JAMA Clinical Guidelines Synopsis

Diagnosis and Treatment of *Clostridium difficile* Infection

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GUIDELINE TITLE Diagnosis and Treatment of *Clostridium difficile* Infections in Adults and Children

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PRIOR VERSION 2010

DEVELOPER Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

FUNDING SOURCE IDSA and SHEA

TARGET POPULATION Patients with suspected or diagnosed *Clostridium difficile* infection (CDI)

MAJOR RECOMMENDATIONS AND RATINGS

- Patients with a high likelihood of CDI manifested by unexplained new-onset watery diarrhea can have a nucleic acid amplification test (NAAT) as a single diagnostic test. When institutional criteria for stool testing to be done only in patients with unexplained diarrhea are not present, a stool toxin test should be obtained as part of a multistep testing strategy to diagnose CDI (weak recommendation; low-quality evidence).
- In adults with a nonfulminant initial CDI episode, treat with vancomycin or fidaxomicin rather than metronidazole (strong recommendation; high-quality evidence).
- For fulminant CDI, use high-dose oral or nasogastric tube–administered vancomycin and intravenous metronidazole. If ileus is present, consider adding rectal vancomycin.
- For adults having their first CDI recurrence, avoid repeating the initial treatment regimen. Use vancomycin (weak recommendation; low-quality evidence) or, potentially, fidaxomicin if metronidazole was used initially. Use pulse-tapered vancomycin (weak recommendation; low-quality evidence) or fidaxomicin (weak recommendation; moderate-quality evidence) if vancomycin was used initially.
- For a second or subsequent recurrence, treat with pulse-tapered vancomycin (weak recommendation; low-quality evidence) or vancomycin for 10 days followed by rifaximin (weak recommendation; low-quality evidence) or fidaxomicin (weak recommendation, low-quality evidence) or use fecal microbiota transplantation (FMT) to treat adults in whom antibiotic therapy has failed (strong recommendation; moderate-quality evidence).

Summary of the Clinical Problem

Clostridium difficile is a common health care–associated infection in the United States with an increasing incidence of community-acquired disease that can be very severe and has a significant risk of mortality. Recurrent CDI is increasing disproportionately to primary CDI.[1] Management of CDI is determined by disease severity, history of CDI, and a patient's risk of recurrence.[2]

Characteristics of the Guideline Source

The guideline was developed and funded by the IDSA and SHEA. They convened a 14-member expert panel from the American Society for Health-Systems Pharmacists, the Society of Infectious Diseases Pharmacists, and the Pediatric Infectious Diseases Society (**Table**).[3] Panel members disclosed all conflicts regardless of relevancy but were not forced to recuse themselves for conflicts. The panel included the search used for the previous (2010) guideline and updated it with an extensive literature search including references through 2016. The panel evaluated the quality of evidence using GRADE methodology and determined the strength of the recommendations. The guideline provides a comprehensive overview of the diagnosis and management of CDI. Four clinically important recommendations in adults are covered herein.

Evidence Base

Recommendations regarding optimal diagnostic strategy for CDI were based on observational data. *Clostridium difficile* infection should be suspected in patients with acute diarrhea who have risk factors such as antibiotic exposure and should also be suspected in patients with chronic unexplained diarrhea. Enzyme immunoassays (EIAs) detecting *C difficile* toxins are less sensitive than either glutamate dehydrogenase immunoassays (GDH) or NAATs. Testing with NAAT alone in a low-risk population may lead to overdiagnosis owing to detection of *C difficile* carriers. Use of EIA alone leads to underdiagnosis because of its lower sensitivity. If institutional criteria for stool submission are not in place (testing only unformed stools in patients without other causes of diarrhea such as laxatives), multistep testing incorporating a toxin EIA is recommended (GDH followed by toxin arbitrated by NAAT for inconsistent results, or NAAT followed by toxin testing). If institutional criteria for

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Fair
Clinical practice guideline–systematic review intersection	Fair
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Fair
Updating	Good
Implementation issues	Fair

testing appropriate patients exist (increasing the probability of CDI), NAAT alone or multistep testing can be used.

