Clostridioides difficile Infection: a Review of Current Diagnostic, Preventative and Therapeutic Guidelines

Despite increased awareness, *Clostridioides* (formerly *Clostridium*[1]) *difficile* remains the most common cause of hospital-acquired diarrhea in the United States.[2] *C difficile* infection (CDI) constitutes a major cause of morbidity and mortality, affecting almost 500,000 people per year in the United States alone and resulting in an estimated 15,000 annual deaths.[3] CDI places a substantial economic burden on the healthcare industry—with an annual cost in the United States totaling $6.3 billion[4]—and presents a persistent and daunting healthcare challenge. Recent advances, however, suggest CDI control is not unattainable; prevention measures, new diagnostic guidelines, and emerging therapeutics offer opportunities for improved CDI management.

Diagnostic Guidelines

Diagnosing CDI is problematic in part because of the diversity of clinical manifestations. These range from asymptomatic carriage to mild or moderate diarrhea, to fulminant pseudomembranous colitis.[5] Fever, abdominal discomfort, and leukocytosis are common, but not consistent, features.[5]

Although clinical manifestations vary, cases of CDI share common risk factors. Recent antibiotic use is present in the overwhelming majority of cases.[5] Additional risk factors that increase clinical suspicion of CDI include advanced age, hospitalization or residence in a nursing home, and a history of CDI.[6] A case definition for typical CDI consists of the presence of diarrhea, megacolon or ileus, in combination with a positive stool test or the presence of pseudomembranous colitis.[5]

Because diarrhea is a characteristic clinical manifestation of CDI, any patient with unexplained, unformed stools with a stool frequency of 3 or more in 24 hours[2] should undergo fecal testing.[7] Although diarrhea is present in the majority of cases, in paralytic ileus, diarrhea may be absent.[5,7] Testing on formed stool samples should be reserved for these patients.[7]

Fecal testing aims to detect both the presence of *C difficile* and the presence of *C difficile*–produced toxin. Multiple tests have been developed with this aim, but all have limitations. Toxin-immunoassays detect fecal toxins but are poorly sensitive, resulting in false negatives.[2,6] Glutamate dehydrogenase enzyme immunoassays (GDH-EIA) detect GDH produced by *C difficile*. However, they do not differentiate toxigenic from

non-toxigenic strains of *C difficile*.[7] Nucleic acid amplification tests (NAAT) detect toxin-producing genes, but, as they detect genes rather than toxin itself, they do not differentiate active toxin production from colonization without toxin production.[7] NAAT tests are consequently unable to distinguish non-CDI diarrhea in patients with colonization from true CDI.

No single fecal test is sufficient to diagnose CDI, so a two-step algorithm is instead recommended.[2,8] As GDH-EIA and NAAT are highly sensitive, they are useful in ruling out CDI, but positive results require additional confirmatory tests. In patients with consistent clinical symptoms, the recommended initial screening test is either NAAT or GDH-EIA.[2,8] If the result is negative, CDI is unlikely. If the result is positive, a second more specific toxin-immunoassay is required to confirm the presence of toxins and to differentiate from colonization.[2]

Infection Prevention and Control

C difficile spores are directly transmitted between patients, as well as via contaminated surfaces, fomites, and healthcare professionals. Basic principles of hygiene, personal protection equipment, and contact precautions are, consequently, paramount in infection control. The implementation of infection prevention programs in long-term care facilities has been found to decrease CDI by as much as 36.1%.[9]

Contact precautions should be applied when there is a reasonable suspicion of CDI, pending confirmatory lab results. Once CDI is confirmed, patients should be hospitalized in an individual room with their own toilet for at least 48 hours after diarrhea has resolved.[2] Daily room cleaning with a sporicidal agent should be considered during outbreaks or in hyperendemic settings, as should the creation of a dedicated CDI healthcare team.[2] Further necessary control measures for healthcare professionals include wearing gloves and gowns, using disposable equipment, and encouraging patients to shower and wash their hands.[2]

