Diagnosis, Prevention, and Treatment of *C. difficile*: Current State of the Evidence

Focus of This Summary

This is a summary of a systematic review that evaluated the recent evidence regarding the accuracy of diagnostic tests and the effectiveness of interventions for preventing and treating *Clostridium difficile* (*C. difficile*) infection. The systematic review included 93 articles published between 2010 and April 2015. The full report, listing all studies, is available at *www.effectivehealthcare.ahrq.gov/c-difficile-update-report/*. This summary is provided to assist in informed clinical decisionmaking. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

C. difficile is a Gram-positive, anaerobic, spore-forming bacterium generally acquired through ingestion. Symptoms of *C. difficile* infection (CDI) can range from mild diarrhea to severe conditions such as pseudomembranous colitis and toxic megacolon that can result in death. The estimated mortality rate for health care-associated CDI ranged from 2.4 to 8.9 deaths per 100,000 in 2011. For people ≥65 years of age, the mortality rate was 55.1 deaths per 100,000.

Effective containment and treatment of CDI depends on accurate and swift diagnosis. CDI is diagnosed using clinical findings and tests such as: (1) nucleic acid amplification using loop-mediated isothermal amplification (LAMP) and the polymerase chain reaction (PCR), (2) tests for disease-generating *C. difficile* toxins (including immunoassays), and (3) test algorithms (these are two-step procedures: the first step is a fast screen for the presence of the organism using a test such as the glutamate dehydrogenase [GDH] assay; if the first test is positive, a second test for toxins is performed).

Efforts to prevent CDI include antimicrobial stewardship, the use of infection-control strategies such as handwashing, and immune-boosting strategies. Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials to reduce microbial resistance and decrease the spread of infections. Handwashing with soap and water is helpful for removing *C. difficile* spores, which are resistant to alcohol rubs or hand sanitizer. Measures that improve a patient's immune defenses include the use of probiotics to promote healthy gut flora and the maintenance of balanced nutrition.

Initial treatment of CDI commonly involves the use of oral antimicrobials such as metronidazole and vancomycin. Mild to moderate initial CDI is often treated with metronidazole, while severe initial CDI is often treated with vancomycin. Treatment with metronidazole and vancomycin can be problematic, however, as they have been implicated in the development of vancomycin-resistant enterococci in immunocompromised patients.

CDI recurs in 15 to 35 percent of patients who have had one previous episode and in 33 to 65 percent of patients who have had more than two previous episodes. Diagnosis and treatment of relapsed or recurrent CDI are challenging. Diagnosis of recurrent CDI is based on the recurrence of clinical symptoms, and repeat testing may not be required. Currently, clinicians choose from a variety of antimicrobials, dosing protocols, and adjunctive treatments (such as probiotics and fecal microbiota transplantation [FMT]) to manage relapsed or recurrent CDI.

The current review aimed to update a 2011 review regarding the accuracy of CDI diagnostic tests and the effects of interventions to prevent and treat CDI in adults.

Conclusions

Diagnosis of CDI: Nucleic acid amplification tests have high sensitivity and specificity for diagnosing CDI (high strength of evidence [SOE]). (*See Table 1.*)

Prevention of CDI: Strategies such as antibiotic stewardship and handwashing campaigns may help prevent CDI (low SOE). Further evidence is needed to confirm that prevention strategies impact patient outcomes such as CDI incidence. (*See Table 2.*)

Treatment of CDI: Vancomycin is more effective than metronidazole for the initial treatment of CDI (high SOE), while fidaxomicin is more effective than vancomycin for the prevention of recurrent CDI (high SOE). Physicians may take into consideration disease and patient characteristics, effectiveness, potential adverse effects, patient preferences, and costs when choosing an antibiotic to treat CDI. Lactobacillus probiotics, when used as an adjunct to antibiotic therapy, may prevent the recurrence of CDI (low SOE); additionally, probiotics are generally safe in otherwise healthy patients. There is low SOE that FMT may be effective for treating recurrent and relapsed CDI; however, there is consistent positive evidence for its effectiveness in patients with recurrent and relapsed CDI. (*See Tables 3, 4, and 5.*)

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Overview of Clinical Research Evidence

Table 1: Summary of Key Findings and Strength of Evidence for the Accuracy of Diagnostic Tests for *C. difficile* Infection

Note: Diagnostic testing is recommended in patients in whom there is a suspicion of CDI based on symptoms and history. CDI is suspected in patients with symptoms of diarrhea (≥3 loose stools in 24 hours) or ileus who have additional risk factors (including use of antibiotics or antineoplastic agents in the previous 8 weeks, hospitalization, and older age). Clinicians should consider the possibility of CDI in hospitalized patients who have unexplained leukocytosis. Testing of stool from asymptomatic patients is not recommended. Testing for *C. difficile* or its toxins should be performed only on diarrheal (unformed) stool, unless ileus due to *C. difficile* is suspected.*

