precautions when ordering CDI testing in children include [2,10]:

- Discourage testing infants less than 12 months of age
- In toddlers 1 to 2 years of age with diarrhea, limit testing to those in whom other infectious or noninfectious causes of diarrhea have been excluded
- In children 3 years of age or older, limit testing to those with prolonged or worsening diarrhea who also have relevant exposures (eg, antibiotic exposure, health care system contact) and/or CDI risk factors

The diagnosis of CDI is most commonly based on laboratory methods to detect *C difficile* toxins or toxin gene s in stools of patients with diarrhea. Unless ileus or toxic megacolon is suspected, laboratory tests for *C difficile* should not be ordered on formed stools. In many institutions the laboratory rejects stool samples that are not liquid or soft (ie, take the shape of the container). This measure can improve the specificity of the tests [2].

Available diagnostic tests include nucleic acid amplification tests (NAATs) to detect genes responsible for the production of toxins A and B, enzyme immunoassay (EIA) to detect free toxins A and B, enzyme immunoassay for glutamate dehydrogenase, toxigenic culture, and the cell culture cytotoxic assay to detect the toxins. These last 2 tests are rarely used for routine testing because they require technical expertise and are labor intensive [2].

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have recently published clinical practice guidelines for CDI [2]. With regard to the most appropriate tests for CDI, they recommend the use of tests that are more specific, such as EIA toxin assays as part of a multitest algorithm rather than NAAT alone for institutions with no clinical data who accept all unformed samples for testing. In contrast, they recommend NAAT alone or a multitest algorithm for institutions that have preagreed criteria for accepting the samples [2].

Tests of cure are not recommended because greater than 60% of patients remain positive even after successful treatment and shedding of *C difficile* in the stools can persist for several months [2,10].

TREATMENT AND PREVENTION

The first consideration when deciding the management of patients with CDI should be the discontinuation of ongoing antibiotic therapy as soon as possible. The continuation of such therapy is associated with suboptimal clinical response and increased risk of recurrence [38,42]. If antibiotics for a

concomitant infection need to be continued, it is advisable to use antibiotics with the narrowest spectrum possible for that infection. Consideration to shorten the duration of antibiotic therapy is also recommended [2].

The use of antimotility drugs (eg, loperamide) has been associated with poor outcomes, and it is generally discouraged [10]. However, it might be safe to use them once specific antibiotic treatment of CDI has been started [2].

Empiric therapy for CDI should be started when the results of testing will be delayed for more than 48 hours and/or when patients show signs of severe or fulminant infection. Otherwise, it is recommended to wait for positive laboratory results before starting treatment [2].

Asymptomatic colonization should not be treated [2,10].

The first-line antibiotics for CDI include vancomycin and metronidazole. Vancomycin, administered orally, is the only US Food and Drug Administration (FDA)–approved agent for the treatment of CDI in children. Because it is not absorbed through the gastrointestinal tract, it achieves high fecal concentrations without the risk of adverse effects with systemic administration. The oral formulation is expensive; however, the intravenous (IV) formulation of vancomycin is less expensive and it can used for oral administration. Vancomycin administered intravenously is not effective for CDI because it does not reach the gastrointestinal tract [10]. The use of oral vancomycin is fraught with concerns about perturbation of the intestinal microbiota and risk of increasing intestinal colonization with vancomycin-resistant enterococci. However, this has been shown to occur with metronidazole as well [43].

Metronidazole, administered orally, is absorbed quickly. It is then excreted through the biliary system and secreted across inflamed intestinal mucosa, achieving high fecal levels. Those levels decline as the mucosal inflammation decreases. Because of systemic absorption, side effects are more common and include nausea, vomiting, abdominal cramps, and metallic taste. Serious complications, such as peripheral neuropathy and encephalopathy, are less common. These complications seem to occur more often in adults, but pediatric cases have been reported [44,45].