Hand hygiene among health professionals is essential before and after contact with a patient with CDI or contact with feces.[2] During a national campaign in the UK promoting hand hygiene, CDI rates decreased from 16.75 to 9.49 cases per 10 000 bed days over a 4-year period.[10] Either soap and water or alcohol-based hand rub can be used in endemic settings,[2,11] but as alcohol-based hand rubs are less effective in vitro against spores,[11] soap and water washing is recommended in outbreaks or hyperendemic settings.[2]

The most influential factor in the prevention of CDI is appropriate antibiotic use.[12] Antibiotics that have been implicated in CDI, particularly fluoroquinolones, clindamycin, and cephalosporins, should be restricted.[2,13] Antibiotic stewardship programs consisting of prescription reviews, prior approval policies, and/or removal of a drug from stock are shown to have a significant protective effect[13] and should form parts of prevention strategies.

Current Treatment Recommendations

Although treatment depends on the severity of CDI, the first step in any CDI treatment is to immediately discontinue the inciting antibiotics.[2,7] If antibiotics are still required to control the primary infection, ones that are less likely to cause CDI should be used, such as parenteral aminoglycosides, sulfonamides, macrolides, vancomycin or tetracycline/tigecycline.[7]

Antibiotic therapy for CDI should be started empirically pending confirmatory results, or when fulminant CDI is suspected.[2]

In an initial, mild/moderate episode of CDI, vancomycin (125 mg PO QID for 10 days)[2] or fidaxomicin (200 mg PO BID for 10 days)[2] have replaced metronidazole as first-line antibiotic choices. Metronidazole has more side effects than vancomycin and has been associated with treatment failures, particularly in infections caused by more virulent strains of *C difficile*.[7] Reasons for metronidazole treatment failure are unclear but appear to be unrelated to resistance.[14] One proposed explanation is that, whereas vancomycin is poorly absorbed systemically and achieves high levels in the colon, metronidazole is well absorbed, and intestinal levels decrease as colonic inflammation subsides.[14] Despite these limitations, when access to vancomycin or fidaxomicin is limited, metronidazole (500 mg PO TID for 10 days) should be used. Repeated or prolonged courses, however, should be avoided because of the risk of neurotoxicity.[2]

Fulminant CDI, characterized by hypotension or shock, ileus, or megacolon,[2] requires close monitoring and supportive care.[7] The treatment of choice is oral vancomycin (500 mg QID) in combination with intravenous metronidazole (500 mg IV q 8 hours). If ileus is present, vancomycin can be administered rectally (500 mg in 100 mL saline q 6 hours) instead of orally.

Surgery should be considered if the patient does not respond to medical therapy or if serum lactate is above 2.2 mmol/L.[7] If surgical management is necessary, the surgeries of choice are either a subtotal colectomy with preservation of the rectum, or a diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes.[2]

Recurrent CDI (defined as repeat CDI within 2-8 weeks[2]) has 3 treatment options depending on prior therapy. For the first recurrent episode, if metronidazole was used to treat the primary episode, a standard 10-day course of vancomycin should be used. If a standard 10-day course of vancomycin was used to treat the primary episode, oral vancomycin can be administered as a tapered and pulsed regimen.[2] Alternatively, a 10-day course of fidaxomicin can be administered.[2]

Patients with more than one recurrence of CDI can be treated with a tapered and pulsed regimen of oral vancomycin; a standard course of oral vancomycin followed by rifaximin; or a course of fidaxomicin.[2] Patients with multiple recurrences of CDI that have been treated with antibiotics can be treated with fecal microbiota transplantation (FMT),[2] where fecal matter is transferred from a healthy donor to a patient with CDI in order to restore normal intestinal microbiota.

Emerging Therapies

The main antibiotics used to treat CDI—metronidazole and vancomycin—are broad-spectrum antibiotics that disrupt intestinal microbiota.[15] This disruption predisposes the gut to further *C difficile* colonization.[16] Fidaxomicin, in contrast, has a narrow spectrum of activity, minimal effect on normal intestinal microbiota and reduced rates of recurrent CDI.[16,17] However, it is prohibitively expensive for first-line treatment.[18] Novel antibiotics with a more narrow spectrum of activity, such as teicoplanin, ridinilazole, surotomycin, and cadazolid have recently been developed. Their role in the treatment of primary and recurrent CDI is currently being investigated.

