Journal of Medicine and Therapeutics

Research Article ISSN: 2399-9799

Clostridioides difficile infection in children with Inflammatory Bowel Disease: challenges in diagnosis and management

Sindhu Mohandas, Shaddy Farid and Sonia Michail*

Clinical Pediatrics, Children's Hospital of Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, California USA

Abstract

Clostridioides difficile infection (CDI) has been increasing in incidence in the general population and particularly in patients with inflammatory bowel disease (IBD). This rise is also seen in pediatric patients with IBD and is associated with increased morbidity and complications. Despite successful treatment, recurrences are also more common in this group. CDI is of particular concern in pediatric patients with IBD both from a diagnostic and management viewpoint. The similar clinical presentation between CDI and IBD poses a diagnostic challenge. Various CDI antibiotics have been used to treat CDI in children. Fecal microbiota transplantation can be successful in curing recurrent CDI when other treatments have failed however its effect on the underlying IBD is not entirely clear. This review article describes the challenging aspects of diagnosis and management of this dual disease and discusses the novel therapies including monoclonal antibodies, vaccines and probiotics. While we currently have good knowledge of this area, however, further research is required to study the unique risk factors for CDI and the diagnostic and management challenges in pediatric patients with IBD.

Introduction

Clostridioides difficile is an anaerobic, gram positive, spore forming, toxin-producing bacillus. It exists in the environment in the spore form, which is resistant to heat, acid and a number of antiseptics. Mode of spread to others is by the fecal-oral route. The important virulence factors are the toxins that it produces, namely toxins A and B. The toxins are responsible for the clinical manifestations, which can range from asymptomatic colonization to severe disease with pseudomembranous colitis [1].

In the last decade the incidence and prevalence of CDI has been rising. Highly communicable strains and enhanced testing capabilities have contributed to an increase in identified cases. For example, emergence of the easily transmissible and highly virulent North American pulsed-field gel electrophoresis type 1 (NAP1) strain of *C. difficile* is one of the contributors to the changing epidemiology of CDI [2-5]. Newer testing modalities are also available which are very sensitive and specific and allow enhanced detection of cases leading to an increased number of identified cases.

C. difficile causes a high burden of disease with an estimated 453,000 infections and 29,300 deaths attributable to CDI, per year in the United States alone [6]. CDI negatively impacts patients with IBD both short term and long term, including rates of colectomy, escalation in IBD therapy and mortality as shown in multiple adult studies [7-12]. It may also result in longer hospitalization, increased readmission rates and increased in-hospital expenditures [7].

CDI is of particular concern in patients with IBD both from a diagnostic and management viewpoint. In this review we try to address the current evidence that can aid in making an informed decision with regards to management of pediatric patients with IBD and CDI.

Incidence and risk factors for CDI in IBD

Cases of CDI have been rising in both adult and pediatric patients with inflammatory bowel disease (IBD). In children, the rise has been larger with one study showing a 5-fold increase in IBD hospitalizations with CDI from 1997-2011 [13]. Patients with IBD not only have an increasing incidence of CDI [14] but also have a higher prevalence of asymptomatic *C. difficile* colonization [15]. There is also a significantly increased prevalence of CDI in children with IBD when compared to children without IB [7,16-17]. Risk factors in children may also differ from those seen in adults [18]. The prevalence of CDI in IBD among pediatric patients is 7.8%-69%, with a higher incidence among patients with ulcerative colitis (UC) as opposed to (CD) [19-22]. A recent study by Melnik et al shows that *C. difficile* is one of two most common enteric infections among pediatric patients with IBD [23]. More importantly, CDI was associated with about a three-fold increase in disease severity; including more frequent relapses, emergency room visits and surgical intervention. Pediatric patients with IBD can also have increased length of hospital stay, cost and need for TPN and blood transfusions [24,25]. The reasons for increased incidence and complications of CDI in patients with IBD are probably multifactorial. Traditionally, and as reported in multiple earlier studies, antibiotic exposure, hospitalization, PPI, H2 blockers, chemotherapy and corticosteroid use are considered significant risk factors for *C. difficile* colonization [26-28]. Since patients with IBD are exposed to most of these risk factors they may have a high rate of colonization as well as infection. In addition, the

Correspondence to: Sonia Michail, Children's Hospital of Los Angeles, Clinical Pediatrics Keck School of Medicine, University of Southern California, Los Angeles, California USA, E-mail: smichail@chla.usc.edu

Received: March 05, 2021; **Accepted:** April 14, 2021; **Published:** April 17, 2021

underlying IBD and its treatment may expose them to additional risk factors including a disrupted gut microbiome, immunocompromised state and repeated exposure to the health care environment. Disruption of gut microbiome and interaction with the intestinal immune system are mechanisms for pathogenesis of both CDI and IBD. Patients with inflammatory bowel disease (IBD) are at higher risk for CDI and host genetics may influence susceptibility to *C. difficile* in these patients [29].

