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Clostridioides Difficile: A Concise Review of Best Practices and Updates

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Abstract

Clostridioides difficile infection (CDI) is one of the most common and severe nosocomial infections worldwide. It can also affect healthy individuals in the community. The incidence of CDI has been on the rise globally for the past decade, necessitating a proactive approach to combat its spread; new strategies are being developed to enhance diagnostic accuracy and optimize treatment outcomes. Implementing the 2-step testing has increased diagnostic specificity, reducing the usage of CD-specific antibiotics with no concomitant increase in surgical complication rates. In 2021, the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) shifted its preference for initial treatment to fidaxomicin over vancomycin and metronidazole due to its lower recurrence rate. It also prioritized fidaxomicin for the treatment of recurrent CDI. There are new developments on the frontiers of fecal microbiota therapies, with RBX2660 and SER-109 approved recently by the FDA for prevention, with other microbiome-based therapies in various development and clinical trials. This review offers providers an updated and practical guide for CDI management.

Keywords

Clostridium difficile infection, treatment, diagnosis, microbiome, fidaxomicin, vancomycin, fecal transplant, update, pseudomembranous colitis, bezlotoxumab

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Introduction

Clostridioides difficile is a spore-forming gram-positive anaerobic bacterium and part of commensal flora. It was discovered in 1935 in newborn stool. In 1978 it was implicated in causing pseudomembranous colitis.[1-3] It is the most common cause of diarrhea in hospitalized patients, but younger and healthier patients in the community are also affected.[4] Mortality attributed to *C. difficile* infection (CDI) is 5%, and all-cause mortality is 15% to 20%.[5] CDI exhibits a spectrum of manifestations, ranging from asymptomatic carriage, which is considered a significant mode of transmission, to non-severe and severe diarrhea, toxic megacolon, and pseudomembranous colitis.[6,7]

Upon spore ingestion, germination is promoted by decreased gut flora diversity, decreased competition for nutrients and attachment sites, reduced presence of bacteriocins, decreased conversion of primary to secondary bile acids, and decreased short-chain fatty acids, which have a role in reducing intestinal inflammation and maintaining homeostasis.[8,9] Studies using mouse models demonstrated that antibiotics alter the bile acid balance besides decreasing bacterial competition, favoring primary bile acids and thus promoting spore germination.[10] *C. difficile* produces 2 main toxins, Toxin A and Toxin B, which function as glycosylating agents, deactivating Rho-GTPases, disrupting the epithelial cytoskeleton (toxin A) and forming pores in the enterocyte membrane (toxin B), causing cell death.[8,11] Some strains produce a binary toxin, an ADP-ribosylating toxin that hampers actin polymerization, facilitating bacterial adherence through the formation of epithelial protrusions.[12]

Antibiotic exposure is the highest risk for CDI.[13] Other risk factors include advanced age >65 years, use of proton pump inhibitors, and various comorbidities such as inflammatory