Teicoplanin is a glycopeptide antibiotic used to treat primary and recurrent CDI.[6] A 2-year prospective observational study comparing teicoplanin with vancomycin found that teicoplanin resulted in a significantly higher clinical cure rate compared with vancomycin (90.7% vs 79.4%, $P = .013$) and a significantly lower recurrence rate (9.3% vs 34.3%, $P < .001$).[19] However, teicoplanin treatment neither accelerated resolution of diarrhea nor decreased overall mortality compared with vancomycin.[19]

Ridinilazole is a highly targeted, novel antibiotic that reduces *C difficile* toxins and spores but preserves normal intestinal microbiota.[6,20–22] Its mechanism of action is unknown but it is thought to disrupt cell division.[23] In a double-blind phase 2 trial comparing ridinilazole with vancomycin, ridinilazole was associated with superior post-treatment clinical response rates (66.7% vs. 42.4%; *P* = .0004).[24] Ridinilazole also was associated with non-inferiority to vancomycin for initial cure rate at the end of treatment.[25] A phase 3 trial is ongoing.

Surotomycin is a novel lipopeptide antibiotic that is highly selective for *C difficile* and minimally absorbed from the gastrointestinal tract.[6] In a phase 2 trial comparing surotomycin with vancomycin, surotomycin demonstrated superior clinical cure rates and lower recurrence rates.[26] However, results from phase 3 trials are conflicting. Of two parallel, double-blind phase 3 trials, one demonstrated clinical cure rates for surotomycin non-inferior to vancomycin,[27] whereas the other failed to show non-inferiority.[28] Neither study showed superiority of surotomycin over vancomycin.[27,28] Further studies are needed to clarify these results.[25]

Cadazolid is a novel oxazolidinone-type antibiotic that inhibits *C difficile* toxin and spore formation.[6] A phase 2 study found cadazolid had higher sustained clinical response rates compared with vancomycin.[29] However, in one of two phase 3 trials assessing clinical cure, cadazolid failed to demonstrate non-inferiority to vancomycin. The results preclude further development of cadazolid for the treatment of CDI.[30]

In contrast to antibiotics, monoclonal antibodies, such as bezlotoxumab, preserve intestinal microbiota[31] and do not promote antibiotic resistance. Bezlotoxumab binds to toxin B, thereby neutralizing its cytotoxic effects.[7,31] Its role in the treatment of primary CDI is unclear, so it is not currently indicated for primary episodes of CDI.[6] However, it is used in combination with standard antibiotic therapy to reduce the recurrence of CDI in patients at high risk of recurrence.[6,31] In phase 3 trials, a combination treatment of bezlotoxumab and antibiotics was associated with a 38% lower rate of recurrence compared with antibiotics alone.[32]

Other potential therapeutic options for primary CDI are spore-based therapy, where non-toxigenic *C difficile* spores are administered to preferentially colonize the gut,[25] and FMT. Although FMT is used successfully as salvage therapy in recurrent CDI, its efficacy and safety in treating primary CDI have not yet been established.[16] In addition to new therapeutic agents, vaccination against *C difficile* offers a new option for CDI management. Currently, two vaccine candidates are being developed.[25] A phase 3 trial

for the Pfizer Clover vaccine is ongoing,[33] and the Valneva VLA84 vaccine has completed a successful phase 2 trial and is awaiting funding for a phase 3 trial.[34]

Conclusion

While CDI remains a major medical challenge, recent advances have improved current practices.[25] Infection prevention strategies and antibiotic stewardship programs can reduce CDI rates. Novel antibiotics, antibiotic-sparing therapies, and vaccines are currently being developed that may replace metronidazole and vancomycin as the treatments of choice. These emerging therapies, along with improved prevention strategies, provide encouraging prospects for the future management of CDI.

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