Pathogenesis of disease

The pathogenesis of IBD (although incompletely understood) is thought to arise from the interactions between environmental and host factors. IBD is characterized by recurring episodes of relapsing inflammation of the gastrointestinal tract with variable clinical manifestations and potential serious complications which include bleeding, perforation and abscess formation. CDI is thought to result from disturbance in the microbiome resulting in dysbiosis and loss of colonization resistance.

Diagnosis of CDI

Accurate diagnosis of CDI is not an easy task due to many factors. Patients may harbor toxigenic strains without clinical disease. It is generally recommended that only symptomatic children (defined as 3 or more loose or liquid stools in a 24-hour period) older than 1 year be tested once other infectious etiologies of diarrhea are addressed. It should be noted that laboratory tests are only recommended for unformed stool sample with many hospitals having a laboratory-based rejection of testing on formed specimens.

Diagnosis of CDI requires presence of diarrhea (≥ 3 unformed stools in a 24 hour period) or radiographic evidence of ileus/toxic megacolon and a positive stool test result indicating the presence of toxigenic C. difficile or colonoscopic/histopathologic findings demonstrating pseudomembranous colitis [30].

There are several diagnostic assays available to assess CDI. Toxigenic cultures and cell cytotoxicity neutralization assays have been used as reference methods. However, both methods are cumbersome, time consuming and lack standardization, and not too many labs use it for diagnosis at the present time. Glutamate dehydrogenase (GDH) immunoassays detect the highly conserved metabolic enzyme (common antigen) present in high levels in all isolates of *C. difficile*. Since this antigen is present in both toxigenic and nontoxigenic strains, GDH immunoassays lack specificity and must be used with algorithms that combine it with a toxin test and/ or a molecular test for toxin gene detection [31,32]. DNA-based tests or nucleic acids amplification tests via polymerase chain reaction (PCR) for C. Difficile toxin genes (tcdA and tcdB) have been found to be more sensitive than toxin A and B enzyme immunoassays (EIA). Currently NAAT alone or a multistep algorithm for testing is (GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) is recommended as the preferred diagnostic testing method for CDI [30].

Repeat testing is not recommended within 7 days during the same episode of diarrhea. Stool testing from asymptomatic patients is not recommended, except for epidemiological studies. There is not enough data to recommend the use of biological markers (fecal lactoferrin) to diagnose CDI. Clostridium difficile testing should not be routinely performed in children with diarrhea who are 1-2 years of age unless other infectious or non-infectious causes have been excluded [30].

Specific challenges in diagnosis and management of CDI in IBD

There is significant overlap in the clinical presentation of IBD and CDI. Patients with either condition often present with abdominal pain, watery diarrhea, mucus, and rectal bleeding. Laboratory evaluation may reveal leukocytosis and hypoalbuminemia in both conditions. Radiologic evaluation is often normal, except in severe disease where it may show megacolon or perforations. Thus, physical examination, laboratory values and radiologic findings do not aid in differentiating CDI from active IBD colitis [24,33].

Further complicating the picture, a percentage of patients may be asymptomatically colonized with C difficile and not have the disease. The prevalence of such colonized individuals is estimated to be between 1 and 4% in healthy adults and higher up to 8% among those with IBD [15]. Furthermore C difficile colonization rates in younger children are higher than in older children and adults with children less than a year of age commonly colonized with *C. difficile* (cross-sectional prevalence 35–40%), decreasing to adult rates of ~3% by ~8 years (34) A pediatric study by Leibowitz et al. showed an asymptomatic colonization rate by PCR of 24% [34,35].

Currently there is no definite way to differentiate asymptomatic colonization from disease, which makes this determination in a patient with IBD presenting with diarrheal disease extremely challenging. In addition, the two conditions can often co-exist and CDI can potentially trigger an acute flare of the underlying IBD [33,36]. There has also been a rise in CDI among IBD patients in the last few decades as shown in multiple single center and national studies [7-9,17].