Rifaximin is a rifamycin derivative approved for treatment of travelers' diarrhea in individuals 12 years of age or older. Because it is minimally absorbed, well tolerated, and active against *C difficile*, its role for treatment of CDI has been investigated with promising results. In a small, prospective, single-blind, single-center study comparing the efficacy and recurrence rate of metronidazole with rifaximin in children between 12 and 18 years of age with IBD and mild to moderate CDI, the investigators found no significant difference between the two regimens. This finding suggests that rifaximin could be a good choice for these patients, especially if they do not tolerate metronidazole [46]. Other studies of rifaximin for treatment of recurrent CDI have shown a modest decrease in the rate of recurrent diarrhea when used immediately after a standard anti-CDI course [47,48]. The major concern with its use is the issue of resistance: the rate of resistance among *C difficile* isolates [49] and the risk of inducing resistance to all rifamycins among intestinal flora [50].

Nitazoxanide is an antiparasitic agent with good activity against anaerobic bacteria, including *C difficile* [51]. A few small studies have shown nitazoxanide's efficacy to be comparable with vancomycin and metronidazole in the treatment of CDI [52], and a good response to it in patients who failed treatment with metronidazole [53].

Fidaxomicin has not been FDA approved for use in children with CDI. In spite of this, 16% of pediatric infectious diseases specialists who responded to a survey about their practices related to CDI reported using it for severe or recurrent CDI [54]. In a phase 2a open-label study in children with CDI, fidaxomicin for 10 days had promising results, with good tolerability and excellent clinical response rate (92%). However, the recurrence rate was higher than in some adult studies (31.4% vs 12.7%–15.4%) [55]. Phase 3 clinical trials in children are ongoing.

There is limited information available about the antibiotic susceptibility of *C difficile* isolates obtained from children. A single-center study found that most of the pediatric isolates were susceptible to first-line and second-line antibiotics (100% susceptible to vancomycin and metronidazole and 98% susceptible to rifaximin), and had favorable minimum inhibitory concentrations to fidaxomicin. This susceptibility pattern did not differ between the initial and subsequent isolates from children with recurrent CDI [55]. Adult populations tend to have more resistant strains [49,56,57].

The definitive treatment of CDI depends on the age of the patient; whether it is the first episode, first recurrence, or subsequent recurrences; and the severity of the illness.

For example, in adults, there is substantial evidence that vancomycin is superior to metronidazole for CDI. In contrast, fidaxomicin seems to be better than vancomycin [58]. This superiority has been proved particularly in patients in whom concomitant antibiotics for other infections cannot be discontinued [42]. Therefore, for adults with a first or recurrent episode of CDI, either vancomycin or fidaxomicin is recommended rather than metronidazole. Metronidazole is only considered acceptable for an initial CDI episode if it is nonsevere and if the access to vancomycin or fidaxomicin is limited [2].

In children, comparative data for different regimens are lacking. There are limited data suggestive of inferiority of metronidazole compared with vancomycin with regard to failure rates [34]. Metronidazole seems to work well for the first episode of CDI in children, and it is the preferred regimen of most pediatric infectious diseases specialists in North America for a mild first episode of CDI in children without comorbidities [54]. In addition, because complications and mortality in children with CDI are rare, it is difficult to compare the outcomes with different regimens. The new clinical practice guidelines from IDSA and SHEA recommend either metronidazole or vancomycin for the initial or first recurrent CDI episode in children, as long as it is nonsevere. For a severe first episode and for second or greater recurrence, vancomycin should be used [2]. Metronidazole should not be used for subsequent recurrences because of the risk for neurotoxicity [10,44]. The best treatment

of children with second or greater episodes of recurrent CDI has not been studied well. Recommendations are extrapolated from limited data in adults [59], and include the use of tapered or pulse regimens of vancomycin alone or followed by rifaximin or nitazoxanide [10]. Table 1 provides a summary of the treatment recommendations for the first episode of CDI and Table 2 shows recommended regimens for recurrent CDI in children.

Newer antibiotics being developed to treat *C difficile* include surotomycin (a lipopeptide), cadazolid (a novel oxazolidinone-fluoroquinolone hybrid), and ridinilazole (a novel, narrow-spectrum, nonabsorbable antibiotic) [60].