Diagnostic Test	Outcome	No. Studies	Summary of Key Findings	Sensitivity or Specificity (95% CI)	Strength of Evidence
Nucleic Acid Amplification Test: loop-mediated isothermal amplification	Sensitivity	12	Sensitive for CDI	0.95 (0.90 to 0.97)	●●●
	Specificity	12	Specific for CDI	0.98 (0.96 to 0.99)	●●●
Nucleic Acid Amplification Test: polymerase chain reaction	Sensitivity	31	Sensitive for CDI	0.95 (0.93 to 0.96)	●●●
	Specificity	31	Specific for CDI	0.97 (0.96 to 0.98)	●●●
Immunoassays for *C. difficile* Toxins A/B	Sensitivity	58	Not sensitive for CDI	0.70 (0.66 to 0.74)	●●○
	Specificity	58	Specific for CDI	0.98 (0.97 to 0.99)	●●○
Tests for Glutamate Dehydrogenase	Sensitivity	10	Sensitive for CDI	0.90 (0.78 to 0.96)	●●○
	Specificity	10	Not specific for CDI	0.94 (0.89 to 0.97)	●●○
Test Algorithms†	Sensitivity	11	Not sensitive for CDI	0.73 (0.62 to 0.82)	●○○
	Specificity	11	Specific for CDI	1.00 (0.99 to 1.00)	●○○

CDI = *Clostridium difficile* infection; CI = confidence interval

* Information drawn from: Cohen SH, Gerding DN, Johnson S, et al; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010 May;31(5):431-55. PMID: 20307191.

† These are two-step procedures. The first step is a fast screen for the presence or absence of *C. difficile* using a test such as the glutamate dehydrogenase assay. If the first test gives a positive result, a second test for *C. difficile* toxins is performed.

Table 2: Summary of Key Findings and Strength of Evidence for Interventions To Prevent *C. difficile* Infection

Intervention	No. Studies	Summary of Key Findings	Strength of Evidence
Antibiotic Stewardship	6	Appropriate prescribing practices were associated with decreased CDI.	●○○
Handwashing Campaigns	1	Handwashing campaigns reduced CDI incidence (rates fell from 16.75 to 9.49 cases per 10,000 bed days).	●○○
Multicomponent Prevention Interventions**	4	Multicomponent interventions were sustainable over several years.	●○○

CDI = *Clostridium difficile* infection

** Multicomponent interventions consisted of using multiple prevention strategies to reduce CDI rates (e.g., the simultaneous use of education, isolation, handwashing, contact precautions, and environmental disinfection).

Strength of Evidence Scale††

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence either is unavailable or does not permit a conclusion.

†† The overall evidence grade was assessed based on the ratings for the following domains: study limitations, directness, consistency, precision, and reporting bias. Other domains were considered, as appropriate: dose-response association, plausible confounding, and strength of association (i.e., magnitude of effect). For additional details on the methodology used to assess strength of evidence, please refer to: Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

Overview of Clinical Research Evidence (*Continued*)

Table 3: Summary of Key Findings and Strength of Evidence for the Effectiveness of Antimicrobials in Treating Initial *C. difficile* Infections and Reducing Their Recurrence

Antimicrobial	Outcome	No. Studies	No. Subjects	Summary of Key Findings	Strength of Evidence
Vancomycin vs. metronidazole	Initial cure of CDI	4	872	Favors vancomycin: 83.9% vs. 75.7% of patients achieved initial cure (RR 1.08, 95% CI 1.02–1.15).	●●●
	Prevention of CDI recurrence	4	705	No significant difference: 16.5% vs. 18.7% of patients had recurrent CDI (RR 0.89, 95% CI 0.65–1.23).	●●○
Fidaxomicin vs. vancomycin	Initial cure of CDI	2	1111	No significant difference: 87.6% vs. 85.6% of patients achieved initial cure (RR 1.02, 95% CI 0.98–1.07).	●●○
	Prevention of CDI recurrence	2	962	Favors fidaxomicin: 14.1% vs. 26.1% of patients had recurrent CDI (RR 0.55, 95% CI 0.42–0.71).[§]	●●●
Any antimicrobial	Treatment effect by disease severity	3	NR	Treatment results did not differ by disease severity.	●○○

CDI = *Clostridium difficile* infection; CI = confidence interval; NR = not reported; RR = relative risk

[§] Limited evidence suggested that there was a lower rate of recurrence in patients receiving fidaxomicin when the infecting organism was a non-epidemic (non-nucleosome assembly protein 1) strain (●○○).