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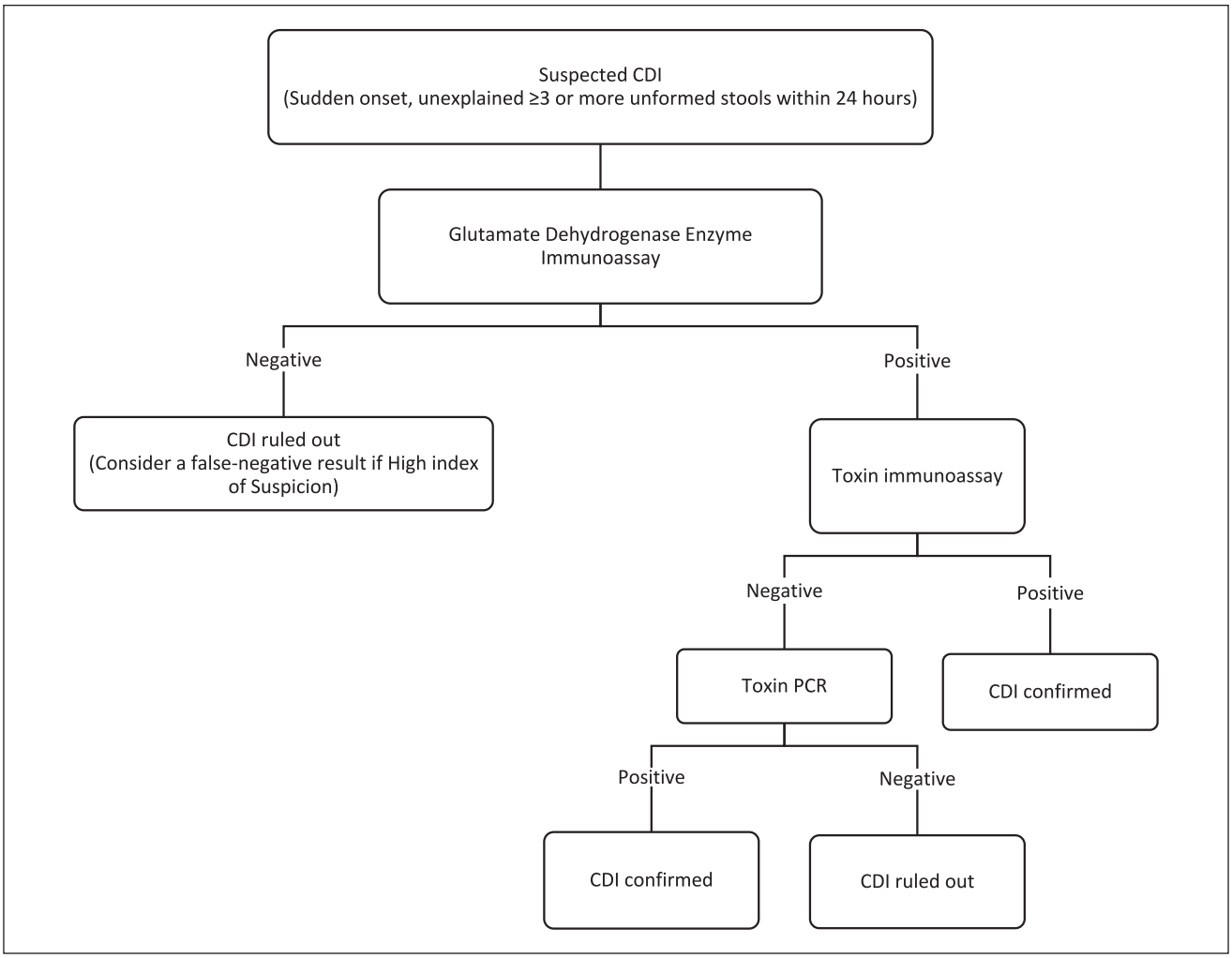

Figure 1. Algorithm for CDI diagnosis.

bowel disease, lymphoma, leukemia, chronic kidney disease, chemotherapy, obesity, or gastric bypass surgery.[8,14-19]

Diagnosis

Clostridioides difficile infection is diagnosed in patients experiencing unexplained, sudden onset of 3 or more unformed stools within 24 h.[20,21] Laboratories should only process liquid or formless stool samples, Bristol type 6 or type 7, to prevent testing asymptomatic carriers, except in cases of paralytic ileus, where rectal swabs may be accepted for toxigenic cultures or nucleic acid amplification testing (NAAT).[20,21]

In the 2021 guidelines from the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) and the American College of Gastroenterology recommend a 2-step testing approach for the presence of the bacterium and its toxin. It uses a combination of enzyme-based immunoassay (EIA), glutamate dehydrogenase (GDH), which are highly sensitive but not specific for differentiation between toxigenic and non-toxigenic strains, and EIA for toxin A/B. GDH is used as a screening test; if the result is negative, it rules out CDI. A diagnosis of CDI is made if the combined tests are positive. Discordant tests such as positive GDH and negative toxin are further clarified with polymerase chain reaction (PCR). A negative PCR rules out infection, and a positive PCR diagnoses CDI.[4,22,23] (Figure 1).

