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Review Article

Clostridioides difficile Infection: A Review of Emerging Practices for Infection Treatment and Prevention of Recurrence

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Abstract

Clostridioides difficile infection (CDI) is associated with significant morbidity and mortality and carries a high risk of recurrence. Given the substantial healthcare burden and the evolving nature of CDI, understanding the role of emerging treatment strategies is essential. While oral vancomycin remains a mainstay of CDI treatment, the past decade has brought several notable advances in agents and practices that may be used for CDI treatment and prevention. Fidaxomicin or vancomycin are now recommended for an initial episode of CDI, with several guidelines giving preference to fidaxomicin based on its demonstrated ability to reduce recurrent CDI. Promising developments have emerged regarding the use of fecal microbiota-based therapies in the management of CDI, including conventional fecal microbiota transplantation and the approved live biotherapeutic products, Rebyota and Vowst. These therapies help restore the microbiota of the colon to treat severe CDI and prevent recurrence in select patients. Several strategies have emerged to prevent recurrent CDI, including bezlotoxumab, a single-dose, weight-based IgG1 monoclonal antibody that may be given to patients at high risk of recurrence. Additional pipeline therapies, such as vaccines, beta-lactamases, and bacteriophages, may provide future opportunities for CDI management. This narrative review aimed to summarize societal guideline recommendations for CDI management, describe the evidence for key therapies used in CDI treatment, and review recent updates on emerging treatment modalities.

Introduction

Clostridioides difficile (C. difficile) is a spore-forming, gram-positive, anaerobic, toxin-producing bacillus. *C. difficile* infection (CDI) is one of the most common healthcare-associated infections and is associated with significant morbidity and mortality.[1,2] The presentation of CDI is heterogeneous, ranging from asymptomatic carriage to life-threatening colitis. CDI can present as mild to diffuse diarrhea, severe colitis, and toxic megacolon.[3] Most commonly, patients experience cramping abdominal pain with mild to moderate diarrhea, followed by recovery within three to five days of antimicrobial therapy.[4] Risk factors for CDI include antibiotic use, female gender, advanced age, select comorbidities (renal disease, liver disease, rheumatoid arthritis, multiple sclerosis, diabetes, and inflammatory bowel disease), immunosuppressed status, recent hospitalization, and a history of corticosteroid, proton pump inhibitor, or lipid-lowering therapy use.[3] The risk of recurrent CDI is high, with 20% to 30% of patients developing a recurrent infection within two weeks of completing therapy. The rate of additional recurrences doubles after two or more recurrences.[5] This is partly due to the ability of *C. difficile* spores to germinate into toxin-producing vegetative cells after cessation of antibiotic therapy.[2] The incidence of CDI and associated hospitalizations increased in the early 2000s, largely due to the emergence of the epidemic BI/NAP1/027 strain and the introduction of more sensitive *C. difficile* assays, such as nucleic acid amplification tests.[6,7] This has led to a significant expansion of efforts by the Centers for Disease Control and Prevention and the Department of Health and Human Services to monitor changes in the epidemiology of CDI and reduce the incidence and burden of disease.[6,8,9] Given the substantial healthcare burden and the evolving nature of CDI, understanding the appropriate treatment measures and strategies for preventing recurrent

Keywords: *Clostridioides difficile*; Clostridium difficile; *Clostridioides difficile* infection; Clostridium difficile infection; Infectious diseases; Fidaxomicin; Fecal microbiota transplant; Fecal microbiome transplantation; Bezlotoxumab.

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Table 1. Guideline recommended treatments for *Clostridioides difficile* infection

	IDSA/SHEA recommendations	ESCMID recommendations	ACG recommendations
Primary CDI	Fidaxomicin 200 mg BID × 10 days (preferred); Vancomycin 125 mg QID × 10 days (alternative); Metronidazole 500 mg TID × 10–14 days (alternative for non-severe CDI, if Fidaxomicin and Vancomycin unavailable); [a]Consider Bezlotoxumab 10 mg/kg	Fidaxomicin 200 mg BID × 10 days (SoC 1st line); Vancomycin 125 mg QID × 10 days (SoC 2nd line); Metronidazole 500 mg TID × 10 days (if SoC unavailable). If High Risk of Recurrence: Fidaxomicin 100 mg BID × 10 days (1st line) Add Bezlotoxumab to SoC regimen (2nd line)	Non-Severe Treatment Options: Vancomycin 125 mg QID × 10 days; Fidaxomicin 200 mg BID × 10 days; Metronidazole 500 mg TID × 10 days (for low-risk patients only). Severe Treatment Options: Vancomycin 125 mg QID × 1 0 days; Fidaxomicin 200 mg BID × 10 days; FMT; [b]Bezlotoxumab 10 mg/kg
First recurrence	Fidaxomicin 200 mg BID × 10 days (preferred); Fidaxomicin 200 mg BID × 5 days, then daily every other day × 20 days (preferred); Vancomycin taper and pulse (alternative) Vancomycin 125 mg QID x10 days (alternative if metronidazole used for primary CDI); Bezlotoxumab in patients with a CDI episode in the past six months	If Fidaxomicin Used for Primary CDI: SoC + Bezlotoxumab (1st line). If Vancomycin Used for Primary CDI: Fidaxomicin 200 mg BID × 10 days (2nd line). Preferred Options Unavailable: Vancomycin taper and pulse	Vancomycin taper and pulse; Fidaxomicin 200 mg BID × 10 days (unless Fidaxomicin used for primary CDI); [b]Bezlotoxumab 10 mg/kg
Second or Subsequent Recurrence	Fidaxomicin 200 mg BID × 10 days (preferred); Fidaxomicin 200 mg BID × 5 days, then daily every other day × 20 days (preferred); Vancomycin taper and pulse (alternative); Vancomycin 125 mg QID × 10 days, then rifaximin 400 mg TID × 20 days (alternative); FMT (alternative); Bezlotoxumab in patients with a CDI episode in the past six months	SoC + Bezlotoxumab for Recurrence: FMT (1st line). Fidaxomicin for Recurrence: FMT (1st line); SoC + Bezlotoxumab (2nd line). Preferred Options Unavailable: Vancomycin taper and pulse	FMT; [b]Bezlotoxumab 10 mg/kg
Fulminant CDI	Vancomycin 500 mg QID PLUS metronidazole IV 500 mg TID; Add vancomycin rectal 500 mg in 100 mL saline QID if ileus present	Vancomycin or Fidaxomicin; Multidisciplinary approach with surgical consult; Consider Tigecycline IV and FMT when refractory	Vancomycin 500 mg QID PLUS Metronidazole IV 500 mg TID; Add vancomycin rectal 500 mg QID (if ileus present); FMT

[a]Consider in patients who are age ≥ 65 years, immunocompromised, or have severe CDI. [b]Add Bezlotoxumab in patients age ≥ 65 years who have one of the following: CDI within the past six months, are immunocompromised, or have severe CDI. ACG, American College of Gastroenterology; BID, twice daily; CDI, *Clostridioides difficile* infection; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; FMT, fecal microbiota transplantation; IDSA, Infectious Disease Society of America; IV, intravenous.; QID, four times daily; SHEA, Society for Healthcare Epidemiology of America; SoC, standard of care; TID, three times daily.

infections is paramount. While oral vancomycin remains a mainstay of CDI treatment, the past decade has brought several notable advances in agents and practices for CDI treatment and prevention. As such, understanding the role of each agent and the evidence supporting its use is essential. This narrative review aimed to summarize societal guideline recommendations for CDI management, describe the evidence for key therapies used in CDI treatment, and review recent updates on emerging treatment modalities.