For an initial CDI episode, the guideline recommends treating with vancomycin or fidaxomicin; metronidazole may be used if vancomycin or fidaxomicin are unavailable or contraindicated (eg, due to allergy). Pooled analysis from 2 randomized trials demonstrated higher rates of clinical response with vancomycin (vancomycin, 81.1% [210/259] vs metronidazole, 72.7% [202/278]).[3] Fidaxomicin is noninferior to vancomycin for clinical response (fidaxomicin, 88% vs vancomycin, 86%) but more effective for preventing recurrence (recurrence rate: fidaxomicin, 15.4% vs vancomycin, 25.3%; difference in modified intention-to-treat analysis was 9.9%; 95% CI, −16.6% to −2.9%; $P = .005$).[4]

There are limited data to guide treatment of a first recurrence. The guideline recommends that the same regimen used initially not be used to treat a recurrence. Thus, if metronidazole was used initially, vancomycin or, potentially, fidaxomicin are recommended, given their superior efficacy and lower adverse event rate compared with metronidazole. In a study of 128 patients with first recurrence, rates of second recurrence were lower with fidaxomicin compared with vancomycin (19.7% vs 35.5%).[5] Tapered-pulse vancomycin or fidaxomicin may be used if vancomycin was used initially.

Multiple randomized trials have demonstrated that fresh or freeze-thawed donor FMT is more effective than vancomycin or autologous FMT in patients with multiply recurrent CDI.[6] The guideline recommends that FMT be considered for multiply recurrent CDI after failure of antibiotic treatments (at least 2 recurrences; ie, 3 CDI episodes).

Benefits and Harms

Clostridium difficile infection is less common than antibiotic-associated diarrhea and irritable bowel syndrome. There is significant concern about overdiagnosis and subsequent overtreatment of CDI with increasing use of NAATs, especially when applied inappropriately to patients who do not have diarrhea or for patients with another cause of diarrhea. This can lead to CDI overdiagnosis and delay in diagnosis and treatment of the actual underlying cause. Overdiagnosis can be countered by appropriate patient selection (eg, testing only unformed stools) and using multistep testing to reduce false-positive test results.[7] The increased cost of multistep testing (GDH plus toxin arbitrated by NAAT, or NAAT plus toxin) may be offset by decreased CDI overdiagnosis and decreased hospital penalties by regulatory agencies due to CDI.

Considering recent data on treatment efficacy, the guideline recommends more effective initial therapies (vancomycin or fidaxomicin over metronidazole) for CDI to reduce treatment failure and recurrence. The guideline did not consider drug costs. Fidaxomicin, vancomycin, and FMT are more expensive than metronidazole, but the costs of these drugs could be offset by fewer recurrence rates.

Discussion

This guideline includes significant changes to both testing and treatment recommendations for CDI. A multistep algorithm and recommended modes for diagnosing CDI are included based on whether stool testing guidelines are followed at an institution. The 2010 guideline did not definitively recommend a single testing mode. The 2010 guideline recommends using laboratory markers of elevated leukocyte count and creatinine to define the severity of CDI and guide therapy (metronidazole or vancomycin).

Areas in Need of Future Study or Ongoing Research

More sensitive EIA toxin tests are being developed and may eventually replace multistep testing. Studies of various FMT preparations and delivery techniques have demonstrated its short-term efficacy and safety. The long-term safety of FMT is being evaluated in a prospective national registry of 4000 FMT recipients and several ongoing clinical trials. Narrower-spectrum antibiotics for treating CDI, such as ridinilazole, are being developed. A monoclonal antibody against toxin B, bezlotoxumab, was recently approved for treatment of CDI in patients at high recurrence risk based on 2 trials that demonstrated lower recurrence rates with adjunctive bezlotoxumab vs placebo (17% vs 28% and 16% vs 26% in the 2 trials).[8]

Related guidelines and other resources

American College of Gastroenterology Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections; 2013

ARTICLE INFORMATION

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