Frequently Asked Questions About the Treatment of *Clostridioides difficile* Infection (CDI)

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1. Why is fidaxomicin recommended over vancomycin for treatment of initial and recurrent CDI? If fidaxomicin cannot be obtained, how suboptimal is vancomycin?

- In patients with initial CDI and recurrent CDI while clinical cure between vancomycin and fidaxomicin is comparable, fidaxomicin has a lower rate of recurrence (higher sustained response at 30 days).

As opposed to the “old” 2017 IDSA/SHEA CDI treatment guidelines, which recommended vancomycin or fidaxomicin as treatment for non-fulminant initial and recurrent episodes of CDI, in 2021 in a “focused update” of the IDSA/SHEA guidelines fidaxomicin is now recommended over oral vancomycin for the same indications.

For initial CDI, the new guidelines incorporate two additional RCTs (totaling four) evaluating the efficacy of fidaxomicin compared to oral vancomycin in patients with confirmed CDI. In a pooled analysis of these RCTs, when compared to vancomycin, fidaxomicin had comparable initial rates of CDI cure (RR 1.00, 95% CI 0.96-1.04) as well as increased sustained response four weeks after the end of therapy (RR 1.16, 95% CI 1.09-1.24) without an increased risk of adverse drug events.

To assess the benefit in patients with rCDI, pooled subgroup analyses of three RCTs was performed and the same pattern was observed: compared to vancomycin, fidaxomicin had comparable rates of clinical cure (RR 1.03, 95% CI 0.94-1.14) and an increase sustained response of CDI cure 30 days after end of antimicrobial therapy (RR 1.27, 95% CI 1.05-1.54). It should be noted that for rCDI, because subgroup analyses of randomized controlled trials may not have been adequately powered, recommendations favoring fidaxomicin over vancomycin in the 2021 guidelines are made with a low level of certainty. Currently there are no studies comparing the optimal regimen for multiply recurrent CDI, therefore we recommend an ID consult in patients with multiple recurrences.

Fidaxomicin is administered less frequently than vancomycin (2 vs 4 times daily) and some studies have shown increased cost effectiveness of fidaxomicin over vancomycin by reducing recurrent CDI. Obtaining fidaxomicin in the outpatient setting may be logistically challenging and prior authorizations may be needed, therefore, coordination of outpatient coverage should be started when fidaxomicin is initiated.

2. Can fidaxomicin be used in fulminant disease?

- There is insufficient data to recommend the use of fidaxomicin in patients with fulminant CDI.

There is insufficient data to formally recommend the use of fidaxomicin in patients with fulminant CDI. For the treatment of fulminant CDI, the 2021 IDSA/SHEA guidelines recommend the use of oral vancomycin with intravenous metronidazole and to consider the addition of rectal vancomycin for patients with ileus.

3. How should CDI be treated if a fidaxomicin course must be partially finished with vancomycin?

- Based on fidaxomicin pharmacokinetics, it is reasonable to start oral vancomycin therapy when the next dose of fidaxomicin is due to finish a combined 10-day course (see text for taper recommendations).
- Such a scenario may be encountered if an inpatient is started on fidaxomicin cannot get access to the drug on discharge.

Access to fidaxomicin upon discharge should be addressed early. There is no published literature or data to recommend how to adjust CDI therapy based in the setting of a regimen change midway through a treatment course. Considering that the half-life of fidaxomicin is estimated to be $11.7 \pm 4.80$ hours and both fidaxomicin and oral vancomycin are poorly absorbed after oral administration, it is reasonable to start oral vancomycin therapy.
4. **There is an alternative every other day dosing for fidaxomicin, how does this compare to the standard 10-day regimen?**
   - There is no data directly to suggest that efficacy of a standard 10-day course of fidaxomicin differs from an extended-pulse regimen.
   - A 10-day regimen is recommended to maximize patient adherence.

