



Updates and Opinions in Diagnosis and Treatment of *Clostridioides difficile* in Pediatrics

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Abstract

Purpose of review *Clostridioides difficile* infection (CDI) has unique challenges for diagnosis and treatment in pediatrics. Though new antibiotics and biologics are being approved or developed for adults, most of the pediatric therapies still rely on multiple or extended antibiotic courses. This review aims to highlight emerging evidence and our clinical experience with CDI in children and can help inform readers' approach to pediatric CDI.

Recent findings Use of fidaxomicin for CDI in pediatrics has been shown to be non-inferior to vancomycin and is associated with higher global cure rates and decreased risk of recurrence. Fecal microbiota transplant is a successful emerging therapy with cure rates of up to 90%, though safety alerts should be noted. Diagnostic laboratory testing for *C. difficile* remains a challenge as it still cannot definitively distinguish between colonization and true infection, and this is particularly relevant to pediatric patients as they have the highest rates of colonization.

Summary The diagnosis and treatment of *C. difficile* infection in pediatrics remain challenging and recommendations lag behind advances made in the adult field. Recent data suggests that use of fidaxomicin both as treatment of first episode or recurrences may be beneficial in pediatrics just as in adults. At an experienced center, FMT is associated with high cure rates. Bezlotuxumab a monoclonal antibody to toxin B that is already recommended for use in adults is being studied in children and should be available for clinical use soon. Oral vancomycin prophylaxis is also an emerging strategy for high-risk patients. Finally, a possible vaccine may be on the horizon for pediatrics.

Introduction

Clostridioides difficile (formerly *Clostridium difficile*) is the most common cause of healthcare-associated diarrhea and has unique challenges and presentations in the pediatric population [1]. *C. difficile* is an anaerobic gram-positive rod with spore formation that makes disinfection challenging. It is associated with toxin production that causes diarrheal illness [2]. Furthermore, the majority of cases in pediatrics are now thought to be community acquired, a shift

in a classically nosocomial illness [3–5]. Presentation varies from asymptomatic colonization to true illness comprising of profuse, pungent, watery, and at times, bloody diarrhea. Most severe forms include pseudomembranous colitis, ileus, toxic megacolon, and intestinal perforation, though surgical complications occur in <2% of pediatric patients. The majority (66%) of pediatric patients with CDI have at least one comorbidity [6].

Epidemiology

The incidence of CDI in pediatrics ranges from 20 to 30 per 100,000 persons and has been increasing steadily [1, 5, 7]. Acquisition of *C. difficile* occurs via fecal–oral route and once it has colonized the lower intestines, toxin proliferation and disrupted gut microbiome cause disease. The epidemiology of *C. difficile* infection in pediatrics is unique because of the high rates of asymptomatic colonization in infants, even up to 50% under age one. Most experts do not think a diagnosis of CDI should be considered under 1 year of age as it is likely nonpathogenic in that age group and should be made cautiously between the ages of 1 and 2. In these young infants, other common pathogens for diarrheal illness should be considered first [2]. Asymptomatic carriage decreases with age, however, and in hospital-exposed patients, up to 25% of pediatric patients may still be colonized [8]. The incidence of CDI in the general population increases with age, with the lowest incidence in the 1–17 age group. Risk factors for CDI include recent antibiotic exposure, frequent exposure to the healthcare system, comorbidities such as inflammatory bowel disease (IBD), cancer, transplant recipient, exposure to proton pump inhibitors, and/or history of abdominal surgery such as gastrostomy or colostomy (Fig. 1). Previous antibiotic exposure, hospitalization, and immunodeficiency remain the most significant risk factors and almost all antibiotics have been linked to CDI [8–10]. Cancer and IBD have been reported to be

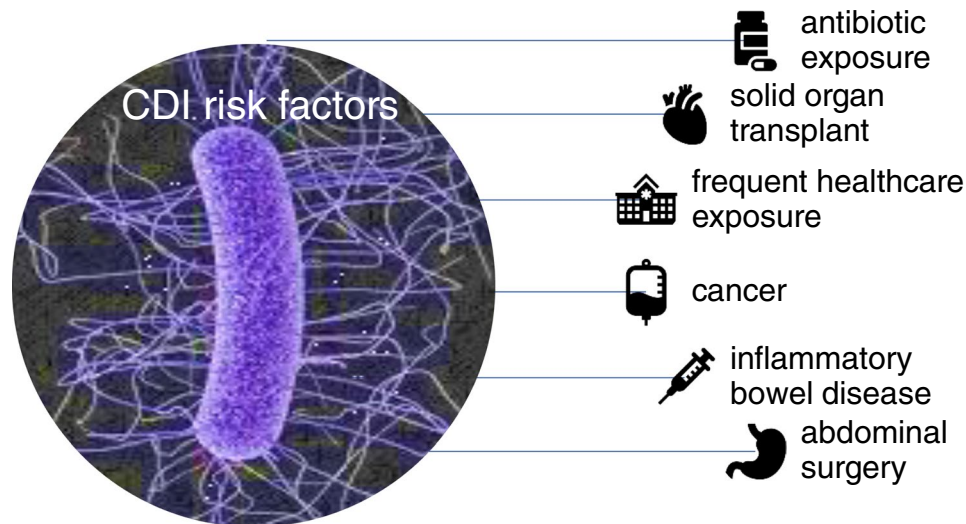


Fig. 1 Important risk factors for pediatric *C. difficile* infection. Image adapted from <https://phil.cdc.gov/> [51]