Treatment measures

The recommendations for the preferred agent in the initial management of CDI have evolved over the past decades, particularly in the management of non-severe CDI.[10–12] This evolution has largely been driven by emerging data on differences in treatment success based on disease severity, as well as differences in sustained response and the risk of disease recurrence between agents.[13,14] In 2021, the Infectious Diseases Society of America (IDSA), in conjunction with the Society for Healthcare Epidemiology of America (SHEA), the American College of Gastroenterology (ACG), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), each published updated clinical practice guidelines for the management of CDI.[10–12] Treatment selection in CDI is primarily based on disease severity, with CDI classified as non-severe, severe, or fulminant (severe complicated).[10–12] Guideline treatment recommendations are summarized in Table 1 and are discussed in further detail below.

Treatment of an initial CDI episode: fidaxomicin vs. vancomycin

Fidaxomicin and oral vancomycin are the recommended agents for the management of an initial episode of CDI. Both agents have minimal systemic absorption, concentrate well in the gut lumen, and have a low incidence of adverse effects.[10–12] Fidaxomicin is available as a 200 mg tablet and oral suspension, typically given twice daily, although extended dosing schemes have been studied and are described below.[15,16] Oral vancomycin is available as an oral suspension as well as capsules and is given four times daily.[17,18] Both medications are typically administered for 10 days in cases of non-severe CDI.[10–12] One of the most notable updates in the most recent IDSA and ESCMID guidelines is the preference for fidaxomicin over oral vancomycin in this setting, although the ACG guidelines do not favor one agent over the other.[10–12] Fidaxomicin is a macrolide antibiotic that binds to RNA polymerase to inhibit RNA synthesis. It possesses a narrower spectrum of activity compared to oral vancomycin.[19] Additionally, it has limited activity against other enteric commensal bacteria, preserves the intestinal microbiome during therapy, and reduces toxin re-expression.[20] These properties have translated into improved sustained clinical

response and lower recurrence rates for fidaxomicin compared to oral vancomycin. A meta-analysis of two pivotal trials compared cure rates, sustained response, and recurrence rates for fidaxomicin versus vancomycin in CDI.[13] This study found that fidaxomicin demonstrated noninferiority to vancomycin for clinical cure, and superiority to vancomycin for CDI recurrence and global cure ($p < 0.0001$). The study noted a 37% reduction in persistent diarrhea or death through day 12 in the fidaxomicin group, demonstrating the potential for substantially improved outcomes with fidaxomicin compared to vancomycin.[13] More recently, Guery and colleagues evaluated the utility of an extended-pulsed regimen of fidaxomicin to facilitate sustained clinical cure through prolonged *C. difficile* suppression and gut microbiota recovery.[16] Patients received an extended-pulsed regimen of fidaxomicin (200 mg twice daily on days 1–5, followed by once daily on alternate days from days 7–25) compared to oral vancomycin (125 mg capsules four times daily for 10 days). Investigators found that significantly more patients who received extended-pulsed fidaxomicin achieved sustained clinical cure 30 days after completion of therapy compared to those in the oral vancomycin group (70% *vs.* 59%, $p = 0.03$). They also noted a decrease in recurrence with the extended-pulsed fidaxomicin regimen compared to that seen with standard dosing regimens in prior studies.[16] No studies have directly compared standard and extended-pulsed fidaxomicin dosing.[16] The IDSA/SHEA guidelines note that, although fidaxomicin is well-tolerated and effective, it is cost-prohibitive without adequate insurance coverage, limiting its widespread use in some practice settings. Although fidaxomicin is now recommended as the preferred agent for an initial CDI episode, both the IDSA/SHEA and ESCMID recommend vancomycin as an acceptable alternative when fidaxomicin is not available.

Treatment of severe CDI

Severe CDI is defined by the IDSA/SHEA and ACG as CDI, along with an increase in white blood cell count to ≥15,000 cells per microliter or a serum creatinine level of >1.5 mg per deciliter. These factors are considered predictive of unfavorable outcomes.[10,11] ESCMID guidelines provide additional criteria for the consideration of severe CDI, such as distension of the large intestine, pericolonic fat stranding, or colonic wall thickening on imaging.[12] It is important to note that current literature does not clearly define whether fidaxomicin or vancomycin should be preferred for the management of an initial episode of severe CDI. Most of the currently available data favoring fidaxomicin over vancomycin in severe CDI is derived from subgroup analyses of studies involving the treatment of initial CDI episodes with infections ranging from mild to moderate severity. Therefore, societal guidelines do not provide differing recommendations for which agent should be preferred in severe initial episodes of CDI.[10–12] In one study of patients receiving fidaxomicin or vancomycin for CDI, there was no significant difference in clinical cure at the end of therapy between the groups. However, in a subgroup analysis of patients with severe CDI, there was a lower risk of recurrence in the fidaxomicin group compared to the vancomycin group (13.0% *vs.* 26.6%, $p = 0.05$) when using a modified intention-to-treat analysis.[19] In contrast, a retrospective propensity-score matched analysis in Veterans Affairs patients compared fidaxomicin to vancomycin in severe CDI patients. No difference was found between fidaxomicin and vancomycin for the combined outcome of clinical failure or 90-day recurrence (31.9% *vs.* 25.5%), but there was a higher incidence of clinical failure in the fidaxomicin group compared to the vancomycin group (9.39% *vs.* 1.41%, $p < 0.001$).[21] The optimal agent for the initial treatment of severe CDI is still unclear, and further prospective randomized-controlled trials are needed to determine the best approach. It should also be noted that guidelines recommend against the use of metronidazole for severe CDI.[11,22] In patients with severe CDI who are not responding to therapy, fecal microbiota-based therapies may be considered, as recommended by the American Gastroenterological Association, which is discussed in further detail below.[23]

Management of fulminant CDI

Fulminant CDI is defined as meeting the criteria for severe CDI, in addition to hypotension, shock, ileus, or megacolon.[10,11] For fulminant CDI, guidelines recommend high-dose oral vancomycin (500 mg four times daily, by mouth or nasogastric tube). If ileus is present, rectal instillation of vancomycin should be considered. Intravenous metronidazole should be administered in addition to oral vancomycin in this setting.[10,11] The recommended addition of intravenous metronidazole is largely based on a small, retrospective, single-center study by Rokas and colleagues, which demonstrated that adding intravenous metronidazole to oral vancomycin in critically ill patients resulted in a significant decrease in mortality compared to oral vancomycin monotherapy (15.9% *vs.* 36.4%, $p = 0.03$).[24] The higher recommended dose of vancomycin (500 mg four times daily) is not primarily based on outcomes data but rather on expert opinion, which suggests that the potential benefit outweighs any risks, especially in the absence of evidence that this intervention is harmful.[10,11] There is supporting data showing that fecal concentrations of vancomycin increase proportionally with higher oral doses, leading to higher concentrations of vancomycin in the stool.[25] Fidaxomicin is not recommended by the IDSA/SHEA or ACG for the management of fulminant CDI.[10,11] These guidelines note a lack of data on fidaxomicin in this setting, as fulminant CDI is uncommon, and most of the studies cited above excluded patients with fulminant CDI. ESCMID guidelines, however, list fidaxomicin as a potential option for the management of fulminant disease, although they emphasize the lack of clear evidence demonstrating superiority of fidaxomicin over vancomycin in this context.[12] The optimal treatment regimen for fulminant disease remains an area that warrants further study.