The extended-pulse regimen (every other day dosing) of fidaxomicin originated from an *in vitro* human gut model study that suggested that persistent fidaxomicin above inhibitory concentrations may prolong *C. difficile* suppression and facilitate gut microbiota recovery. Subsequently, the EXTEND trial comparing extended-pulse fidaxomicin (200 mg PO twice daily on days 1-5, then 200 mg once daily on days 7-25) with a standard regimen of oral vancomycin (125 mg PO 4 times daily for 10 days) found that 70% of patients treated with fidaxomicin achieved sustained clinical cure 30 days after treatment, compared to 59% in the vancomycin group (p=0.30). The findings of this trial were similar to previous trials demonstrating the advantage of 10-day regimens of fidaxomicin over vancomycin for sustained clinical cure and no study has directly compared the standard 10-day regimen to the extended-pulse regimen. Therefore, we recommend treating patients with the standard 10-day regimen of fidaxomicin, as every other day administration and 20 days of antimicrobial therapy may be challenging for patient adherence.

5. **When should bezlotoxumab be considered?**
   - Bezlotoxumab may be considered as adjunctive therapy in the following scenarios:
     - Recommended by Infectious Diseases
     - Recurrent CDI within the last six months
     - Initial CDI episode treated with oral vancomycin with 2 or more of the following risk factors for recurrence: Age ≥ 65, Immunocompromised host, Severe CDI
   - Bezlotoxumab did not show benefit vs. placebo in patients without risk factors, or in patients younger than 65 years, regardless of presence of risk factors. Due to limited data, it is unclear if adjunctive bezlotoxumab provides benefit when fidaxomicin is used as primary CDI therapy.

The 2021 IDSA/SHEA guidelines recommend the co-administration of bezlotoxumab with standard of care anti-CDI medications in those with recurrent CDI episode within the last six months (this is a conditional recommendation based upon very low certainty of evidence). They also state, when barriers of care are not an issue, patients with primary CDI episode and risk factors for recurrence (age ≥ 65, immunocompromised host, and severe CDI) may also benefit from receiving bezlotoxumab. The FDA acknowledges that the data on the use of bezlotoxumab when fidaxomicin is used as the standard of care antibiotic is limited. At SHC, we recommend the use of bezlotoxumab in addition to vancomycin therapy in those with recurrent CDI episode within the last six months and in those with initial CDI episodes with 2 or more risk factors (age ≥ 65, immunocompromised host, and severe CDI). If feasible for logistical and cost reasons, the administration of bezlotoxumab should preferably occur in the outpatient setting.
The efficacy of bezlotoxumab was demonstrated in two phase 3 randomized, placebo-controlled, clinical trials: MODIFY I and MODIFY II. In the MODIFY trials, the majority of patients (73%) had a first CDI episode and most patients (77%) had one or more risk factors for CDI recurrence. CDI treatment was predominantly vancomycin (48%) and metronidazole (47%). Only 4% received fidaxomicin. Compared with placebo, patients who received bezlotoxumab had less recurrence within 12 weeks (MODIFY I: 17% vs 28%, 95% CI -15.9--4.3, p<0.001; MODIFY II 16% vs 26%, 95% CI -15.5--4.3, p<0.001). The highest relative risk reduction for those with risk factors for recurrence was found in those with severe CDI (52.4%), ≥ 65 years old (50.9%), immunocompromised patients (46.8%), and ≥ 1 CDI episode in the past six months (39.2%). Of note, immunocompromise was not well defined in the studies, and severe CDI defined using the Zar score, which differs than the traditional guideline definition (elevated WBC or Scr). The Zar score ranges from 1 to 8, with 1 point given for age ≥ 60 years old, temperature > 38.3°C, albumin < 2.5 g/dL, and WBC > 15,000/mm³ within 48 hours and 2 points given for endoscopic evidence of pseudomembranous colitis and treatment in the ICU.

As mentioned earlier, only 4% of patients received fidaxomicin as primary CDI therapy, limiting generalizability to patients receiving fidaxomicin for first occurrence. In a multicenter retrospective cohort study evaluating the rate of CDI recurrence in patients receiving bezlotoxumab in addition to standard of care antibiotics, the rate of recurrence at 90 days was comparable in those who received vancomycin and fidaxomicin (vancomycin fixed dose 13.7%, vancomycin taper 18.3%, and fidaxomicin 15.2%, p=0.76). Of note, bezlotoxumab did not show significant benefit vs. placebo in patients without risk factors for recurrence and in patients younger than 65 years, regardless of presence of risk factors.