the most significant risk factors for recurrent disease [11]. The health of the gut microbiome and interplay of gut bacteria with *C. difficile* toxin has also been shown to play a role in risk and severity of CDI [12, 13].

Though previously considered a nosocomial infection, rates of community-acquired infection (CA-CDI) have been rising, accounting for 41–75% of cases in pediatrics now [3, 5]. In adult patients, exposure to an infant < 1 was also shown to be a risk factor in those with CA-CDI. The emergence of a more virulent strain, the North American pulsed-field gel electrophoresis type 1 strain (NAP-1), has also contributed to a rising incidence of CA-CDI over the past 10–20 years in otherwise low-risk patients [9]. Though not as prevalent in pediatrics, about 19% of *C. difficile* strains in a children's hospital were found to be NAP-1, which accounted for 11% of severe cases [14, 15].

Diagnosis

Asymptomatic carriage of *C. difficile* can make the diagnosis of true infection difficult in children, and therefore must rely on clinical assessment and exclusion of other diagnoses before the diagnosis is considered and testing done. The clinical presentation should include greater than 3 episodes of watery, unformed, diarrhea in a 24-h period in an appropriate host (> 1 year old with risk factors). Other clinical features such as fever, abdominal pain, tenesmus, or bloody diarrhea can be seen, with associated leukocytosis or hypoalbuminemia. In severe cases, imaging findings concerning for ileus, toxic megacolon, intestinal perforation or colonoscopy findings of pseudomembranous colitis in the setting of positive *C. difficile* testing can make the diagnosis. A recurrent CDI episode is defined as being 2–8 weeks from a prior episode,

and multiply recurrent CDI is defined as 3 or more episodes of mild to severe CDI with failure to respond to an extended vancomycin taper [2].

Diagnostic confirmation with laboratory testing is challenging. Laboratories are advised not to accept formed stool for testing given the high rate of asymptomatic carriage in children. Cell cytotoxic neutralization assays and toxigenic stool cultures are the gold standard for diagnostic testing but are too time consuming and user dependent and so are no longer regularly used. Institutions are recommended to use either a multi-step testing algorithm or a nucleic acid amplification test (NAAT) alone in specific cases. Multi-step testing can include a glutamate dehydrogenase (GDH) immunoassay with toxin enzyme immunoassay (EIA) confirmatory testing (with or without further confirmatory NAAT testing if toxin negative) or NAAT with toxin EIA confirmatory testing. GDH and toxin EIA should not be used alone. GDH testing is highly sensitive but not specific to *C. difficile* or a toxigenic strain, so is mostly useful as a screening tool, and toxin EIA has lower sensitivity resulting in false negatives if used alone [16]. NAAT can be used alone if the institution has agreed on strict criteria for stool submission. Despite all these measures, testing can still be challenging given the high sensitivity but lower positive predictive value of NAAT. A recent pediatric study suggests that the combination of NAAT and EIA still cannot distinguish between asymptomatic colonization and true infection in pediatrics and cannot predict disease severity, so should still be used with caution [17]. Although imperfect, our recommended method would be to use the multi-step algorithm with NAAT as initial screening followed by toxin EIA testing. This would increase the overall sensitivity and specificity of results. In the appropriate clinical situation, a positive NAAT with a negative toxin EIA may be useful in distinguishing colonization from disease. Tests of cure are not recommended given the high frequency of continued asymptomatic shedding after an infection and repeat testing within 7 days should not be done. Multiplex gastrointestinal pathogen panels are also an emerging diagnostic technique but are associated with increased detection of *C. difficile* colonized patients and should be interpreted with caution [18•].

Special patient populations in pediatrics

Patients with IBD

Inflammatory bowel disease is a significant risk factor for CDI in pediatrics, with patients with IBD having a significantly higher prevalence and risk of recurrence [19–22]. Patients with IBD are exposed to many of the risk factors for CDI including frequent antibiotics, frequent hospital visits, exposure to PPIs, corticosteroids, and immunosuppressants. This is further exacerbated by an inflamed colon which contributes to a disrupted gut microbiome. There is increased morbidity in patients with IBD, with increased hospital stay, severity of symptoms, and risk for surgical interventions. However, asymptomatic colonization in IBD patients is also higher than the general population [23, 24]. Furthermore, given the similarities of clinical presentation of CDI with

an IBD flare, it can be often hard to tease out if a positive test signifies colonization in the setting of an IBD flare or CDI. This is particularly important to differentiate as treatment for the two conditions differs significantly. Immunosuppressants used for an IBD flare are associated with worse outcomes in CDI, whereas untreated CDI can trigger an IBD flare [19, 21, 24]. Until better testing strategies are available, distinguishing asymptomatic colonization versus acute infection in patients with an IBD flare will continue to be challenging.

