INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Clostridioides Difficile*

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Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a clinical review of treatment of *Clostridioides difficile* Infection (CDI) at the Winter 2023 NPTC meeting. Prior to this review, the National Core Formulary (NCF) included metronidazole as a treatment option for management of this condition. Following clinical, pharmacoeconomic and IHS utilization trend analysis, the NPTC voted to **ADD oral vancomycin to the NCF.**

CDI is one of the most common healthcare-associated infections among adults and is a significant cause of morbidity, mortality, and healthcare associated utilization and costs. CDI is estimated to cause almost half a million illnesses in the United States each year, and an estimated 29,300 deaths annually. The organism is spread via the oral-fecal route and involves a disruption in fecal microbiota. CDI occurs when the bacterium produces a toxin that causes diarrhea and inflammation of the colon and is the causative organism of antibiotic-associated colitis.[22]

Discussion:

CDI is defined as ≥3 unformed stools in a 24-hour period without an alternative explanation and a positive stool test for C. difficile. Clinical spectrum of infection ranges from colonization to mild, moderate, and severe or fulminant infection. Antibiotic exposure, previous CDI, age >65, exposure to healthcare settings, as well as having underlying immunocompromising conditions increase a person's risk for developing CDI. People are 7 to 10 times more likely to get CDI while taking an antibiotic and during the month after, and approximately 1 in 6 patients who get CDI will get it again in the subsequent 2-8 weeks.[19-20]

Management options include both pharmacologic and non-pharmacologic interventions. Infection control measures, antibiotic stewardship efforts, and appropriate pharmacologic treatment options are effective ways to reduce the incidence of CDI. Testing algorithms should include a highly sensitive and specific testing modality in order to help distinguish colonization from active infection.[4]

In non-severe CDI, the American College of Gastroenterology and Infectious Disease Society of America recommend the use of fidaxomicin or oral vancomycin given orally for 10 days. Alternatively, if previously mentioned agents are unavailable, metronidazole may be considered for treatment in low-risk patients. Metronidazole should be limited to one course and not considered for treatment of a second recurrence or for prolonged therapy because of the potential neurotoxicity risk associated with this medication. [4-5.] A Cochrane review of 22 trials concluded that vancomycin was more effective than metronidazole (72% vs. 79%, RR 0.90, 95% CI: 0.84 to 0.97) and that fidaxomicin was more effective than vancomycin (71% vs. 61%, RR 1.17, 95% CI: 1.04 to 1.31) for achieving symptomatic cure.[8] Additionally, a meta-analysis by Di et al. found metronidazole to be inferior to vancomycin in both initial cure and sustained cure rates (RR 0.91, 95% CI: 0.84-0.98; *p*=0.02 and RR 0.88, 95% CI: 0.82-0.96; *p*=0.003). Inferiority of metronidazole was even more pronounced in patients with moderate to severe disease. [21] Finally, Louie et al. assessed clinical cure and recurrence rates when comparing fidaxomicin to vancomycin for treatment of CDI. Fidaxomicin was found to be non-inferior when assessing rates of clinical cure and fewer patients in the fidaxomicin group had CDI recurrence within 30 days (modified ITT: 15.4% vs 25.3%; *p*=0.005, Per Protocol: 13.3% vs. 24%; *p*=0.004).[6] In the case of first CDI recurrence, fidaxomicin or tapered or prolonged courses of oral vancomycin is recommended.

Based on the MODIFY trials, adjunct therapy with bezlotoxumab resulted in significant reductions in CDI recurrence compared with placebo (17% vs 28% in MODIFY I; 16% vs 26% in MODIFY II; *p*<0.001).[15] It may be appropriate to utilize this adjunctive therapy in patients experiencing recurrence or with additional risk factors for recurrence. However, caution is advised when considering the use of bezlotoxumab in patients with heart failure due to unexplained increased risk of heart failure noted (2.2% BEZ vs 0.9% placebo) for patients with underlying congestive heart failure in phase III trials. Additionally, bezlotoxumab should only be used in conjunction with antibacterial drug treatment of CDI. Use of rifaximin may also be useful against recurrent CDI as adjunctive therapy following oral vancomycin treatment taking into consideration potential resistance, high cost and lack of randomized, controlled trials (RCTs) to support its use. Studies with larger, more diverse populations should be conducted before efficacy of rifaximin can be conclusively stated.