Given the fact that the management of the two conditions differs significantly and IBD-targeted therapy may potentially adversely affect the progression of CDI, management of immunosuppression in patients with IBD who with CDI can be challenging.

Endoscopy

The classically described endoscopic appearance of *C. difficile* colitis is the 'pseudomembrane', a collection of necrotic debris and secretions from sloughing of the mucosa [37,38]. However this classic finding is not very commonly seen in patients underlying IBD (8, 14). Pseudomembranes are also seen though less commonly in other conditions like Behcet's disease, collagenous colitis, inflammatory bowel disease, ischemic colitis, other infections organisms (e.g. bacteria, parasites, viruses) and few drugs and toxins [39].

Endoscopy is however useful in these patients as it is helpful to assess the severity of the active disease as well as to obtain biopsies to rule out other infections such as cytomegalovirus which can present in some patients with severe steroid refractory colitis [16].

Management

Medical management

Non-CDI antibiotics should be stopped or narrowed whenever possible once a patient is diagnosed with CDI. In mild CDI this alone may be enough to achieve cure. In patients with IBD however most patients will be treated with antibiotics against CDI. Infection control procedures should be in place when hospitalized patients are diagnosed with CDI.

CDI antibiotics

As *C. difficile* toxin acts locally in the gut, activity of CDI antibiotics depends on achieving adequate intraluminal concentrations. There

have been considerable changes over the past decade regarding recommendations for the agent of choice to treat CDI.

Metronidazole

Metronidazole was the recommended first line antibiotic for treating first episode of CDI until recently. With recent randomized control clinical trials showing increased failure rates in patients on metronidazole [40] and release of the Infectious diseases Society of America (IDSA) guidelines in 2017 metronidazole has made place for oral vancomycin as the first line drug in adult patients with first episode of CDI. In children however studies comparing the two are lacking and metronidazole continues to be recommended as the first line antibiotic for first episode of non-severe CDI. In pediatric patients with severe CDI or recurrence of CDI vancomycin is the recommended first line antibiotic [30]. There are also concerns for peripheral neuropathy with repeated or prolonged exposure to metronidazole.

Vancomycin

Orally administered vancomycin is not absorbed significantly in the small intestine and achieves fecal concentrations several- fold higher than the ratio of fecal concentration-to-maximum mean inhibitory concentration achieved with metronidazole making it an effective CDI antibiotic.

Vancomycin is now the recommended antibiotic of choice in adults for the first episode of CDI.

Either vancomycin or metronidazole is recommended for the treatment of initial episode or first recurrence of a non-severe CDI in children. However, for an initial severe episode of CDI, oral vancomycin is recommended over metronidazole (IDSA) [30,41].

Fidaxomicin

Fidaxomicin is minimally absorbed from the gut and has a very narrow spectrum of activity leading to minimal disruption of microbiota with its use. Randomized controlled trials comparing oral vancomycin to oral fidaxomicin for the treatment of CDI showed that resolution of diarrhea at end of treatment was similar in both groups however sustained clinical response (no recurrence 25 days after treatment) was superior for fidaxomicin [42,43]. Patients treated with fidaxomicin were also less likely to have acquisition and overgrowth of vancomycin-resistant *Enterococcus* and *Candida* species [41].

Based on these 2 large clinical trials and meta-analyses, fidaxomicin is recommended along with vancomycin as the drug of choice for an initial episode of CDI in adult patients by the IDSA. IDSA guidelines do not incorporate fidaxomicin for treatment of pediatric CDI, however a recent large multicenter, randomized, single-blind clinical trial showed that compared with vancomycin, fidaxomicin was well tolerated and demonstrated significantly higher rates of global cure (confirmed clinical response without CDI recurrence 30 days after the end of treatment) [44]. Fidaxomicin may thus be an attractive alternative to vancomycin in pediatric CDI however widespread use is limited due to cost considerations and lack of incorporation in national guidelines for pediatric CDI.

Other CDI antibiotics

Other agents that have been used for treatment but have less supportive evidence include nitazoxanide, fusidic acid, rifaximin, tigecycline, and bacitracin. Rifaximin has been studied as an adjunctive post vancomycin treatment regimen in patients with recurrent CDI and is recommended following a standard course of Vancomycin for second of subsequent recurrence of CDI in children [30].

