JPPT | Review

An Updated Review of *Clostridium difficile* Treatment in Pediatrics

Christopher T. Campbell, PharmD; Margaret Oates Poisson, PharmD; and Elizabeth Oates Hand, PharmD

Clostridium difficile infection (CDI) continues to have clinical and economic impact across all health care settings. Pediatrics accounts for a small percentage of worldwide infection; however, screening and diagnosis are confounded by asymptomatic colonization in young infants. Metronidazole and oral vancomycin have historically been the agents used to manage CDI in both pediatrics and adults. Newer agents and alternative therapies, such as fecal microbiota transplantation, may offer additional benefit. Recent guidelines updates from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America separate pediatric and adult recommendations for epidemiology, diagnosis, and treatment. This review will discuss the risk factors, management, prevention, and updated guideline recommendations for CDI in the pediatric population.

ABBREVIATIONS AAP, American Academy of Pediatrics; CA, community-acquired; CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant; FDA, US Food and Drug Administration; GDH, glutamate dehydrogenase; HA, hospital-acquired; IDSA, Infectious Diseases Society of America; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; PPI, proton pump inhibitor; RCDI, recurrent *Clostridium difficile* infection

KEYWORDS antibiotic; *Clostridium difficile*; diarrhea; pediatrics

J Pediatr Pharmacol Ther 2019;24(2):90–98

DOI: 10.5863/1551-6776-24.2.90

Introduction

Clostridium difficile is an anaerobic, spore-forming, Gram-positive bacillus infamous for health care–associated diarrhea and is an increasing culprit in community-acquired infectious diarrhea. The threat of *C difficile* infection (CDI) has been well documented in the literature, and the rates by which these health care–associated infections continue to grow present a clinical and economic challenge to a health care system.[1,2] Pediatric CDI remains a small percentage of this growing health epidemic. It was recently estimated that the incidence of CDI was 147.2 per 100,000 persons in all age groups and 24.2 per 100,000 persons in the pediatric population.[3] Population-based epidemiologic studies demonstrate an increase in pediatric CDI cases from 1991 to 2009 despite pediatric hospital discharge rates remaining unchanged from 2001 to 2010.[1,4]

Clostridium difficile infection is an independent risk factor for increased length of stay, higher rates of colectomy, and mortality.[2] Within pediatrics, screening and diagnosis of CDI are further complicated by the high rates (9%–37%) of asymptomatic colonization in infants and children younger than 2 years.[5] In 2017, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America published an update to the clinical practice guidelines for CDI in adults and children.[6] One of the largest modifications from 2010 was the inclusion of pediatric considerations as well as separation of pediatric and adult recommendations for epidemiology, diagnosis, and treatment. In comparison, the recommendations for adults changed drastically, whereas the recommendations for pediatrics were relatively unchanged from current clinical practice.[6] The purpose of this review article is to discuss the current literature surrounding the risk factors, management, and prevention of CDI in the pediatric population as well as to review updated guideline recommendations.

Risk Factors

McFarland et al[7] describe a triad of risk factors that are common among both adult and pediatric CDI: disruptive factors, host factors, and increased exposure to *C difficile* spores. Risk factors have also been defined according to location of exposure, community acquired (CA) or hospital acquired (HA), although they both share similar associations. Efforts should be made to reduce disruptive factors by limiting antibiotic and gastric suppression usage. Host factors should be identified and interventions can be made to reduce hospital length of stay to limit exposure of *C difficile* spores in the health care setting.

Disruptive Factors. Disruptive factors include antibiotic use, surgery, feeding tubes, and other medications. Antibiotic use and gastric acid suppression are consistent risk factors across settings.[7–9] While

reviewing 1331 children with CA-CDI, Adams et al[10] identified the greatest contributing disruptive factor as recent exposure of antibiotics in the last 12 weeks. Fluoroquinolones, clindamycin, and third-generation cephalosporin antibiotics were most strongly associated, although several other antibiotic classes, including macrolides, sulfonamides, and penicillins, were also implicated to a lesser degree. Of those patients who received antibiotics prior to their CDI episode (n = 795), more than 40% of them were on multiple antibiotics.[10] A previous retrospective study confirmed that antibiotic use, specifically that of cephalosporins, may have significant associations when used within 30 days (OR 3.32; 95% CI 1.1–10.01).[11] Samady et al[9] also noted a significant relationship between antibiotic use in both CA-CDI and HA-CDI (OR 2.8; p = 0.001), with no difference between locations of exposure (CA-CDI 68% vs HA-CDI 65%; p = 0.84).

Proton pump inhibitor (PPI) use has been associated with both CA-CDI and HA-CDI. Adams et al[10] found that PPI use was essentially equivalent to the odds of CA-CDI due to antibiotic exposure (OR 8.17; 95% CI 2.35–28.38). Several other studies have confirmed this association, with reported ORs between 2.36 and 7.66.[12,13] In opposition, Brown and colleagues[14] found that although PPI use at home was not a significant risk factor (OR 1.05; 95% CI 0.69–1.59), the use of a histamine-2 receptor antagonist at home was associated with an increased risk of CA-CDI (OR 2.56; 95% CI 1.44–4.54). For hospitalized patients, Turco et al[15] also found an association between PPI use and HA-CDI infection (OR 4.5; 95% CI = 1.4–14.4). A meta-analysis of 56 studies in 2017 confirmed that PPI use regardless of setting of location was significantly associated with CDI (pooled OR 1.99; 95% CI 1.73–2.30).[16] It should be noted that meta-analyses have not been able to determine doses and durations of acid-suppressive medications that predispose a patient to CDI. These medications should be used judiciously for well-established indications.