6. **Is bezlotoxumab effective in the treatment of an acute episode of CDI?**
   - No, the addition of bezlotoxumab to CDI antibiotic therapy (e.g. vancomycin, metronidazole, or fidaxomicin) does not influence rates of clinical cure in acute CDI.

No. Bezlotoxumab does not treat CDI and is only indicated as an adjunctive treatment to reduce the risk of recurrence. In phase 3 clinical trials, there was no difference in initial clinical cure for those who received bezlotoxumab and those who received placebo (80% vs 80%).

7. **What risk factors are strongly associated with recurrent CDI?**
   - Risk factors associated with CDI recurrence include: advanced age, immunocompromised host, history of inflammatory bowel disease, long-term proton-pump inhibitor (PPI) use, administration of antibiotics, and prior CDI episodes.
   - Among these, modifiable risk factors include systemic antibiotic and long-term PPI therapy, stewardship of these therapies is highly recommended in patients at risk for CDI or with a history of CDI.

Risk factors for CDI recurrence include prior CDI episodes, advanced age (30-65%), immunocompromised host (20%), history of inflammatory bowel disease (33%), long-term PPI use, and the administration of antibiotics during or after treatment of CDI. Recurrent CDI occurs in approximately 10-30% of patients who are treated with anti-CDI therapy. The risk of recurrence significantly increases with each subsequent CDI episode, with recurrence rates of 40-65% after the 2nd recurrence.

There are limited modifiable risk factors that can influence CDI recurrence. Therefore, it is essential to limit the unnecessary use of antibiotics and acid suppression therapy. The use of antibiotics has been associated with an increased incidence rate of 30-75%, while the use of PPIs is associated with a 50-60% increased risk. Limit repeat
antibiotic use and PPI use without a clear indication as these are the epidemiologic risk factors most associated with recurrence.

8. **What can be used to control diarrhea in patients with CDI?**
   - In patients with fulminant CDI or patients who are not yet on CDI therapy, antimotility agents should be avoided.
   - In patients with non-fulminant CDI who have been initiated on CDI therapy, antimotility agents may be considered on an as-needed basis, but should be used with caution.

Historically, administering antimotility agents to patients with CDI has led to bad outcomes. The 2017 IDSA/SHEA guidelines make no recommendation on antimotility agents, however they state that the administration of an antimotility agent such as loperamide may be used as long as it is given adjunct with anti-CDI therapy. This recommendation originates from a literature review describing 55 patients with CDI exposed to antimotility agents. Twenty-three patients who received anti-CDI therapy co-administered with an antimotility agent experienced no-complications, however thirty six patients in the study either died or had unknown outcomes. The 2021 ACG guidelines, state that the addition of psyllium husk as a bulking agent may help with diarrheal symptoms, but make no specific recommendation on symptomatic management of CDI diarrhea. In their discussion they state that antimotility agents should be avoided in untreated CDI and in patients with fulminant infection, however, they may be used on an as-needed basis once patients have initiated anti-CDI therapy.

9. **Can metronidazole monotherapy still be used to treat CDI?**
   - Metronidazole monotherapy is inferior to oral vancomycin (and, by extension, fidaxomicin) for clinical cure in most patients.
   - Metronidazole monotherapy may be considered in exceptional circumstances in non-severe CDI episodes in low-risk patients ≤ 65 years old when fidaxomicin and vancomycin are completely unavailable. In such circumstances, caution is advised.

The 2021 IDSA/SHEA guidelines recommend the use of metronidazole as monotherapy only in initial non-severe CDI episodes when fidaxomicin and vancomycin are unavailable. This recommendation remains unchanged from the 2017 iteration of the guidelines.

The recommendation to use metronidazole only as alternative therapy is supported by previously conducted randomized placebo controlled trials that have shown that oral vancomycin is superior to metronidazole. In the study by Zar et al., 150 patients were randomized to receive either vancomycin 125 mg 4 times daily or metronidazole 250 mg 4 times daily, the overall cure rate was 97% in the vancomycin group and 84% in the metronidazole group (p=0.006). In patients with severe CDI, the cure rate for vancomycin was 97% compared to 76% for metronidazole (p=0.02). In a separate study by Johnson et al., comparing 266 patients who received vancomycin 125 mg PO 4 times daily and 289 patients who received metronidazole 250 mg PO 4 times daily, the clinical success rate of metronidazole was 72.7% whereas vancomycin was 81.1% (p=0.02).

