Long-Term Care Updates

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C. difficile infection in adults: updated IDSA/SHEA treatment guidelines

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Introduction

Clostridioides difficile (*C. difficile*) is a gram-positive toxin-producing bacillus that can cause diarrhea upon infection. Its vegetative spores transmit through a fecal-oral route and cause symptoms that can range from watery diarrhea to life threatening pseudomembranous colitis, toxic megacolon, perforation of the colon, and sepsis. *C. difficile* infection (CDI) is most often associated with the use of antibiotics such as clindamycin, broad spectrum cephalosporins or penicillins, and fluoroquinolones.[1]

CDI is one of the major causes of nosocomial or healthcare acquired diarrhea in the United States with an estimated 500,000 cases occurring annually. CDI is also a major concern in long term care (LTC) facilities.[2] It is estimated that 36% of CDI cases occurring every year are associated with LTC facilities. Geriatric patients, immune compromised individuals, chemotherapy recipients, and patients in healthcare facilities with or without antibiotic use are at higher risk for CDI. Infection recurrence is also of significant concern with rates as high as 20 to 30%. Forty to sixty percent of patients who have a recurrent infection are at risk of subsequent recurrence.[3] Because most patients in LTC facilities fit the high-risk category, CDI can be a cause of significant morbidity and mortality in this population.

CDI treatment is directed by clinical practice guidelines established by the Infectious Diseases Society of America (IDSA) and Society of Healthcare Epidemiology of America (SHEA). These organizations revise practice guidelines every two years and more frequently if needed. CDI treatment guidelines were updated in 2021 and incorporated some important changes.[4]

Treatment

Treatment of CDI depends on the severity of the infection and history of CDI for the patient. Guidelines include criteria for determining CDI severity as measured by white blood cell (WBC) count and serum creatinine (SCr) level.[4-6] Criteria for infection severity is summarized in Table 1.

Table 1. CDI severity classification[4-6]

Infection severity	Lab or symptom parameters
Non-severe infection	WBC count ≤15000 cells/mL AND SCr <1.5mg/dL
Severe infection	WBC count ≥15000 cells/mL OR SCr >1.5mg/dL
Fulminant CDI	Presence of hypotension/shock, ileus, or megacolon

The updated guidelines focus on treatment of CDI in adult patients and implement several new recommendations. Two of these are pertinent to treatment of an initial episode and first recurrence. A third recommendation addresses the use of an adjunctive treatment for recurrent CDI infections.[4] Recommendations for treatment of CDI are summarized in Table 2.

Table 2. IDSA/SHEA treatment recommendations for CDI in adults[4-6]

Infection type	Recommended treatments
Initial episode	Preferred: Fidaxomicin 200mg by mouth twice a day for 10 days Alternative: Vancomycin 125mg by mouth four times a day for 10 days Alternative for non-severe infection if other agents are unavailable: Metronidazole 500mg by mouth three times a day for 10-14 days
First recurrence	Preferred: Fidaxomicin 200mg by mouth twice a day for 10 days OR twice a day for 5 days followed by once every other day for 20 days Alternative: Vancomycin by mouth in a tapered and pulsed regimen Tapered/pulsed vancomycin regimen example: 125mg four times a day for 10-14 days, then twice a day for 7 days, then daily for 7 days, then every 2-3 days for 2-8 weeks Alternative if metronidazole was used for initial infection: Vancomycin 125mg by mouth four times a day for 10 days Adjunctive therapy: Bezlotoxumab 10mg/kg given intravenously (IV) once during administration of standard of care antibiotics (recommended for patients with CDI in previous 6 months; may also be considered in those with risk factors for recurrence)
Second or subsequent recurrence	Fidaxomicin 200mg by mouth twice a day for 10 days OR twice for 5 days followed by once every other day for 20 days OR Vancomycin by mouth in a tapered and pulsed regimen OR Vancomycin 125mg by mouth four times a day for 10 days followed by rifaximin 400mg by mouth three times a day for 20 days OR Fecal microbiota transplantation (after at least 3 episodes of appropriately treated CDI) Adjunctive therapy: Bezlotoxumab 10mg/kg IV given once during administration of standard of care antibiotics (recommended for patients with CDI in previous 6 months; may also be considered in those with risk factors for recurrence)
Fulminant infection	Vancomycin 500mg four times a day (given by mouth or via nasogastric tube) AND Metronidazole 500mg IV every 8 hours If ileus is present, consider adding rectal instillation of vancomycin (500mg in 100mL normal saline given as a retention enema every 6 hours)

