JAMA Clinical Guidelines Synopsis

Treatment of Clostridioides difficile Infection

Kanika Sehgal, MBBS; Adam S. Cifu, MD; Sahil Khanna, MBBS, MS

GUIDELINE TITLE  ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections

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PRIOR VERSION  2013

DEVELOPER  American College of Gastroenterology (ACG)

FUNDING SOURCE  ACG

TARGET POPULATION Adults with suspected or diagnosed Clostridioides difficile infection (CDI)

MAJOR RECOMMENDATIONS

- Initial CDI should be treated with vancomycin or fidaxomicin (strong recommendation; moderate-quality evidence). Metronidazole may be considered in low-risk patients with nonsevere infection (strong recommendation; moderate-quality evidence).
- Fulminant CDI should be treated with high-dose vancomycin (strong recommendation; very low-quality evidence). Combination therapy with parenteral metronidazole can be considered (conditional recommendation; very low-quality evidence). If ileus is present, vancomycin enemas are recommended (conditional recommendation; very low-quality evidence). Severe or fulminant CDI refractory to antibiotic therapy may be treated with fecal microbiota transplantation (FMT) (strong recommendation; low-quality evidence).
- A first CDI recurrence is treated with tapered-pulsed vancomycin if vancomycin, fidaxomicin, or metronidazole was used initially (strong recommendation; very low-quality evidence) or with fidaxomicin if vancomycin or metronidazole was used initially (strong recommendation; moderate-quality evidence). Second or further CDI recurrences are treated with antibiotics followed by FMT (strong recommendation; moderate-quality evidence), which may be repeated for recurrences within 8 weeks (conditional recommendation; very low-quality evidence).
- Bezlotoxumab is recommended for high-risk patients for recurrence prevention (conditional recommendation; moderate-quality evidence).

Evidence Base

Clostridioides difficile infection is diagnosed by a stool assay for presence of the organism or the toxin in patients with otherwise unexplained diarrhea (≥3 watery or loose stools in 24 hours). A leukocyte count of 15 × 10⁹/L or greater or a creatinine level greater than 1.5 mg/dL defines severe CDI. Fulminant infection is defined by the presence of hypotension, shock, ileus, or megacolon. High-risk patients include those aged 65 years or older or who have had prior CDI, have severe CDI, or are immunocompromised.

Vancomycin or fidaxomicin is recommended for initial treatment of nonsevere CDI. Metronidazole is recommended only for low-risk patients. Fidaxomicin has been demonstrated to be noninferior to vancomycin for initial response (ie, resolution of diarrhea with treatment) and is associated with fewer recurrences (absolute risk reduction, 9.9%).

Fulminant CDI should be treated with high-dose vancomycin. Lower mortality has been observed with vancomycin and metronidazole (15.9%) vs vancomycin alone (36.4%; P = .03). If ileus is present, vancomycin enemas should be administered, although limited data exist to support this recommendation. Severe or fulminant CDI refractory to antibiotic therapy may be treated with FMT. A trial of 56 patients with severe refractory CDI demonstrated 75% efficacy for CDI resolution with single FMT infusions and 100% efficacy with multiple FMT infusions after vancomycin.

For recurrent infection, tapered-pulsed vancomycin is recommended. Tapered-pulsed vancomycin regimens (standard vancomycin course for 10-14 days followed by decreasing the dose by 25%-50% every 1-2 weeks with no skipped days and then pulsed at a 125-mg dose, skipping 1 to 2 days, for 2-4 weeks) are more effective than vancomycin regimens using pulse alone (weighted resolution rate, 83% vs 54%) or taper alone (weighted resolution rate, 83% vs 68%). Based on data from a clinical trial of 128 patients with recent CDI, fidaxomicin is recommended for recurrent CDI if vancomycin or metronidazole was used initially. Initial response

Summary of the Clinical Problem

Clostridioides difficile infection is a common nosocomial and community-acquired cause of diarrhea, with an estimated 453,000 cases per year in the United States. Treatment of CDI is based on severity and recurrence risk.

