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Management of *Clostridioides difficile* Infection: Diagnosis, Treatment, and Future Perspectives

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ABSTRACT

Clostridioides difficile infection is the most common healthcare-associated infection in the United States, with potential life-threatening complications and a significant impact on the costs of care. Antibiotic stewardship as well as discontinuation of chronic acid suppressive therapy are key for its prevention and treatment. Effective infection management requires appropriate interpretation of diagnostic tests, as well as the use of vancomycin and fidaxomicin as first-line treatment. Novel treatments such as Bezlotoxumab, fecal microbiota transplant, and live biotherapeutic products are proven effective in recurrent *C. difficile* infection and address dysbiosis.

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INTRODUCTION

Clostridioides difficile infection is a common nosocomial and community-acquired cause of diarrhea and one of the most prevalent healthcare-associated infections.[1,2] Improved understanding of its pathophysiology has increased availability of testing modalities. *C. difficile* treatment has also evolved, shifting from the previous standard metronidazole or vancomycin to now vancomycin or fidaxomicin as first-line treatments. The primary focus of treatment has been eliminating active toxigenic *C. difficile* bacteria with antibiotics. Vancomycin and fidaxomicin have shown effectiveness in the short-term relief of symptoms but fail to address underlying residual dysbiosis, which can lead to spore germination and recurrent infections. Restoration of the intestinal microbiome after antibiotic treatment is essential in addressing recurrence and completing treatment.[3,4] Restoring the microbiome through therapies like fecal microbiota transplant and live biotherapeutic products has demonstrated efficacy in recurrent *C. difficile* infection, addressing dysbiosis and increasingly establishing itself as a treatment option for patients with recurrent *C. difficile* infection.[5-8]

EPIDEMIOLOGY

C. difficile infection remains the leading cause of healthcare-associated diarrhea and the most commonly identified cause of healthcare-associated infection in adults in the United States.[1] The improper use of antibiotics increases the probability of contracting *C. difficile* infection, with more than half of hospitalized patients receiving unnecessary antibiotics during their stay.[9] *C. difficile* infection prevalence in the general population is growing, and it is estimated that more than 41% of current cases are community-acquired, impacting groups not previously at risk (younger patients and those without antibiotics exposure during the 12 weeks prior to infection).[2,9] *C. difficile*

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infection affects approximately 500,000 patients each year in the United States.[10] More recent data from 2021, the CDC showed a *C. difficile* infection incident rate of 110.2 cases per 100,000 persons, with community-associated cases accounting for 55.9 cases per 100,000 persons and hospital-associated cases slightly lower at 54.3 cases per 100,000 persons.[11,12] Of those who contracted *C. difficile* infection, approximately 29,000 patients experienced fatal outcomes within a month of diagnosis, with 15,000 of these deaths directly attributable to the infection.[9] Around 83,000 patients diagnosed with *C. difficile* infection experienced at least 1 recurrence, and among them, 29,000 died within 30 days of the initial diagnosis. These emerging data trends have begun to reshape our perception of *C. difficile* infection.

CLINICAL SIGNIFICANCE

- *C. difficile* is a highly contagious nosocomial and community-acquired infectious diarrhea, associated with antibiotic overuse and antisecretory therapy.
- Antibiotic stewardship and avoidance of routine antacid therapy are paramount for its prevention.
- Effective infection management requires appropriate interpretation of diagnostic tests.
- Vancomycin and fidaxomicin are first-line treatments.
- Novel treatments such as Bezlotoxumab, fecal microbiota transplant, and live biotherapeutic products are proven effective in recurrent *C. difficile* infection and address dysbiosis.