Host Factors. Host factors include demographic information, including age, sex, and comorbidities. Younger age (1–5 years) and comorbidities such as cancer, immunosuppressive conditions, solid organ transplantation, and inflammatory bowel disease have been implicated across all health care settings.[7–9,17,18] Cystic fibrosis patients are at high risk of *C difficile* colonization despite their infection rate remaining low. The causative factors include frequent hospitalizations, broad-spectrum antibiotics, and gastric acid suppression.[19] In the pediatric hematology-oncology population specifically, patients who were ages 0 to 3 years, had longer durations of neutropenia, and used more than 4 antibiotics had higher rates of CDI than matched comparators.[20] In a multivariate analysis, a significant risk reduction was seen in older age, specifically in those ages 4 to 6 years (OR 0.07; 95% CI 0.01–0.41) and older than 7 years (OR 0.11; 95% CI 0.02–0.54). A higher risk was also seen with longer durations of neutropenia (OR 1.11; 95% CI 1.01–1.22). Because of the concomitant administration of antibiotics during episodes of neutropenia, the potential risk with neutropenia could not be separated from the increased risk of antibiotic administration.[20] The presence of solid organ tumors (OR 6; 95% CI 2.4–15.7) and hospitalization in a hematology-oncology ward (OR 7.8; 95% CI 2–29.9) were also associated with higher rates of CDI.[21] For patients with hematopoietic cell transplants, Boyle et al[22] identified that inpatient stay within the previous 3 days was significant in univariate analysis, yet failed to remain significant in their multivariate model.

Other CA-CDI host risk factors identified include outpatient health care visits (OR 1.35; 95% CI 1.31–1.39) and a gastrointestinal feeding device (OR 2.59; 95% CI 1.07–6.3).[10,11] Other HA-CDI host risk factors include recent hospitalization within 48 weeks, malnutrition (OR 7; 95% CI 1.33–36.7), presence of congenital heart diseases (OR 4.6; 95% CI 1.13–18.7), and hospitalization in the pediatric intensive care unit (OR 15.6; 95% CI 3.2–75.8).[8,11]

Colonization Versus Infection

Many institutions are actively working to raise their awareness and lower their incidence rates of CDI. Most antimicrobial stewardship programs focus on appropriate initiation and discontinuation of antibiotics through prospective audit and feedback along with specific antimicrobial restrictions.[23,24] Other prevention strategies include education around hand washing and equipment cleaning.[23,24] *Clostridium difficile* infection may also be overdiagnosed in pediatric patients because of the early colonization in neonates and infants (9%–37%).[5] Historically, the American Academy of Pediatrics (AAP) recommended against testing in patients younger than 1 year and recommended avoiding testing in those younger than 3 years unless other etiologies have been ruled out because of this high rate of colonization.[25] Stewardship programs are also addressing how decreasing inappropriate *C difficile* testing can prevent a misdiagnosis.[26]

Nicholson and colleagues[26] initiated a computerized physician order entry alert describing the AAP guidelines to display when providers order *C difficile* testing for patients younger than 3 years. They noted a decrease in the average monthly testing rate for those children ages 0 to 11 months (11.5 vs 0 per 10,000 patient-days; p < 0.001) and 12 to 35 months (61.6 vs 30.1 per 10,000 patient-days; p < 0.001).[26] The most common reasons for overriding the alert were previous antibiotic use in the past 30 days, bloody diarrhea with close contact with *C difficile*, and Hirschsprung disease or gastrointestinal motility disorder.[26] The authors concluded that the alert encouraged thoughtful testing while avoiding unnecessary treatment and additional health care costs.

Current recommendations from the IDSA 2017 update provide slightly different recommendations than the AAP. The IDSA similarly strongly recommends against routine testing for CDI in neonates or infants younger than 1 year. In children 2 years or older, testing is recommended in the setting of prolonged or worsening diarrhea with additional risk factors (such as inflammatory bowel disease and immunocompromising conditions) or where there are potential exposures and disruptive factors. For patients between the ages of 1 and 2 years, there is little evidence to support the use of *C difficile* testing. Testing should not be routinely ordered unless other causes have been ruled out.[6] In addition, it is recommended that subsequent testing not be performed within 7 days of the same diarrhea episode.[6] Stewardship programs can continue to develop processes to eliminate testing in those younger than 2 years and reduce testing in those between ages 2 and 3 years when other causes have not been ruled out.

