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Clostridium difficile Infection in Pediatric Inflammatory Bowel Disease

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Abstract: Children with inflammatory bowel disease (IBD) are disproportionately susceptible to *Clostridium difficile* infection (CDI) and the incidence is increasing. There has also been growing recognition of asymptomatic *C. difficile* colonization in pediatric IBD, which can sometimes be very difficult to distinguish from symptomatic *C. difficile*-associated disease in this population. In this study, we discuss the current knowledge of *C. difficile* infection in children with IBD, reviewing epidemiology, risk factors, and outcomes that often differ from the adult IBD population, and discuss the complexities and dilemmas of diagnosing and treating CDI in pediatric IBD.

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Key Words: *Clostridium difficile* infection, pediatric, children, inflammatory bowel disease

Clostridium difficile infection (CDI) is now the leading cause of gastroenteritis-associated death and the number one health care-associated infection in the United States and is increasing in prevalence both in adult and pediatric populations, with estimates of almost half a million infections per year.^{1–3} Individuals with inflammatory bowel disease (IBD) are at increased risk of CDI.⁴ The cooccurrence of IBD and CDI was first noted in the 1980s with CDI proposed to complicate IBD.^{5,6} Over the last decade, possibly correlating with the rising incidence of CDI, there has been growing attention again to the complex relationship of CDI in IBD, with many uncertainties regarding the clinical implications, diagnosis, and treatment options.

In the general population, CDI is typically more common in adults compared with children,³ and most studies to date examining the link between CDI and IBD have been conducted in adults. However, it is known that children with IBD have high rates of intercurrent CDI, comparable with adults with IBD.⁷ The pathogenesis and risk factors for CDI in children with IBD may differ from adults with IBD for many reasons including increased asymptomatic colonization of *C. difficile* in children, the dynamic

developing intestinal microbiome in children, especially the very young, and differing patterns of IBD in children compared with adults.^{8–10} In this study, we review published studies looking at CDI in children with IBD and discuss special considerations that may be important in this population.

THE BASICS

Toxigenic *C. difficile* is a gram-positive, anaerobic, spore-producing bacterium that primarily infects the colon and can produce 2 protein exotoxins, toxin A (gene *tcdA*) and toxin B (gene *tcdB*). Most toxigenic *C. difficile* secrete both toxin A and toxin B, although strains producing only toxin B exist and are known to induce disease. Nontoxigenic strains of *C. difficile* also exist but are not associated with clinical disease; hence the importance of documenting that a patient is infected with a toxin-producing strain as only toxin-producing strains induce disease. The terminology used to discuss CDI can be confusing, but the clinical focus is on distinguishing asymptomatic *C. difficile* colonization and symptomatic disease that ranges from mild diarrhea to life-threatening pseudomembranous colitis. Symptomatic *C. difficile* infection is often referred to as *C. difficile*-associated disease (CDAD). Thus, herein, use of the term CDI will refer to both asymptomatic *C. difficile* colonization and CDAD because “infection” represents a continuum from being asymptomatic to toxic megacolon.^{3,11} A further point of confusion is the evolving diagnostic methods to detect CDI with an increasing shift from insensitive but specific enzyme immunoassays that detect the protein toxins in the stool to highly sensitive and specific DNA-based tests that detect the *C. difficile* toxin genes in the stool.^{11,12} The diagnostic approach to identifying infection with toxigenic *C. difficile* will be discussed in more detail later, but the clinician must understand the method of detection used for their patient to interpret the test

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results. Importantly, diagnosis requires use of a fecal test that detects toxin B or the *tcdB* gene because disease-inducing strains of toxigenic *C. difficile* that secrete only toxin B (or express only the *tcdB* gene) exist. Hence, use of fecal tests that detect only toxin A or *tcdA* can lead to false results as no toxigenic *C. difficile* secreting only toxin A (or expressing only the *tcdA* gene) have yet been identified as causing CDAD. In this review, the data on the intersection of pediatric IBD and toxigenic *C. difficile* will be discussed.