It is no longer necessary to test more than 1 proper sample, and it is advised not to retest within 7 days of the same diarrheal episode, as many patients continue to excrete spores and toxins after diarrheal symptoms have ceased.[22,23]

Classification of CDI According to Severity

Clostridioides difficile infections are categorized into non-severe, severe, and fulminant; according to IDSA guidelines (2021), non-severe CDI is defined as an infection with

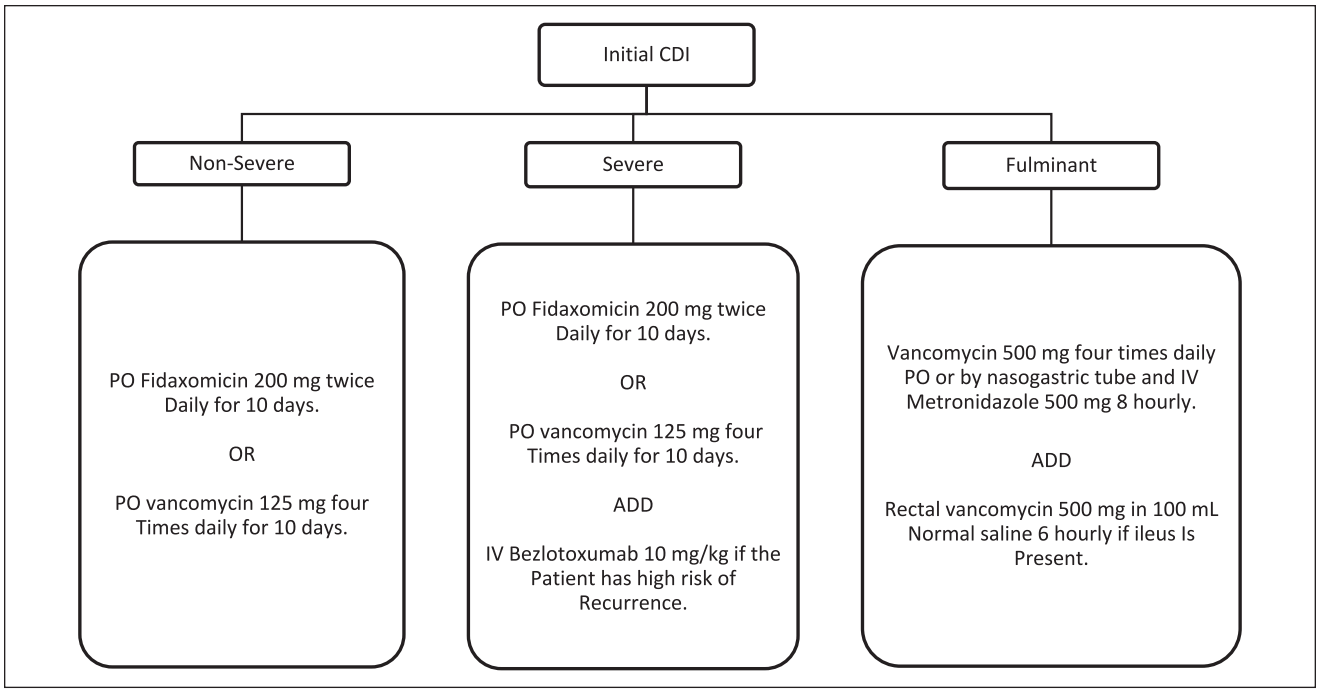

Figure 2. Treatment of an initial CDI.