The approach of using vancomycin or metronidazole for primary or secondary prophylaxis has gained attention in recent years and has been tried anecdotally. Literature on this is limited to a few retrospective studies using vancomycin in high-risk adults, showing promising results [61–63], and 1 prospective study using metronidazole [64]. The ideal dose and duration have not been determined, and there are no data in children. At this time, there are not sufficient robust data to support this approach.

Given the limitations of standard antibiotic therapy against recurrent CDI, and based on the understanding of the role of intestinal dysbiosis in the pathogenesis of CDI, several biotherapeutic approaches have been developed for

Table 1
Recommended regimens for the treatment of first episode of *Clostridium difficile* infection in children

Severity	Antimicrobial agent	Dose and duration
Mild to moderate	Metronidazole[a]	30 mg/kg/d PO every 6 h (preferred)
	Or	Or
		IV every 6 h for 10 d (maximum 500 mg/dose)
	Vancomycin	40 mg/kg/d, PO, every 6 h for 10 d (maximum 125 mg/dose)
Severe[b]	Vancomycin	40 mg/kg/d, PO, every 6 h for 10 d (maximum 125 mg/dose)
Severe and complicated[c]	Vancomycin[d] Plus metronidazole	Same doses as above for 10 d

Abbreviation: PO, by mouth.

[a]Consider switching to vancomycin if failure to respond in 5 to 7 days [10].

[b]Severe: should be considered in the presence of severe abdominal pain and distension, hemodynamic instability, hypoalbuminemia, worsening renal function, leukocytosis, and lactic acidosis [10,14,21].

[c]Complicated: intensive care unit admission, hypotension or shock, pseudomembranous colitis, pneumatosis intestinalis, toxic megacolon, intussusception, rectal prolapse, gastrointestinal perforation, surgical intervention because of CDI and/or sepsis [10,14,21].

[d]If complicated with ileus or toxic colitis and/or significant abdominal distension, add vancomycin, 500 mg/100 mL normal saline enema, as needed every 8 hours until improvement [10].

Adapted from McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018; 66:e1–48; and American Academy of Pediatrics. Clostridium difficile. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018;288–92.

Table 2
Recommended regimens for the treatment of recurrent *Clostridium difficile* infection in children

For first recurrent episode of CDI		
Severity	Antimicrobial agent	Dose and duration
Mild to moderate	Metronidazole Or	30 mg/kg/d PO every 6 h (preferred), OR IV every 6 h for 10 d (maximum 500 mg/dose)
	Vancomycin	40 mg/kg/d, PO, every 6 h for 10 d (maximum 125 mg/dose)
Severe	Vancomycin	40 mg/kg/d, PO, every 6 h for 10 d (maximum 125 mg/dose)

For second or greater episode of recurrent CDI		
Initial dose of vancomycin	Tapered dose of vancomycin	Additional agent
10 mg/kg/dose (maximum 125 mg) PO 4 times a day for 7 d	Then same dose, 3 times a day for 7 d Then twice a day for 7 d Then once a day for 7 d Then once every other day for 7 d Then every 72 h for 7 d	None
10 mg/kg/dose (max. 125 mg) PO 4 times a day for 14 d	Then same dose, twice a day for 7–14 d Then once daily for 7–14 d Then every 2–3 d for 2–8 wk	None
10 mg/kg/dose (max. 125 mg) PO 4 times a day for 14 d	None	Then rifaximin[a] PO 400 mg 3 times a day for 14 d Or Nitazoxanide PO twice a day for 10 d: 100 mg: 1–3 y of age 200 mg: 4–11 y of age 500 mg: ≥12 y of age

[a]Rifaximin is not FDA approved in children less than 12 years of age, but it is poorly water soluble and minimally absorbed. It should be avoided if the patient recently has received rifaximin for CDI or another indication [2,10].

Adapted from McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018; 66:e1–48; and American Academy of Pediatrics. Clostridium difficile. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018;288–92.

the treatment and prevention of CDI. Clinical trials are ongoing for some of them and some are being used for salvage therapy with varying degrees of success. They include fecal microbiota transplant (FMT), oral administration of nontoxigenic *C difficile* spores, and probiotics [65].