RISK FACTORS AND TRANSMISSION

Identifying *C. difficile* in asymptomatic patients is known as colonization, and such patients act as a reservoir. *C. difficile* is highly contagious and spreads via the fecal-oral route through the ingestion of spores.[1,4] Current colonization status with the organism at the time of hospitalization increases the likelihood of developing symptomatic *C. difficile* infection by 6 times.[4] The main risk factors for an active infection include contact with the hospital environment, age (≥65 years), and antibiotic usage. Additional risk factors include white race, cardiac disease, chronic renal disease, and inflammatory bowel disease.[1,3,4] Antibiotics alter the normal colonic microbiota's barrier function, disrupting normal intestinal flora, and *C. difficile* starts to dominate and colonize the large intestine.[4,13] Although any antibiotic can predispose to colonization, the most commonly linked to *C. difficile* infection include broad-spectrum penicillins and cephalosporins, clindamycin, and fluoroquinolones.[2] The use of multiple antibiotics, broad-spectrum antimicrobials, and prolonged antibiotic treatment impacts the incidence of *C. difficile* infection.[14] Antisecretory therapy with proton pump inhibitors or histamine 2 receptor antagonists has been linked to an increased risk of *C. difficile* infection; therefore, the necessity for the continuation of antisecretory treatment should be reevaluated in patients who present with *C. difficile* infection.[15] Patients with inflammatory bowel disease have up to 5 times increased risk of *C. difficile* infection.[4] Associated with increased rates of community-acquired *C. difficile* infection and recurrent infection, 13% inflammatory bowel disease compared to 7%.[4] Therefore, patients with a history of inflammatory bowel disease presenting with a suspected acute flare and diarrhea should be tested for *C. difficile*.

MICROBIOLOGY

C. difficile is an anaerobic gram-positive, spore-forming, toxin-producing bacillus.[11] *C. difficile* spores are considered the primary causality for *C. difficile* transmission. Spores are resistant to heat, antibiotics, and bile acids which allows for a long dormant state. Spore germination in the intestines is thought to be affected in part by bile acids. Primary bile acids promote spore germination, and in contrast, secondary bile acids tend to inhibit this process.[13] Fecal microbiota transplantation and live biotherapeutic products are promoting a shift towards secondary bile acid composition contributes to an environment not conducive to *C. difficile* growth. *C. difficile* infection is mediated by 2 potent exotoxins that mediate colitis and diarrhea: toxin A and toxin B, which disrupt tight junctions and destroy the actin cytoskeleton of the mucosal lining cells of the colon (colonocytes), inducing fluid secretion, neutrophil adhesion, and local inflammation with formation of pseudomembranes.[13] The organism is rarely invasive, nontoxigenic strains do not cause *C. difficile* infection, and not all colonized patients develop *C. difficile* infection. This implies that additional variables (immune response and gut microbiota balance) play a significant role in disease pathogenesis.[2]

CLINICAL CHARACTERISTICS OF *C. DIFFICILE* INFECTION

The clinical presentation of *C. difficile* infection ranges from an asymptomatic carrier state to fulminant illness with a toxic megacolon.[13] *C. difficile* infection typically presents as watery diarrhea (≥3 loose stools in 24 hours). Additional symptoms include cramping, lower abdominal discomfort, a low-grade fever, nausea, and anorexia.[4,13] Mucus or occult blood may be present in diarrhea, yet melena or hematochezia are uncommon. Lower abdomen tenderness may be demonstrated on physical examination.

Severe *C. difficile* infection is defined as a leukocyte count of 15×10^9/L or above or a creatinine level of ≥1.5 mg/dL. Hypotension, shock, ileus, or megacolon (>7 cm diameter in the colon and/or >12 cm diameter in the cecum) are signs of a fulminant infection. Patients 65 years or older, have a history of *C. difficile* infection, severe *C. difficile* infection, or are immunocompromised