A large retrospective study has suggested that the use of metronidazole may be considered in patients with an initial episode of mild CDI in low-risk patients ≤ 65 years old. This study was conducted at 125 Veterans Affairs (VA) centers nationally and 3,656 patients with mild CDI were treated with oral metronidazole. The clinical success rate with oral metronidazole was found to be 89.7%. A multivariable analysis identified patients ≤ 65 years old were 1.63 times more likely to experience success (95% CI 1.29-2.06).
10. **What are the clinical considerations for antimicrobial prophylaxis for CDI if my patient is also receiving systemic antibiotics alongside CDI treatment?**

- There is very limited data to recommend extended anti-CDI treatment or anti-CDI prophylaxis. However, its use may be considered in those with a history of CDI with a high risk of recurrence.
- If extending anti-CDI treatment is being considered, ID consultation should be considered.

The use of systemic antibiotics alongside CDI treatment decreases clinical response and increase recurrence rates, therefore the risks versus benefits must be appropriately assessed. Consider obtaining an ID consult, as antimicrobials and duration of therapy may be optimized. There is limited data to suggest the routine use of long-term suppressive antibiotics or prophylaxis antibiotics in patients with a history of CDI. This is not addressed in the 2021 IDSA/SHEA guidelines, however the 2017 guidelines state that there is insufficient evidence to recommend extending CDI treatment beyond the standard treatment course or restarting CDI treatment empirically for those who require the use of antibiotics.

The 2021 ACG guidelines make “conditional recommendations with limited evidence” to consider long-term suppressive oral vancomycin to prevent recurrences in those who are not candidates for FMT, relapse after FMT, or require ongoing courses of antibiotics, and to consider oral vancomycin prophylaxis during systemic antibiotic use in patients with high risk of recurrence. High-risk patients are defined as those 65 years or older, immunocompromised, and previously hospitalized for severe CDI in the past 3 months. ID consultation should be considered in cases where long term suppressive oral vancomycin is being considered. Studied regimens for long-term suppressive therapy include vancomycin 125 mg PO daily (increase frequency to twice or three times daily if loose stools continue). A studied regimen for prophylaxis is vancomycin 125 mg PO daily continued until 5 days after completion of systemic antibiotics.

The use of oral vancomycin for long-term suppression and prophylaxis is not without consequences. In addition to increased cost, there is a risk of further disruption of the gut microbiome and theoretical selection for VRE, though studies thus far have failed to demonstrate this. The use of fidaxomicin for CDI prophylaxis is promising, but limited data exists. In an underpowered randomized controlled trial by Mullane et al., for adults undergoing hematopoietic stem cell transplant taking broad spectrum antimicrobials, fidaxomicin (200 mg daily) compared to placebo was associated with lower incidence of confirmed CDI (4.3% vs 10.7%, p=0.0014).

11. **What are the clinical considerations for use of probiotics?**

- Probiotics are not recommended for the prevention of CDI.
- Probiotics are discouraged in patients who are immunocompromised, have central lines, or have a compromised GI tract.

Available evidence for use of probiotic preparations (capsules, powder, yogurts) to prevent CDI occurrence is equivocal due to heterogeneity in studies, and these are not recommended for CDI prevention in the 2021 ACG guidelines and 2017 IDSA/SHEA guidelines (not addressed in 2021 guidelines). Use is discouraged in immunocompromised patients, patients with central lines, and in those with a compromised GI tract due to documented risk of superinfection with the probiotic organism.
12. Is there a vaccine for CDI?

- There is currently no vaccine for CDI.

Currently, there is no FDA approved vaccine for CDI, however there are ongoing clinical trials in this area.

Recently, the phase 2 study evaluating the safety of the *C. difficile* vaccine for adults age 65 to 85 found the vaccine to be safe, well tolerated, and immunogenic. The phase 3 *Clostridium Difficile Vaccine Efficacy Trial (CLOVER)* is ongoing with an anticipated completion date of September 2021.

References


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