EPIDEMIOLOGY

The rising incidence of CDI in the general pediatric population over the last 2 decades has been more than paralleled by children with IBD who have a disproportionately higher rate of CDI that is increasing.⁷ A study using a statewide database of hospital discharges showed that between 2009 and 2012 the overall prevalence of hospitalizations with CDI was 46.0 per 1000 in children with a diagnosis of IBD compared with 4.1 per 1000 hospitalizations in those without IBD, representing over a 10-fold difference ($P < 0.0001$).⁷ Furthermore, a retrospective cross-sectional analysis of discharges from 1997 to 2011 using the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (NIS), considered nationally representative, of youth in the United States revealed a 5-fold increase in IBD hospitalizations with CDI (P for trend < 0.01) compared with a 2-fold increase in IBD hospitalizations without CDI (P for trend < 0.01).¹³ When evaluating hospitalizations with an admitting diagnosis of diarrhea, a retrospective, single-center, observational, case-control study from Italy reported a CDI prevalence of 24.7% in pediatric patients with IBD compared with 8.9% in those without this diagnosis ($P = 0.004$).¹⁴ Moreover, there is a high recurrence of CDI in pediatric IBD, with a retrospective case-control study of hospitalized children showing an increased rate of recurrence in those with IBD and CDI compared with those with CDI alone (34% versus 7.5%, respectively, $P < 0.0001$).¹⁵ Clinically significant, symptomatic CDI (i.e., CDAD), as opposed to asymptomatic *C. difficile* colonization, is assumed in these studies based on study design and patients given a diagnosis of CDI by providers, although this is difficult to ascertain with certainty from retrospective studies given the overlap between the symptoms of CDAD and IBD.

Children with newly diagnosed IBD also appear to have a high rate of CDI with 8% reported in a US study¹⁶ compared with 47% in a Polish study¹⁷; the differing results may represent geographical differences. With the high prevalence rate of CDI in pediatric IBD, some advocate testing all cases of suspected new onset pediatric IBD for CDI,¹⁶ although it is unclear whether detection of *C. difficile* at onset of IBD is colonization versus disease and with the argument that repeated treatment of *C. difficile* may delay the final diagnosis of underlying IBD.

COLONIZATION

In addition to the high rate of CDAD in pediatric IBD, there is also a high rate of asymptomatic, presumed clinically

insignificant, colonization of *C. difficile*. Using a combination of culture to detect the organism and PCR to detect the *C. difficile* toxin B gene (*tcdB*), asymptomatic carriage in children with clinically quiescent IBD in the outpatient setting has been reported at 17% compared with 3% in children without IBD ($P = 0.012$)¹⁸; namely, none of the children in this study had clinically significant gastrointestinal symptoms at the time stool was collected for testing. This asymptomatic colonization appears to be higher than in adults with IBD using similar methodology (8.2% in IBD versus 1% in healthy volunteers, $P = 0.02$).¹⁹ An overall higher rate of asymptomatic colonization of toxigenic *C. difficile* in children may contribute to the higher rate of asymptomatic colonization seen in pediatric IBD compared with adult IBD,⁸ although asymptomatic toxigenic *C. difficile* colonization is more prevalent in infants and younger children,^{20,21} presumably with decreased colonization with age as the intestinal microbiome matures.²² Similar results were also seen in children in a prospective multicenter study with detection of *C. difficile* toxins A and B by enzyme immunoassay giving a 10-fold higher detection in children with IBD compared with children with celiac disease (7.5% versus 0.8%; $P = 0.008$); this study however included both symptomatic and asymptomatic subjects.²³ Interestingly, a further study did not find a significant difference in the prevalence of toxigenic *C. difficile* between pediatric patients with IBD and controls using PCR to detect the toxin B gene (*C. difficile* detection of 11.6% in patients with Crohn's disease, 18.4% in patients with ulcerative colitis [UC], and 11.8% in controls [$P = 0.25$]); however, this study looked at both inpatients and outpatients, and also likely symptomatic and asymptomatic colonization because some patients who tested positive also had diarrhea.²⁴ Furthermore, as compared with enzyme-linked immunoassay testing, PCR testing for detection of the toxin B gene of *C. difficile* is significantly more sensitive.¹² The range of results of toxigenic *C. difficile* detection in IBD may be due to differences in detection methods and prevalence of toxigenic *C. difficile* in the differing control populations, but nevertheless most studies to date show a high prevalence of both CDAD and *C. difficile* colonization in pediatric IBD.