Antibiotics in Fulminant CDI

Fulminant CDI is severe disease that may be characterized by hypotension, shock, ileus or megacolon. In such cases higher doses of oral vancomycin along with intravenous (IV) metronidazole is used [30,45]. There are also case reports suggesting that rectally administered vancomycin may be of benefit when ileus is present and this is thus also recommended [46,47] Both IV metronidazole and rectally administered vancomycin should be used in combination with oral vancomycin as rectal vancomycin does not reach the entire colon and treatment failures are reported with IV metronidazole alone [46,48-49]. Fulminant CDI may need may need surgical management if these measures fail.

Antibiotics in Recurrent CDI

Patients with IBD are 33% more likely to suffer recurrent CDI. The treatment of recurrent CDI beyond the first recurrence is often initiated through tapering and/or pulsed doses of vancomycin for 2-8 weeks [50,51]. Another strategy is the use of a "chaser" like rifaximin with a narrower spectrum of activity following vancomycin which still prevents CDI from relapsing while allowing the microbiota to recover [50]. As discussed above Fidaxomicin with its narrower spectrum of action is an alternative to vancomycin in patients with recurrent CDI and has demonstrated increased efficacy in preventing recurrence. If appropriate antibiotic treatment for at least two recurrences fails fecal microbiota transplantation can be considered.

Other agents

Intravenous Immunoglobulin

Lower antitoxin levels may in part contribute to CDI severity and this is the rationale behind use of intravenous immunoglobulin (IVIG) in patients with refractory disease. However, case series that report use of passive immunotherapy with IVIG have not shown convincing efficacy and no controlled trials have been performed [52]. IVIG may have a role in patients with IBD and underlying immunoglobulin deficiency.

Probiotics

Probiotics are theorized to work by restoring the balance of intestinal flora however they have not demonstrated convincing efficacy in the treatment of CDI. A Cochrane review found insufficient evidence to recommend probiotic therapy as an adjunct to antibiotic therapy for C. difficile colitis and no evidence to support the use of probiotics alone in the treatment of C. difficile colitis [53]. Further studies are necessary to determine if there is a role in CDI in patients with IBD. A large metaanalysis on the role of probiotics in preventing CDI found that probiotic prophylaxis may be a useful and safe CDI prevention strategy, particularly among participants taking 2 or more antibiotics and in hospital settings [54].

Bezlotoxumab

Bezlotoxumab, a monoclonal antibody directed against toxin B, has been approved as adjunctive therapy for adult patients who are receiving antibiotic treatment for CDI and who are at high risk for recurrence. In patients being treated for primary or recurrent CDI with antibiotics addition of bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo [55]. Bezlotoxumab was

more effective at reducing recurrences in patients who were *C. difficile* toxin positive via EIA testing than who were positive by PCR alone [56]. Studies in pediatrics are currently underway.

Fecal microbiota transplantation

There is increasing recognition of the critical role the microbiome plays in human health and disease. Changes in microbial composition are associated with immune dysregulation and have been linked to multiple diseases including inflammatory bowel disease, obesity, autoimmune diseases, cancer, and infections [57,58]. A recent study showed that adults with *C. difficile* colonization (CDC) and CDI have significantly decreased bacterial diversity compared to controls, however overall microbial composition was significantly different between control, CDC and CDI patients [59]. Strategies aimed at normalizing the gut microbiota include fecal microbiota transplantation (FMT) with donated stool delivered into the gut of an affected individual to restore the microbiota to a healthy state. Indeed, FMT has successfully been used in the management of recurrent CDI (rCDI) in adults with several high quality RCTs demonstrating efficacy, with cure rates approaching 90% [60-65]. Most large controlled studies have been performed in adults. However, many small case series and case reports indicate treatment success and safety in children with recurrent CDI comparable to adults. Recently NASPGHAN special interest group collected data on children with rCDI in the USA and showed that FMT was successful in 81% of the children after a first FMT and this number approached 90% when patients who received a second FMT were included [66]. Therefore, in carefully selected pediatric patients with rCDI (≥3 infections including a 6- to 8-week tapering course of CDI-directed antibiotics or at least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity) and those with severe or fulminant CDI without response to standard treatment for >48 hours FMT may be considered.

Vaccines

C. difficile vaccine is a novel toxoid vaccine developed by Sanofi Pasteur and currently under evaluation in global Phase III clinical trial. It consists of genetically and chemically detoxified, purified toxins A and B. It demonstrated good safety and immunogenicity in Phase I and Phase II trials in the USA [67,68]. It may be an option in the future especially for patients at high risk of developing severe CDI.