FMT consists of the administration of fecal content from a healthy donor into the gastrointestinal tract of a patient with CDI, with the goal of providing a preformed healthy balanced intestinal flora to patients with recurrent CDI in order to achieve a cure [66]. Beneficial effects include restoration of the recipient's gastrointestinal microbiota, which then inhibits *C difficile* colonization, and eliciting an immunologic response that facilitates the eradication of *C difficile* [67]. It has proved to be effective in adults with recurrent CDI with high success rates. In a systematic review, the rate of resolution of symptoms without recurrences was 75% in 2 randomized controlled trials (RCTs), and 85% in 21 case-series studies [68]. The routes of delivery include nasoenteric tubes, colonoscopy, enemas, and oral capsules with concentrated fecal microbes. However, it has not been shown that the route affects the efficacy of FMT. Adverse events are uncommon, and include gastrointestinal symptoms (eg, nausea, vomiting, flatulence, bloating, abdominal and/or rectal discomfort), headaches, and transient fever [67–69]. There are no published RCTs in children and the experience, although limited, is increasing.

A recent review summarizes the current pediatric data on FMT [69]. As of 2017, the investigators had found 45 reported cases of the use of FMT in children aged 1.1 to 19 years with recurrent CDI. After the intervention, there was symptomatic improvement in 89% of the children. There was a relapse in only 4% of the children. However, the follow-up period varied from 2 months to 4 years. Of note, 29% of these children had IBD. No serious adverse events (SAEs) or infectious complications were reported, and mild adverse events (eg, transient abdominal pain and mucoid stools) related to FMT occurred in 6% [69]. One of the concerns with FMT is the risk for acquired infections, especially when used in immunocompromised hosts. In a multicenter retrospective review of FMT in immunocompromised patients (75 adults and 5 children), the investigators found a cure rate of 78% (62 out of 80) after a single FMT, and an overall cure (defined as resolution of CDI after 1 or more FMTs) of 89%. After a follow-up period of 12 weeks, they found no infections related to the procedure. However, 15% of the patients experienced SAEs that included 10 hospitalizations and 2 deaths (1 was related to aspiration during the sedation for the FMT, the second death was unrelated) [70]. Adequate screening of donors minimizes infectious complications.

Even with limited pediatric data, 23 of 125 (18%) pediatric infectious diseases specialists who reported using alternative therapies for recurrent or severe CDI would recommend using FMT, especially for the third or later recurrence [54]. Perceived advantages of FMT include less risk of drug allergy; fewer exposures to antibiotics, which decreases development of antimicrobial resistance; higher cure rates in adults; and potential lower cost (considering avoiding multiple course of antibiotics and hospitalizations for recurrences) [65,66]. Based on evidence from studies done in the adult population and limited pediatric data, it seems reasonable to consider FMT for children with multiple recurrences, following standard treatment courses [2]. Potential benefits should be weighed against known and theoretic risks.

Nontoxigenic *C difficile* (NTCD) therapy focuses on the ability of this strain to outcompete and replace the toxigenic strain. A phase 2 randomized, double-blind, placebo-controlled trial showed significant difference in CDI recurrence rate compared with the placebo group (11% vs 30%; $P = .006$). Reduced recurrence rate correlated with NTCD colonization. However, colonization was transient (100% of patients lost colonization by 22 weeks) [65,71].

The efficacy and safety of probiotics in the prevention of CDI in adults and children undergoing antibiotic therapy have been studied in randomized trials. Based on a recent systematic review, the evidence suggests with moderate certainty that probiotics are effective in reducing the risk of CDI in these patients. The calculated reduction was 60% and the results were similar in adults and in children, inpatients and outpatients, and with different products and doses. However, the reduction was significantly higher (70%) in patients at higher risk for CDI. In the same review, probiotics also seemed to be safe [72].