WBC ≤15 000 cells/mL and serum creatinine of <1.5 mg/dL. The ESCMID guidelines of (2021) have a similar WBC count cut-off point but add that creatinine level should be ≤50% above baseline and core temperature ≤38.5°C at presentation.[23-25]

The IDSA defines severe infection as a WBC >15 000 and a serum creatinine of 1.5 mg/dL. The ESCMID guidelines stipulate the same WBC as IDSA or creatinine level >50% of baseline or core body temperature >38.5° with additional supporting factors, if available, such as dilatation of the large intestine, colonic wall thickening, or a pericolonic fat stranding at imaging.[23-25] Fulminant CDI is denoted by hypotension or shock, ileus, or megacolon, according to the IDSA guidelines. The ESCMID guidelines define it as the presence of hypotension, septic shock, elevated lactate, ileus, toxic megacolon, bowel perforation, or a fulminant course attributed to CDI.[23-25]

Treatment of Initial CDI

Treatment of CDI is based on severity.

Oral metronidazole has less efficacy than vancomycin (72% vs 79% or 59% vs 89%).[4] It is only recommended in settings where vancomycin is unavailable or affordable.[4,26] For an initial episode of CDI, vancomycin has similar cure rates as fidaxomicin. Still, fidaxomicin leads to 40% fewer relapses (it causes less dysbiosis) and decreases mortality by half to 1.2% from 2.9%.[4,23,25,27,28] The cost of fidaxomicin is justified as it prevents relapses and hospitalization.[29] Bezlotoxumab is a monoclonal antibody against toxin B. A single dose decreases the recurrence rate by 10% in patients at high risk of recurrence[30] (Figure 2). It is cost effective as it prevents relapse and hospitalization in patients >65 years, immunocompromised, or with severe CDI.[31]

An initial episode of non-fulminant CDI is treated for 10 days with oral fidaxomicin 200 mg twice daily or oral vancomycin 125 mg 4 times daily.

Oral metronidazole 500 mg 3 times daily for 10 to 14 days can be considered if fidaxomicin or vancomycin is unavailable.

If the patient has risk factors for recurrence including a previous CDI, consider using fidaxomicin 200 mg twice daily for 10 days over vancomycin or using an extended fidaxomicin regimen (fidaxomicin 200 mg twice daily for 5 days then every other day for up to day 25) and adding 1 dose of IV bezlotoxumab 10 mg/kg.[4,25,32,33] Metronidazole is not an acceptable treatment for severe CDI.

Bezlotoxumab provides more protection against recurrence for up to 12 weeks when used with antibiotics compared to treating only with antibiotics.[34,35] Due to the risk of exacerbating congestive heart failure, it should be used with caution in such patients.[23,25,36,37]

Fulminant CDI is treated orally or via nasogastric tube vancomycin 500 mg 4 times daily with consideration of adding intravenous metronidazole 500 mg every 8 h. Adding rectal vancomycin 500 mg in 100 mL normal saline every 6 h should be considered if ileus is present.[25,38]

Table 1. The 2 FDA Approved Oral Capsules and Enema for Prevention of Recurrence.

FDA Approved microbiome-based therapies	
Fecal microbiota, live-jslm (RBX2660) (approved in 2022)	Single dose enema 24-72 h from the last antibiotic dose.
Fecal microbiota spores, live-brpk (SER-109) (approved in 2023)	Administered orally 4 times daily for 3 days after the antibiotic treatment.

Treatment of Recurrent CDI

Recurrent *C. difficile* infection (rCDI) is defined as relapse of symptoms within 2 to 8 weeks following successful CDI treatment. About 15% to 30% of patients recur after an initial episode of CDI, and the recurrence rate increases with each recurrence, to 40% to 60%.[39-41] Recurrence often involves the same strain rather than a new infection. For management of recurrence, an infectious disease specialist should be consulted.