A decreased role for metronidazole in CDI

The role of oral metronidazole in the initial management of CDI has declined over time. While a course of oral metronidazole was previously recommended as a low-cost first-line treatment for non-severe CDI, literature has demonstrated metronidazole's inferiority to oral vancomycin in patients with severe CDI.[14] A trial conducted by Zar and colleagues compared vancomycin and metronidazole for the treatment of CDI and stratified patients by disease severity. Overall, there was no significant difference between metronidazole and vancomycin in clinical cure rates (90% *vs.* 98%, $p = 0.36$).[14] However, among patients with severe CDI, clinical cure was significantly lower in the metronidazole group compared to the vancomycin group (76% *vs.* 97%, $p = 0.02$). There was a similar incidence of recurrent symptoms between the groups.[14] More recently, Stevens and colleagues compared the effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with CDI.[26] They found no difference in recurrence between patients treated with vancomycin or metronidazole based on disease severity. However, vancomycin significantly reduced the risk of all-cause 30-day mortality compared to metronidazole, which was largely driven by a decrease in mortality among patients with severe CDI (15.3% *vs.* 19.8%, $p = 0.01$).[26]

Table 2. AGA guideline recommendations for fecal microbiota-based therapies in CDI

Patient population	Recommendation details	Certainty of evidence
Immunocompetent adults with nonsevere, nonfulminant recurrent CDI	Suggests the use of fecal microbiota-based therapies (conventional FMT or LBPs) upon the completion of standard of care antibiotics after a second recurrence (third episode) of CDI or in select patients at high risk of either recurrent CDI or a morbid CDI recurrence	Conditional recommendation, low certainty of evidence
Mildly or moderately immunocompromised adults with recurrent CDI	Suggests the use of conventional fecal microbiota transplant upon completion of standard of care antibiotics	Conditional recommendation, very low certainty of evidence
Severely immunocompromised* adults with recurrent CDI	Suggests against the use of fecal microbiota-based therapies upon completion of standard of care antibiotics	Conditional recommendation, very low certainty of evidence
Adults hospitalized with severe or fulmionant CDI not responding to antibiotics	Suggests the use of conventional fecal microbiota transplant over no fecal microbiota transplant in hospitalized patients not responding to standard of care antibiotics, generally within two to five days after initiating CDI treatment	Conditional recommendation, very low certainty of evidence

*Severely immunocompromised includes patients receiving active cytotoxic therapy for solid tumors and hematologic malignancies, patients who have received chimeric antigen receptor T-cell therapy or hematopoietic cell transplant (only when neutropenic), any form of neutropenia, patients with severe primary immunodeficiency, and patients with advanced or untreated HIV infection. AGA, American Gastroenterological Association; CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; LBPs, live biotherapeutic products.

Metronidazole is now recommended only for non-severe CDI in patients who cannot tolerate oral vancomycin or fidaxomicin, or when preferred therapies are unavailable.[10–12] Guidelines do not recommend the use of oral metronidazole in patients with severe CDI. Intravenous metronidazole is recommended by the IDSA/SHEA and ACG as part of the management of fulminant CDI, as discussed above.[10,11]

Fecal-microbiota transplantation in CDI treatment

Fecal microbiota transplantation (FMT) is a treatment modality that has only recently been endorsed by societal guidelines for the management of severe and fulminant CDI.[23] Antibiotics such as oral vancomycin and fidaxomicin can eradicate toxin-producing *C. difficile* bacteria but do not kill *C. difficile* spores, which can germinate into toxin-producing vegetative cells after antibiotic treatment is completed.[2] Conventional FMT refers to the process in which a fecal solution from a donor is administered into the gastrointestinal (GI) tract of a recipient via colonoscopy, enema, capsule, or other methods.[27] This procedure helps restore colonic homeostasis.[28] Recently published guidelines by the American Gastroenterological Association (AGA) provide recommendations that include the use of FMT in patients with CDI.[23] A summary of the AGA guideline recommendations for the use of FMT in CDI patients is provided in Table 2. For adult patients hospitalized with severe or fulminant CDI who are not responding to antimicrobial therapy, the AGA suggests the use of conventional fecal microbiota transplant over no transplant.[23] This recommendation applies only to conventional FMT and does not include live biotherapeutic products (LBPs), which are discussed in further detail under prevention of recurrence. The AGA notes that this recommendation is based on five observational studies involving 647 patients with severe or fulminant CDI, comparing conventional FMT with standard of care, including colectomy. FMT treatment was associated with a reduced risk of mortality compared to standard care (RR = 0.37), a finding consistent in both severe and fulminant CDI.[23] No increase in serious adverse events was observed in these studies, but the AGA emphasizes that the use of FMT in this setting warrants shared decision-making with a multidisciplinary team, including surgical colleagues, to acknowledge the low certainty of evidence and consider alternative therapies.[23] Other societal guidelines provide varying recommendations on the utility of FMT in patients with severe and fulminant CDI. The ACG recommends FMT be considered in severe and fulminant CDI refractory to standard care antibiotics, ESCMID suggests FMT as a rescue therapy for patients with fulminant CDI who have deteriorated, and the IDSA/SHEA does not comment on the use of FMT in an initial CDI episode.[10–12] Further studies are needed to elucidate the role of FMT in managing primary CDI episodes.

Treatment of recurrent CDI (rCDI)

rCDI is typically defined as the recurrence of diarrhea with a positive confirmatory test for CDI within eight weeks after treatment of an initial episode.[11] Infection recurrence is common in patients with CDI, and the risk of subsequent recurrences increases with each episode. Therefore, in the setting of rCDI, guidelines emphasize therapies that can prevent further recurrences. The 2021 IDSA/SHEA CDI guidelines recommend fidaxomicin (given as a standard or extended-pulsed dosing regimen) for patients with recurrent CDI episodes, rather than a standard course of vancomycin. However, they list oral vancomycin as an acceptable alternative, either in a tapered and pulsed regimen or a standard course, for a first recurrence.[10] As discussed above, fidaxomicin has been shown in three studies to reduce the risk of recurrence compared to standard courses of vancomycin.[13,16] The pooled analysis of these fidaxomicin studies demonstrated that fidaxomicin had a higher sustained response at 30 days after the end of therapy compared with vancomycin (RR = 1.27).[10] Additionally, the EXTEND study of extended-pulsed fidaxomicin versus oral vancomycin, which included patients with one or two prior CDI episodes, demonstrated a non-significant trend towards improved sustained clinical response in patients who received fidaxomicin compared to vancomycin. The EXTEND study also reported a notably low rate of recurrent CDI (2%) at 40 days in the extended-pulsed fidaxomicin arm.[16] The IDSA/SHEA concludes that the overall balance of benefits and harms favors the use of fidaxomicin over vancomycin (low certainty of evidence).[10] The IDSA/SHEA also lists rifaximin as an option for patients with multiple recurrences of CDI, to be used as follow-up therapy after a standard course of vancomycin. This practice was shown to be

potentially beneficial in the RAPID study, where investigators randomized patients with CDI who had been successfully treated with vancomycin or metronidazole to receive follow-up treatment with rifaximin or placebo after their standard antibiotics. Rifaximin was given 400 mg three times a day for two weeks, followed by 200 mg three times a day for an additional two weeks. Recurrence at 12 weeks was lower in the rifaximin arm (13.7%) compared to placebo (29.5%), although investigators failed to meet the statistical power in this study ($p = 0.06$).[29]

ACG recommendations for rCDI are similar to those made by the IDSA/SHEA. They recommend either a tapering-pulse vancomycin regimen or fidaxomicin for patients experiencing a first recurrence of CDI. However, they recommend against using fidaxomicin if it was used during the initial course of therapy.[11] The ACG concurs with the IDSA/SHEA's assessment that multiple studies have demonstrated a decrease in recurrence with fidaxomicin compared to a standard course of vancomycin but notes that there is no data comparing tapering-pulsed vancomycin to fidaxomicin.[11] The evidence supporting the use of tapering-pulsed vancomycin in the management of CDI is limited, but societal guidelines recommend it as an appropriate option for rCDI. Vancomycin tapered and pulsed regimens were shown to be safe and effective in a retrospective study by Sirbu and colleagues.[30] They studied tapering-pulsed regimens in 100 patients with rCDI. After a taper of oral vancomycin to once-daily dosing, patients either received every-other-day (QOD) vancomycin dosing or QOD followed by every third-day dosing (Q3D). Patients who received Q3D dosing had a significantly longer duration of treatment than the QOD group (86 days *vs.* 60 days), but the cure rate was higher for the Q3D group compared to the QOD group (81.1% *vs.* 61.1%, $p = 0.03$).[30] Finally, both the ACG and IDSA/SHEA recommend that bezlotoxumab be considered in addition to antibiotic therapy for patients with recurrence within six months.[10,11] Bezlotoxumab is discussed further under prevention of recurrence.