Immunologic therapies for CDI include passive infusion of antibodies and active immunization. Serum antitoxin antibody levels are higher in patients with asymptomatic *C difficile* colonization than in patients with CDI, suggesting a protective effect [65]. The potential benefits of IV immunoglobulin have led to anecdotal use and retrospective evaluation, showing promising results. However, controlled clinical trials have not been done. In contrast, monoclonal antibodies against toxin A (actoxumab, Merck & Co., Inc) and toxin B (bezlotoxumab [Zinplava], Merck & Co., Inc.) have been developed and studied in clinical trials. In 2 phase III RCTs, patients receiving bezlotoxumab alone or combined with actoxumab had lower CDI recurrences than placebo (15.7% and 14.9% vs 25.7%, respectively; $P = .0003$). Actoxumab alone did not decrease the recurrence rate compared with placebo. The combination of both monoclonal antibodies did not offer an advantage compared with bezlotoxumab alone, suggesting that antibodies against toxin B could play a more important role in the prevention of recurrences [65,73]. Bezlotoxumab was FDA approved in October 2016 for the prevention of recurrent CDI in patients 18 years of age or older.

Vaccines targeted against *C difficile* toxins have the potential to provide longer-term protection compared with the monoclonal antibodies, and 3 candidate vaccines, targeting both toxins, have been developed and are undergoing RCTs. In phase II trials, all of them showed high immunogenicity and satisfactory safety. The Sanofi Pasteur toxoid vaccine is currently undergoing a phase III trial [60].

INFECTION PREVENTION AND CONTROL

Prevention of transmission of *C difficile* is challenging because the spores are resistant to commonly used alcohol-based hand sanitizers and cleaning agents, they can persist on environmental surfaces for months, and they can be transmitted from person to person through direct contact, via contaminated environmental surfaces and through the contaminated hands of other people, including health care personnel. Guidelines for infection prevention and control were

published recently within the clinical practice guidelines from IDSA and SHEA [2] and are summarized as follows:

1. Whenever possible, patients with suspected or confirmed CDI should be isolated in a private room. If this is not possible, patients infected or colonized with the same organisms (eg, MRSA, VRE) can be cohorted.
2. Health care personnel must wear gloves and gowns on entry to a room of a patient with CDI, and while caring for that patient.
3. Health care personnel should perform hand hygiene before and after contact with a patient with CDI, and after removal of gloves. Soap and water or alcohol-based product can be used in routine or endemic settings. However, soap and water is preferred in outbreaks or hyperendemic settings, because it is more efficacious in removing spores from the hands.
4. Use disposable patient equipment when possible. When reusable equipment is used, it should be cleaned and disinfected thoroughly. A sporicidal agent (eg, hypochlorite) is preferred.
5. Consider terminal room cleaning or daily cleaning with a sporicidal agent in hyperendemic or outbreaks settings, or when there are repeated CDI cases in the same room. There is not consistent evidence that this measure reduces CDI in nonoutbreak situations.
6. Quality of environmental cleaning should be monitored.

Another important aspect of infection prevention and control for CDI is the reduction of patients' susceptibility to CDI. Because antibiotic exposure is the most important risk factor for HA-CDI, avoiding or minimizing this exposure is essential. To this end, it is recommended to minimize the frequency and duration of high-risk antibiotics (eg, fluoroquinolones, clindamycin and cephalosporins) to reduce the risk for CDI and to implement of an antibiotic stewardship program [2]. The effect of antibiotic stewardship programs (ASPs) on the incidence of CDI and infections with antibiotic-resistant bacteria was analyzed in a systematic review. The investigators found that ASPs reduced the incidence of CDI by 32% [74].

Infection prevention and control efforts should include not only hospital settings but also outpatient settings, especially in patient populations at increased risk of CDI because of the shift of care of these patients to ambulatory settings.

SUMMARY

It is important for pediatricians to recognize the increasing incidence of CDI in children, not only in the health care settings but also in the community. There are many risk factors for CDI in children, but the exposure to antibiotics is still the most important risk factor. The challenges clinicians face include a 20% to 30% rate of recurrent CDI and the occurrence of rare but severe and complicated disease. Standard therapies are not always effective. New treatment and prevention strategies are promising, but more studies involving children are urgently needed. The role of infection prevention and control, as well as antibiotic stewardship, is of utmost importance.

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