Probiotics

Probiotics are believed to restore the gut microflora during antibiotic administration and thus decrease the incidence of antibiotic-associated diarrhea. A recent Cochrane meta-analysis of 23 studies (3939 patients) found a beneficial effect of probiotics in reducing antibiotic-associated diarrhea in children (RR 0.46; 95% CI 0.35–0.61).[27] It should be noted that data were pooled from studies using various combinations of different probiotic strains. In an earlier Cochrane meta-analysis of 4492 adults and children in 31 studies, the authors demonstrated a 64% reduction in the risk of developing a CDI (RR 0.36; 95% CI 0.26–0.51).[28] A similar reduction was seen in the subgroup analysis of the 3 included pediatric studies (RR 0.4; 95% CI 0.17–0.96). Goldenberg and colleagues[29] updated their results in 2017. In this analysis, 31 studies with 8672 patients were included. Again, the evidence suggests that probiotics reduce the risk of CDI: 1.5% with probiotics and 4% without (RR 0.4; 95% CI 0.30–0.52). Baseline CDI rates from the included studies ranged from 0% to 40%, with only those studies with baseline CDI rates >5% (n = 13) showing a significant reduction in CDI risk. The subgroup analysis of 6 pediatric studies with 1141 patients demonstrated a 65% reduction in the risk of CDI (RR 0.35; 95% CI 0.19–0.63).[29] Another systematic review by Shen and colleagues[30] confirmed these previous results, but meta-regression analysis also uncovered that if probiotics were administered within 2 days of starting antibiotics in adult patients, there was a higher probability of efficacy (p = 0.02).[30] Additionally, a pharmacoeconomic study suggests that in certain scenarios (age >65 years or when the baseline risk of CDI exceeded 1.6%), probiotics can be cost-effective to prevent CDI in hospitalized adult patients receiving antibiotics.[31] The potential benefit seen here should be tempered with the risk of *Saccharomyces* and *Lactobacillus* bacteremia in patients who are immunocompromised with central lines.[32,33]

The 2010 update of the IDSA CDI guidelines recommends against the use of probiotics to prevent primary CDI because there were limited data at the time. The 2017 update to the IDSA guidelines, however, provides no recommendation on the use of probiotics because of insufficient data to support or refute their use.[6,34] With the currently available data, there is a suggestion that probiotics can reduce the risk of developing CDI in pediatric patients, especially if administered soon after beginning antibiotics. No specific strain or formulation has been found to be more efficacious at this point. Future studies should be designed to control for type of antibiotic, length of treatment, and strain of probiotic.

Initial Management

Because of the lack of well-designed studies, conflicting CDI definitions, and widespread *C difficile* colonization rates in infants, management of pediatric CDI has focused on children older than 1 year.[35] Since 2010, the IDSA guidelines have distinguished mild/moderate from severe CDI based on supportive clinical data (white blood cell count >15,000 cells/mcL and serum creatinine ≥1.5 times the premorbid concentration). The CDI episodes were further classified as complicated with the presence of hemodynamic changes, ileus, or megacolon.[34] *Clostridium difficile* infection was also classified according to initial episode, first recurrence, and second recurrence. At that time, metronidazole was the drug of choice for initial, mild/moderate CDI (A-I recommendation), with vancomycin (oral or rectal) reserved for both initial episode of severe CDI (B-I recommendation) as well as for treatment of the second or later recurrence of CDI (B-III recommendation). Combination therapy was recommended for those with severe, complicated disease (C-III recommendation).[34]

These recommendations remain virtually unchanged for pediatric patients in the updated 2017 guidelines, with slight changes to the clinical definitions.[6] Severity of illness is now defined as non-severe, severe, or fulminant. The old mild/moderate classification is now considered non-severe, and the complicated classification is now fulminant. Recurrence is defined similarly as first recurrence, and second or subsequent recurrence. The supportive clinical data definitions, including white blood cell count, have remained unchanged despite age-specific differences in normal values.

The updated 2017 guidelines recommend oral vancomycin or oral metronidazole for the initial, non-severe episode (weak recommendation; low quality of evidence; Table 1). For initial severe or fulminant disease, vancomycin with or without intravenous metronidazole is recommended.[6] The subtle change is the addition of combination therapy for initial, severe CDI (weak recommendation; low quality of evidence).[6] The primary management approach for CDI still includes discontinuing

Table 1. Summary of Current Recommended Pediatric Dosing for *Clostridium difficile* Management[6,37–43,50]

Clinical Definition	Treatment	Dose	Maximum Dose
Initial, non-severe[6]	Oral: metronidazole × 10 days, *or*	7.5 mg/kg 3 or 4 times a day	500 mg
	Oral: vancomycin × 10 days	10 mg/kg 4 times a day	125 mg
Initial, severe/ fulminant[6,43]	Vancomycin × 10 days, *with or without*	Oral: 10 mg/kg 4 times a day Rectal: 1–3 yr: 250 mg/50 mL every 6 hr; Rectal: 4–9 yr: 375 mg/75 mL every 6 hr; Rectal: ≥10 yr 500 mg/100 mL every 6 hr	500 mg (oral and rectal)
	IV: metronidazole × 10 days	10 mg/kg 3 times a day	500 mg
First recurrence, non-severe[6]	Oral: metronidazole × 10 days, *or*	7.5 mg/kg 3 or 4 times a day	500 mg
	Oral: vancomycin × 10 days	10 mg/kg 4 times a day	125 mg
Second or subsequent recurrence[6,44]	Oral: vancomycin in a tapered and pulsed regimen, *or*	10 mg/kg 4 times a day × 10–14 days 10 mg/kg 2 times a day × 7 days 10 mg/kg daily × 7 days 10 mg/kg/dose every 2 days for 2–8 wk	125 mg
	Oral: vancomycin × 10 days, *followed by*	10 mg/kg 4 times a day	500 mg
	Oral: rifaximin × 20 days* *or*	10 mg/kg 3 times a day	400 mg
	Oral: fidaxomicin × 10 days† *or*	≥18 yr: 200 mg 2 times a day	200 mg
	nitazoxanide × 10 days‡ *or*	1–3 yr: 100 mg 2 times a day 4–11 yr: 200 mg 2 times a day ≥12 yr: 500 mg 2 times a day	Based on age
	IVIG§ *or*	400 mg/kg every 3 wk	Not established
	FMT	N/A	N/A

FDA, US Food and Drug Administration; FMT, fecal microbiota transplantation; IV, intravenous; IVIG, intravenous immunoglobulin; N/A, not applicable

* Recommended dosing; No FDA approval for use in ages <12 years; no pediatric approved dosing for *C difficile*.