Characteristics of the Guideline Source

The ACG funded the guideline and commissioned experts in the management of CDI, who collaborated with the ACG’s Practice Param-

Table. Guideline Ratings

<table>
<thead>
<tr>
<th>Standard</th>
<th>Rating</th>
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<tbody>
<tr>
<td>Establishing transparency</td>
<td>Good</td>
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<tr>
<td>Management of conflict of interest in the guideline development group</td>
<td>Fair</td>
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<tr>
<td>Guideline development group composition</td>
<td>Fair</td>
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<tr>
<td>Clinical practice guideline-systematic review intersection</td>
<td>Fair</td>
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<tr>
<td>Establishing evidence foundations and rating strength for each of the guideline recommendations</td>
<td>Good</td>
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<tr>
<td>Articulation of recommendations</td>
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<td>External review</td>
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<td>Updating</td>
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<td>Implementation issues</td>
<td>Fair</td>
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was similar for vancomycin and fidaxomicin, but higher recurrences were seen with vancomycin (35.5% vs 19.7%; \( P = .045 \)).

If patients have experienced a recurrence of CDI, they are at an increased risk of further recurrences typically within 8 weeks (multiply recurrent CDI), for which antibiotics followed by FMT are recommended. This treatment regimen may be repeated for recurrent CDI (multiply recurrent CDI), for which antibiotics followed by FMT are recommended. This treatment regimen may be repeated for recur-

Benefits and Harms
Adoption of a guideline that recommends high-efficacy regimens should improve cure rates and reduce rates of recurrence. Treatment favored in this guideline, including vancomycin, fidaxomicin, bezlotoxumab, and FMT, can be expensive, and the shift from use of metronidazole will lead to higher initial costs. There is evidence supporting cost-effectiveness, specifically for fidaxomicin and FMT.

Discussion
These guidelines reflect the evolving evidence base for CDI treatment. Fidaxomicin and vancomycin are recommended over metronidazole, and fidaxomicin is the preferred antibiotic for high-risk patients. Intravenous bezlotoxumab is recommended to prevent recurrences in high-risk patients. Microbiota restoration therapies such as FMT effectively prevent recurrent CDI.

Areas in Need of Future Study or Ongoing Research
Most recommendations in this guideline are supported by moderate- to low-quality evidence. Rigorous trials supporting these therapies are needed. Data are needed to determine the positioning of prolonged vancomycin and fidaxomicin regimens in the treatment algorithm. An extended-pulsed fidaxomicin (same number of doses as a regular course) is more effective than standard-regimen vancomycin for sustained clinical cure owing to fewer recurrences.

Fidaxomicin is more cost-effective in patients with a high risk of recurrence (those aged \( \geq 65 \) years or with severe comorbidities, continued systemic antibiotics, or elevated creatinine), reducing the number needed to treat.

Data on FMT for acute CDI are limited; 1 trial with 21 patients demonstrated that FMT had similar efficacy as metronidazole. With high success rates of FMT but ongoing heterogeneity and newly reported serious adverse events such as Escherichia coli bacteremia and Shiga toxin-producing E coli infection, standardized stool-based microbiota restoration therapies and defined microbial consortia are being developed. The safety of FMT or standardized microbiota-based therapies as first-line therapy requires more evidence.

Nontoxicogenic C difficile administration for reducing recurrent CDI has shown promise in a phase 2 trial (NCT01259726), and a phase 3 trial is being planned. A trial investigating the efficacy of bezlotoxumab and FMT vs FMT alone in patients with inflammatory bowel disease and CDI is underway (NCT03829475). Oral vancomycin prophylaxis (NCT03462459) is being studied to prevent recurrences.

**Associated Guidelines and Other Resources**
Clinical Practice Guideline by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America: 2021 Focused Update Guidelines on Management of Clostridioides difficile infection in Adults
https://www.idsociety.org/practice-guideline/clostridioides-difficile-2021-focused-update/