PATHOGENESIS

The healthy intestinal microbiome is protective against *C. difficile*, with dysbiosis and decreased diversity associated with CDI acquisition and recurrence.²⁵ By 16s rRNA gene sequencing, those with recurrent CDI compared with control subjects without CDI and those with a single episode of CDI were shown to have a significantly decreased diversity using the Shannon-Weiner diversity index and decreased overall species richness.²⁵ Moreover, microbiome compositional changes have been reported in those with recurrent CDI before treatment with fecal microbiota transplantation (FMT) compared with healthy fecal donors and with themselves after FMT with CDI eradication. For example, increased abundance of the phyla Proteobacteria, predominantly from the order Enterobacteriales^{26,27} and decreased Bacteroidetes²⁷ have been detected in children with recurrent CDAD

before FMT. In the general population, antibiotic exposure is a major risk factor for CDI,^{11,28} by causing pervasive shifts in the intestinal microbiota and decreased diversity,²⁹ allowing for colonization with pathogens such as toxigenic *C. difficile*.³⁰ In pediatric IBD, antibiotic exposure has not been found to be the major risk factor for CDAD or *C. difficile* colonization.^{18,23} Instead, it is proposed that the underlying dysbiosis with decreased diversity of species that is found in IBD, in both Crohn's disease and UC, predisposes to the loss of colonization resistance to *C. difficile* in IBD, leading to increased rates of CDI in this population.^{31,32} Moreover, increased Proteobacteria and decreased Bacteroidetes have also been reported in those with IBD compared with non-IBD controls,³² similar to some reports of microbiome changes in recurrent CDI.²⁷ Host genetic polymorphisms have also been known to impact microbiota composition in IBD³³ and it can be hypothesized that certain genetic polymorphisms associated with IBD increase the risk of CDI. In a study looking at adults with UC, with and without a history of CDI (n = 319, 29 with CDI), 163 risk loci for IBD were examined for an association with CDI; 6 genetic polymorphisms were associated with increased risk whereas 2 loci were inversely associated.³⁴ The UC-specific locus with the strongest association was TNFRSF14, is thought to play an important role in maintaining the colonic barrier against pathogenic bacteria, and so it is plausible that it may have a role in CDI in IBD. However, much larger studies are needed to examine genetic associations and this key area has not been studied in children to date.

RISK FACTORS

IBD Type

In adults, CDAD and toxigenic *C. difficile* colonization are more common in UC compared with Crohn's disease.^{4,19,35} However, in children, there seems to be no difference in the rate of CDAD and toxigenic *C. difficile* colonization between UC and Crohn's disease.^{7,13,17,18} However, overall, colonic IBD is associated with CDI in pediatric IBD.^{14,18,24} A reason why no difference in IBD type is found in pediatric studies may be because young children have a different pattern of IBD compared with adults, with colonic CD being prominent.¹⁰

Disease Severity

CDI has been reported to be increased in more severe and active IBD.^{14,17,23} Worsening dysbiosis of the microbiome has been reported in more severe pediatric IBD,³⁶ possibly increasing loss of colonization resistance to *C. difficile*, causing some to propose toxigenic *C. difficile* detection in IBD is more a marker of underlying IBD severity. Thus, it is very difficult to parse out the relationship between the clinical severity of IBD and CDI, as in these cases it is unclear whether patients have severe IBD and asymptomatic colonization of toxigenic *C. difficile* versus severe IBD and severe CDAD because of the large overlap in symptoms.

Medications

In adults with IBD, increased risk for CDI has been associated with immunomodulator use³⁷ and corticosteroid use.³⁸ Although CDI is generally more common in the immunosuppressed pediatric population,³⁹ the type of IBD therapy, including the major immunosuppressant agents of glucocorticoids and biological treatments, has not been found to increase the risk of CDAD or *C. difficile* colonization in IBD in children.^{14,18,23} However, these studies were not specifically designed to address this question and so may have been underpowered to detect a difference. Antibiotic use, a traditional risk factor for CDI, has not been reported to increase the risk of CDAD or *C. difficile* colonization in IBD in children.^{14,18,23} Proton pump inhibitor use increases the risk of CDI in children,⁴⁰ and these medications are commonly used in IBD; however, proton pump inhibitor use has not been found to be associated with CDAD in IBD²³ but is associated with increased risk of *C. difficile* colonization.¹⁸ Importantly, the Food and Drug Administration issued a drug safety alert in 2012 regarding the association of gastric acid suppressants and risk for CDAD.