† Recommended dosing; No FDA approval for use in ages <18 years.

‡ Recommended dosing; FDA approved for the treatment of *Cryptosporidium* and *Giardia* infection in children ages ≥1 year; no pediatric approved dosing for *C difficile*.

§ Limited evidence to support; no optimal dosing established.

offending antimicrobial agents, if possible, correcting fluid and electrolyte imbalances, avoiding antiperistalsis agents, and initiating treatment immediately in severe or fulminant CDI.[36]

Prior to the release of the 2017 guidelines, there was widespread consensus in the literature and among pediatric infectious disease physicians across North America to treat with oral metronidazole for mild CDI in an immunocompetent host. In the setting of underlying comorbidities, including underlying intestinal tract disease, immunosuppression, severe CDI, or CDI recurrence, there was wide variation in clinical practice. Children with chronic comorbidities may be at increased risk for CDI and subsequent complications, and limited data exist on optimal treatment for this population. The AAP *Red Book* recommends oral vancomycin as initial therapy for patients with underlying intestinal tract disease and in patients with severe CDI, with or without metronidazole.[45,46] Similarly, IDSA guidelines also recommend oral vancomycin for severe CDI, with add-on intravenous metronidazole specifically in fulminant CDI. In addition, consideration of rectal vancomycin instillation is recommended if a complete ileus is present.[6] Rectal dosing in pediatrics has not been established, but recommended volumes have been proposed by some experts.[44] Despite these recommendations, 30% of pediatric infectious disease physicians still prefer metronidazole alone for severe disease.[45]

The most substantial change from the previous guidelines is the difference in treatment recommendations for initial, non-severe episodes in adults. There is now a strong recommendation for adult patients to receive vancomycin or fidaxomicin for all initial episodes regardless of severity, based on high quality

Table 2. Summary of Cost and Most Common Adverse Reactions[37–43,50]

Drug	Cost (AWP)	Commonly Reported Adverse Reactions
Metronidazole	250-mg tablet: $0.25–0.58/tablet 500-mg tablet: $0.23–0.69/tablet 100 mg/mL suspension: $0.85/mL 500 mg/100 mL IV solution: $0.01–0.06/mL	Headache, nausea, vaginitis
Vancomycin	25 mg/mL solution: $0.75/mL 50 mg/mL solution: $1/mL 125-mg capsule: $12–$34.80/capsule 250-mg capsule: $21.6–$64.14/capsule	Abdominal pain, dysgeusia (oral solution), nausea
Rifaximin	200-mg tablet: $23.03/tablet 550-mg tablet: $43.90/tablet	Peripheral edema, dizziness, fatigue, ascites, nausea, headache
Fidaxomicin	200-mg tablet: $220.90/tablet	Nausea, abdominal pain, vomiting
Nitazoxanide	100 mg/5 mL suspension: $10.44/mL 500-mg tablet: $123.60/tablet	Headache, abdominal pain, nausea, urine discoloration
IVIG	100 mg/mL IV: Gammagard $15.99/mL 100 mg/mL IV: Gamunex-C $13.15/mL 100 mg/mL IV: Privigen $16.68/mL	Hypotension, tachycardia, bradycardia, infusion site reaction, headache, muscle cramps, fever

AWP, average wholesale price; IV, intravenous; IVIG, intravenous immunoglobulin

of evidence. Following the 2010 IDSA guidelines, the US Food and Drug Administration (FDA) approved the use of fidaxomicin in adults with CDI on the basis of 2 randomized controlled trials that showed non-inferiority to oral vancomycin.[47,48] Updated adult clinical practice guidelines in 2013 from the *American Journal of Gastroenterology* reviewed the latest data on CDI treatment and the potential role of fidaxomicin in therapy. These guidelines concluded that metronidazole remains the drug of choice for mild to moderate disease, and fidaxomicin is not supported because of limitations in the comparison studies with oral vancomycin and the significantly higher cost (Table 2).[49]

The lack of recommendation for fidaxomicin in pediatrics remains unchanged from the 2010 guideline because of a lack of clinical data. It is important to note that the recommendations for the treatment of CDI in adults for all initial episodes are based on strong, high levels of evidence, whereas pediatric recommendations are weak and low quality.[6] The FDA granted orphan drug designation for all formulations of fidaxomicin to treat CDI in pediatric patients. Since that time, studies evaluating the safety and tolerability of fidaxomicin in pediatric patients have been published. In a pharmacokinetic study of 40 pediatric patients (ages 11 months to 17 years) with CDI, fidaxomicin was shown to exhibit a pharmacokinetic profile similar to that of adults. Despite more than half of the patients (60.5%) having a history of CDI, a significant percentage exhibited not only an early response rate (92.1%) but also a sustained clinical response 28 days after treatment (65.8%), with most reported adverse effects given as mild (Table 2).[50]

Although fidaxomicin received approval for initial CDI treatment, the potential role for this drug was intended for recurrent CDI episodes because of the significantly lower rate of recurrence reported when compared to oral vancomycin and the tremendous cost associated with it; however, fidaxomicin is now seen throughout the updated guideline for not only recurrence but initial treatment in adult patients.[6,47] The weak recommendations and low quality of evidence with regard to the management of CDI in pediatric patients from the updated guideline highlights the necessity for well-designed, multicenter clinical trials in pediatrics.

