CME

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

Colleen R. Kelly, MD, AGAF, FACG[1], Monika Fischer, MD, MSc, AGAF, FACG[2], Jessica R. Allegretti, MD, MPH, FACG[3], Kerry LaPlante, PharmD, FCCP, FIDSA[4], David B. Stewart, MD, FACS, FASCRS[5], Berkeley N. Limketkai, MD, PhD, FACG (GRADE Methodologist)[6] and Neil H. Stollman, MD, FACG[7]

***Clostridioides difficile* infection occurs when the bacterium produces toxin that causes diarrhea and inflammation of the colon. These guidelines indicate the preferred approach to the management of adults with *C. difficile* infection and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation process. In instances where the evidence was not appropriate for Grading of Recommendations Assessment, Development, and Evaluation but there was consensus of significant clinical merit, key concept statements were developed using expert consensus. These guidelines are meant to be broadly applicable and should be viewed as the preferred, but not the only, approach to clinical scenarios.**

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INTRODUCTION

The American College of Gastroenterology last published guidelines on the diagnosis, treatment, and prevention of *Clostridium difficile* infection in 2013 (1). Since that publication, there was a change in the taxonomic classification in 2016, with the organism assigned to a new genus and now called *Clostridioides difficile* (2). The US Centers for Disease Control and Prevention has adopted the new nomenclature, which has become standard throughout the scientific literature. Other developments include the increased recognition of diagnostic challenges in the era of nucleic acid amplification–based testing, new therapeutic options for treatment and prevention of recurrence, and increasing evidence to support fecal microbiota transplantation (FMT) in recurrent and severe infection.

These guidelines are intended to be complementary to the recently updated Infectious Disease Society of America (IDSA) and Society of Healthcare Epidemiologists of America (SHEA) guidelines (3–5). The goal of the authors was to provide an evidence-based, clinically useful guideline for the diagnosis, management, and prevention of *C. difficile* infection (CDI). We chose to expand on areas of particular interest to gastroenterologists, including diagnostic issues around diarrhea and distinguishing *C. difficile* colonization from active infection, and the evaluation and management of CDI in the setting of inflammatory bowel disease (IBD). We also addressed the current evidence and best practices around FMT.

Each section presents recommendations followed by a summary of the evidence. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to grade the strength of the recommendations and the quality of the evidence (Table 1) (6). The strength of a recommendation is graded as strong, when the evidence shows the benefit of the intervention or treatment clearly outweighs any risk, and as conditional, when uncertainty exists about the risk-benefit ratio. The quality of the evidence is graded as follows: high if further research is unlikely to change our confidence in the estimate of the effects; moderate if further research is likely to have an important impact and may change the estimate; and low if further research is very likely to change the estimate. Key concepts are statements that are not amenable to the GRADE process because of either the structure of the statement or the available evidence. In most instances, key concepts are based on extrapolation of the evidence and/or expert opinion. Tables 2 and 3 summarize the GRADED recommendations and key concepts in this guideline.

EPIDEMIOLOGY AND RISK FACTORS

Between 2001 and 2012, there was an increase in the annual CDI incidence of 43%; however, cases of multiply recurrent CDI (rCDI) increased 188% over that same period (7). Surveillance data from 2011 estimated the number of CDI in the United States to be 453,000 annually, with nearly 14,000 deaths directly

[1]Division of Gastroenterology, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA; [2]Division of Gastroenterology, Indiana University, Indianapolis, Indiana, USA; [3]Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [4]Department of Pharmacy Practice, University of Rhode Island College of Pharmacy, Kingston, Rhode Island, USA; [5]Department of Surgery, University of Arizona Health Sciences, Tucson, Arizona, USA; [6]Division of Digestive Diseases, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California, USA; [7]Division of Gastroenterology, Alta Bates Summit Medical Center, East Bay Center for Digestive Health, Oakland, California, USA.
Correspondence: Colleen R. Kelly, MD, AGAF, FACG. E-mail: ckelly91@brown.edu.
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Table 1. Quality assessment criteria (6)