Patients with cancer

Pediatric oncology and hemopoietic stem cell transplant (HSCT) recipients are at significantly higher risk for CDI compared to the general pediatric population due to many non-modifiable risk factors including frequent exposure to the healthcare system, frequent antibiotic exposure, and a disrupted gut microbiome [25, 26]. Colonization rates are also high, with studies showing that up to 30% of pediatric oncology patients may be asymptotically colonized with *C. difficile*. A recent large cohort study of pediatric oncology patients showed that liquid tumors were associated with higher rates of infection than HSCT and solid tumors. Admission at the same time as another patient with CDI was also a risk factor with an odds ratio of 84.7 emphasizing the importance of infection prevention practices. CDI admissions were found to delay chemotherapy significantly longer than non-CDI admissions and chemotherapy delays are associated with reduced disease free survival [25].

Patients with abdominal surgeries

Abdominal surgeries, including gastrostomy, ileostomy, colostomy, intestinal transplant, and colectomy (particularly in patients with IBD), are all known risk factors for CDI, with a 1.4–2.2% prevalence documented in colorectal surgical patients [27, 28]. Pediatric intestinal transplant recipients are also at particularly high risk for CDI, with a prevalence of 39% in a 2020 study, exceeding the rates in other solid organ transplants [29]. Small bowel infection is a known extra-colonic manifestation of CDI, though rare, and can carry high mortality if not treated aggressively. Risk is highest in the post-operative period and should especially be considered in patients with known *C. difficile* carriage prior to colectomy. Use of oral antibiotics as bowel prep for colectomy has been associated with reduced risk of post-operative CDI [28]. Small bowel enteritis typically presents with similar symptoms to *C. difficile* colitis but is more severe and more often associated with systemic symptoms [30]. Disease is typically worse in the ileum and retrograde vancomycin flushes through the ileum can be considered [27]. Previous case series of small bowel enteritis are few and mostly in adults, as old age is one of the most significant risk factors [30]. However, in our experience, pediatric

patients with abdominal surgeries have presented similarly and are frequently challenging to treat.

New developments in treatment options and future directions

Treatment guidelines

Current guidelines in pediatrics recommend the use of metronidazole or oral vancomycin for the initial and first recurrence of a mild to moderate episode of CDI. Oral and rectal vancomycin with or without IV metronidazole is suggested for a severe/fulminant episode. Subsequent recurrent episodes can be treated with a tapered oral vancomycin regimen lasting 4–10 weeks longer than a standard course, or a standard oral vancomycin course followed by 20 days of rifaximin, or fecal microbiota transplant (FMT) [2]. Treatment guidelines used in our institution based on experience, literature review, and consensus between pediatric infectious diseases and gastroenterology specialists are detailed in Table 1.

First episode: metronidazole vs oral vancomycin?

Pediatric IDSA guidelines currently suggest metronidazole can be used for initial or first recurrence for mild to moderate CDI though this is no longer recommended in adult guidelines. This is because studies comparing metronidazole to oral vancomycin in pediatrics are lacking compared to adults. Given lower morbidity and mortality and lower rates of recurrence in pediatrics, it is reasonable to use metronidazole for the first mild episode in low-risk patients. However, for moderate to severe cases or in patients with high risk of recurrence, oral vancomycin should be preferred given the clear benefit seen in adult patients, though pediatric data lags [31, 32]. Some providers may choose to indeed go with vancomycin as the first line for even milder presentations. Emerging evidence also supports the use of fidaxomicin initially in pediatrics, over metronidazole or oral vancomycin, which would be in line with the current adult recommendations.

Fidaxomicin in pediatrics

In adults, fidaxomicin has been approved since 2011 for treatment of *C. difficile* and has been shown to be noninferior to vancomycin in achieving clinical cure with decreased risk of recurrence after treatment. Additional benefits of fidaxomicin include a narrower spectrum of activity, less frequent dosing, and rarity of resistance [33]. IDSA 2021 updated guidelines specifically address the use of fidaxomicin in adults, now recommending its use for both the first episode of *C. difficile*, and now also in recurrent episodes over vancomycin [34•]. An extended pulsed regimen of fidaxomicin, like for vancomycin, is

