Implementing AHRQ Effective Health Care Reviews

Helping Clinicians Make Better Treatment Choices

Clostridium difficile Infection: Prevention and Treatment

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Key Clinical Issue

How effective are interventions to prevent and treat *Clostridium difficile* infection?

Evidence-Based Answer

Antibiotic stewardship and handwashing campaigns reduce *C. difficile* infection without reported harms. (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) Vancomycin has a higher initial cure rate than metronidazole, although the recurrence rate is equal between the two drugs. Fidaxomicin has a lower recurrence rate than vancomycin, although there is no difference in the initial cure rate. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) There is low strength but consistent evidence that *Lactobacillus,* multiorganism probiotics, and fecal microbiota transplantation are effective in reducing *C. difficile* infection recurrence.[1] (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

There are an estimated 350,000 *C. difficile* infection–related hospitalizations in the United States every year with approximately 9% ending in death. The number of patients discharged from the hospital with any *C. difficile*–related diagnosis has more than doubled since the 1990s.[2] In 2008, *C. difficile* infection was estimated to account for $4.8 billion in health care expenses.[3]

This Agency for Healthcare Research and Quality (AHRQ) review update included 93 articles published between 2010 and April 2015. Based on a systematic review that included one randomized controlled trial (RCT) and five interrupted time series studies, antibiotic stewardship is associated with decreased *C. difficile* infection. No studies found harms associated with antibiotic stewardship. Handwashing campaigns reduced *C. difficile* infection rates from 16.8 to 9.5 cases per 10,000 bed days. There is insufficient evidence to determine the effectiveness of chlorhexidine gluconate baths, hydrogen peroxide vapor with terminal room cleaning, daily cleanings with hydrogen peroxide disposable wipes, and pulsed xenon ultraviolet light after terminal room cleaning. Fifteen single-hospital studies assessed multicomponent prevention strategies. Although there is insufficient evidence to assess the effectiveness of these strategies, four studies demonstrated that they are sustainable over time.[1]

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to produce evidence to improve health care and to make sure the evidence is understood and used. A key clinical question based on the AHRQ Effective Health Care Program systematic review of the literature is presented, followed by an evidence-based answer based upon the review. AHRQ's summary is accompanied by an interpretation by an *AFP* author that will help guide clinicians in making treatment decisions. For the full review, clinician summary, and consumer summary, go to https://effective-healthcare.ahrq.gov/topics/c-difficile-update/clinician/.

This series is coordinated by Kenny Lin, MD, MPH, Associate Deputy Editor for *AFP* Online.

A collection of Implementing AHRQ Effective Health Care Reviews published in *AFP* is available at http://www.aafp.org/afp/ahrq.

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 167.

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Summary of Key Findings and Strength of Evidence for Interventions to Prevent *Clostridium difficile* Infection

Intervention	Number of studies	Summary of key findings	Strength of evidence
Antibiotic stewardship	6	Appropriate prescribing practices were associated with decreased *C. difficile* infection.	●○○
Handwashing campaigns	1	Handwashing campaigns reduced *C. difficile* infection 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.	●○○

Strength of evidence scale

●●● **High:** High confidence that the evidence reflects the true effect. Further research is very unlikely to change the confidence in the estimate of effect.

●●○ **Moderate:** Moderate confidence that the evidence reflects the true effect. Further research may change the 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 the confidence in the estimate of effect and is likely to change the estimate.

○○○ **Insufficient:** Evidence either is unavailable or does not permit a conclusion.

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

Adapted from the Agency for Healthcare Research and Quality, Effective Health Care Program. Diagnosis, prevention, and treatment of C. difficile: *current state of the evidence. Clinician summary. Rockville, Md.: Agency for Healthcare Research and Quality; May 2017. https://ahrq-ehc-application.s3.amazonaws.com/media/pdf/c-difficile-update_clinician.pdf. Accessed November 6, 2017.*

Regarding treatment, this AHRQ review found high strength of evidence based on four RCTs that oral vancomycin has higher initial *C. difficile* infection cure rates compared with metronidazole (83.9% vs. 75.7%; number needed to treat [NNT] = 12; 95% confidence interval [CI], 7 to 35), and no difference between fidaxomicin and vancomycin in initial cure. When assessing *C. difficile* infection recurrence rates, fidaxomicin is favored over vancomycin (14.1% vs. 26.1%; NNT = 8; 95% CI, 6 to 15), and there is no difference between vancomycin and metronidazole. Notably, two RCT subgroup analyses found that differences in disease severity did not significantly affect the results.[1]

Three RCTs and 23 case series described the use of fecal microbiota transplantation. In most studies, it

Summary of Key Findings and Strength of Evidence for the Effectiveness of Fecal Microbiota Transplantation in Treating Recurrent and Relapsed *Clostridium difficile* Infection