CDI in special populations

Older adults

Certain patient populations, such as older adults, children, and immunosuppressed individuals, may face higher risks, increased severity, and worse outcomes from CDI. Advanced age is a major risk factor for developing CDI and is associated with increased morbidity and mortality, as well as a higher risk of recurrence.[31,32] Older adults are particularly vulnerable to CDI due to several factors, including underlying health conditions, frequent antibiotic exposure, and reduced gut microbiota diversity. These individuals often suffer from multiple comorbidities, which not only increase their risk of infection but also complicate CDI treatment and recovery.[31,33] The risk of CDI in elderly patients is increased during systemic antimicrobial therapy and within a month thereafter.[31,33] Therefore, discontinuing unnecessary antibiotics is essential in treating CDI in older adults.[31] The antimicrobials with the highest risk include cephalosporins, clindamycin, and fluoroquinolones.[33] For elderly patients with CDI, therapeutic decisions should be guided by the severity of CDI, underlying comorbidities, and the patient's goals of care.[33] Further research is needed to identify poor prognostic indicators in the elderly and validate interventions that may improve outcomes in this population.[33]

Children

Although CDI is less common in children, its incidence has increased over time.[34] Despite recent progress in understanding the epidemiology, risk factors, and management of CDI in children, much of current practice is still adapted from adult studies. In contrast to CDI in adults, infection in children is most commonly community-associated.[34] The prevalence of *C. difficile* in the stools of children varies by age, with the incidence of infant asymptomatic carriage exceeding 40% within the first year.[35] For unclear reasons, infants appear protected from clinical disease, with some theorizing that infants lack the receptors for binding *C. difficile* toxins.[34] The high incidence of asymptomatic colonization among the pediatric population makes it challenging to differentiate between active disease and asymptomatic carriage.[36] Certain pediatric populations, such as those with inflammatory bowel disease, cystic fibrosis, cancer, and transplant recipients, are predisposed to higher rates of colonization, which serves as a risk factor for subsequent infection and diarrhea.[34] However, diarrhea in children with these chronic diseases may be multifactorial, complicating the separation of CDI from other causes of diarrhea.[35] Recurrent CDI is as common in children as in adults, occurring in approximately 20% to 30% of cases.[34] The 2017 IDSA and SHEA guidelines recommend using either metronidazole or vancomycin for the treatment of children with an initial episode of non-severe CDI, with preference given to oral vancomycin in cases of severe CDI.[22] Although severe CDI is poorly defined in children and less common compared to adults, it occurs in up to 8% of children with CDI.[37] Guidelines note a lack of high-quality evidence to guide the preference for vancomycin over metronidazole in children with non-severe cases, but suggest that the decision should balance the positive experience with metronidazole in children with emerging data indicating a potential advantage for vancomycin.[22] Fidaxomicin has also been approved for the treatment of CDI in children aged six months and older.[34] The SUNSHINE study, the first clinical trial conducted in children with CDI, randomized 142 children to receive either fidaxomicin or vancomycin for 10 days.[38] The median age of participants was 60 months in the fidaxomicin group compared to 48 months in the vancomycin group. There was no difference in clinical response at the end of therapy between groups; however, the fidaxomicin group had a higher rate of sustained response at 30 days following the end of therapy (68%) compared with vancomycin (50%).[38] Societal guidelines have not yet addressed the use of fidaxomicin in children. There is minimal evidence for the use of FMT in children, though one case report described the successful use of FMT in an eight-year-old child with cystic fibrosis.[39] Despite the decreased severity of disease among children, they may still serve as a means of transmission of *C. difficile*, making infection control practices essential.[34]

Immunocompromised hosts

Immunocompromised individuals, such as those receiving chemotherapy, solid organ transplant recipients, and those with human immunodeficiency virus, are at an increased risk for CDI. The incidence of CDI in hematology-oncology patients is higher than in the general population and ranges from 6% to 33%.[40] Additionally, immunocompromised hosts are more likely to experience severe CDI compared to the general population.[41] Given that these populations frequently experience diarrhea due to other causes such as antibiotic exposure, graft-*vs*-host disease, chemotherapy, and mucositis, it can be difficult to differentiate *C. difficile* diarrhea from diarrhea caused by other factors.[42] Therefore, IDSA guidelines recommend the use of a toxin assay as part of a multistep diagnostic algorithm to differentiate *C. difficile* colonization from active CDI.[22] *C. difficile*-colonized patients are likely to be nucleic acid amplification test positive, making a toxin assay ben-

Table 3. Guideline recommendations on interventions for the prevention of *Clostridioides difficile* infection and recurrence

	IDSA/SHEA recommendations	ESCMID recommendations	ACG recommendations
Antibiotics for secondary prevention of CDI (Oral Vancomycin Prophylaxis)	Insufficient evidence	Consider in select patients with multiple recurrences	OVP in patients who cannot do FMT or require frequent antibiotics. Consider OVP in patients at high risk of recurrence
Bezlotoxumab	In certain patients with recurrent infection in the past six months	First and subsequent recurrences	In certain patients at high risk for recurrence
FMT	Consider for ≥2 recurrences	Consider for ≥2 recurrences	Consider for ≥2 recurrences
Discontinuation of Acid suppression with proton pump inhibitors	Insufficient evidence to recommend discontinuation as a prevention measure	Review use	Recommends against discontinuation if an appropriate indication exists
Probiotics for primary prevention	Insufficient evidence	Not routinely recommended	Not recommended

Please refer to the shonna.mcbride@emory.edu for further details. ACG, American College of Gastroenterology; CDI, *Clostridioides difficile* infection; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; FMT, fecal microbiota transplantation; IDSA, Infectious Disease Society of America; OVP, oral vancomycin prophylaxis; SHEA, Society for Healthcare Epidemiology of America.

eficial in this setting.[40] Of particular concern is the risk of poor outcomes from CDI in immunosuppressed hosts, with studies demonstrating an increase in mortality as well as additional markers of morbidity, such as renal failure, bloodstream infections, and pneumonia.[43] There are no specific recommendations for initial agent selection in immunocompromised individuals due to a lack of high-quality data, with most studies being retrospective, single-center studies. Therefore, treatment in this setting typically mirrors guideline recommendations for immunocompetent individuals.[40] CDI recurrence may be higher among immunocompromised individuals. In a study of 100 patients with hematologic malignancies, 41% experienced CDI recurrence, with severe CDI and salvage lymphoma chemotherapy identified as factors associated with recurrence.[44] In immunocompromised adults with recurrent *C. difficile*, the AGA recommends the use of conventional FMT after the completion of standard of care antibiotics.[23] This recommendation applies only to mildly or moderately immunocompromised adults, while the AGA recommends against the use of FMT in severely immunocompromised adults. They define severely immunocompromised patients as those receiving active cytotoxic therapy for solid tumors and hematologic malignancies, those who have received chimeric antigen receptor T-cell therapy or hematopoietic cell transplantation (only when neutropenic), any neutropenia, patients with severe primary immunodeficiency, or patients with advanced or untreated human immunodeficiency virus infection.[23] The AGA made this recommendation based on observational studies of FMT in immunocompromised individuals, which found similar rates of prevention of CDI recurrence compared to RCTs that evaluated FMT in immunocompetent individuals. Many of these observational studies excluded severely immunocompromised patients.[23]

Prevention of CDI and recurrence

Given that approximately 35% of patients who experience CDI will develop rCDI, and that 65% of those who experience at least one recurrence will suffer a subsequent recurrence, identifying and implementing strategies to prevent rCDI is essential.[45] The following section reviews societal guideline recommendations and emerging trends for rCDI prevention. Societal guideline recommendations are summarized in Table 3.