Surgical management

Patients with fulminant or complicated CDI who develop megacolon or colonic perforation require may require emergent surgery. The timing of surgery is debated however protracted antibiotic treatment in those with severe underlying disease may increase the likelihood of complications if the patient eventually needs surgery. Mortality in patients requiring surgery remains high (40–60%) owing to both the severity of illness and underlying IBD related comorbidity [69,70]. If surgical management is necessary for severely ill patients, subtotal colectomy with preservation of the rectum is recommended. Segmental resection or hemicolectomy have been associated with worse outcomes. The early involvement of the surgical team in patients with severe and fulminant CDI is associated with superior outcomes [71].

Managing immunosuppression

Management of concurrent immunosuppression can be challenging in patients with IBD who have CDI. Presentation of both IBD flare and CDI is often similar, but the treatment paths are markedly divergent with the escalation of immunosuppression for an IBD flare compared with reduction in immunosuppression in those with active CDI. Significant uncertainty exists among practitioners with regards to the initiation of corticosteroid therapy and its safety in the context of an ongoing CDI-mediated colitis.

Indeed, in a prior survey, the approach that seems to be favored by 56% of the American and Canadian gastroenterologists is to use both antibiotics and immunomodulators together whereas 46% would use antibiotics alone to treat the CDI [72]. Treating for both conditions however may not always be the best approach as shown in a multicenter study, which found increased risk of mortality in patients treated with both antibiotics and immunomodulators [73]. AGA expert review recommends postponing escalation of steroids in the setting of acute CDI until 72 to 96 hours after the initiation of appropriate antibiotic therapy [74]. It is our practice that we treat both clostridium difficile infection and the flare of IBD colitis simultaneously as this has resulted in the best outcome.

Conclusions and future directions

Multiple challenges exist in the diagnosis and management of CDI in pediatric patients with IBD. Recognition of C. *difficile* colonization versus active CDI is especially challenging given the high rates of asymptomatic *C. difficile* colonization rates in children with IBD. Similar clinical presentation further confounds the clinician's ability to make the distinction between acute flare of IBD and CDI. We have addressed in this review the current data and evidence available and the approach to diagnosis and management of CDI in patients with IBD, however there continues to be much uncertainty in multiple areas that would benefit from more data and further research.

FMT has shown great success in the management of CDI however the role of microbiome in IBD is more complex. A better understanding of the role of microbiota in patients with IBD with and without CDI is urgently needed and could significantly influence diagnostics and therapeutics. Further research is required to identify better diagnostic markers that differentiate the two conditions and optimal timing of immunosuppressive therapy. The hopes of *C. difficile* vaccine in the future will be an important step forward to protect patients with IBD from CDIs.

References

1. Viscidi RP, Bartlett JG (1981) Antibiotic-associated pseudomembranous colitis in children. *Pediatrics* 67: 381-386. [Crossref]

2. Lessa FC, Mu Y, Winston LG, Dumyati GK, Farley MM, et al. (2014) Determinants of Clostridium difficile Infection Incidence Across Diverse United States Geographic Locations. *Open Forum Infect Dis*. 1: ofu048.

3. McDonald LC, Killgore GE, Thompson A, Owens RC, Jr., Kazakova SV, et al. (2005) An epidemic, toxin gene-variant strain of Clostridium difficile. N Engl J Med 353: 2433-2441. [Crossref]

4. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, et al. (2005) A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med* 353: 2442-2449. [Crossref]

5. Warny M, Pepin J, Fang A, Killgore G, Thompson A, et al. (2005) Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. *Lancet* 366: 1079-1084. [Crossref]

6. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, et al. (2015) Burden of Clostridium difficile infection in the United States. *N Engl J Med* 372: 825-834. [Crossref]

7. Ananthakrishnan AN, McGinley EL, Binion DG (2008) Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. *Gut* 57: 205-210. [Crossref]

8. Issa M, Vijayapal A, Graham MB, Beaulieu DB, Otterson MF, et al. (2007) Impact of Clostridium difficile on inflammatory bowel disease. *Clin Gastroenterol Hepatol* 5: 345-351. [Crossref]

9. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 103: 1443-1450. [Crossref]

10. Jodorkovsky D, Young Y, Abreu MT (2010) Clinical outcomes of patients with ulcerative colitis and co-existing Clostridium difficile infection. *Dig Dis Sci* 55: 415-420. [Crossref]

