Guidelines and Future Trends in *Clostridioides difficile* Diagnosis, Management, and Prevention

By Suzanne Morris, DVM

Clostridioides difficile, formerly known as *Clostridium difficile*, is the most common nosocomial pathogen in the United States, with increasing global incidence.[1,2] *C difficile* infection (CDI) most often occurs from hospitalization, antibiotic and immunosuppressive use, and after organ or stem cell transplant.[3,4] However, up to 40% of CDIs, which are transmitted by the fecal-oral route, are contracted outside of healthcare settings.[1,2,5] A gram-positive spore-producing anaerobe, *C difficile* classically causes diarrhea, hematochezia, abdominal discomfort, pseudomembranous colitis, and, rarely, megacolon and ileus.[2,5,6] Complications can include flare-up of inflammatory bowel disease and death.[2] The pathogenic effects of *C difficile* derive from its exotoxins A (TcdA) and B (TcdB), which disrupt the epithelial tight junctions of the gastrointestinal tract.[6]

CDI diagnosis is based on clinical signs along with a positive stool test result.[2] Enzyme-linked immunoassays (EIAs) were used to detect TcdA and TcdB prior to polymerase chain reaction (PCR) testing, which has become the more frequently selected test.[7] There is currently a suspected overdiagnosis of CDI due to the increased use of PCR testing, which detects the toxin-producing gene, but not the toxin.[3,7] Hence, a positive PCR test result does not distinguish between a colonized patient (asymptomatic carrier) and an infected patient.[3,7] Misdiagnosis of CDI in a carrier can lead to unnecessary treatment resulting in in immunosuppression, additional hospitalization, and antibiotic resistance.[3]

To decrease the overdiagnosis of CDI, diagnostic stewardship has been incorporated into clinical guidelines and diagnostic algorithms.[3,7,8] Criteria for PCR testing comprise clinical signs (eg, diarrhea, abdominal discomfort, fever), CDI risk factors (eg, age over 60 years, antibiotic use, surgery), and testing only unformed stool.[3] The Infectious Diseases Society of America (IDSA) also recommends pairing PCR testing with EIA, pairing a glutamate dehydrogenase (GDH) test with EIA or PCR, or combining all three assays.[2,4,7,8]

A recent study of organ transplant recipients paired a computerized diagnostic algorithm with hospital staff education, the combination of which decreased *C difficile* testing by 33% ($P < .001$). In the study, duplicate negative ($P = .004$) and duplicate positive results ($P = .023$) were decreased.[3] The same study found no significant difference in mortality rates between the algorithm-intervened group and the non-intervened group ($P = 0.742$).[3] In a clinical trial review, Kong et al discussed the possibility that PCR testing may be undermining therapeutic evaluation by referring to a trial that involved an oral microbiota treatment wherein "only 15 of 31 patients who tested positive by PCR also tested positive for the presence of *C difficile* free toxin upon retesting."[7] Therefore, more than one type of test on unformed stool has been recommended by the IDSA and the Society for Healthcare Epidemiology of America (SHEA).[2,8]

The treatment of CDI has traditionally involved antibiotics and continues to do so, albeit with additional considerations. Metronidazole has historically been used to treat CDI, but the US Food and Drug Administration (FDA), IDSA, and SHEA discourage its use for this purpose.[2]

Vancomycin is recommended by the IDSA and SHEA for the treatment of an initial CDI episode. Metronidazole is considered appropriate if no other recommended therapeutics are available.[2,8] However, neither vancomycin nor metronidazole are sporicidal, which could allow for recurrent CDI (rCDI).[2] Fidaxomicin, the most recently approved therapeutic for CDI, is bactericidal and binds *C difficile* spores and, like vancomycin, is indicated for initial CDI occurrence.[1,2] Rifaximin is an antibiotic with gut-specific broad-spectrum action that is recommended in the treatment of rCDI by the IDSA/SHEA, but is not recommended for CDI treatment by the FDA.[2,8] The IDSA and SHEA recommend that antibiotic use be altered for treatment of rCDI episodes.[2,8] Additional antibiotics cadazolid, ridinilazole, and surotomycin are under investigation.[2] Pulse antibiotic therapy has been investigated and has reduced rCDI rates in recent studies.[1,2]