Emerging data for fecal microbiota-based therapies

Perhaps the most exciting recent developments in the realm of rCDI prevention are related to fecal microbiota-based therapies, including conventional FMT and emerging LBPs. Antibiotics such as oral vancomycin and fidaxomicin can eradicate toxin-producing *C. difficile* bacteria, but they do not kill *C. difficile* spores, which can germinate into toxin-producing vegetative cells after antibiotic treatment is complete.[2] Following standard-of-care antibiotics, the gut microbiota is typically at its most deficient state, necessitating regrowth to replace the preexisting *Bacteroides* and *Firmicutes*.[46] A sustained clinical response to CDI is dependent on restoring the host microbiome, which can be achieved with FMT. FMT has been found to be highly effective in the treatment of recurrent and refractory CDI. A systematic review with meta-analysis of 37 studies conducted by Quraishi and colleagues found that FMT was more effective than vancomycin in resolving recurrent and refractory CDI (RR = 0.23), with a clinical resolution across all studies of 92%.[47] FMT has been found to be overall well tolerated, with short-term adverse effects typically consisting of mild GI symptoms such as abdominal pain, bloating, constipation, diarrhea, flatulence, nausea, and vomiting.[47,48] Certain routes of administration may confer a more benign adverse effect profile, with capsules and enemas being better tolerated than colonoscopy.[27] The long-term adverse effects of conventional FMT have not yet been clearly established. Notably, there have been cases reported of pathogenic bacteria being transmitted via FMT, so proper screening of donor stool is essential.[49] Donor stool may be screened for viral pathogens, parasites, and pathogenic bacteria, including resistant strains of *Escherichia coli*. The most recent IDSA/SHEA, ACG, and ESCMID guidelines, published in 2021, recommend FMT after at least the second recurrence of CDI, to be administered after the completion of standard-of-care antibiotics.[10–12] However, more recent data and agent approvals, including novel LBPs, demonstrate increased promise for the utility of fecal microbiota-based therapies in rCDI prevention.

Two novel LBPs, fecal microbiota live-jslm (Rebyota) and fecal microbiota spores live-brpk (Vowst), were approved by the FDA in November 2022 and April 2023, respectively. LBPs differ from conventional FMT in that they require extensive screening, good manufacturing practices, and clinical trials prior to approval.[2] Re-

byota (previously known as RBX2660) contains *Bacteroides* and was the first LBP approved as a result of the PUNCH CD3 study.[50] The PUNCH CD3 study randomized participants with rCDI (defined as one or more recurrences after a prior episode) to receive RBX2660 (Rebyota) or placebo, each administered rectally after a washout period of 24–72 h following completion of a full course of standard-of-care antibiotic therapy. Treatment success, defined as the absence of CDI diarrhea within eight weeks of study treatment, occurred in 70.6% of the RBX2660 (Rebyota) group compared with 57.5% in the placebo group (posterior probability 0.991). Of the patients with treatment success, 92.1% remained free of CDI recurrence at six months. RBX2660 (Rebyota) was overall well tolerated, with treatment-emergent adverse effects most commonly being mild gastrointestinal events. Investigators theorized that the favorable safety profile may be in part due to rigorous screening of donor samples against GI pathogens.[50] RBX7455 is an oral product manufactured using the same suspension used for RBX2660 (Rebyota). This product is currently under investigation and could allow patients to take an oral LBP instead of a rectally administered suspension.[2,51]

Fecal microbiota spores live-brpk (Vowst), formerly known as SER-109, was approved as a result of the ESCOPOR III and IV studies.[52,53] Vowst is distinct from conventional FMT in that it contains a narrow consortium of *Firmicutes* spores. It is isolated from human donor stool and purified using ethanol solvent and sequential purification and bioburden testing. This process removes vegetative forms of bacteria, fungi, parasites, and viruses.[46] The ESCOPOR III study randomized patients who had three or more episodes of CDI to receive SER-109 (Vowst) or placebo, administered as four capsules daily for three days. The percentage of patients with recurrent CDI at eight weeks was 12% in the SER-109 (Vowst) group compared with 40% in the placebo group. Additionally, a sustained response was maintained in 88% of the SER-109 (Vowst) group compared to 60% in the placebo group. The occurrence of adverse events was similar between groups, with the events primarily characterized by mild to moderate GI effects.[52] The ESCOPOR IV study was a phase 3, open-label, single-arm study which included two cohorts. One cohort consisted of rollover patients from the ESCOPOR III study who had rCDI, and the second cohort included patients with at least one CDI recurrence. SER-109 (Vowst) was administered to both groups orally as four capsules daily for three days following symptom resolution after standard-of-care antibiotic treatment, the same dosing regimen as in the ESCOPOR III study. Overall, 4/29 (13.8%) of patients in cohort 1 and 19/234 (8.1%) in cohort 2 had recurrent CDI at week 8, which remained low at 13.7% in both cohorts through 24 weeks. The occurrence of treatment-emergent adverse events was 53.6%, primarily consisting of mild to moderate gastrointestinal effects such as diarrhea, flatulence, nausea, and abdominal pain. Serious treatment-emergent adverse events occurred in 12.5% of patients, but none were considered treatment-related by the investigators. The authors concluded that SER-109 (Vowst) was well tolerated and that the study supported the benefit of SER-109 (Vowst) for patients with CDI.[53]

AGA recommendations for fecal microbiota-based therapies

The AGA recently published a Clinical Practice Guideline supporting the use of fecal microbiota-based therapies for select gastrointestinal diseases, including rCDI and severe to fulminant CDI.[23] This includes the novel LBPs described above, which were not included in other society guidelines published in 2021. A summary of AGA recommendations can be found in Table 2. In immunocompetent adults with rCDI, the AGA suggests the use of fecal microbiota-based therapies upon completion of standard-of-care antibiotics. These therapies include conventional FMT, Rebyota, and Vowst as appropriate options in this setting.[23] The AGA recommends considering fecal microbiota-based therapies after the second recurrence (third episode) of CDI, which is consistent with prior society guidelines published in 2021, as discussed above.[10–12] The AGA also states that fecal microbiota-based therapies may be considered in select patients at high risk of recurrent CDI or a morbid CDI recurrence. This includes patients who have recovered from severe, fulminant, or particularly treatment-refractory CDI, as well as those with significant comorbidities.[23] The AGA recommends that a vancomycin-tapered-pulsed regimen, tapered-pulsed fidaxomicin, or bezlotoxumab be considered as reasonable alternatives to prevent rCDI in patients who are not interested in fecal microbiota-based therapies. In mildly or moderately immunocompromised adults with rCDI, the AGA suggests only conventional FMT as an option to prevent further recurrence upon completion of standard-of-care antibiotics. Rebyota and Vowst are not included as alternatives based on a lack of data on safety and efficacy in this setting. In severely immunocompromised adults, the AGA recommends against the use of any fecal microbiota-based therapies.[23] Despite the significant advances in fecal microbiota-based therapies over the past decade, many unanswered questions remain, and several agents have recently completed or are currently undergoing clinical trials.[2]