Recurrence

Rates of recurrent CDI (RCDI) cases in pediatrics are reported to be as high as 25%. Recurrence can be defined as a subsequent clinical CDI within 8 weeks of the day the previous CDI was diagnosed.[51] The etiology of the relapse infection is thought to be due to the original strain or re-infection of susceptible patients exposed to new strains. Malignancy, tracheostomy tube dependence, and toxin B gene (tcdB) polymerase chain reaction (PCR) cycle threshold were all identified in this case-control study of 30 children as being statistically significant risk factors for RCDI.[51] Other factors that place patients at an increased risk of recurrence are similar to those defined above for initial CDI. Lack of hand washing may be a substantial risk factor in RCDI because of the potential to ingest spores from contaminated hands.[6] The risk of having a recurrence is highest in patients with inflammatory bowel disease, most notably ulcerative colitis, solid organ transplant patients, chronic kidney disease, and end-stage renal disease, and hematopoietic stem cell transplant patients.

Repeat Testing. The 2017 updated IDSA guidelines provide clear recommendations on when to test and

retest a patient for potential CDI. Because of the colonization of *C difficile* in the colon, a positive test is not always indicative of infection. Testing of CDI by PCR is very sensitive and can result in false positives from detecting the toxin gene even if it is not actively producing toxin.[52] Furthermore, repeat testing, even 6 weeks after treatment is completed, can result in a positive PCR test.[53] A study evaluating the currently available laboratory tests for diagnosing CDI illuminates the importance of assessing clinical suspicion, risk factors, and interpretation of the test being performed to appropriately diagnose CDI.

The gold standard for diagnosing CDI has been the cell cytotoxic neutralization assay. Compared with the glutamate dehydrogenase (GDH) assay it is more sensitive and specific. A GDH assay requires a confirmatory test because of the potential for false positives because both toxigenic and non-toxigenic strains produce GDH. Enzyme immunoassays were among the first assays for the detection of CDI. Enzyme immunoassays are advantageous in cost and ability to perform but are inconsistent, resulting in the Society for Healthcare Epidemiology of America and IDSA guidelines to recommend against toxic detection by enzyme immunoassay alone for the diagnosis of CDI. Nucleic acid amplification tests, which are now commonly used to detect other infections, are superior to other tests in their sensitivity, specificity, speed, and ability to perform without a culture. Similar to GDH, however, nucleic acid amplification tests can detect strains that do not produce toxins and have a high sensitivity, which can lead to false positives.[54]

Treatment of Recurrence. Both previous and current IDSA CDI guidelines recommend using the same agent used during the initial episode for the first recurrence in pediatric patients, unless the recurrence is deemed severe. For patients with severe and/or fulminant infection, the guidelines recommend vancomycin (oral or rectal) first line, with or without intravenous metronidazole, because of the associated higher risk for developing complications. Metronidazole is reserved for first recurrences only because of the risk of neurotoxicity when used long term.[6,34] A small retrospective, multicenter, observational study of pediatric patients in Italy reported a 5-fold higher risk of developing recurrence with initial metronidazole therapy compared with vancomycin monotherapy, or vancomycin or metronidazole combined with probiotics. In a multivariate analysis, the route of metronidazole showed that the risk was not substantiated with the intravenous route, but the authors reported the lack of difference in the result could be due to the small portion of children who received the intravenous dose.[55] Although no other pediatric comparative studies of recurrence rates between metronidazole and vancomycin exist, there are several adult studies examining the difference. In a 2015 meta-analysis the superiority for vancomycin over metronidazole was significant for initial clinical cure (RR 0.91; 95% CI 0.84–0.98) and sustained cure (RR 0.88; 95% CI 0.82–0.96) rates in the treatment of CDI, whereas recurrence rates and all-cause mortality remained similar.[56] More recently, a 2017 retrospective study of 47,471 adult patients reported a significantly reduced risk of all-cause 30-day mortality in patients with severe CDI treated with vancomycin (adjusted RR 0.79; 95% CI 0.65–0.97).[57] Although they still showed a lack of difference in the risk of recurrence between patients treated with vancomycin compared with metronidazole, the above findings support the conclusions in the recent adult CDI guidelines to use vancomycin as the initial therapy. There is currently not enough data to support that same conclusion in pediatrics.[56,57] Alternative drug therapies, such as nitazoxanide, rifaximin, and intravenous immunoglobulin (IVIG), as well as non-drug therapies, such as fecal microbiota transplants (FMTs), have emerged as potential treatment modalities following the first recurrence (Table 1).[44]