Hospitalizations

Hospitalization has traditionally been considered a strong risk factor for CDI, although there has been a dramatic increase in community-onset CDI recently.^{3,41} In studies in children with IBD and CDI, recent hospitalization has not been associated with increased risk^{15,23} and many cases seem to be community acquired,⁴² including for *C. difficile* colonization.¹⁶ However, the Centers for Disease Control and Prevention have reported that most patients with "community-onset" or "community-acquired" CDI do have health care exposures, including outpatient clinic exposures, with only 6% of all patients with *C. difficile* infections having no health care exposures at all.⁴³

DIAGNOSIS

IBD exacerbation and CDAD can be very difficult to distinguish from each other, due to a high overlap of symptoms. Usually, in CDAD, other factors such as leukocytosis raised fecal lactoferrin or calprotectin, and raised intestinal inflammatory biomarkers⁴⁴ can help distinguish disease from asymptomatic colonization. However, these tests are less helpful in the setting of active IBD where these biomarkers are often elevated due to the underlying intestinal inflammation. Although endoscopy is rarely performed for diagnosis of CDI in children, the classic pseudomembranes of non-IBD-associated CDAD seen at colonoscopy are rarely seen with CDI in IBD.^{38,45} The reason for this is unclear and pseudomembranes with CDI in IBD do not seem to be associated with immunosuppressant drugs or IBD characteristics.⁴⁵ Possible hypotheses include lack of pseudomembrane formation due to preexisting mucosal changes and chronic inflammation.³⁷ Alternatively, symptoms may be due to IBD rather than CDI and, thus, pseudomembranes may be less likely to occur. Currently, DNA-based PCR assays for diagnosis of *C. difficile* are used in

approximately 50% of US laboratories due to the high sensitivity, specificity, and quick turnaround time and in general they have high diagnostic value.⁴⁶ There is concern, however, that the high sensitivity permits for detection of low levels of toxigenic *C. difficile* of unclear clinical relevance. In the setting of IBD in children where there seems to be a high rate of asymptomatic colonization of *C. difficile*, this adds to the complexity of determining whether *C. difficile* should be considered disease-inducing in certain cases of IBD. It is important to highlight that clinicians should only test for *C. difficile* when it is clinically appropriate and the patient is symptomatic.⁴⁷ By Centers for Disease Control and Prevention criteria, this requires 3 or more loose stools in 24 hours. What the appropriate criteria are in the setting of IBD are unknown; 1 possibility is to test if there is change in baseline clinical status and/or a change from usual disease pattern.

TREATMENT

Guidelines exist for the treatment of CDI in children,⁴⁷ but none specifically pertain to CDI in children with IBD. Data from a retrospective observational study in adults with IBD showed fewer readmissions and shorter lengths of stay in those with UC and CDI treated with vancomycin compared with metronidazole,⁴⁸ leading to the proposal that in adults with IBD oral vancomycin should be considered first-line therapy for CDI. This is mirrored by recent studies in adults without IBD that strongly suggest that overall outcome is improved with initial vancomycin therapy.⁴⁹ There are few CDI treatment studies in pediatric IBD; however, a small retrospective single-center study showed equal success with using metronidazole or vancomycin for initial treatment of CDAD, with treatment success defined as documented resolution of symptoms or *C. difficile* toxin test negativity after treatment.⁵⁰ Initial treatment failure was very high at 57%,⁵⁰ regardless of IBD type or initial treatment used for CDAD, seemingly much higher compared with the general pediatric population.⁴⁷ Intercurrent use of aminosalicylates was positively associated with initial antimicrobial treatment success, although previous use of steroids, thiopurine, and methotrexate immunomodulators, or anti-tumor necrosis factor alpha treatments did not affect initial treatment success.⁵⁰ The reasons for this are unclear, although they may possibly be a reflection of CDI being easier to clear in less severe IBD with less inflammation, and this cannot be directly derived from this study. To add to the complexity, assessing treatment success of CDAD in IBD can be problematic as improvement in symptoms may be a response of the underlying IBD to antibiotics, rather than due to treatment of *C. difficile*.⁵¹ However, test of cure after therapy of CDI is not standard of care as persistent detection of toxigenic *C. difficile* of variable duration is common (similar to other enteric pathogens) despite clinical improvement.