Bezlotoxumab

Bezlotoxumab is an IgG1 human monoclonal antibody approved for the prevention of CDI recurrences. It binds to and neutralizes *C. difficile* toxin B, preventing it from entering the gastrointestinal cell layer and causing colonic damage.[11] Toxins A and B are enterotoxins essential for the pathogenesis of *C. difficile*. Toxin A induces inflammation, cytokine release, and fluid secretion, while toxin B causes epithelial damage, inflammation, and increased mucosal permeability.[54] The utility of bezlotoxumab in the prevention of CDI recurrence was demonstrated in the MODIFY I and MODIFY II trials.[55] In these studies, bezlotoxumab was given in addition to standard antibiotics to patients with primary or recurrent CDI. It was administered intravenously over 60 m as a single 10 mg/kg dose. Bezlotoxumab was found to significantly reduce the rates of recurrent CDI compared to placebo in both the MODIFY I (17% *vs.* 28%) and MODIFY II (16% *vs.* 26%) trials. The rates of adverse effects were similar between treatment groups, with nausea (6.6%) and diarrhea (6%) being common in the bezlotoxumab arm. It is important to note that most patients in these studies received oral vancomycin or metronidazole as their standard CDI treatment, with only approximately 4% receiving fidaxomicin.[55] A post hoc analysis of the MODIFY I and II data evaluated the effectiveness of bezlotoxumab in study participants with characteristics associated with an increased risk of rCDI or CDI-related adverse events.[56] The five pre-specified factors included: age ≥ 65 years, a history of CDI in the previous six months, compromised immunity, a Zar score of ≥2 points at the time of randomization, and isolation with a strain associated with poor outcomes (ribotypes 027, 078, or 244). The Zar score is a CDI severity assessment tool developed by Zar and colleagues.[14] Patients receive one point each for meeting the criteria of age > 60 years, temperature > 38.3°C, albumin < 2.5 mg/dL, or WBC count of >15,000 cells/mm^3. Patients receive two points for endoscopic evidence of pseudomembranous colitis or for requiring intensive care unit treatment. Patients with a score of ≥2 are considered to have severe CDI.[14] The post hoc

analysis of the MODIFY I and II trials found that bezlotoxumab reduced the rate of rCDI among participants with each of the five risk factors. Among participants with ≥1 risk factor, bezlotoxumab reduced the rate of CDI recurrences compared to placebo (21.2% *vs.* 37.2%), with an even greater reduction among participants with ≥3 risk factors (21.2% *vs.* 46.1%). Notably, bezlotoxumab did not demonstrate significant benefit in patients who had none of the prespecified factors.[56]

The 2021 IDSA and SHEA Clinical Practice Guidelines recommend using bezlotoxumab in addition to standard-of-care antibiotics for patients with a recurrent CDI episode within the last six months. They also recommend bezlotoxumab for patients with a primary CDI episode and additional risk factors for recurrent CDI, such as those aged ≥ 65 years, immunocompromised hosts, and individuals with severe CDI at presentation.[10] Similarly, the 2021 ACG Clinical Guidelines recommend considering bezlotoxumab for prevention of CDI recurrence in those at high risk, defined as those aged 65 years or older with at least one additional risk factor (second episode of CDI within six months, immunocompromised, or severe CDI).[11] Guidelines suggest avoiding bezlotoxumab in patients with a history of congestive heart failure, noting the higher incidence of treatment-emergent adverse effects, serious adverse effects, and deaths among patients with congestive heart failure who were treated with bezlotoxumab compared to placebo in clinical trials.[10,11] The 2021 IDSA and SHEA Guidelines also note the challenges of routinely using bezlotoxumab due to its high cost and logistical limitations.[10] Despite its cost, several cost-effectiveness studies have found bezlotoxumab to be cost-effective compared to oral vancomycin monotherapy. A recent systematic review and meta-analysis found that eight of nine identified cost-effectiveness analyses demonstrated that bezlotoxumab, in addition to standard-of-care antibiotics, is more cost-effective compared to standard-of-care antibiotics alone.[57] However, a study published in 2021 by Chen and colleagues found that a standard course of fidaxomicin was more cost-effective compared to bezlotoxumab plus vancomycin when using a willingness-to-pay threshold of $150,000.[58] This raises questions regarding which of the newer, yet higher-cost therapies are most feasible to routinely utilize, taking into account the varying willingness-to-pay of individuals and institutions.

Oral vancomycin prophylaxis (OVP)

Oral vancomycin has been utilized not only as a treatment option for CDI but also as a prophylactic measure in certain patients. Its effectiveness against *C. difficile*, ease of availability, overall favorable adverse effect profile, and relatively low cost compared to other prophylactic measures make it an attractive option for preventing rCDI. However, the lack of high-quality evidence supporting OVP and concerns about potential long-term negative effects on the host gut microbiome have limited its widespread use. Several studies have noted an impact of oral vancomycin on the host's microbiota, including the presence of vancomycin-resistant bacteria and overgrowth of certain organisms.[59] To date, 12 original studies have been published evaluating the utility of OVP in the prevention of primary or recurrent *C. difficile* infection. However, these studies show notable heterogeneity in the populations studied, timing of OVP initiation, and dosing regimens and durations utilized. The patient populations studied include adults, lung and renal transplant recipients, adults with hematopoietic stem cell transplantation or hematologic malignancies, and pediatric patients.[60] Additionally, of the 12 published studies, only one was a prospective RCT, published in 2020 by Johnson and colleagues.[61] Johnson and colleagues sought to evaluate the effectiveness of OVP in preventing healthcare facility-onset CDI. They randomized 100 patients to receive either 125 mg of OVP dosed once daily or no OVP, with 50 patients in each arm. They evaluated patients aged 60 years or older who were hospitalized for at least 72 h, had been hospitalized ≤ 30 days prior to their index hospitalization, and had received systemic antibiotics during their prior hospitalization. The incidence of healthcare facility-onset CDI was 0% in the OVP group, compared to 12% in the group that did not receive OVP ($p = 0.03$). This study suggests that OVP is effective in preventing CDI in targeted patients. It also suggested that OVP was cost-effective, citing that the six cases of CDI in the no OVP arm added an estimated additional cost of $15,892.86, compared to $1,302 spent on OVP in the intervention arm.[61]

Given the low quality of currently available evidence, clinical practice guidelines do not make strong recommendations for the routine use of OVP. While the 2021 IDSA Focused Update does not address OVP, the 2021 ACG *C. difficile* Clinical Practice Guidelines recommend considering OVP in high-risk patients (age ≥ 65 years or significantly immunocompromised, who were hospitalized for severe CDI within the past three months) who have been recently treated for CDI and require subsequent systemic antibiotics.[10,11] The ACG suggests that a dose of 125 mg of oral vancomycin once daily may be effective in preventing recurrence in most patients.[11] More recently, a systematic review, meta-analysis, and trial sequential analysis conducted by Maraolo and colleagues pooled and evaluated the results from 11 published OVP studies.[62] They found that OVP exerted a strong protective effect against CDI occurrence, with an odds ratio of 0.14, though they noted moderate heterogeneity between the included studies. They also noted no difference between the two groups regarding the development of vancomycin-resistant *Enterococcus* infections, a concern highlighted in prior literature. The authors concluded that OVP is a promising preventive strategy for CDI and rCDI but emphasized the need for high-quality RCTs to answer unanswered questions, such as the optimal OVP dose, duration, and target patient population.[62] Currently available data may suggest that a 125 mg daily dose balances the risk of CDI recurrence with the potential negative impact of oral vancomycin on the host microbiome, though no prospective data has compared the risk-benefit profile of different OVP dosing regimens. More high-quality evidence is necessary before routine use of OVP can be considered.