For the second recurrence, oral vancomycin is either recommended in a tapered approach or as a 10-day course of vancomycin followed by rifaximin for 20 days. Alternatively, FMT is also recommended as an option first line (Table 1).[44] There is no FDA-approved pediatric dosing for rifaximin in *C difficile*; however, rifaximin has been compared to metronidazole in the treatment of *C difficile* in pediatric patients with inflammatory bowel disease and has been shown to be equally efficacious.[58] In the study patients randomized to rifaximin received varying dosages every 8 hours based on weight (200 mg every 8 hours, 200 mg–400 mg–200 mg, 400 mg–200 mg–400 mg, or 400 mg every 8 hours). Recommended dosing for rifaximin in pediatrics for the management *of C difficile* is based on currently approved indications. Rifaximin's role in RCDI is based on the benefit shown in observational studies.[59] Fidaxomicin is still not approved by the FDA for children ages <18 years and therefore is not mentioned in the updated guidelines in the management of recurrent pediatric CDI. Another agent not mentioned in the guidelines but shown to have similar cure and relapse rates to the standard of therapy is nitazoxanide, an antiparasitic agent. The dosing of nitazoxanide for RCDI is extrapolated from pediatric dosing for the treatment of *Cryptosporidium* and *Giardia* infection.[44]

For a third recurrence and beyond, FMT is recommended first line with IVIG (400 mg/kg IV every 3 weeks) as a secondary alternative to preventing RCDI through the provision of antibodies against the *C difficile* toxin; however, evidence is extremely limited.[44] Fecal microbiota transplant alone is recommended for second or subsequent recurrence in the updated guidelines, but again, with weak recommendation and very low quality of evidence.[6] Fecal microbiota transplant has been used as a treatment modality related to CDI since 1958. First used for the curative treatment

of severe pseudomembranous colitis due to CDI, FMT has gained renewed interest in the area of RCDI.[60,61] It is widely known that the human microbiome plays an important role in immune function. Although the exact mechanism is unknown, it is hypothesized that FMT can restore the disrupted intestinal microbiota and prevent *C difficile* spores from causing active disease through the provision of a healthy donor's microbiota.[60,61] Positive outcomes following FMT for the treatment of RCDI in adult patients led researchers to look into pediatric application because of the microbiome differences between adult and children. Although there are fewer data compared with adults, similar results were seen in children with RCDI without a compromise in safety.[62] In addition to the positive outcomes seen, when compared to other currently available therapies for RCDI, FMT may result in huge cost savings.[63] Although the results of FMT are promising, the logistical issues (e.g., donor screening and processing, collection, preparation, and route of administration) and unknown long-term consequences pose potential limitations and concerns for this treatment modality. There are significant donor considerations that have yet to be investigated, including donor diet and the use of age-matched donors, that must be examined if FMT is pursued.[64]

In summary, the preferred management of RCDI is not clearly established, although there may be more evidence to support the management of a first recurrence. According to the updated guidelines, pediatric patients who develop a first recurrence should be treated with oral metronidazole or oral vancomycin. A repeated course of standard oral vancomycin followed by oral rifaximin, a course of oral vancomycin as a tapered and pulsed regimen, or treatment with fidaxomicin is recommended in the guidelines for patients with more than 1 recurrence. There are several other agents proposed for the management of secondary recurrences but little evidence to support their use (Table 1). Fecal microbiota transplant still remains a last-line option in a patient with multiple recurrences who has failed standard antibiotic treatments. Overall, it is more important to assess a patient's signs and symptoms of CDI compared with repeat testing to diagnose initial or recurrent CDI because of the potential limitations of currently available assays.

Conclusions

Clostridium difficile infection in pediatrics has been associated with increased morbidity and mortality. There are risk factors in both the community and the hospital that predispose patients to infection. Providers can identify a patient's risk factors and consider interventions to reduce the possibility of CDI. Pediatric antimicrobial stewardship programs are working diligently to prevent misdiagnosis and true infection. The updated guidelines highlight the recommendation change in adult patients from more traditional therapies to more intensive regimens but leave gaps in pediatric recommendations because of a lack of evidence. Future randomized controlled pediatric studies comparing oral vancomycin, fidaxomicin, FMT, and combination regimens will provide better-quality evidence to help clarify their role in the pediatric population. Evaluation of length of treatment and the necessity for tapering regimens should be conducted to streamline antibiotic therapy and limit unnecessary antibiotic exposure.

ARTICLE INFORMATION

Affiliations Department of Pharmacotherapy and Translational Research (CTC), University of Florida College of Pharmacy, Gainesville, Florida, Department of Pharmacy (CTC), University of Florida Health Shands Children's Hospital, Gainesville, Florida, Department of Pharmacy (MOP), Augusta University Medical Center, Augusta, Georgia, College of Pharmacy (EOH), The University of Texas at Austin College of Pharmacy, San Antonio, Texas

Correspondence Christopher T. Campbell, PharmD; campbellc@cop.ufl.edu

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Accepted September 20, 2018

REFERENCES

1. Pechal A, Lin K, Allen S, Reveles K. National age group trends in *Clostridium difficile* infection incidence and health outcomes in United States community hospitals. *BMC Infect Dis*. 2006;16(1):682.
2. Gupta A, Pardi DS, Baddour LM, et al. Outcomes in children with *Clostridium difficile* infection: results from a nationwide survey. *Gastroenterol Rep (Oxf)*. 2016;4(4):293–298.
3. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med*. 2015;372(9):825–834.
4. Khanna S, Baddour LM, Huskins WC, et al. The epidemiology of *Clostridium difficile* infection in children: a population-based study. *Clin Infect Dis*. 2013;56(10):1401–1406.
5. Jangi S, Lamont JT. Asymptomatic colonization by *Clostridium difficil*e in infants: implication for disease in later life. *J Pediatr Gastroenterol Nutr*. 2010;51(1):2–7.
6. McDonald CL, 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(7):987–994.