The antibiotics used in treating CDI can cause gut microbiome disruption, which may result in dysbiosis, a predisposing factor for CDI and rCDI.[1] Reintroducing a healthy microbiome via fecal microbiota transplantation (FMT) dates to fourth century China and has been effective in rCDI treatment; although, FMT is still considered investigational, and long-term safety data are scant.[1,2,4,8] FMT evaluation is complicated by its variability (eg, differences in donor, volume, storage methods, and administration). Investigations into these variations have suggested that frozen and fresh stool produce similar efficacy and that implantation in the lower GI tract improved cure rates over upper GI tract implantations.[2]

Trials have shown decreased rCDI rates with the use of nontoxigenic *C difficile* spores, which hinder the growth of toxigenic strains.[2] Other stool elements may play a therapeutic role, as suggested by one case series in which the transfer of sterile filtrates eliminated CDI patients' symptoms.[1] Current trials are evaluating standardized microbiota products including spore-containing oral capsules.[1,2] Immune system target therapeutics have also been employed against CDI. Bezlotoxumab, a TcdB-targeting antibody, has been approved by the FDA for rCDI treatment.[1,2] In a phase 3 trial, bezlotoxumab reduced rCDI rates but was not curative for CDI.[1]

Additional therapeutics under investigation target *C difficile* exotoxins, pathogenic spores, and exotoxin-induced mucosal damage. Recent molecular research involved the construction of ankyrin repeat proteins (DARPins) that bind and neutralize TcdB, with the end goal being an orally administered anti-toxin protein.[6] One particular constructed DARPin has demonstrated a 33-fold greater potency than bezlotoxumab in TcdB neutralization.[6] This same constructed dimer improved survival in mice challenged with TcdB ($P = 0.04$).[6] DARPin protease resistance, however, requires improvement.[6] Another approach employs iron oxide nanoparticles (IONPs) that are treated with vancomycin (van-IONPs).[5] The IONPs function as a spore-neutralizing therapeutic.[5] In a recent investigation, IONPs were shown to have a high affinity for binding *C difficile* spores and prevented spore germination.[5] For spores already undergoing germination, the antibiotic component of van-IONPs significantly inhibited germinated spore growth as compared with treatments comprised of IONPs or vancomycin alone ($P < 0.001$).[5]

Although promising, these molecular target investigations are not currently clinically applicable, unlike misoprostol. The authors of a study of misoprostol use and CDI in mice aimed to address the association between nonsteroidal anti-inflammatory (NSAID) use and CDI.[9] NSAIDs inhibit prostaglandin production, and studies have shown that NSAID use disrupts the GI microbiome

and tight junction maintenance.[9] Prostaglandins mediate the maintenance of tight junctions, which are protective against bacterial translocation.[9] Misoprostol, a PGE_1 analogue FDA-approved for the treatment of upper GI tract ulceration, was proposed in this recent study as a potential protective agent against the tight junction-destabilizing effects of *C difficile* toxins.[9] Zackular et al found that misoprostol treatment of *C difficile*-challenged mice provided dose-dependent protection against CDI mortality and clinical signs ($P < .05$).[9] The study also showed that misoprostol treatment allowed for significant microbiota recovery following antibiotic challenge in mice ($P < .001$).[9] Although further investigation is recommended by the study authors, they proposed a potential repurposing of misoprostol for CDI treatment or prevention.[9]

Basic preventive measures against CDI or rCDI involve isolating colonized and symptomatic hospitalized patients and using sporicidal disinfectants, personal protective measures, and hygienic practices (eg, gloves, gowns, and handwashing) while caring for these patients.[4,8,10] Prevention strategies proposed in relation to CDI also involve antimicrobial stewardship, which entails judicious antibiotic use in patients in order to avoid gut microbiota disruption.[4] Other proposed CDI prevention strategies include the use of probiotics, prophylactic antibiotics, bezlotoxumab, and FMT.[4] Probiotics, although not FDA-approved for such purposes, have been proposed as a preventive measure against CDI.[4] However, their efficacy and safety have yet to be demonstrated—particularly with respect to transplant or immunosuppressed patients.[4,8]