Probiotics

The potential role of probiotics in the prevention of CDI has been explored in many studies. Probiotics are live microbial preparations that, when given in adequate numbers, may provide health benefits.[63] It is theorized that probiotics may help in the prevention of CDI through several mechanisms, including enhanced colonization resistance, improved mucosal integrity and barrier function, and neutralization of *C. difficile* toxins.[63] Probiotics may contain a single or multiple microbial strains, with *Saccharomyces boulardii* and *Lactobacillus sp.* having the most data supporting their use. Probiotics are generally considered safe, with most patients experiencing only mild gastrointestinal adverse effects such as abdominal cramping, nausea, soft stools, or flatulence.[64] Cases of bacteremia and fungemia have been observed in patients with certain risk factors, such as intensive care unit stay, those receiving parenteral or enteral feeding, immunosuppressed individuals, intravenous drug use, and gastrointestinal surgery. Therefore, probiotics should be used with caution in these settings.[65]

Despite the theoretical benefits and overall tolerability of probiotics, societal guidelines do not endorse their use in the prevention

of CDI.[10–12] Several factors contribute to this, including variability in study design and findings, small study sizes, and the wide variety of probiotic formulations being studied. Much of the evidence supporting probiotic use comes from meta-analyses of pooled small studies. A 2017 Cochrane Review on the use of probiotics in the prevention of CDI found that probiotics were effective in trials with a baseline CDI risk greater than 5%, but not in trials with a baseline CDI risk ≤ 5%. Among 13 studies with a baseline risk > 5%, the incidence of CDI in the probiotic group was 3.1% (43/1,370), compared to 11.6% (126/1,084) in the control group (RR 0.86, 95% CI 0.67 to 1.10).[66] The 2021 ESCMID Guidelines questioned whether a baseline CDI risk of >5% is representative of typical clinical practice.[12] In contrast to the 2017 Cochrane Review, the PLACIDE study, a large, prospective RCT published in 2013, found no significant decrease in the incidence of CDI between patients who received a probiotic preparation of Lactobacilli and Bifidobacteria or placebo (0.8% *vs.* 1.2%).[67] Despite conflicting opinions and evidence, the use of probiotics in the prevention of CDI persists due to their potential benefits, widespread availability, and relatively low risk of serious adverse effects.

Discontinuation of proton pump inhibitors

Given the significant morbidity, mortality, and risk of recurrence associated with CDI, avoiding medications that are strongly associated with CDI may be prudent. Many clinicians suspect that proton pump inhibitors (PPIs) increase the risk of developing CDI. PPIs inhibit gastric acid production, which may the proliferation of *C. difficile* spores and their ability to convert to their vegetative form.[68] PPIs have been found in numerous studies to be associated with an increased risk of CDI, however, there is notable heterogeneity between studies and findings have been conflicting.[10,11] A meta-analysis conducted by Kwok and colleagues evaluated the risk of CDI with acid suppressing drugs (including PPIs and histamine-2 receptor antagonists) and antibiotics to assess the association between PPI use and rCDI, as well as the potential benefit of switching to histamine-2 receptor antagonists (H2RAs). Their study found a significant association between PPI use and risk of developing CDI (OR 1.74) and a significantly increased risk of recurrent CDI (OR 2.51). Concomitant PPI use and antibiotics conferred an even greater risk of CDI compared to PPIs alone (OR 1.96). Notably, use of H2RAs as an alternative carried a lower risk of CDI compared to PPIs (OR 0.71) demonstrating they may be a less harmful alternative acid suppressant.[69] Both the IDSA/SHEA and ACG acknowledge the association between PPI use and CDI but state that there is insufficient evidence to recommend discontinuing PPIs specifically to prevent CDI. They do, however, suggest that the appropriateness of PPI use should be evaluated, and unnecessary PPIs should be discontinued.[10,11]

Avoidance of high-risk antibiotics

Antibiotic use is the most significant risk factor for CDI, with 60% of CDI cases having used antibiotics in the four months prior to infection.[3] Antibiotic exposure alters the gut flora, allowing *C. difficile* to proliferate.[70] Due to the varying mechanisms of action and spectra of activity of different antibiotic classes, some antibiotics confer a higher risk of CDI than others. Ampicillin, amoxicillin, cephalosporins, clindamycin, and fluoroquinolones are the antibiotics most commonly associated with CDI, though most antibiotics confer some degree of risk.[3] A systematic review and meta-analysis demonstrated that carbapenems and third- and fourth-generation cephalosporins carry the strongest associations with CDI, with cases more than twice as likely to have had recent exposure to these antibiotics prior to developing healthcare facility-associated CDI. Fluoroquinolones, clindamycin, and beta-lactamase inhibitor combination penicillin antibiotics also showed modest associations with healthcare facility-associated CDI.[70] Another study by Webb and colleagues found that prior antibiotic use was the dominant risk factor for CDI, with each additional day of antibiotic therapy increasing the odds of CDI by 12.8%.[71] These findings emphasize the importance of antimicrobial stewardship and surveillance practices in preventing exposure to high-risk antibiotics and optimizing antibiotic therapy durations.

Future opportunities for CDI treatment and prevention

Vaccines for CDI prevention

Vaccines have long been a cornerstone of infection prevention for many diseases. Antibiotic stewardship and public health interventions have reduced the incidence of healthcare-associated CDI, but community-acquired cases have remained largely unchanged.[6] Vaccines have been proposed as a means of CDI prevention, but previous vaccines have failed to demonstrate a reduction in CDI cases.[72] More recently, PF-06425090, a genetically detoxified *C. difficile* vaccine formulated with modified toxins A and B, showed promise in phase 1 and 2 studies, eliciting a robust immune response against toxins A and B. However, a recently published phase 3 study failed to demonstrate a reduction in CDI episodes with three doses of PF-06425090.[73] The vaccine did, however, reduce the duration of symptoms for patients who developed CDI and the need for CDI-related medical attention and antibiotic treatment. The authors highlighted the vaccine's tolerability and its potential to reduce CDI-associated healthcare burden.[73]

Ribaxamase

Ribaxamase has a novel mechanism for CDI prevention compared to other approved agents. It is an oral beta-lactamase designed to be administered with intravenous beta-lactam antibiotics to degrade them in the upper GI tract before they can disrupt the normal gut microbiome, thus preventing CDI.[2,74] In a phase 2b trial involving patients receiving ceftriaxone for lower respiratory tract infections, those who received ribaxamase four times daily during ceftriaxone therapy had a lower incidence of *C. difficile* within four weeks of antibiotic treatment compared to the placebo group (1% *vs.* 3.4%, $p = 0.045$). Adverse effects were similar between groups, but there were more deaths in the ribaxamase group, which investigators attributed to cardiac-associated causes.[74] While ribaxamase may prove beneficial for the prevention of primary or recurrent CDI, no further clinical trials for this agent are currently ongoing.