7. McFarland LV, Ozen M, Dinleyici EC, et al. Comparison of pediatric and adult antibiotic-associated diarrhea and *Clostridium difficile* infections. *World J Gastroenterol*. 2016;22(11):3078–3104.
8. Samady W, Pong A, Fisher E. Risk factors for the development of *Clostridium difficile* infection in hospitalized children. *Curr Opin Pediatr*. 2014;26(5):568–572.
9. Samady W, Bush R, Pong A, et al. Predictors of *Clostridium difficile* infections in hospitalized children. *J Hosp Med*. 2014;9(2):94–98.
10. Adams DJ, Eberly MD, Rajnik M, et al. Risk factors for community-associated *Clostridium difficile* infections in children. *J Pediatr*. 2017;186:105–109.
11. Crews JD, Anderson LF, Waller DK, et al. Risk factors for community-associated *Clostridium difficile*-associated diarrhea in children. *Pediatr Infect Dis J*. 2015;34(9):919–923.
12. Freedberg DE, Lamouse-Smith ES, Lightdale JR, et al. Use of acid suppression medication is associated with risk for *C. difficile* infection in infants and children: a population-based study. *Clin Infect Dis*. 2015;61(6):912–917.
13. Nylund CM, Eide M, Gorman GH. Association of *Clostridium difficile* infections with acid suppression medications in children. *J Pediatr*. 2014;165(5):979–984.
14. Brown KE, Knoderer CA, Nichols KR, et al. Acid-suppressing agents and risk for *Clostridium difficile* infection in pediatric patients. *Clin Pediatr (Phila)*. 2015;54(11):1102–1106.
15. Turco R, Martinelli M, Miele E, et al. Proton pump inhibitors as a risk factor for paediatric *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2010;31(7):754–759.
16. Trifan A, Stanciu, C, Girleanu I. Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: systematic review and meta-analysis. *World J Gastroenterol*. 2017;23(35):6500–6515.
17. Cozar-Llisto A, Ramos-Martinez A, Cobo J. *Clostridium difficile* infection in special high-risk populations. *Infect Dis Ther*. 2016;5(3):253–269.
18. Mhaissen MN, Rodriguez A, Gu Z, et al. Epidemiology of diarrheal illness in pediatric oncology patients. *J Pediatric Infect Dis Soc*. 2017;6(3):275–280.
19. Com G, Cetin N, O'Brien CE. Complicated *Clostridium difficile* colitis in children with cystic fibrosis: association with gastric acid suppression? *J Cyst Fibros*. 2014;12(1):37–42.
20. Daida A, Yoshihara H, Inai I. Risk factors for hospital-acquired *Clostridium difficile* infection among pediatric patients with cancer. *J Pediatr Hematol Oncol*. 2017;39(3):e167–e172.
21. Karaaslan A, Soysal A, Yakut N, et al. Hospital acquired *Clostridium difficile* infection in pediatric wards: a retrospective case-control study. *Springerplus*. 2016;5(1):1329.
22. Boyle NM, Margaret A, Stednick Z, et al. Evaluating risk factors for *Clostridium difficile* infection in adult and pediatric hematopoietic cell transplant recipients. *Antimicrob Resist Infect Control*. 2015;14(4):41.
23. Dubberke ER, Carling P, Carrico R, et al. Strategies to prevent *Clostridium difficile* infections in acute care hospitals: 2014 Update. *Infect Control Hosp Epidemiol*. 2014;35(6):628–645.
24. Barker A, Ngam C, Musuuza J, et al. Reducing *Clostridium difficile* in the inpatient setting: a systematic review of the adherence to and effectiveness of *C. difficile* prevention bundles. *Infect Control Hosp Epidemiol*. 2017;38(6):639–650.
25. Schutze GE, Willoughby RE. *Clostridium difficile* infection in infants and children. *Pediatrics*. 2013;131(1):196–200.
26. Nicholson MR, Freswick PN, Di Pentima MC, et al. The use of a computerized provider order entry alert to decrease rates of *Clostridium difficile* testing in young pediatric patients. *Infect Control Hosp Epidemiol*. 2017;38(5):542–546.
27. Goldenberg JZ, Lytvyn L, Steurich J, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev*. 2015;(12):CD004827
28. Goldenberg JZ, Ma SS Y, Saxton JD, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev*. 2013;(5):CD006095.
29. Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev*. 2017;(12):CD006095.
30. Shen NT, Maw A, Tmanova LL, et al. Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: a systematic review with meta-regression analysis. *Gastroenterology*. 2017;152(8):1889–1900.
31. Shen NT, Leff JA, Schneider Y, et al. Cost-effectiveness of probiotic use to prevent *Clostridium difficile* infection in hospitalized adults receiving antibiotics. *Open Forum Infect Dis*. 2017;4(3):ofx148.
32. Enache-Angoulvant A, Hennequin C. Invasive *Saccharomyces* infection: a comprehensive review. *Clin Infect Dis*. 2005;41(11):1559–1568.
33. Gouriet F, Million M, Henri M, et al. *Lactobacillus rhamnosus* bacteremia: an emerging clinical entity. *Eur J Clin Microbiol Infect Dis*. 2012;31(9):2469–2480.
34. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431–455.
35. Faust SN, Wilcox MH, Banaszkiewicz A, et al. Lack of evidence for an unmet need to treat *Clostridium difficile* infection in infants aged <2 years: expert recommendations on how to address this issue. *Clin Infect Dis*. 2015;60(6):912–918.
36. Shim JO. *Clostridium difficile* in children: to treat or not to treat? *Pediatr Gastroenterol Hepatol Nutr*. 2014;17(2):80–84.
37. Metronidazole. Lexicomp. Riverwoods, IL: Wolters Kluwer Health Inc. http://online.lexi.com. Accessed January 19, 2019.
38. Vancomycin. Lexicomp. Riverwoods, IL: Wolters Kluwer Health Inc. http://online.lexi.com. Accessed January 19, 2019.
39. Rifaximin. Lexicomp. Riverwoods, IL: Wolters Kluwer Health Inc. http://online.lexi.com. Accessed January 19, 2019.
40. Fidaxomicin. Lexicomp. Riverwoods, IL: Wolters Kluwer Health Inc. http://online.lexi.com. Accessed January 19, 2019.
41. Nitazoxanide. Lexicomp. Riverwoods, IL: Wolters Kluwer Health Inc. http://online.lexi.com. Accessed January 19, 2019.