Furthermore, fecal microbiota transplantation (FMT) can also be considered in second or subsequent CDI recurrence.[5] Reintroduction of normal flora via donor feces is thought to correct the imbalance and re-establish normal bowel function. A systematic review and meta-analysis by Du et al. found that oral FMT resulted in ~82% efficacy which was similar to that achieved with colonoscopy-based FMT administration. Secondary analysis found no difference in efficacy between various formulations of oral FMT although not compared directly. Due to heterogeneity of included studies, non-inferiority could not be assessed therefore clinical applicability of this analysis is limited.[17] Recently, the FDA approved a novel

microbiota-based live biotherapeutic agent, Rebyota®, for prevention of recurrence of CDI in adults following antibiotic treatment for recurrent CDI. A phase III, double-blind, RCT evaluated efficacy and safety and found that this agent reduces CDI recurrence with low risk of adverse events.[18] There is an ongoing open-label study that includes a more diverse recurrent CDI population and also allows enrollment of patients with immunocompromised and chronic conditions. While oral FMT provides an attractive option that reduces procedural risk and costly resources, there are few large, prospective, well controlled studies that have compared oral FMT to well established colonoscopy-based FMT.

Initially, in severe CDI (leukocyte count >15 x 10^3/μL or renal failure with creatinine >1.5mg/dL) oral vancomycin or fidaxomicin is recommended. A meta-analysis of 5 RCTs found that, in severe CDI cases, clinical effects of vancomycin were significantly higher than those of metronidazole (RR 1.19, 95% CI: 1.02-1.39; *p*=0.03).[10] FMT should be considered for patients with severe and fulminant CDI (hypotension or shock, ileus, megacolon) refractory to antibiotic therapy. Ancillary strategies include discontinuation of inciting antibiotics and if further antibiotics are still indicated it is important to utilize the agent with narrowest spectrum and avoid agents associated with strong association with CDI (i.e., fluoroquinolones, clindamycin, and third- and fourth-generation cephalosporins). [22]

Findings:

CDI is a common and potentially life-threatening cause of diarrhea and colitis. Host factors (immune status and comorbidities), exposure (hospitalizations, community sources, long-term care facilities), and colonic microbiome disruption (antibiotics, other medications, surgery) all contribute as potential risk factors for developing CDI. Healthcare professionals can help prevent transmission of CDI by optimizing antibiotic prescribing, utilization of screening and diagnostic tests that provide the most accurate results, and by rapidly identifying and isolating patients with CDI. Supportive cares include good hand hygiene (soap and water), wearing personal protective equipment, and proper cleaning of the environment.[22-23]

CDI is a challenging problem and recurrence is common, occurring in ~20% of patients. Antibiotic therapy is the primary treatment, and in severe or recurrent cases, FMT may be used. The choice of antibiotic therapy depends on the severity of the infection, patient factors, and local antimicrobial susceptibility patterns. Based on recent literature and current guideline recommendations, fidaxomicin or oral vancomycin should be used over metronidazole as first line treatment.

Metronidazole is a relatively inexpensive and well-tolerated however, use should be limited to patients with an initial episode or non-severe CDI where access to vancomycin or fidaxomicin is limited. Vancomycin is the drug of choice for severe CDI and multiple trials have shown that vancomycin is more effective than metronidazole. Fidaxomicin, a newer oral antibiotic has been shown to be more effective than vancomycin in preventing *C. diff* recurrence. It may be appropriate to consider additional adjunctive therapies with bezlotuxumab or oral FMT in patients with recurrent or refractory CDI when appropriate antibiotic treatments have failed.[4]

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