Clinical Guideline Highlights for the Hospitalist: Diagnosis and Management of *Clostridium difficile* in Adults

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TARGET POPULATION: Adult and pediatric patients at risk for or diagnosed with *Clostridium difficile* infection based on a literature review with a defined search period of 2009–2016. This review will focus on adult patients.

Clostridium difficile, now referred to as *Clostridioides difficile* (*C. difficile*), is the most commonly identified cause of healthcare-associated infection among adults in the United States.[1] Because *C. difficile* infection results in significant mortality and inpatient costs, its persistence threatens to undermine patient safety and the value of healthcare delivery.[1] A standardized, evidence-based approach to diagnosis and management is crucial. However, inconsistencies remain with regard to the appropriate threshold for testing, the type of diagnostic tests used, and treatment. Knowledge of these areas has progressed since the publication of the previous *C. difficile* guidelines in 2010. These guidelines contain 53 recommendations across 35 sections based on a systematic weighting of the strength of recommendation and quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation system. Herein, we have chosen to highlight five of these recommendations most relevant to hospitalists.

KEY RECOMMENDATIONS FOR THE HOSPITALIST

Recommendation 1. Patients with unexplained and new-onset ≥3 unformed stools within 24 hours are the preferred target population for testing for *C. difficile* infection *(weak recommendation, very low quality of evidence)*. Do not perform repeat testing (within seven days) during the same episode of diarrhea and do not test stool from asymptomatic patients (*strong recommendation, moderate quality of evidence*).

In the recent past, healthcare facilities employed *C. difficile* tests with limited sensitivity, leading to frequent and repeat testing of hospitalized patients. Excess testing puts patients at risk for false positive results and unnecessary or prolonged treatment courses. Proper testing requires consideration of pretest probability, including analysis of the alternative causes of diarrhea. Duration of hospitalization and antibiotic exposure are the most significant modifiable risk factors for *C. difficile* infection in adult inpatients.[2] Laxative use within the previous 48 hours, enteral tube feeding, and underlying medical conditions, such as inflammatory bowel disease (IBD), are common causes of improper testing.[3] This decision may be difficult, as some underlying causes of diarrhea, such as IBD and enteral tube feeding, also increase the risk of *C. difficile* infection.[3] Laboratories can help by rejecting specimens that are not liquid or soft and employing a multistep algorithm using a combination of nucleic acid testing, antigen testing, and toxin detection to maximize sensitivity and specificity. Because recurrent *C. difficile* infection is relatively common, repeat testing is appropriate only for recurrence of symptoms following successful treatment and should focus on detection of *C. difficile* toxin because the persistence of the organism itself can occur after successful treatment.[4]

Recommendation 2. Either vancomycin (125 mg orally four times per day for 10 days) or fidaxomicin (200 mg twice daily for 10 days) is recommended over metronidazole for an initial episode of nonsevere or severe *C. difficile* infection (*strong recommendation, high quality of evidence*). For fulminant *C. difficile* infection, the regimen of choice is a vancomycin dos-

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age of 500 mg orally four times per day (per rectum every six hours if with ileus) in addition to intravenous metronidazole (*strong recommendation, moderate quality of evidence*).

For several decades now, metronidazole has been the primary antibiotic agent for initial treatment of nonsevere *C. difficile* infection. Two recent randomized, placebo-controlled trials, however, have found oral vancomycin to be superior to metronidazole for producing a clinical cure and resolution of diarrhea without recurrence.[5,6] Oral vancomycin remains the treatment of choice for severe *C. difficile* infection. Fidaxomicin, a recently FDA-approved antibiotic, can also be used as initial treatment in place of oral vancomycin. One study found fidaxomicin to be superior to oral vancomycin for producing a sustained clinical response, that is, resolution of diarrhea at the end of treatment without recurrence 25 days later.[7] Fulminant disease, which is characterized by hypotension or shock, ileus, or megacolon, requires a higher dose of oral vancomycin (or vancomycin enema if with ileus) in addition to intravenous metronidazole.

Recommendation 3. Treat a first recurrence of *C. difficile* infection with oral vancomycin as a tapered and pulsed regimen rather than a second standard 10-day course of vancomycin or metronidazole *(weak recommendation, low quality of evidence)*.