11. Ananthakrishnan AN, McGinley EL, Saeian K, Binion DG (2011) Temporal trends in disease outcomes related to Clostridium difficile infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 17: 976-983.[Crossref]

12. Jen MH, Saxena S, Bottle A, Aylin P, Pollok RC (2011) Increased health burden associated with Clostridium difficile diarrhoea in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 33: 1322-1331. [Crossref]

13. Sandberg KC, Davis MM, Gebremariam A, Adler J (2015) Disproportionate rise in Clostridium difficile-associated hospitalizations among US youth with inflammatory bowel disease, 1997-2011. *J Pediatr Gastroenterol Nutr* 60: 486-492. [Crossref]

14. Bossuyt P, Verhaegen J, Van Assche G, Rutgeerts P, Vermeire S (2009) Increasing incidence of Clostridium difficile-associated diarrhea in inflammatory bowel disease. *J Crohns Colitis* 3: 4-7. [Crossref]

15. Clayton EM, Rea MC, Shanahan F, Quigley EM, Kiely B, et al. (2009) The vexed relationship between Clostridium difficile and inflammatory bowel disease: an assessment of carriage in an outpatient setting among patients in remission. *Am J Gastroenterol* 104: 1162-1169. [Crossref]

16. Ananthakrishnan AN, Binion DG (2010) Impact of Clostridium difficile on inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 4: 589-600. [Crossref]

17. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD (2007) Incidence of Clostridium difficile infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 5: 339-344. [Crossref]

18. Pascarella F, Martinelli M, Miele E, Del Pezzo M, Roscetto E, et al. (2009) Impact of Clostridium difficile infection on pediatric inflammatory bowel disease. *J Pediatr* 2009 154: 854-858. [Crossref]

19. Wultanska D, Banaszkiewicz A, Radzikowski A, Obuch-Woszczatynski P, Mlynarczyk G, et al. (2010) Clostridium difficile infection in Polish pediatric outpatients with inflammatory bowel disease. *Eur J Clin Microbiol Infect Dis* 29: 1265-12 70.[Crossref]

20. Mezoff E, Mann EA, Hart KW, Lindsell CJ, Cohen MB (2011) Clostridium difficile infection and treatment in the pediatric inflammatory bowel disease population. *J Pediatr Gastroenterol Nutr* 52: 437-441. [Crossref]

21. Mir SA, Kellermayer R (2013) Clostridium difficile infection in newly diagnosed pediatric inflammatory bowel disease in the mid-southern United States. *J Pediatr Gastroenterol Nutr* 57: 487-488. [Crossref]

22. Martinelli M, Strisciuglio C, Veres G, Paerregaard A, Pavic AM, et al. (2014) Clostridium difficile and pediatric inflammatory bowel disease: a prospective, comparative, multicenter, ESPGHAN study. *Inflamm Bowel Dis* 20: 2219-2225. [Crossref]

23. Melnik P, Soffair N, Matar M, Shamir R, Assa A (2021) Positivity of Stool Pathogen Sampling in Pediatric Inflammatory Bowel Disease Flares and Its Association With Disease Course. *J Pediatr Gastroenterol Nutr* 72: 61-66. [Crossref]

24. Goodhand JR, Alazawi W, Rampton DS (2011) Systematic review: Clostridium difficile and inflammatory bowel disease. *Aliment pharmacol Ther* 33: 428-441. [Crossref]

25. Pant C, Anderson MP, Deshpande A, Altaf MA, Grunow JE, et al. (2013) Health care burden of Clostridium difficile infection in hospitalized children with inflammatory bowel disease. *Inflamm Bowel Dis* 19: 1080-1085. [Crossref]

26. Loo VG, Bourgault AM, Poirier L, Lamothe F, Michaud S, et al. (2011) Host and pathogen factors for Clostridium difficile infection and colonization. *N Engl J Med* 365: 1693-1703. [Crossref]

27. Hutin Y, Casin I, Lesprit P, Welker Y, Decazes JM, et al. (1997) Prevalence of and risk factors for Clostridium difficile colonization at admission to an infectious diseases ward. *Clin Infect Dis* 24: 920-924. [Crossref]

28. Morgan DJ, Leekha S, Croft L, Burnham CA, Johnson JK, et al. (2015) The Importance of Colonization with Clostridium difficile on Infection and Transmission. *Curr Infect Dis Rep* 17: 499. [Crossref]

29. Ananthakrishnan AN, Oxford EC, Nguyen DD, Sauk J, Yajnik V, et al. (2013) Genetic risk factors for Clostridium difficile infection in ulcerative colitis. *Aliment Pharmacol Ther* 38: 522-530. [Crossref]

30. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, et al. (2018) 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* 66: 987-994. [Crossref]

31. Burnham CA, Carroll KC (2013) Diagnosis of Clostridium difficile infection: an ongoing conundrum for clinicians and for clinical laboratories. *Clinical microbiology reviews* 26: 604-630.