After diagnosis of CDI is confirmed, antibiotics that may have caused the infection should be immediately discontinued to prevent further exacerbation of the disease. Since watery diarrhea is a hallmark symptom of the infection, fluid loss is a significant concern. A patient's fluid and electrolyte status should be closely monitored and replenished as needed.[6]

The 2021 guideline update recommends a treatment duration of 10 days as opposed to the previously recommended 14 days. A shorter treatment duration may have a smaller impact on the gastrointestinal tract microbiome.[7]

For patients with non-severe CDI, fidaxomicin is recommended as first line treatment for initial episodes.[4] Fidaxomicin is a macrolide antibiotic indicated for patients 6 years or older.[7] It was first approved in May 2011 shortly after the first CDI guidelines were published in 2010. Fidaxomicin is only indicated for treatment of *C. difficile* diarrhea as it has minimal systemic absorption and reaches high fecal concentrations. Minimal systemic absorption means less drug-related adverse events. The usual adult dose for initial CDI is 200mg twice a day for 10 days. Treatment duration can be individualized and extended to 14 days if clinical resolution (defined as resolution of diarrhea) is not achieved after 10 days.[7]

Prior to the 2021 CDI update, oral vancomycin was recommended as first line treatment. Since the approval of fidaxomicin, randomized controlled trials have compared vancomycin to fidaxomicin for CDI treatment. A combined analysis of four randomized controlled trials showed that there was no difference in clinical cure rates between fidaxomicin and vancomycin. However, fidaxomicin resulted in a higher sustained clinical response to infection 4 weeks after the end of therapy. Fidaxomicin did not cause an increase in drug-related adverse events or mortality. Several small cost-effective analyses were completed to compare fidaxomicin and vancomycin. It was deduced that even though fidaxomicin is more expensive in the short term, it is more cost effective in the long run due to sustained clinical response and lesser need for treatment of recurrent infections. Additionally, treatment with fidaxomicin may be advantageous as it is only dosed twice daily as compared to vancomycin which is dosed four times a day.[4]

Fidaxomicin is also recommended as the preferred treatment for first, second or subsequent recurrent CDI episodes. Standard or pulsed dose fidaxomicin can be used. Pulsed dose fidaxomicin can be achieved with 200mg twice daily for 5 days followed by 200mg once every other day for 20 days.[4] Both standard dose and pulsed dose regimens use the same number of tablets per treatment. Although standard dose fidaxomicin is effective at eliminating actively dividing *C. difficile* bacteria, it does not kill the vegetative spores. The purpose of using a pulsed dose is to eliminate the vegetative spores during the antibiotic free period.[7]

Vancomycin remains an acceptable option for the treatment of CDI if fidaxomicin is not available. The recommended standard dose is 125mg given orally four times a day for 10 days, but the dose may be pulsed or tapered for recurrent infections.[4]

Oral metronidazole is no longer recommended as first line for treatment of CDI as it was in the 2010 guidelines. Recently, use of metronidazole has been associated with an increase in treatment failure and an increased 30-day mortality for patients with severe disease.[7] Metronidazole remains an acceptable alternative for non-severe infections if no other options are available.[4]

Adjunctive therapy

The updated guidelines address the role of bezlotoxumab as adjunctive treatment for CDI.[4] Bezlotoxumab is a human monoclonal antibody approved by the FDA in October 2016. It binds to *C. difficile* toxin B and is approved for patients who are at least 18 years of age and are at high risk for CDI recurrence. The recommended dose is 10mg/kg given as a single dose intravenous infusion over 1 hour. Bezlotoxumab is not an antibiotic and should only be used in combination with an antibiotic

approved for CDI treatment. Caution should be used while using bezlotoxumab in patients with a history of congestive heart failure (CHF). Two phase 3 trials reported that patients treated with bezlotoxumab had a higher incidence of heart failure as compared to placebo. Risk of heart failure was more profound in patients with a history of heart disease.[9] The guidelines state that patients who are diagnosed with a recurrent CDI episode and have at least one risk factor for recurrence (age >65 years, history of CDI, immunocompromised, severe CDI, and infection with certain virulent strains) can benefit from a bezlotoxumab infusion. If bezlotoxumab availability and affordability is not an issue, it can be considered as adjunctive treatment for an initial episode of CDI with the presence of at least one other risk factor for recurrence.[4]

Conclusion

In conclusion, new guidelines recommend that oral fidaxomicin be used preferentially for the treatment of initial and recurrent CDI. However, vancomycin remains an acceptable alternative. Metronidazole should be avoided, but it can be used for non-severe infection if no other approved antibacterial agent is available. Bezlotoxumab can be considered as adjunctive therapy for patients with risk factors for recurrence.

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