Despite the improved treatment response with oral vancomycin, one in four patients will experience recurrence. For a first recurrence of *C. difficile* infection after a 10-day course of oral vancomycin, an extended taper or pulsed course of vancomycin should be attempted. Various regimens have been tried and found to be effective. For a second recurrence, providers can consider addition of rifaximin following oral vancomycin. Fecal microbiota transplantation is recommended for patients with multiple recurrences of *C. difficile* infection who have failed these antibiotic treatments.

Recommendation 4. Minimize the frequency and duration of high-risk antibiotic therapy (based on local epidemiology) and the number of antibiotic agents prescribed to reduce *C. difficile* infection risk *(strong recommendation, moderate quality of evidence)*.

Antibiotic stewardship is a necessary component of any successful effort to reduce *C. difficile* infections. Antibiotic stewardship programs, which are now commonplace in US hospitals, largely rely on educational initiatives or committee-based order review. Hospitalists should take a structured approach emphasizing the four critical questions of antibiotic prescribing: Does this infection require antibiotics? Have I ordered appropriate cultures and the correct empiric therapy? Can I stop, narrow, or switch to oral agents? Finally, what duration of therapy is needed at discharge?[8] Initial efforts should focus on the restriction of fluoroquinolones, clindamycin, and cephalosporins (except for surgical antibiotic prophylaxis) given their known risk to cause *C. difficile* infection.

Recommendation 5. Contact precautions should be maintained for at least 48 hours after diarrhea has resolved *(weak recommendation, low quality of evidence)*.

Although *C. difficile* is undetectable in stool samples from most patients by the time diarrhea has resolved, skin and environmental contaminations remain high. No studies demonstrating a benefit to further extending contact precautions beyond 48 hours after resolution of diarrhea are yet available.

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Methods in Preparing Guidelines

The guideline committee consisted of an interdisciplinary team of healthcare providers with extensive experience in the diagnosis, infection control, treatment, and management of *C. difficile*. The literature search accessed five different databases (Medline, Embase, Cochrane, Health Technology Assessment, and Database of Abstracts of Reviews and Effects), relevant journals, conference proceedings, and regulatory websites published over the search period of 2009-2016.

A major strength of these guidelines is the extensive work that went into their preparation. The committee reviewed over 14,000 pieces of literature and performed a detailed analysis of each one to determine the quality of evidence in support of each recommendation.

Sources of Potential Conflict of Interest or Bias

To reduce bias, the committee's work was funded by Infectious Disease Society of America and Society for Healthcare Epidemiology of America. Some authors received funding for work outside of this guideline by companies that manufacture diagnostic assays, vancomycin, and fidaxomicin. These potential conflicts were listed at the end of the article.

Generalizability of the Guideline

Not all studies included in the guideline contain exclusively hospitalized patients, but much of the guideline content is applicable to hospitalized patients. Because *C. difficile* infection is such a widespread public health problem and these guidelines represent a significant update in knowledge since 2010, the specific recommendations highlighted in this review will impact numerous hospitalists, regardless of the practice setting.

Areas in Need of Future Study

Based on the current literature, as well as statements in the guideline, we expect future guidance around potential screening for and isolation of asymptomatic carriers, including closer guidance on stool transplantation focusing on timing and route, as further data emerge in these areas.

Other Resources

- Grading of Recommendations Assessment, Development, and Evaluation system (http://www.gradeworkinggroup.org)
- Universal Screening for *C. difficile* in a Tertiary Hospital: risk factors for carriage and clinical disease (https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(19)30048-5/fulltext)
- Effectiveness of Isolating *Clostridium Difficile* Asymptomatic Carriers on the Incidence of Infections (https://clinicaltrials.gov/ct2/show/NCT03223415)
- Effect of Detecting and Isolating *Clostridium difficile* Carriers at Hospital Admission on the Incidence of C difficile

Infections (https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2516765)

- Clinical Trial Testing Fecal Microbiota Transplant for Recurrent Diarrheal Disease Begins (https://www.nih.gov/news-events/news-releases/clinical-trial-testing-fecal-microbiota-transplant-recurrent-diarrheal-disease-begins)

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