32. Eastwood K, Else P, Charlett A, Wilcox M (2009) Comparison of nine commercially available Clostridium difficile toxin detection assays, a real-time PCR assay for C. difficile tcdB, and a glutamate dehydrogenase detection assay to cytotoxin testing and cytotoxigenic culture methods. *J Clin Microbiol* 47: 3211-3217. [Crossref]

33. Berg AM, Kelly CP, Farraye FA (2013) Clostridium difficile infection in the inflammatory bowel disease patient. *Inflamm Bowel Dis* 19: 194-204. [Crossref]

34. Enoch DA, Butler MJ, Pai S, Aliyu SH, Karas JA (2011) Clostridium difficile in children: colonisation and disease. *J Infect* 63: 105-113. [Crossref]

35. Leibowitz J, Soma VL, Rosen L, Ginocchio CC, Rubin LG (2015) Similar proportions of stool specimens from hospitalized children with and without diarrhea test positive for Clostridium difficile. *Pediatr Infect Dis J* 34: 261-266. [Crossref]

36. Kelsen JR, Kim J, Latta D, Smathers S, McGowan KL, et al. (2011) Recurrence rate of clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 17: 50-55. [Crossref]

37. Kelly CP, LaMont JT (1998) Clostridium difficile infection. *Annu Rev Med* 49: 375-390. [Crossref]

38. Fekety R, Shah AB (1993) Diagnosis and treatment of Clostridium difficile colitis. *JAMA* 269: 71-75. [Crossref]

39. Farooq PD, Urrunaga NH, Tang DM, von Rosenvinge EC (2015) Pseudomembranous colitis. *Dis Mon* 61: 181-206. [Crossref]

40. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB (2007) A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 45: 302-307.

41. Nerandzic MM, Mullane K, Miller MA, Babakhani F, Donskey CJ (2012) Reduced acquisition and overgrowth of vancomycin-resistant enterococci and Candida species in patients treated with fidaxomicin versus vancomycin for Clostridium difficile infection. *Clin Infect Dis* 55: S121-126. [Crossref]

42. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, et al. (2011) Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med* 364: 422-431. [Crossref]

43. Lee C, Louie TJ, Weiss K, Valiquette L, Gerson M, et al. (2016) Fidaxomicin versus Vancomycin in the Treatment of Clostridium difficile Infection: Canadian Outcomes. *Can J Infect Dis Med Microbiol* 2016: 8048757. [Crossref]

44. Wolf J, Kalocsai K, Fortuny C, Lazar S, Bosis S, et al. (2019) 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* p. 71. [Crossref]

45. Debast SB, Bauer MP, Kuijper EJ, European Society of Clinical Microbiology and Infectious Diseases. (2014) European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect* 20: 1-26. [Crossref]

46. Apisarnthanarak A, Razavi B, Mundy LM (2002) Adjunctive intracolonic vancomycin for severe Clostridium difficile colitis: case series and review of the literature. *Clin Infect Dis* 35: 690-696.

47. Musgrave CR, Bookstaver PB, Sutton SS, Miller AD (2011) Use of alternative or adjuvant pharmacologic treatment strategies in the prevention and treatment of Clostridium difficile infection. *Int J Infect Dis* 15: e438-48. [Crossref]

48. Bublin JG, Barton TL (1994) Rectal use of vancomycin. *Ann pharmacother* 28: 1357-1358. [Crossref]

49. Olson MM, Shanholtzer CJ, Lee JT, Jr., Gerding DN (1994) Ten years of prospective Clostridium difficile-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982-1991. *Infect Control Hosp Epidemiol* 15: 371-381. [Crossref]

50. Bagdasarian N, Rao K, Malani PN (2015) Diagnosis and treatment of Clostridium difficile in adults: a systematic review. *JAMA* 313: 398-408. [Crossref]