Table 4: Summary of Key Findings and Strength of Evidence for the Effectiveness of Probiotics in Reducing Recurrence of *C. difficile* Infection

Interventions Compared (as an adjunct to standard antibiotic treatment)	Outcome	No. Studies	No. Subjects	Summary of Key Findings	Strength of Evidence
Lactobacillus vs. placebo	Prevention of CDI recurrence	6	1251	Favors Lactobacillus: RR 0.27, 95% CI 0.15–0.49	●○○
***Saccharomyces boulardii* vs. placebo**	Prevention of CDI recurrence	6	1244	No significant difference: RR 0.77, 95% CI 0.38–1.54	●○○
Multiorganism probiotics vs. placebo	Prevention of CDI recurrence	5	3960	Favors multiorganism probiotics: RR 0.50, 95% CI 0.28–0.88	●○○

CDI = *Clostridium difficile* infection; CI = confidence interval; RR = relative risk

Table 5: Summary of Key Findings and Strength of Evidence for the Effectiveness of Fecal Microbiota Transplantation in Treating Recurrent and Relapsed *C. difficile* Infection

Intervention Studied	Outcome	No. Studies	No. Subjects	Summary of Key Findings	Strength of Evidence
Fecal microbiota transplantation	Resolution of diarrhea and prevention of relapse	3 RCTs and 23 case series	751	Resolves diarrhea and prevents relapse in patients with recurrent CDI	●○○

CDI = *Clostridium difficile* infection; RCT = randomized controlled trial

Overview of Clinical Research Evidence (*Continued*)

Table 6: Adverse Effects Associated With Interventions Used To Prevent and Treat *C. difficile* Infection

Note: The adverse effects listed here have been drawn from the systematic review and from U.S. Food and Drug Administration (FDA) labels.

Intervention	Adverse Effects
Metronidazole	■ Abdominal pain, nausea, vomiting, diarrhea, headache, loss of appetite, and metallic taste in the mouth. ■ Rare but serious adverse effects include neurotoxicity, seizures, or neuropathy with long-term use.
Vancomycin	■ Abdominal pain, nausea, and low serum-potassium levels.
Fidaxomicin	■ Abdominal pain, nausea, vomiting, anemia, neutropenia, and gastrointestinal bleeding.
Probiotics	■ No adverse effects were reported in studies in which probiotics were used as adjunctive treatment. ■ Fungemia has been reported in critically ill and immunocompromised patients with use of *Saccharomyces*.
Fecal Microbiota Transplantation	■ Adverse effects reported in the RCTs include diarrhea, cramps, belching, nausea, and constipation. ■ Rare adverse effects include secondary infection and microperforation of the colon.

RCT = randomized controlled trial

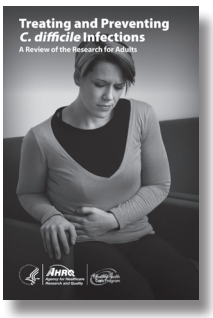
Gaps in Knowledge and Additional Issues

- Future research should include studies to identify subgroups of patients who derive the most benefit from the various treatments for CDI.
- The costs of the antibiotics used to treat CDI vary significantly. Fidaxomicin is significantly more expensive than vancomycin and metronidazole.
- The use of probiotics and FMT as adjuntive or alternative treatments for CDI needs additional research.
- The FDA has specific guidance on FMT as treatment for CDI and on the role of donors and stool banks. The guidance is available at *www.fda.gov*.

What To Discuss With Your Patients and Their Caregivers

- The role that use or overuse of antibiotics, including those used to treat CDI, may play in the development of CDI
- The available antibiotic treatments for CDI and the evidence for their effectiveness and adverse effects
- That probiotics may be helpful in preventing recurrent CDI and that patients should be aware that there is wide variation in the quality of over-the-counter probiotics
  - » Some manufacturers provide information on the potency and stability of their products.
- For patients with recurrent CDI that is difficult to treat, the benefits and harms of FMT for reducing the risk of relapse and that patients will be referred to a center with expertise in this procedure for treatment
- The importance of cleaning hands frequently with soap and water (and not hand sanitizer) to prevent the spread of CDI spores
  - » *C. difficile* spores are resistant to alcohol hand rubs and other routinely used antiseptics.

Companion Resource for Patients



Treating and Preventing C. difficile *Infections: A Review of the Research for Adults* is a free companion to this clinician research summary. It can help patients and their caregivers talk with their health care professionals about the various options that are available for treating *C. difficile* infections.

Ordering Information

For electronic copies of this clinician research summary, the companion patient resource, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/c-difficile-update-report/*. To order free print copies of the patient resource, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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