For recurrent CDI, FMT has been shown to be effective in randomized controlled trials in the general adult population.^{52,53} FMT has been successfully used to treat CDI in pediatric IBD in case series data.^{27,54} In these reports, FMT was given to children with IBD through colonoscopy with reported success in both

those with UC and Crohn's disease; no adverse effects and no change in baseline IBD status were reported, although the studies were not designed to robustly assess this. Immediately after FMT, there was an increase in fecal microbiome diversity in children with and without IBD.²⁷ Interestingly, however, FMT-restored fecal diversity was sustained only in children without IBD, whereas in those with IBD, bacterial diversity returned to the pre-FMT baseline by 6 months.²⁷ This suggests IBD host-related mechanisms modify fecal microbiome diversity and possibly that children with IBD may still be at risk of recurrent CDI even after FMT. Longer term longitudinal studies are needed.

OUTCOMES

CDI in IBD represents an increased health risk and burden. From studies using nationally representative databases, hospitalized children with IBD and CDI have been reported to have significantly lengthier hospital stays, higher charges, and greater need for parenteral nutrition and blood transfusions than IBD alone.^{13,55} Moreover, from a retrospective case-control study of hospitalized children, those with IBD and CDI have been reported to have an increased chance of being readmitted to the hospital with a disease exacerbation within 6 months of a CDI (57%) compared with those with IBD alone (30%) ($P < 0.001$), secondary to disease exacerbation.¹⁵ Furthermore, in children with a history of IBD and CDI, an increased rate of escalation of IBD therapy has been reported.^{15,23} The effects of asymptomatic *C. difficile* colonization on the natural history of pediatric IBD have not been well elucidated, although some children with stool positive for toxigenic *C. difficile* were not thought to have symptoms compatible with CDAD in the aforementioned study.²³

In adults with IBD, some studies report an increased rate of colectomy with intercurrent CDI, whereas others show little impact of CDI on colectomy rate.⁵⁶ In pediatric studies addressing this, CDI was actually associated with a decreased risk of bowel surgery and colectomy in IBD.^{13,55} The reasons for the discrepancies between pediatric and adult surgery rates with intercurrent CDI and IBD are unclear, with possible hypotheses of increased reluctance to perform operation in children with IBD, especially with intercurrent infections⁵⁵ and study design that only evaluated colectomy rates during current and not subsequent hospitalizations.¹³ There is a need for studies in children addressing this question with more access to detailed clinical information.

Dilemmas and Future Directions

As discussed, a major dilemma is being able to differentiate CDAD from an IBD flare with *C. difficile* colonization and this is likely even more relevant in pediatric IBD, as children in general have a higher rate of toxigenic *C. difficile* colonization. Equally complex is when to consider toxigenic *C. difficile*, a disease-inducing pathogen in IBD, or whether detection is more a reflection of severe disease with the quagmire of whether an IBD flare led to *C. difficile* colonization or vice versa. The only cases of certain *C. difficile* colonization are detection of the toxigenic

organism in an asymptomatic patient, which is rarely the case in clinical practice in pediatric IBD. Further research looking at differentially raised inflammatory markers and systemic immune responses such as specific cytokines between CDAD and IBD may prove useful to begin to address this dilemma.

Furthermore, given high failure rates of CDAD treatment in pediatric IBD and increased negative outcomes in those with CDI, it is must be considered whether a different or more aggressive treatment algorithm is needed to combat CDAD in children with concurrent IBD. Prospective randomized controlled trials are desperately needed to address this concern. Moreover, it is currently unknown whether *C. difficile* colonization also has a negative impact on the pediatric IBD course, but this is suggested from data in some studies.²³ There are no current guidelines on the management of *C. difficile* colonization in IBD. Large prospective longitudinal studies are needed to examine the effect of *C. difficile* colonization on the natural history and progression of IBD in relation to disease severity and complications. If asymptomatic colonization leads to an accelerated IBD course, then routine screening for asymptomatic toxigenic *C. difficile* colonization with subsequent treatment needs to be tested in prospective controlled trials. Last, there is growing interest in microbiome manipulation, including FMT, in the treatment of IBD and this may hold further promise and opportunities to address concurrent CDI.

CONCLUSIONS

There has been growing attention to CDI in pediatric IBD in the last decade, with the recognition of both high rates of CDAD and toxigenic *C. difficile* colonization, and worse outcomes for those with both CDI and IBD. However, many questions remain unanswered including distinguishing CDAD from asymptomatic *C. difficile* colonization, the optimal treatment for CDAD in IBD and the effect of toxigenic *C. difficile* colonization on the natural history of pediatric IBD. Prospective longitudinal studies are greatly needed to address these dilemmas and help fight CDI and improve outcomes in children with IBD.

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