Table 1 Updated guidelines for treatment of pediatric *C. difficile* infection at a US Children’s Hospital (based on experience, literature review, and expert consensus and does not reflect current IDSA guidelines)

| Treatment | Previously healthy | Presence of comorbid illnesses ¹ |
|--|--|---|
| CDI episode | | |
| Initial episode, non-severe | <p>Age < 18 years Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 10 days OR Metronidazole 10 mg/kg/dose PO Q8H (max 500 mg/dose) × 10 days</p> <p>Age ≥ 18 years Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 10 days</p> | <p>Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 10 days OR Fidaxomicin 16 mg/kg/dose PO Q12H (max 200 mg/dose) × 10 days</p> |
| First recurrence² (i.e., the second episode) | <p>Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 10 days OR Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 14 days, then Q12H × 7 days, Qday × 7 days, every 2–3 days × 2–8 weeks OR Fidaxomicin 16 mg/kg/dose PO Q12H (max 200 mg/dose) × 10 days (fidaxomicin is preferred particularly in patients with comorbid illness, previously treated with oral vancomycin)</p> | <p>Fidaxomicin 16 mg/kg/dose PO Q12H (max 200 mg/dose) × 10 days OR Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 14 days, then Q12H × 7 days, Qday × 7 days, every 2–3 days × 2–8 weeks OR Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 10 days, then rifaximin × 20 days</p> |
| Second recurrence or more (i.e., the third episode or more) | <p>Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 10 days, then rifaximin × 20 days And Start evaluation for FECAL microbiota transplant (ID and GI consultation)</p> | <p>Vancomycin 10 mg/kg/dose PO Q6H (max 125 mg/dose) × 10 days OR Metronidazole 10 mg/kg/dose IV Q8H (max 500 mg/dose) × 10 days (ID and GI consultation, pediatric surgery consultation if appropriate)</p> |
| Severe episode vs fulminant episode | | |
| Severe³ episode Criteria: WBC > 15 K/μL OR Elevated serum Cr (> 1.5 × baseline) | | |
| Fulminant episode Criteria: hypotension, shock, ileus, toxic megacolon, or perforation | | |

¹Presence of comorbid illnesses including immunocompromised patients (e.g., neutropenic, BMT, SOT) or patients with underlying GI diseases including IBD, Hirschsprung’s disease, intestinal dysmotility, gut GVHD

²Definitions of recurrent CDI: It is defined as an episode of CDI and positive CDI testing result occurring within 8 weeks of a previous episode

³Definitions of severe CDI: There are no validated criteria for disease severity in children. These definitions are based on adult criteria

also suggested. Pediatric patients with comorbidities such as inflammatory bowel disease, immunosuppressed condition, or with abdominal surgical procedures (i.e., g-tubes, colostomy) face a significant risk of recurrence after the initial episode; however, currently fidaxomicin is only used off-label. The SUNSHINE study, a multicenter, investigator-blind, phase 3 trial study, supports the use of fidaxomicin in pediatrics as a non-inferior and safe option to vancomycin [35•]. The patients in this study had one or more comorbidities. It demonstrated safety, as the rate of adverse events was similar, and indeed fewer in the fidaxomicin group. It demonstrated efficacy, with similar rates of resolution of diarrhea in the fidaxomicin vs vancomycin group (75.5% vs 72.7%), shorter time to resolution in fidaxomicin group (58 h vs 97 h), and fewer rates of recurrence (11.8% vs 29%) [35•]. This study shows that in pediatrics, fidaxomicin is associated with a higher rate of clinical response without recurrence. This data suggests that fidaxomicin should potentially be considered as a first-line option for treating CDI particularly in patients at high risk for recurrence. At our institution, fidaxomicin is frequently used for recurrent CDI especially in patients with IBD and other underlying risk factors. Cost and availability continue to be issues with fidaxomicin.

Fecal microbiota transplant in pediatrics

Fecal microbiota transplant in pediatrics is recommended for recurrent CDI or severe CDI that does not respond to standard therapies within 48 h [36•]. The practical challenges in arranging for FMT in pediatrics make it more commonly an outpatient, scheduled procedure for recurrent CDI. FMT is overall associated with high clinical cure rates in adults (80–90%) especially in comparison to vancomycin, but no controlled clinical trial has been done in pediatrics. However, a large retrospective review showed a similar (81% with single FMT and 86.6% with single and repeat) success rate in pediatrics [37]. FMT can be delivered in many forms, with no difference found between fresh or frozen specimens in adults in a prospective trial [38], though fresh specimens were associated with better outcomes in the pediatric retrospective study. Delivery methods include through tube (NG, NJ, ND), gastrostomy, colonoscopy, enema, or through a capsule. In patients with inflammatory bowel conditions, delivery via colonoscopy is more prudent, but otherwise similar success rates have been shown with the other forms of administration as well in adults. Nicholson et al. also found a higher odds ratio of success for colonoscopy in pediatrics [39]. However, safety considerations limit use of FMT to cases that are non-responsive to standard therapies. Though safely used in both immunocompetent and immunocompromised children successfully, rigorous donor screening, close follow-up, and an experienced center are key. In 2020, the FDA released safety alerts due to transmission of *E. coli* after FMT in 6 patients. Two of the patients died following the FMT. This alert has slowed down the administration of FMTs. Furthermore, the COVID-19 pandemic created more challenges for large institutions to run an FMT program

that are still recovering. The 2021 updated adult IDSA guidelines have not changed their recommendations on FMT but document these safety alerts.