51. McFarland LV, Elmer GW, Surawicz CM (2002) Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. *Am J Gastroenterol* 97: 1769-1775. [Crossref]

52. O'Horo J, Safdar N (2009) The role of immunoglobulin for the treatment of Clostridium difficile infection: a systematic review. *Int J Infect Dis* 13: 663-667. [Crossref]

53. Pillai A, Nelson R (2008) Probiotics for treatment of Clostridium difficile-associated colitis in adults. *Cochrane Database Syst Rev* 1: CD004611. [Crossref]

54. Johnston BC, Lytvyn L, Lo CK, Allen SJ, Wang D, et al. (2018) 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* 39: 771-781. [Crossref]

55. Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, et al. (2017) Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection. *N Engl J Med* 376: 305-317. [Crossref]

56. Wilcox MH, Rahav G, Dubberke ER, Gabryelski L, Davies K, et al. (2019) 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* p. 6. [Crossref]

57. Wu HJ, Wu E (2012) The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes* 3: 4-14. [Crossref]

58. Thaiss CA, Zmora N, Levy M, Elinav E (2016) The microbiome and innate immunity. *Nature* 535: 65-74. [Crossref]

59. Crobach MJT, Ducarmon QR, Terveer EM, Harmanus C, Sanders I, et al. (2020) The Bacterial Gut Microbiota of Adult Patients Infected, Colonized or Noncolonized by Clostridioides difficile. *Microorganisms* p. 8. [Crossref]

60. Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, et al. (2014) Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. *Clin Infect Dis* 58: 1515-1522. [Crossref]

61. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, et al. (2013) Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med* 368: 407-415. [Crossref]

62. Lee CH, Steiner T, Petrof EO, Smieja M, Roscoe D, et al. (2016) Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. *JAMA* 315: 142-149. [Crossref]

63. Cammarota G, Masucci L, Ianiro G, Bibbo S, Dinoi G, et al. (2015) Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. *Aliment Pharmacol Ther* 41: 835-843. [Crossref]

64. Malani PN, Rao K (2016) Expanded Evidence for Frozen Fecal Microbiota Transplantation for Clostridium difficile Infection: A Fresh Take. *JAMA* 315: 137-138. [Crossref]

65. Kassam Z, Lee CH, Yuan Y, Hunt RH (2013) Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. *Am J Gastroenterol* 108: 500-508. [Crossref]

66. Davidovics ZH, Michail S, Nicholson MR, Kociolek LK, Pai N, et al. (2019) 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* 68: 130-143. [Crossref]

67. Foglia G, Shah S, Luxemburger C, Pietrobon PJ (2012) Clostridium difficile: development of a novel candidate vaccine. *Vaccine* 30: 4307-4309. [Crossref]

68. de Bruyn G, Saleh J, Workman D, Pollak R, Elinoff V, et al. (2016) Defining the optimal formulation and schedule of a candidate toxoid vaccine against Clostridium difficile infection: A randomized Phase 2 clinical trial. *Vaccine* 34: 2170-2178. [Crossref]

69. Chan S, Kelly M, Helme S, Gossage J, Modarai B, et al. (2009) Outcomes following colectomy for Clostridium difficile colitis. *Int J Surg* 7: 78-81. [Crossref]

70. Longo WE, Mazuski JE, Virgo KS, Lee P, Bahadursingh AN, et al. (2004) Outcome after colectomy for Clostridium difficile colitis. *Dis Colon Rectum* 47: 1620-1626. [Crossref]

71. Hall JF, Berger D (2008) Outcome of colectomy for Clostridium difficile colitis: a plea for early surgical management. *Am J Surg* 196: 384-388. [Crossref]

72. Yanai H, Nguyen GC, Yun L, Lebwohl O, Navaneethan U, et al. (2011) Practice of gastroenterologists in treating flaring inflammatory bowel disease patients with clostridium difficile: antibiotics alone or combined antibiotics/immunomodulators? *Inflamm Bowel Dis* 17: 1540-1546. [Crossref]

73. Ben-Horin S, Margalit M, Bossuyt P, Maul J, Shapira Y, et al. (2009) Combination immunomodulator and antibiotic treatment in patients with inflammatory bowel disease and clostridium difficile infection. *Clin Gastroenterol Hepatol* 7: 981-987. [Crossref]

74. Khanna S, Shin A, Kelly CP (2017) Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol* 15: 166-174. [Crossref]