Bacteriophage therapy

As discussed previously, antibiotic use is a major risk factor for CDI and recurrence. Dysbiosis caused by antibiotic use or malnutrition can initiate CDI, with increasing *C. difficile* toxin concentrations and colonization in the gut leading to severe disease.[75] Bacteriophages offer a potential alternative to antibiotic therapy as a next-generation treatment method, given that they do not have the same disruptive impact on the host microbiome. Bacteriophages are viruses that infect bacteria and cause bactericidal effects.[76] *C. difficile*-specific phages have been investigated as potential new therapies for CDI, and many CDI specific phages are currently being studied. However, none of the *C. difficile*-specific phages investigated to date have proven effective treatments for CDI.[75] One

trial demonstrated the utility of a specific bacteriophage in reducing the burden of *C. difficile* cells and toxin production *in vitro*, but no late-phase clinical trials are currently in progress.[77]

Artificial intelligence and predictive risk models

The emergence of artificial intelligence and machine learning (ML) presents promising future avenues for CDI surveillance and prevention. Data on these practices in CDI are limited, but they may provide cost-effective solutions for detection and prevention. One study compared the effectiveness of rectal swab surveillance with daily risk estimates generated by a previously validated ML model to identify patients at high risk for developing CDI in the ICU setting. This prospective cohort study used rectal swabs to identify patient carriage of toxigenic *C. difficile* through anaerobic culture and PCR analysis. The ML model used this data to generate a daily risk score for each patient starting on calendar day 3 of admission. Swab results and risk predictions were compared to eventual CDI status.[78] In total, 2,979 admissions representing 2,044 patients resulted in 39 cases of CDI. Swab surveillance identified nine true positive (TP) and 87 false positive cases of CDI. In comparison, the ML model identified nine TP and 226 false positive cases. Notably, only one TP case overlapped between the swab surveillance and ML model.[78] The ML model demonstrated a 3.8% positive predictive value but a 98.3% negative predictive value. The authors concluded that the relatively lower cost and flexibility of the ML approach could add value in infection prevention and early identification of CDI but called for additional studies to further explore the benefits of ML models.[78] Predictive risk scores may also prove valuable in identifying patients at high risk for CDI. A study by Aukes and colleagues compared demographic and clinical characteristics of patients with and without laboratory-confirmed CDI.[79] Patients with CDI were typically older, female, white, and had more hospitalizations, emergency department visits, SNF stays, as well as higher rates of antibiotic and proton pump inhibitor use, and specific comorbidities. Based on this data, they developed a risk score model that performed excellently in predicting the likelihood of developing CDI within 31–365 days after hospital discharge (C-statistic 0.848).[79] It may be beneficial to combine risk score models with artificial intelligence and ML to develop low-cost methods of identifying patients at high risk for CDI or rCDI.

Epidemiological factors in CDI management

Hypervirulent strains of CDI

The *C. difficile* species comprises hundreds of strain types.[80] Certain hypervirulent strains have been associated with more severe disease outcomes and increased rates of recurrence compared to other strains. The BI/NAP1/027 strain is a hypervirulent strain of CDI that emerged in the early 2000s, characterized by severe nosocomial outbreaks in North America, Europe, and Australia.[80,81] This strain produces an additional toxin known as binary toxin, which modifies actin and disrupts cellular cytoskeleton organization.[82] It also produces higher amounts of toxin A and toxin B, which may further increase the severity of infection compared to other *C. difficile* strains.[83] Additionally, the BI/NAP1/027 strain is associated with increased antibiotic resistance, including higher minimum inhibitory concentrations to several antibiotics, particularly fluoroquinolones. This allows BI/NAP1/027 strain to thrive in healthcare settings where broad-spectrum antibiotic use is prevalent.[84] While this strain of *C. difficile* is associated with more severe disease and worse outcomes, treatment recommendations do not differ from non-NAP1 strains, and as a result, many clinical laboratories do not routinely test for its presence.[1] A study by Louie and colleagues compared fidaxomicin to vancomycin for CDI treatment.[19] This study found a 36% incidence of the BI/NAP1/027 strain among participants. While no difference in clinical cure rates was observed between fidaxomicin and vancomycin for patients infected with the NAP1 strain, cure rates were notably higher for non-NAP1 strains.[19]

Epidemiological trends in CDI

Incidence and mortality rates associated with CDI vary significantly worldwide.[85] These trends may be influenced by factors such as the timing of country development, changes in population, surveillance and prevention practices, and public health measures. A trend analysis from 2010 to 2019 in the United States showed a decrease in mortality rates among hospitalized patients with CDI, from 3.2% to 1.4%.[86] An increase in the adjusted CDI incidence rate was noted from 2010 to 2015, followed by a decrease from 2015 to 2019. The investigators hypothesized that this trend was likely due to increased caution in antimicrobial drug use following the widespread implementation of antimicrobial stewardship programs.[86] Similarly, a study in Scotland observed a decrease in CDI-related mortality, from 20.5% to 15.6% between 2010 and 2016.[87] In contrast, the burden of CDI has increased in most European countries over the past three decades. A study by Ilic and colleagues demonstrated an increase in deaths due to CDI in European countries from 1990 to 2019.[85] The lowest number of deaths recorded in 1990 was approximately 2,100, compared to around 4,600 deaths in 2019. Notably, most of the deaths were reported in Western Europe, though the increase was consistent across countries, sexes, and age groups. The investigators suggested that this increase in CDI deaths correlated with the development of these countries.[85]

This highlights the importance of effective public health measures and antimicrobial stewardship programs in reducing CDI incidence and mortality. A study by Couture and colleagues analyzed the incidence of healthcare-associated CDI (HA-CDI) and antibiotic utilization in two hospitals in Québec from 2003 to 2020.[88] In 2003, many hospitals in Québec experienced an epidemic of CDI, which was linked to increased disease severity and recurrence due to the hypervirulent BI/NAP1/027 strain. Couture and colleagues sought to evaluate the impact of antibiotic stewardship and infection control interventions on HA-CDI incidence and the prevalence of the BI/NAP1/027 strain. They found that the incidence of CDI decreased from 26.5 cases per 10,000 patient days in 2003 to 4.9 cases per 10,000 patient days in 2020. The study also noted a decrease in fluoroquinolone use over this period, which was associated with a significant reduction in HA-CDI incidence and an approximately 80% decrease in the prevalence of the BI/NAP1/027 strain.[88] This study underscores the critical role of infection control measures and antibiotic stewardship in preventing CDI and hypervirulent strains.

Discussion

Although there have been significant developments in the management and prevention of CDI, several questions remain that warrant further study. New agents, such as fidaxomicin and bezlotoxumab, have been approved and show promise in preventing recurrent infections. However, cost and logistical challenges have made their widespread use difficult. There are also several unanswered questions regarding fidaxomicin, including the optimal dosing strategy

(standard *vs.* extended-tapered), its utility in severe and fulminant infections, and its effectiveness in rCDI treatment compared to tapered and pulsed vancomycin regimens. Fecal microbiota-based therapies, including LBPs, have demonstrated notable benefits, though more evidence is needed to fully understand their safety and role in CDI therapy. Additionally, several treatment modalities, such as vaccines, bacteriophages, and beta-lactamases, remain promising avenues for further investigation. Given the substantial morbidity and mortality associated with CDI, the development of an effective vaccine is essential to prevent future disease. Meanwhile, the widespread use of artificial intelligence and machine learning may significantly impact CDI surveillance practices in the coming years. Given the stressed importance of CDI treatment and prevention, many of the treatment strategies discussed in this review are based on moderate to high quality evidence. However, a limitation noted in this review is that several current practices are based on very low to low quality of evidence, including the role of high dose oral vancomycin and intravenous metronidazole in fulminant CDI, and the role of tapered and pulsed vancomycin regimens in the management of rCDI. These common treatment strategies warrant further study to confirm their utility. A limitation of this review is that it primarily focuses on emerging trends in medication therapy for CDI treatment and prevention, without examining the role of broader public health and antibiotic stewardship initiatives in CDI prevention. Although epidemiological surveillance and infection prevention strategies are paramount for reducing the incidence and burden of CDI, they fall outside the scope of this narrative review.

Conclusions

The incidence of healthcare-associated CDI has decreased in many countries over the last two decades. This has been largely driven by the development of novel modalities for CDI treatment and prevention, as well as a significant expansion of efforts to monitor changes in the epidemiology of CDI. Given its substantial and persistent impact on morbidity, mortality, and healthcare costs, continued investigation into optimal medication use practices for CDI remains essential.

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Author contributions

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