Probiotics for the prevention of CDI

Studies on probiotic use in CDI are conflicting. A Cochrane database systematic review did find a benefit of using probiotics to prevent *C. difficile*-associated diarrhea but only in hospitals with a CDI risk > 5% (not the majority of hospitals), which remained true when looking at a pediatrics subgroup as well [40]. A randomized controlled trial showed no benefit [41], and a recent paper using a computer-based clinical decision support tool to prescribe probiotics in high-risk adults in a multicenter study again found no benefit to using probiotics. Usage was not studied in immunocompromised patients and is still not recommended in that population. So far, released CDI guidelines do not support the use of probiotics as there is not enough evidence [42–44]. Given that there is no strong evidence of benefit from probiotics, we do not use it routinely in our practice. If a trial of probiotics is considered, it may be attempted in high-risk, non-immunocompromised patients.

Bezlotoxumab in pediatrics

Bezlotoxumab is the first approved monoclonal antibody against *C. difficile* which works by binding to toxin B [45, 46]. Bezlotoxumab is indicated for prevention of recurrent CDI in high-risk adults, particularly in those with three or more risk factors, but cannot be used alone for treatment. The updated 2021 IDSA guidelines for adults also address the use of bezlotoxumab, now recommending it in addition to standard of care antibiotics for adult patients with a recurrence of CDI within the past 6 months, and a consideration with high-risk patients on their first episode. It can be effective if given at any time before the end of antibiotic treatment [34•]. Currently phase III trials are underway to study the use of bezlotoxumab in children age 1–18 (MODIFY III trial). If approved, this may be an important consideration for high-risk patients, particularly children with IBD, severe episodes, frequent recurrences, or ongoing antibiotic use [47].

C. difficile vaccine.

A phase III trial for a 3-dose toxoid-based *C. difficile* vaccine is currently underway. The toxoid vaccine is produced by expressing genetically detoxified toxins in *C. difficile* and chemically removing the cytotoxicity. The toxoid + adjuvant form of the vaccine delivered at days 0, 7, and 30 was determined to show the most optimal immune response with acceptable safety profile [48, 49]. Currently, the trials have only included patients age 50 or

older (CLOVER trial) so use for pediatrics is still far in the future but may become an essential component to preventing *C. difficile*.

Operative management

Operative management should be reserved for cases of fulminant colitis, as it is associated with high mortality. Although infrequently needed in pediatrics, current surgical recommendations for severe cases include total or subtotal colectomy with end ileostomy, with preservation of rectum. Diverting loop ileostomy with intracolonic lavage and aggressive medical management can be considered in less severe cases.

Oral vancomycin prophylaxis

A recently published study supports the use of oral vancomycin prophylaxis in pediatric patients who are at high risk for recurrence while they are receiving systemic antibiotics [50•]. Although this has been studied and shown to be beneficial in adults, this had not previously been studied in pediatrics. The dosing of oral vancomycin used in this study was 10 mg/kg twice a day (up to a max of 125 mg per dose) during concomitant systemic antibiotics and up to 5 days after completion of systemic antibiotics. A significantly lower incidence of CDI recurrence was seen in the prophylaxis group (3% vs 25% $p=0.02$) with a significant risk reduction (odds ratio of 0.10, 95% CI 0.01–0.86), showing that oral vancomycin prophylaxis was protective [50•]. The majority of patients in this study had a high-risk comorbidity including malignancy, immunosuppressed state, IBD, HSCT, and/or a feeding tube. Although this has not been our practice at our institution, this data is compelling and oral vancomycin prophylaxis may be useful in high-risk patients, such as those included in the study, with a history of recurrences.

Conclusions

Incidence of both hospital and community acquired *C. difficile* infections has been rising and can cause significant morbidity in pediatrics. Diagnosis of *C. difficile* remains a challenge given high rates of asymptomatic colonization in pediatrics and clinicians should have a good understanding of pediatric specific risk factors and recommended testing algorithms. New evidence-based treatment strategies have emerged in the past 5 years supporting changes in practice for pediatric patients, particularly those at high risk for recurrence.