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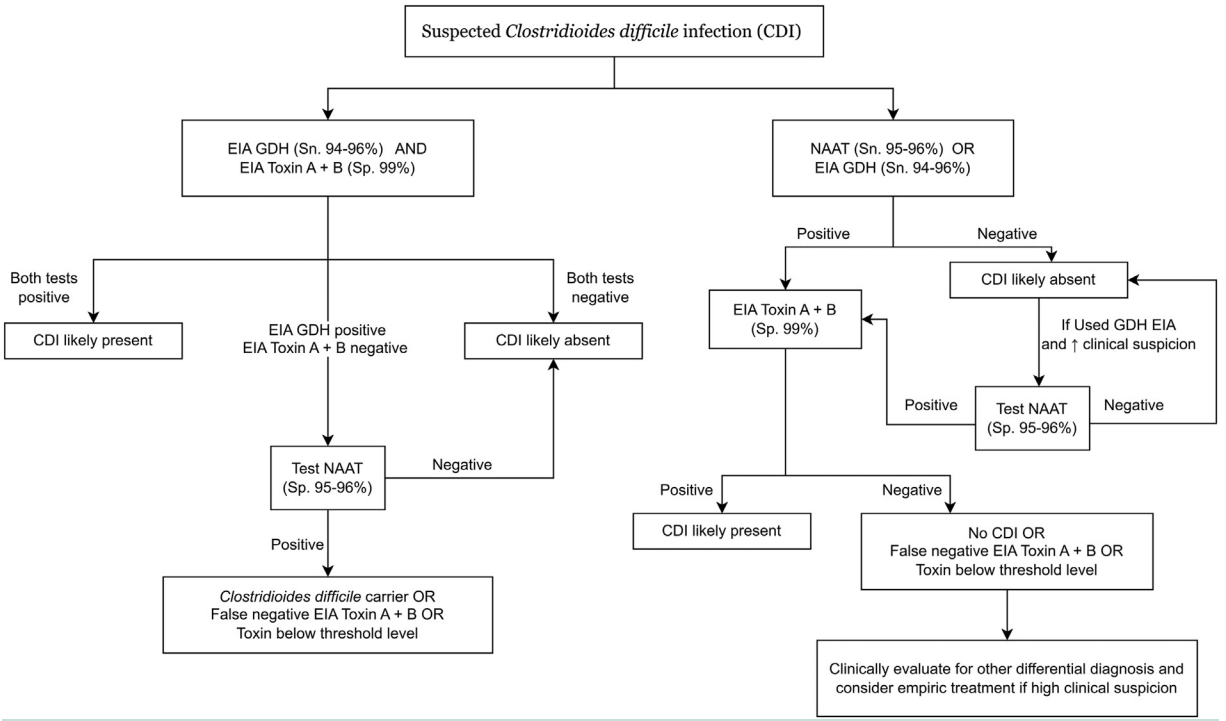

Figure 1 Diagnostic algorithm for *Clostridioides difficile* infection. GDH = glutamate dehydrogenase; EIA = toxin A and B enzyme immunoassay; NAAT = nucleic acid amplification tests; Sn = sensitivity; Sp = Specificity.

are at high risk of developing complications.[3,4,13,16] Recurrent *C. difficile* infection is defined by the remission of *C. difficile* infection symptoms over adequate treatment, followed by recurrence of symptoms and positive assay result within 2 to 8 weeks.[3]

DIAGNOSTIC APPROACH

C. difficile infection is diagnosed by a stool assay for the presence of the organism or the toxin, and only individuals with symptoms suggestive of active infection (unexplained and new-onset diarrhea, ≥3 unformed stools in 24 hours) should be tested.[3,4]

See Figure 1 for the diagnostic algorithm for *C. difficile* infection and Table 1 for a summary of the different diagnostic approaches to *C. difficile* infection.[16] While CCNA and toxic stool culture are the gold standards for identifying infections, their application outside research settings is not practical.[18]

Toxins A and B produced by *C. difficile* can be detected by Enzyme immunoassays (EIAs), providing rapid results with high specificity; however, specimen processing can affect sensitivity. Nucleic acid amplification testing (NAAT), such as polymerase chain reaction and loop-mediated isothermal amplification, detects the presence of the gene encoding toxin, confirming the presence of a toxigenic strain and has comparable sensitivity with toxigenic culture. Detecting glutamate dehydrogenase (GDH) antigen is very sensitive and an effective screening method with a high negative predictive value as both toxic and nontoxic strains generate substantial quantities of this enzyme.

Further testing is necessary when clinical suspicion is strong since false negatives occasionally occur. A positive GDH test necessitates confirmation of a toxigenic strain using either NAAT or EIA. Currently, the Infectious Diseases Society of America (IDSA) recommends using a multistep algorithm to diagnose *C. difficile* infection (GDH plus toxin EIA, GDH plus toxin EIA with NAAT

Table 1 Summary for *Clostridioides difficile* Testing

Diagnostic Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Toxigenic culture	94%	99%*	—	—
Cell culture cytotoxicity neutralization assay (CCNA)	93%	98%	—	—
Glutamate dehydrogenase (GDH)	94%-96%	90%-96%	34%-38%	100%
Toxin A and B Enzyme immunoassay (EIA)	57%-83%	99%	69%-81%	99%
Nucleic acid amplification tests (NAAT)	95%-96%	94%-98%	46%	100%

Adapted from Johnson et al[3] and Kelly et al.[4]
*Combined with presence of toxin.