Oral vancomycin was investigated as a prophylactic in transplant patients. The vancomycin-treated patients developed no CDIs as compared with 20% of the patients who received no prophylaxis ($P < 0.001$).[4] However, because of the microbiome-disruptive activity associated with antibiotic use, cautious assessment is recommended prior to starting vancomycin prophylaxis.[2] A study of fidaxomicin prophylaxis in transplant patients found that fidaxomicin significantly reduced CDI at 30 days post-treatment compared with placebo ($P = .0014$).[4] Bezlotoxumab has been studied as an rCDI preventive in immunosuppressed patients and has significantly reduced rCDI rates.[4]

The efficacy of FMT in treating rCDI has prompted the consideration of its role as a preventive, and a study is currently underway to evaluate its use in CDI prevention.[4] Latter-stage clinical trials are ongoing for multiple anti–*C difficile* vaccines, which include recombinant and inactivated forms of TcdA and TcdB and could be considered for use in higher-risk groups.[1,2]

The complexity of treating CDI with a potentially exacerbating antibiotic regimen has led to the reevaluation of standard treatments as well as of other therapeutic and prophylactic approaches. Clinical trials are underway to elucidate optimal means of gut microbiome modulation.[1] Additionally, dietary influences have been implicated in microbiome composition and further studies of such environmental influences may present possible dietary prevention or management of CDI in the future.[9] In most of the discussed potential therapeutic and prophylactic approaches to CDI, additional studies are recommended.[1,2]

References

[1] Khanna S, Gerding DN. Current and future trends in *Clostridioides (Clostridium) difficile* infection management [Published online ahead of print]. *Anaerobe*. 2019;pii: S1075-9964(19)30077-0. doi: 10.1016/j.anaerobe.2019.04.010. Accessed June 28, 2019.

[2] Saha S, Khanna S. Management of *Clostridioides difficile* colitis: insights for the gastroenterologist [Published online May 6, 2019]. *Therap Adv Gastroenterol*. 2019;12:1756284819847651. doi: 10.1177/1756284819847651. Accessed June 28, 2019.

[3] Madden GR, Sifri CD. Reduced *Clostridioides difficile* tests among solid organ transplant recipients through a diagnostic stewardship bundled intervention [Published online May 28, 2019]. *Ann Transplant*. 2019;304-311. doi: 10.12659/AOT.915168. Accessed June 28, 2019.

[4] Revolinski SL, Munoz-Price LS. *Clostridioides difficile* in transplant patients: early diagnosis, treatment, and prevention. *Curr Opin Infect Dis*. 2019;32(4):307-313. doi: 10.1097/QCO.0000000000000560. Accessed June 28, 2019.

[5] Chen YH, Li TJ, Tsai BY, et al. Vancomycin-Loaded nanoparticles enhance sporicidal and antibacterial efficacy for *Clostridium difficile* infection [Published online May 24, 2019]. *Front Microbiol*. 2019;10:1141. doi: 10.3389/fmicb.2019.01141. Accessed June 28, 2019.

[6] Simeon R, Jiang M, Chamoun-Emanuelli AM, et al. Selection and characterization of ultrahigh potency designed ankyrin repeat protein inhibitors of *C. difficile* toxin B [Published online June 24, 2019]. *PLoS Biol*. 2019;17(6):e3000311. doi: 10.1371/journal.pbio.3000311. Accessed June 28, 2019.

[7] Kong LY, Davies K, Wilcox MH. The perils of PCR-based diagnosis of *Clostridioides difficile* infections: Painful lessons from clinical trials [Published June 12, 2019]. *Anaerobe*. 2019. pii: S1075-9964(19)30098-8. doi: 10.1016/j.anaerobe.2019.06.001. Accessed June 28, 2019.

[8] McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):987-994. doi: 10.1093/cid/ciy149.

[9] Zackular JP, Kirk L, Trindade BC, Skaar EP, Aronoff DM. Misoprostol protects mice against severe *Clostridium difficile* infection and promotes recovery of the gut microbiota after antibiotic perturbation [Published online June 17, 2019]. *Anaerobe*. 2019;pii: S1075-9964(19)30103-9. doi: 10.1016/j.anaerobe.2019.06.006. Accessed June 28, 2019.

[10] FAQs for clinicians about *C. diff*. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/cdiff/clinicians/faq.html#anchor_1529601768432 Reviewed December 17, 2018. Accessed July 2, 2019.