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Declarations

Conflict of Interest

Sanchi Malhotra declares that there is no conflict of interest. Sindhu Mohandas declares that there is no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as: • Of importance

1. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. *N Engl J Med*. 2015;372(9):825–34. <https://doi.org/10.1056/NEJMoa1408913>.
2. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, 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):987–94. <https://doi.org/10.1093/cid/ciy149>.
3. Crews JD, Koo HL, Jiang ZD, Starke JR, DuPont HL. A hospital-based study of the clinical characteristics of Clostridium difficile infection in children. *Pediatr Infect Dis J*. 2014;33(9):924–8. <https://doi.org/10.1097/INF.0000000000000338>.
4. Crews JD, Anderson LR, Waller DK, Swartz MD, DuPont HL, Starke JR. Risk factors for community-associated Clostridium difficile-associated diarrhea in children. *Pediatr Infect Dis J*. 2015;34(9):919–23. <https://doi.org/10.1097/INF.0000000000000767>.
5. Khanna S, Baddour LM, Huskins WC, Kammer PP, Faubion WA, Zinsmeister AR, et al. The epidemiology of Clostridium difficile infection in children: a population-based study. *Clin Infect Dis*. 2013;56(10):1401–6. <https://doi.org/10.1093/cid/cit075>.
6. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001–2006. *Pediatrics*. 2008;122(6):1266–70. <https://doi.org/10.1542/peds.2008-0469>.
7. Enoch DA, Butler MJ, Pai S, Aliyu SH, Karas JA. Clostridium difficile in children: colonisation and disease. *J Infect*. 2011;63(2):105–13. <https://doi.org/10.1016/j.jinf.2011.05.016>.
8. Sandora TJ, Fung M, Flaherty K, Helsing L, Scanlon P, Potter-Bynoe G, et al. Epidemiology and risk factors for Clostridium difficile infection in children. *Pediatr Infect Dis J*. 2011;30(7):580–4. <https://doi.org/10.1097/INF.0b013e31820bfb29>.
9. Sammons JS, Toltzis P, Zaoutis TE. Clostridium difficile Infection in children. *JAMA Pediatr*. 2013;167(6):567–73. <https://doi.org/10.1001/jamapediatrics.2013.441>.
10. Samady W, Bush R, Pong A, Andrews A, Fisher ES. Predictors of Clostridium difficile infections in hospitalized children. *J Hosp Med*. 2014;9(2):94–8. <https://doi.org/10.1002/jhm.2135>.
11. Parmar D, Dang R, Miranda-Katz M, Alabaster A, Greenhow TL. Risk factors for recurrent community-associated Clostridiodes difficile infection in children. *Pediatr Infect Dis J*. 2019;38(11):1073–8. <https://doi.org/10.1097/INF.0000000000002439>.
12. Mohandas S, Soma VL, Tran TDB, Sodergren E, Ambooken T, Goldman DL, et al. Differences in gut microbiome in hospitalized immunocompetent vs. immunocompromised children, including those with sickle cell disease. *Front Pediatr*.