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confirmation if results are discordant, or NAAT plus toxin EIA).[3] Consideration for colonoscopy occurs in situations of diagnostic uncertainty after laboratory testing. This would facilitate the ability to assess for *C. difficile* infection-related changes and evaluate other pathologic causes.

In *C. difficile* infection, lower gastrointestinal endoscopy may be normal or demonstrate a range of abnormalities, from patchy, moderate erythema and friability to severe pseudomembranous colitis (raised yellow mucosal plaques, or "pseudo-membranes").[3,4,13,16] Repeat testing (within 7 days) during the same diarrhea episode or testing asymptomatic patients is not recommended.[1]

TREATMENT

Discontinuing antibiotic therapy in patients with *C. difficile* infection is recommended unless the treatment is necessary. Primary prevention with prophylactic antibiotics in high-risk hospitalized patients is not recommended. Probiotic use as a primary prevention tool has shown varying efficiency depending on when it is started, if the patient is taking antibiotics, and the underlying comorbidities of the patient, and therefore has not been implemented as a standard of therapy.[4] This shifts prevention into 2 main categories: antibiotic stewardship, and minimizing spread with contact precautions.[17] Contact precautions, along with soap and water for hand washing, are also crucial for getting rid of *C. difficile* spores, which are resistant to being killed by alcohol.[4,11,16]

See Table 2 for the current recommendations for antibiotic treatment of *C. difficile.* Vancomycin or fidaxomicin is the first-line initial treatment of nonsevere *C. difficile* infection. In low-risk individuals with nonsevere *C. difficile* infection, metronidazole may be considered.[3,4]

In fulminant *C. difficile* infection, high-dose vancomycin should be used. Consideration may be given to combination treatment with parenteral metronidazole. Vancomycin enemas are recommended if ileus is present. Fecal microbiota transplantation may be used to treat severe or fulminant *C. difficile* infection that is resistant to antibiotic treatment as well as in patients who are poor surgical candidates.[3,4]

First, *C. difficile* infection recurrence is treated with tapered-pulsed vancomycin if vancomycin, fidaxomicin, or metronidazole was used initially. Taper constitutes a standard vancomycin course for 10 to 14 days followed by decreasing the dose by 25% to 50% every 1 to 2 weeks with no skipped days and then pulsed at a 125-mg dose, skipping every 1 to 2 days for 2 to 4 weeks. Fidaxomicin is used for recurrent infection if vancomycin or metronidazole was used initially. Second or further *C. difficile* infection recurrences are treated with antibiotics followed by fecal microbiota transplantation, which may be repeated for recurrences within 8 weeks.[3,4]

Bezlotoxumab, a monoclonal antibody that binds to *C. difficile* toxin B, is advised for high-risk individuals to prevent recurrences.[4] Bezlotoxumab recommended consideration is in those 65 years or older who are either immunocompromised, have severe *C. difficile* infection, or have a second episode of *C. difficile* infection in 6 months.[4]

Microbiota restorative therapy through implementation from fecal microbiota transplantation and live biotherapeutic products after completion of standard antibiotics has proven effective in recurrent *C. difficile* infection and addresses dysbiosis.[18] In fecal microbiota transplantation, feces from a healthy volunteer is screened for pathogens, processed, and administered via endoscopy, colonoscopy,

Table 2 Recommendations for the Treatment of CDI in Adults

Initial Infection Treatment	
Severity	Recommended Treatment
Not severe	Oral vancomycin 125 mg 4 times daily for 10 days, or Oral fidaxomicin 200 mg twice daily for 10 days If vancomycin or fidaxomicin is not available: oral metronidazole 500 mg 3 times a day for 10 days
Severe	Oral vancomycin 125 mg 4 times daily for 10 days, or Oral fidaxomicin 200 mg twice daily for 10 days
Fulminant	Vancomycin 500 mg 4 times daily orally or nasoenterally for >10 days. Vancomycin—enemas, in case of ileus Intravenous metronidazole 500 mg 3 times a day should be administered together with oral or rectal vancomycin, particularly if ileus is present
Treatment of recurrent infection	
Recurrence number	Recommended treatment
First recurrence	Oral vancomycin 125 mg 4 times daily for 10 days if metronidazole was used to treat the initial episode, or Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (oral vancomycin 125 mg 4 times daily for 14 days, followed by 125 mg 3 times daily for 1 week, followed by 125 mg twice daily for 1 week, followed by once daily for a week and then every 2-3 days for 2-8 weeks), or Oral fidaxomicin 200 mg twice daily for 10 days, or Oral fidaxomicin 200 mg twice daily for 5 days, followed by once daily every other day for 20 days
Subsequent recurrences	Vancomycin in a tapered and pulsed regimen, or Oral vancomycin 125 mg 4 times daily for 10 days followed by oral rifaximin 400 mg 3 times daily for 20 days, or Oral fidaxomicin 200 mg twice daily for 10 days, or Fecal microbiota transplant