Intervention studied	Outcome	Number of studies	Number of subjects	Summary of key findings	Strength of evidence
Fecal microbiota transplantation	Resolution of diarrhea and prevention of relapse	3 randomized controlled trials and 23 case series	751	Resolves diarrhea and prevents relapse in patients with recurrent *C. difficile* infection	●○○

Strength of evidence scale

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was performed after antimicrobial therapy. Fecal microbiota transplantation decreased recurrence rates, although studies were small (N < 100), and follow-up time varied from three weeks to eight years.[1] A recent editorial in *American Family Physician* reviewed the evidence and indications for fecal microbiota transplantation (http://www.aafp.org/afp/2017/0315/p351.html).

Seventeen RCTs assessed probiotics as an adjunct to standard antibiotic treatment for the prevention of *C. difficile* infection. Both *Lactobacillus* (NNT = 26; 95% CI, 16 to 58) and multiorganism probiotics (NNT = 91; 95% CI, 52 to 294) are superior to placebo at preventing *C. difficile* infection, but *Saccharomyces* species are not.[1]

Guidelines from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America are largely in concordance with the findings in this review. Notably, these guidelines are being updated, with a target release date of winter 2018.[4]

The U.S. Food and Drug Administration recently approved bezlotoxumab, the first human monoclonal antibody treatment for *C. difficile* infection. A single intravenous dose of bezlotoxumab added to the standard treatment course of metronidazole, vancomycin, or fidaxomicin was found to decrease *C. difficile* infection recurrence rates in two industry-sponsored RCTs.[5]

C. difficile infection is a common problem that causes substantial health and financial burdens.

CLINICAL BOTTOM LINE

Summary of Key Findings and Strength of Evidence for the Effectiveness of Antimicrobials in Treating Initial *Clostridium difficile* Infections and Reducing Their Recurrence

Antimicrobial	Outcome	Number of studies	Number of subjects	Summary of key findings	Strength of evidence
Vancomycin vs. metronidazole	Initial cure of *C. difficile* infection	4	872	Favors vancomycin: 83.9% vs. 75.7% of patients achieved initial cure (RR = 1.08; 95% CI, 1.02 to 1.15)	●●●
	Prevention of *C. difficile* infection recurrence	4	705	No significant difference: 16.5% vs. 18.7% of patients had recurrent *C. difficile* infection (RR = 0.89; 95% CI, 0.65 to 1.23)	●●○
Fidaxomicin vs. vancomycin	Initial cure of *C. difficile* infection	2	1,111	No significant difference: 87.6% vs. 85.6% of patients achieved initial cure (RR = 1.02; 95% CI, 0.98 to 1.07)	●●○
	Prevention of *C. difficile* infection recurrence	2	962	Favors fidaxomicin: 14.1% vs. 26.1% of patients had recurrent *C. difficile* infection (RR = 0.55 ; 95% CI, 0.42 to 0.71)*	●●●
Any antimicrobial	Treatment effect by disease severity	3	349 for initial cure; 91 for recurrence	Treatment results did not differ by disease severity	●○○

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CI = confidence interval; 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 (˜ii).

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CLINICAL BOTTOM LINE

Summary of Key Findings and Strength of Evidence for the Effectiveness of Probiotics in Reducing Recurrence of *Clostridium difficile* Infection

Interventions compared (as an adjunct to standard antibiotic treatment)	Outcome	Number of studies	Number of subjects	Summary of key findings	Strength of evidence
Lactobacillus vs. placebo	Prevention of *C. difficile* infection recurrence	6	1,251	Favors *Lactobacillus:* RR = 0.27; 95% CI, 0.15 to 0.49	●○○
Saccharomyces boulardii vs. placebo	Prevention of *C. difficile* infection recurrence	6	1,244	No significant difference: RR = 0.77; 95% CI, 0.38 to 1.54	●○○
Multiorganism probiotics vs. placebo	Prevention of *C. difficile* infection recurrence	5	3,960	Favors multiorganism probiotics: RR = 0.50; 95% CI, 0.28 to 0.88	●○○

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Based on this AHRQ review, physicians should focus on handwashing and antibiotic stewardship as first-line interventions to prevent the illness. Clinicians may also consider recommending *Lactobacillus* or multiorganism probiotics for patients using antibiotics, especially in those older than 65 years because they are at the highest risk of complication from *C. difficile* infection.[2] Despite the slightly higher cure rate of oral vancomycin, clinicians may want to start treatment with metronidazole because it is more cost-effective and there is no difference in recurrence rates.

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Editor's Note: *American Family Physician* SOR ratings are different from the AHRQ Strength of Evidence (SOE) ratings.

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