Initial recurrence is treated using oral vancomycin or fidaxomicin in a standard dose or tapered regimen. If fidaxomicin was used in the first episode, change to extended fidaxomicin 200 mg twice daily for 5 days, followed by 200 mg every other day for days 6 to 25, or vancomycin pulse and taper 125 mg 4 times daily for 10 days, followed by a tapering dose of twice daily, then once daily, then every other day up to 8 weeks.[42] If vancomycin was used in the first episode, change to fidaxomicin, either in a standard regimen of 200 mg twice daily for 10 days or an extended regimen. If metronidazole was used in the initial treatment, change to fidaxomicin or vancomycin standard doses or extended/tapered and pulsed regimens. Adjunctive therapy with a single dose of Bezlotoxumab IV at 10 mg/kg may be used with antibiotic treatment to decrease recurrence by 13.9%.[4,23,25,30,35]

Second or subsequent recurrences can be managed with a standard dose or extended fidaxomicin or taper and pulse vancomycin. An alternative approach involves a combination of oral vancomycin (125 mg 4 times daily for 10 days) followed by rifaximin (400 mg 3 times a day for 20 days). Bezlotoxumab can be used in conjunction with antibiotics.

Fecal microbiota transplantation (FMT) is recommended for the treatment of a third CDI episode for patients who have relapsed twice despite appropriate antibiotic treatment, and it can be considered in refractory or fulminant CDI.[8,24,25]

Emerging Therapies

Antibiotics kill the vegetative state of *C. difficile* but not the spores, which sporulate after the antibiotic effect wears off. The human gut consists of an estimated 100 trillion microorganisms that include bacteria, viruses, fungi, and archaebacteria. Besides digestion, the microbiome has been shown to be important in maintaining, among other regulatory functions, normal weight, immunity, mental health, and lung function. A healthy microbiome keeps *C. difficile* in low numbers by competing for nutrients and gut wall colonization, producing metabolites important in host defense and colonization resistance. Conversion of primary to secondary bile acids is modulated by Firmicutes. When their numbers decrease, secondary bile acids increase and promote *C. difficile* sporulation.[8,9,43]

Microbiome-based therapies restore microbiota, restore proteins, and bile acids to levels comparable to a healthy individual, and prevent relapse.[5,44] In rCDI, a 1-time treatment of FMT delivered via nasoduodenal tube after a short course of vancomycin has a cure rate of 81%.[44,45] The cure rate increases to 92% after more than 1 treatment. Oral and colonoscopy delivery routes are more efficacious than enema.[4,46] Fresh or frozen stool has the same efficacy.[47] FMT comes with a risk of infection transmission from donor to recipient with reports of Shiga toxin-producing *E. Coli* transmission. Other adverse events include post infection irritable bowel syndrome, transient diarrhea or constipation, and abdominal pain which may be related to therapy or the *C. difficile* infection.[45] There are also concerns of a long term risk of development of autoimmune conditions such as rheumatoid arthritis or peripheral neuropathy due to their potential link to the gut microbiota.[48]

New standardized microbiome-based therapies are being studied. The oral formulations consist of lyophilized intact microbiome and isolated bacterial species or spores: CP101, MET-2, RBX7455, SER-109, SER-262, and VE303. The enema is a stool suspension, RBX2660. Two of these therapies, the oral spores SER-109 and the stool enema RBX2660 received FDA approval for the prevention of recurrence (Table 1).

In trials involving the new FDA approved medications events are mostly mild to moderate gastrointestinal symptoms including abdominal pain, nausea, and flatulence, with no reports of infections related to a causative organism in the transplanted stool. Serious adverse events that lead to death are infrequent and were deemed related to the CDI or a pre-existing condition rather than the treatment itself. This shows that standardization of therapy and good manufacturing can mitigate many potential risks.[49,50]

Stool-Derived Enema

- Fecal microbiota, live-jslm (RBX2660) is a microbiome suspension delivered using a single dose enema