- 2020;8:583446. <https://doi.org/10.3389/fped.2020.583446>.
13. Htwe P, Aung HH, Kywe B, Niang PT, Oo TS, Monhandas S, et al. Endotoxin acts synergistically with *C. difficile* toxin B to increase IL-1 β production: a potential role for the intestinal biome in modifying the severity of *C. difficile* colitis. *J Infect Dis*. 2021. <https://doi.org/10.1093/infdis/jiab165>.
 14. Toltzis P, Kim J, Dul M, Zoltanski J, Smathers S, Zaoutis T. Presence of the epidemic North American Pulsed Field type 1 *Clostridium difficile* strain in hospitalized children. *J Pediatr*. 2009;154(4):607–8. <https://doi.org/10.1016/j.jpeds.2008.10.016>.
 15. Kim J, Shaklee JF, Smathers S, Prasad P, Asti L, Zoltanski J, et al. Risk factors and outcomes associated with severe *clostridium difficile* infection in children. *Pediatr Infect Dis J*. 2012;31(2):134–8. <https://doi.org/10.1097/INF.0b013e3182352e2c>.
 16. Crobach MJ, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect*. 2016;22(Suppl 4):S63–81. <https://doi.org/10.1016/j.cmi.2016.03.010>.
 17. Parnell JM, Fazili I, Bloch SC, Lacy DB, Garcia-Lopez VA, Bernard R, et al. Two-step testing for *Clostridioides difficile* is inadequate in differentiating infection from colonization in children. *J Pediatr Gastroenterol Nutr*. 2021;72(3):378–83. <https://doi.org/10.1097/MPG.0000000000002944>.
 18. • Cotter JM, Thomas J, Birkholz M, Brittan M, Ambroggio L, Dolan S, et al. Impact of multiplex testing on the identification of pediatric *Clostridioides difficile*. *J Pediatr*. 2020;218:157–65.e3. <https://doi.org/10.1016/j.jpeds.2019.11.036>. (As multiplex GI PCRs become more common, the impact on over diagnosis of CDI in children must be considered, which this paper well demonstrates.)
 19. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with *Clostridium difficile* in patients with inflammatory bowel disease. *Gut*. 2008;57(2):205–10. <https://doi.org/10.1136/gut.2007.128231>.
 20. Bossuyt P, Verhaegen J, Van Assche G, Rutgeerts P, Vermeire S. Increasing incidence of *Clostridium difficile*-associated diarrhea in inflammatory bowel disease. *J Crohns Colitis*. 2009;3(1):4–7. <https://doi.org/10.1016/j.crohns.2008.09.003>.
 21. Goodhand JR, Alazawi W, Rampton DS. Systematic review: *Clostridium difficile* and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2011;33(4):428–41. <https://doi.org/10.1111/j.1365-2036.2010.04548.x>.
 22. Jen MH, Saxena S, Bottle A, Aylin P, Pollok RC. Increased health burden associated with *Clostridium difficile* diarrhoea in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2011;33(12):1322–31. <https://doi.org/10.1111/j.1365-2036.2011.04661.x>.
 23. Khanna S, Shin A, Kelly CP. Management of *Clostridium difficile* infection in inflammatory bowel disease: expert review from the clinical practice updates committee of the AGA institute. *Clin Gastroenterol Hepatol*. 2017;15(2):166–74. <https://doi.org/10.1016/j.cgh.2016.10.024>.
 24. Martinelli M, Strisciuglio C, Veres G, Paerregaard A, Pavic AM, Aloï M, et al. *Clostridium difficile* and pediatric inflammatory bowel disease: a prospective, comparative, multicenter, ESPGHAN study. *Inflamm Bowel Dis*. 2014;20(12):2219–25. <https://doi.org/10.1097/MIB.0000000000000219>.
 25. Willis DN, Huang FS, Elward AM, Wu N, Magnusen B, Dubberke ER, et al. *Clostridioides difficile* infections in inpatient pediatric oncology patients: a cohort study evaluating risk factors and associated outcomes. *J Pediatric Infect Dis Soc*. 2021;10(3):302–8. <https://doi.org/10.1093/jpids/piaa090>.
 26. Samady W, Pong A, Fisher E. Risk factors for the development of *Clostridium difficile* infection in hospitalized children. *Curr Opin Pediatr*. 2014;26(5):568–72. <https://doi.org/10.1097/MOP.0000000000000126>.
 27. Napolitano LM, Edmiston CE. *Clostridium difficile* disease: diagnosis, pathogenesis, and treatment update. *Surgery*. 2017;162(2):325–48. <https://doi.org/10.1016/j.surg.2017.01.018>.
 28. Al-Mazrou AM, Hyde LZ, Suradkar K, Kiran RP. Effect of inclusion of oral antibiotics with mechanical bowel preparation on the risk of *Clostridium difficile* infection after colectomy. *J Gastrointest Surg*. 2018;22(11):1968–75. <https://doi.org/10.1007/s11605-018-3837-3>.
 29. Duclaux-Loras R, Berthiller J, Ferroni A, Chardot C, Goulet O, Lacaille F, et al. *Clostridium difficile*: a frequent infection in children after intestinal transplantation. *Transplantation*. 2020;104(1):197–200. <https://doi.org/10.1097/TP.0000000000002795>.
 30. Freiler JE, Durning SJ, Ender PT. *Clostridium difficile* small bowel enteritis occurring after total colectomy. *Clin Infect Dis*. 2001;33(8):1429–31. <https://doi.org/10.1086/322675> (discussion 32).
 31. Gentry CA, Campbell DL, Williams RJ. Outcomes associated with recent guideline recommendations removing metronidazole for treatment of non-severe *Clostridioides difficile* infection: a retrospective, observational, nationwide cohort study. *Int J Antimicrob Agents*. 2021;57(3):106282. <https://doi.org/10.1016/j.ijantimicag.2021.106282>.
 32. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302–7. <https://doi.org/10.1086/519265>.