42. Immune Globulin (Gammagard®). Lexicomp. Riverwoods, IL: Wolters Kluwer Health Inc. http://online.lexi.com. Accessed January 19, 2019.
43. D'Ostroph AR, So T. Treatment of pediatric *Clostridium difficile* infection: a review on treatment efficacy and economic value. *Infect Drug Resist*. 2017;10:365–375.
44. Tamma PD, Sandora TJ. *Clostridium difficile* infection in children: current state and unanswered questions. *J Pediatric Infect Dis Soc*. 2012;1(3):230–243.
45. Sammons JS, Gerber JS, Tamma PD, et al. Diagnosis and Management of *Clostridium difficile* infection by pediatric infectious disease physicians. *J Pediatric Infect Dis Soc*. 2014;3(1):43–48.
46. Pickering L. *Clostridium difficile*. Committee on Infectious Diseases Red Book: *2012 Report of the Committee on Infectious Diseases.* 29th Elk Grove Village, IL American Academy of Pediatrics 2012; pp. 285–287.
47. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for C*lostridium difficile* infection. *N Engl J Med*. 2011;364(5):422–431.
48. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012;12(4):281–289.
49. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013;108(4):478–498.
50. O'Gorman MA, Michaels MG, Kaplan SL, et al. Safety and pharmacokinetic study of fidaxomicin in children with *Clostridium difficile*-associated diarrhea: a phase 2a multicenter clinical trial. *J Pediatric Infect Dis Soc*. 2018;7(3):210–218.
51. Kociolek LK, Palac HL, Patel SJ. Risk factors for recurrent *Clostridium difficile* infection in children: a nested case-control study. *J Pediatr*. 2015;167(2):384–389.
52. Deshpande A, Pasupuleti V, Rolston DD, et al. Diagnostic accuracy of real-time polymerase chain reaction in detection of Clostridium difficile in the stool samples of patients with suspected Clostridum difficile infection: a meta-analysis. *Clin Infect Dis*. 2011;53(7):e81–90.
53. Fekety R, Silva J, Kauffman C, et al. Treatment of antibiotic-associated *Clostridium difficile* colitis with oral vancomycin: comparison of two dosage regimens. *Am J Med*. 1989;86(1):15–19.
54. Martinez-Melendez A, Camacho-Ortiz A, Morfin-Otero R, et al. Current knowledge on the laboratory diagnosis of *Clostridium difficile* infection. *World J Gastroenterol*. 2017;23(9):1552–1567.
55. Lo Vecchio A, Lancella L, Tagliabue C, et al. *Clostridium difficile* infection in children: epidemiology and risk of recurrence in a low-prevalence country. *Eur J Clin Microbiol Infect Dis.* 2017;36(1):177–185.
56. Di X, Bai N, Zhang X, et al. A meta-analysis of metronidazole and vancomycin for the treatment of *Clostridium difficile* infection, stratified by disease severity. *Braz J Infect Dis*. 2015;19(4):339–349.
57. Stevens V, Nelson R, Schwab-Daugherty E, et al. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with *Clostridium difficile* infection. *JAMA Intern Med*. 2017;177(4):546–553.
58. Gawronska A, Banasiuk M, Lachowicz D, et al. Metronidazole or rifaximin for treatment of *Clostridium difficile* in pediatric patients with inflammatory bowel disease: a randomized clinical trial. *Inflamm Bowel Dis*. 2017;23(12):2209–2214.
59. Garey KW, Ghantoji SS, Shah DN, et al. A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with *Clostridium difficile* infection. *J Antimicrob Chemother*. 2011;66(12):2850–2855.
60. Wang AY, Popov J, Pai N. Fecal microbial transplant for the treatment of pediatric inflammatory bowel disease. *World J Gastroenterol*. 2016; 22(47):10304–10315.
61. Van Beurden YH, Nieuwdorp M, van de Berg PJEJ, et al. Current challenges in the treatment of severe *Clostridium difficile* infection: early treatment potential of fecal microbiota transplantation. *Therap Adv Gastroenterol*. 2017;10(4):373–381.
62. Hourigan SK, Oliva-Hemker M. Fecal microbiota transplantation in children: a brief review. *Pediatr Res*. 2016;80(1):2–6.
63. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Infect Control Hosp Epidemiol*. 2015;36(4):438–444.
64. Barnes D, Park KT. Donor considerations in fecal microbiota transplantation. *Curr Gastroenterol Rep*. 2017;19(3):10.