24 to 72 h from the last antibiotic dose. A phase III trial showed a success rate of 70.6% (defined as the absence of CDI diarrhea within 8 weeks of treatment) versus 57.5% with placebo. In November 2022, RBX2660 became the first FDA-approved live biotherapeutic product for CDI.[8,51,52]

Stool-Derived Oral Capsules

- Fecal microbiota spores, live-brpk (SER-109) is a lyophilized oral capsule consisting of spore-forming Firmicute bacteria extracted and purified from donors. It is administered orally 4 times daily for 3 days after standard of care antibiotic treatment. Phase III trials showed an 88% sustained clinical response at 8 weeks compared to placebo. It received FDA approval in 2023, becoming the second approved live microbiome-based drug for CDI.[8,53,54]
- CP101 is a stool-derived oral capsule; after collection of stools from donors, it is lyophilized and processed before its encapsulation. It is stored in a freezer and administered in a healthcare setting. The regimen is a 1-time capsule that does not require prior bowel preparation. In 2023, Finch Therapeutics announced the discontinuation of the phase III trial.[8,51,55,56]
- RBX7455 is also a capsule-based microbiome-modifying therapy. Stools from donors are lyophilized or freeze-dried before casualization and given in a 3-dose regimen. It does not require controlled storage and hence can be administered at home. Phase l trials resulted in 90% success rates.[8,51,53,55,56]
- MET-2 is an oral capsulated formulation consisting of 40 lyophilized species. About 84% of the patients had no recurrence by day 130 in phase I trial. Phase II trial is currently planned.[8]
- Synthetic oral capsules:
- VE303 uses nonpathogenic, non-toxigenic commensal strains of Clostridia that do not require a donor and are grown in the lab. Phase II trial demonstrated that high dose VE303 was superior to placebo in preventing recurrence. A phase III trial is underway.[8,33,51,55,56]
- SER-262 is a consortium comprising 12 strains of anaerobic commensal bacteria in spore form prepared by fermentation. Its development is on hold due to the need for significant differences between treatment groups according to phase I trial.[8]

New Antibiotics

-Ridinilazole is a narrower spectrum antibiotic, and its mechanism of action is incompletely understood; it is thought to disrupt *C. difficile* cell division, where the production of toxin A drops by 91% and toxin B by 100%. In clinical trials, ridinilazole resulted in fewer recurrences than vancomycin.[55,56]

Prevention and Infection Control

Antibiotic stewardship is key in reducing CDI, while other measures like limiting PPI use, prescribing probiotics, or isolation of asymptomatic carriers lack substantial evidence.[20,21,23,57] Instead, patients with CDI should be isolated with personal toilet access, encouraged to wash their hands and shower regularly to reduce the spore burden. Isolation should be continued for 48 h after the diarrhea subsides or until discharge. Healthcare personnel should follow contact precautions and soap and water hand washing before and after entering a patient's room. Sporicidal activity of soap is superior to alcohol-based sanitizers. Rooms should be cleaned with a sporicidal agent daily with terminal cleaning at discharge. Disposable equipment should be utilized, and if equipment must be reused, disinfection with a sporicidal agent is recommended.[20,23,38] Several vaccines are currently under development none of which have been approved to date. Pfizer's toxoid-based vaccine failed to achieve its primary endpoint in a phase III trial back in 2022. However, another phase III trial published in 2023 demonstrated the production of neutralizing antibodies when given for 3 doses to healthy individuals aged 65 to 85. A phase II extension revealed a sustained antibody response up to 48 months after the third dose with additional immunogenic effect observed after a fourth dose.[58,59]

Conclusion

Clostridioides difficile infections are a significant challenge and a burden on healthcare resources. Improved diagnosis and treatment will continue to improve rates if we are good stewards of antibiotic use. Implementing a 2-step testing approach improves diagnostic accuracy and aligns with the 2021 treatment guidelines, reducing recurrence rates. The promising new therapies hold the potential for further improvements in addressing this challenge.

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