33. Al Momani LA, Abughanimeh O, Boonpheng B, Gabriel JG, Young M. Fidaxomicin vs vancomycin for the treatment of a first episode of *Clostridium difficile* infection: a meta-analysis and systematic review. *Cureus*. 2018;10(6):e2778. <https://doi.org/10.7759/cureus.2778>.
34. Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis*. 2021. <https://doi.org/10.1093/cid/ciab549>. (This IDSA 2021 update to adult guidelines is also important for readers as it indicates what might be on the horizon for pediatric care. The guidelines recommend usage of fidaxomicin for both first episode and for recurrences, and for the first time recommend usage of bezlotoxumab in adults to prevent recurrence. With ongoing pediatric trials, these may be the recommendations for pediatrics in the future as well.)
35. Wolf J, Kalocsai K, Fortuny C, Lazar S, Bosis S, Korczowski B, et al. Safety and efficacy of fidaxomicin and vancomycin in children and adolescents with *Clostridioides* (*Clostridium*) *difficile* infection: a phase 3, multicenter, randomized, single-blind clinical trial (SUNSHINE). *Clin Infect Dis*. 2020;71(10):2581–8. <https://doi.org/10.1093/cid/ciz1149>. (This 2020 randomized clinical trial shows that fidaxomicin, which is already recommended first line in adults, is an equally attractive option for pediatrics. Fidaxomicin was safe, well tolerated, non-inferior to vancomycin for treatment, and had statistically significant better global cure rates than vancomycin in pediatrics, with lower risk of recurrence.)
36. Davidovics ZH, Michail S, Nicholson MR, Kocielek LK, Pai N, Hansen R, et al. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection and other conditions in children: a joint position paper from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2019;68(1):130–43. <https://doi.org/10.1097/MPG.0000000000002205>. (This 2019 joint position paper supporting FMT in pediatrics is important for providers to read as it summarizes the safety, efficacy, indications, and methods of FMTs in pediatrics when used at an experienced center.)
37. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol*. 2013;108(4):500–8. <https://doi.org/10.1038/ajg.2013.59>.
38. Lee CH, Steiner T, Petrof EO, Smieja M, Roscoe D, Nematallah A, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection: a randomized clinical trial. *JAMA*. 2016;315(2):142–9. <https://doi.org/10.1001/jama.2015.18098>.
39. Nicholson MR, Hourigan SK, Conrad M, Goyal A, Jensen K, Kelsen J, et al. Current challenges in fecal microbiota transplantation for *Clostridioides difficile* infection in children. *Am J Gastroenterol*. 2021. <https://doi.org/10.14309/ajg.0000000000001350>.
40. Goldenberg JZ, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev*. 2017;12:CD006095. <https://doi.org/10.1002/14651858.CD006095.pub4>.
41. Allen SJ, Wareham K, Wang D, Bradley C, Hutchings H, Harris W, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2013;382(9900):1249–57. [https://doi.org/10.1016/S0140-6736\(13\)61218-0](https://doi.org/10.1016/S0140-6736(13)61218-0).
42. Johnston BC, Lytvyn L, Lo CK, Allen SJ, Wang D, Szajewska H, et al. Microbial preparations (probiotics) for the prevention of *Clostridium difficile* infection in adults and children: an individual patient data meta-analysis of 6,851 participants. *Infect Control Hosp Epidemiol*. 2018;39(7):771–81. <https://doi.org/10.1017/ice.2018.84>.
43. McFarland LV, Johnson SB, Evans CT. Perils and pitfalls of probiotic quasi-experimental studies for primary prevention of *Clostridioides difficile* infection: a review of the evidence. *Am J Infect Control*. 2021;49(3):375–84. <https://doi.org/10.1016/j.ajic.2020.08.003>.
44. Musgrave CR, Bookstaver PB, Sutton SS, Miller AD. Use of alternative or adjuvant pharmacologic treatment strategies in the prevention and treatment of *Clostridium difficile* infection. *Int J Infect Dis*. 2011;15(7):e438–48. <https://doi.org/10.1016/j.ijid.2011.03.017>.
45. Gerding DN, Kelly CP, Rahav G, Lee C, Dubberke ER, Kumar PN, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection in patients at increased risk for recurrence. *Clin Infect Dis*. 2018;67(5):649–56. <https://doi.org/10.1093/cid/ciy171>.
46. Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, Birch T, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med*. 2017;376(4):305–17. <https://doi.org/10.1056/NEJMoa1602615>.
47. Wilcox MH, Rahav G, Dubberke ER, Gabryelski L, Davies K, Berry C, et al. Influence of diagnostic method on outcomes in phase 3 clinical trials of bezlotoxumab for the prevention of recurrent *Clostridioides difficile* infection: a post hoc analysis

- of MODIFY I/II. *Open Forum Infect Dis*. 2019;6(8). <https://doi.org/10.1093/ofid/ofz293>.
48. de Bruyn G, Saleh J, Workman D, Pollak R, Elinoff V, Fraser NJ, et al. Defining the optimal formulation and schedule of a candidate toxoid vaccine against *Clostridium difficile* infection: a randomized phase 2 clinical trial. *Vaccine*. 2016;34(19):2170–8. <https://doi.org/10.1016/j.vaccine.2016.03.028>.
49. Foglia G, Shah S, Luxemburger C, Pietrobon PJ. *Clostridium difficile*: development of a novel candidate vaccine. *Vaccine*. 2012;30(29):4307–9. <https://doi.org/10.1016/j.vaccine.2012.01.056>.
50. • Bao H, Lighter J, Dubrovskaya Y, Merchan C, Siegfried J, Papadopoulos J, et al. Oral vancomycin as secondary prophylaxis for. *Pediatrics*. 2021;148(2) <https://doi.org/10.1542/peds.2020-031807>. (This 2021 study showed that use of oral vancomycin prophylaxis in high-risk pediatric patients during concomitant antibiotics is effective for preventing CDI recurrence. Although oral vancomycin is rarely used in pediatrics, this paper supports that it should be highly considered in appropriate clinical settings.)
51. Oosthuizen J. *Clostridium difficile*. CDC Public Health Image Library ID #16786. *CDC's Antibiotic Resistance Threats in the United States, 2019*: Centers for Disease Control; 2014.

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