Adapted from Johnson et al[3] and Kelly et al.[4]

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or enema to restore protective gut flora.[6] Fecal microbiota transplantation is primarily considered in cases of recurrent *C. difficile* infection and in cases of severe or fulminant *C. difficile* infection that do not respond to antibiotic therapy.[6] The first FDA-approved method of fecal microbiota transplantation was REBYOTA (rectal administered, RBX2660) in November 2022, with the indication for recurrence prevention in adults following antibiotic treatment for recurrent *C. difficile* infection. The treatment success rate was 70.6% with RBX2660 versus 57.5% with placebo.[19] VOWST (live BRPK, formerly SER-109), the first oral live biotherapeutic product intended for *C. difficile* infection is composed of Firmicutes spore colony-forming units in capsule form. SER-109 use after standard antibiotic treatment showed a 68% lower risk of recurrent infection than antibiotics alone, with a 3.6 number needed to treat to prevent 1 recurrent infection.[7,8] There were no significant adverse events associated with the use of SER-109, and comparable rates of adverse events were observed between SER-109 (51%) and placebo (52%).

A surgical evaluation may be beneficial for patients with toxic megacolon, acute abdomen, septic shock, or in patients in whom all medical therapies have failed.[16] Depending on the patient's tolerance and the surgeon's best judgment, total colectomy with an end ileostomy and a stapled rectal stump or a diverting loop ileostomy with colonic lavage and intraluminal vancomycin is currently performed.[4]

Patients should be monitored for signs of clinical improvement, such as the resolution of fever, a decrease in bowel frequency, an improvement in bowel consistency, normalization of abdominal exam findings, as well as resolution of leukocytosis if applicable.[16] As it is typical for patients to continue testing positive for *C. difficile* after symptoms have subsided and treatment of asymptomatic carriers is not suggested, repeated stool testing is not advised to check for a cure.[3] Individuals should be retested if their symptoms recur after receiving effective therapy.

FUTURE WITH MICROBIOME THERAPY

The success of microbiota restoration therapy regarding *C. difficile* infection has expedited the growing recognition of the potential influence of intestinal dysbiosis on other gastrointestinal disorders and those outside the digestive tract. Other possible clinical indications for microbiota therapy include treating toxic megacolon, inflammatory bowel disease, primary sclerosing cholangitis, alcoholic hepatitis, neurodegenerative disorders including multiple sclerosis, Alzheimer's disease, Parkinson's disease, and metabolic syndrome.[20] Indiana University has implemented endoscopic delivery of fecal microbiota transplantation in treating severe and severe-complicated *C. difficile* infection with a 91% cure rate and no serious adverse events attributable to fecal microbiota transplantation.[6,21] The preliminary results of microbiota restorative therapy across various medical disciplines are encouraging; standardized trials are a necessary next step, and live biotherapeutic products may serve as a conduit to help bridge the investigative gap.[21]

CONCLUSIONS

C. difficile infection is one of the most dangerous nosocomial diseases. It is critical to remember that *C. difficile* infection prevention begins with healthcare worker education on proper contact precautions, hand washing with soap and water, glove use, thorough cleaning of medical devices and the patient's surroundings, and the prudent use of antibiotics. Effective infection management requires appropriate interpretation of diagnostic tests, as well as the use of vancomycin and fidaxomicin as first-line treatment. Restoring microbiota through the application of fecal microbiota transplantation and live biotherapeutic products after completion of antibiotics has proven effective in recurrent *C. difficile* infection and addresses dysbiosis.

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