Study design	Quality of evidence	Lower if	Higher if
Randomized trial	High	Risk of bias	Large effect
		−1 serious	+1 large
		−2 very serous	+2 very large
	Moderate	Inconsistency	Dose response
		−1 serious	+1 evidence of a gradient
		−2 very serious	
		Indirectedness	All plausible confounding
		−1 serious	+1 would reduce demonstrated effect or
		−2 very serious	+1 would suggest a spurious effect when results show no effect
Observational trial	Low	Imprecision	
		−1 serious	
		−2 very serious	
	Very low	Publication bias	
		−1 likely	
		−2 very likely	

attributable to the infection (8). A more recently published study showed a 24% decrease in the estimated national burden of CDI between 2011 and 2017, driven by a decrease in healthcare-associated infections, suggesting that efforts at reducing CDI in hospitals and other healthcare facilities have been successful (9). Long-term care facilities saw a 55% decrease in the incidence of CDI between 2011 and 2015 (10).

C. difficile colonization, defined as detection of the organism in the absence of symptoms, is common, occurring in 4%–15% of healthy adults, up to 21% of hospitalized adults, and 15%–30% of residents in long-term care facilities (11,12). Colonization with the organism at the time of admission to the hospital increases the risk of developing CDI 6-fold (13). Contact with the healthcare environment, advanced age (65 years or older), and antibiotic use are the biggest risk factors for developing an active infection. Healthcare-associated CDI has higher rates of recurrence and death, which may be partly due to the North American pulsed-field electrophoresis type 1 (NAP1) strain being more common in healthcare-associated cases (8,9). Fortunately, infections with this more virulent strain seem to be declining (14). Although patients in hospitals and long-term care facilities remain at highest risk, of great concern is the rise of community-associated infections, which now account for 35%–48% of CDI diagnoses (8,9). Risk factors of community-acquired infections, apart from antibiotic treatment, include White race, cardiac disease, chronic kidney disease, and IBD (15). Observed racial differences in CDI risks may represent healthcare access disparities (16).

PREVENTION OF CDI

Although previous ACG guidelines included statements regarding infection control and prevention, we chose not to make GRADE recommendations around the subject in this document. Other published guidelines are available, which provide comprehensive recommendations for preventing CDI. Clinical practice guidelines from the IDSA/SHEA and European Society of Clinical Microbiology and Infectious Diseases recommend isolating patients with suspected or confirmed CDI, use of full-barrier precautions (i.e., gowns and gloves) while caring for these patients, and hand hygiene before and after contact with patients with CDI, preferably using soap and water (3,17,18). None of these guidelines recommend contact precautions in asymptomatic carriers. Antibiotic stewardship programs that restrict high-risk antimicrobials and minimize unnecessary antimicrobials were shown to be to be effective in outbreak and nonoutbreak settings and are recommended to control rates of CDI (17).

PROBIOTICS

Recommendations

1. We recommend against probiotics for the prevention of CDI in patients being treated with antibiotics (primary prevention) (conditional recommendation, moderate quality of evidence).
2. We recommend against probiotics for the prevention of CDI recurrence (secondary prevention) (strong recommendation, very low quality of evidence).

Summary of evidence. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (19). Proposed mechanisms of effect include colonization and normalization of perturbed intestinal microbial communities, competitive exclusion of pathogens and bacteriocin (antibiotic) production, and modulation of the immune system and various metabolic functions, which maintain the integrity of the gut mucosa (20). Although high quality evidence to support probiotics for most conditions is scarce, the notion that probiotics provide natural health benefits is appealing to patients, leading to industry of a 40-billion-dollar a year (21). Probiotics are marketed as dietary supplements, with vague claims to "improve gut health," without the strict oversight by the US Food and Drug Administration (FDA) required for drugs. Therefore, manufacturers have little incentive to conduct clinical trials to

Table 2. Summary and strength of GRADED recommendations for the management of *Clostridium difficile*

Prevention
1. We recommend against probiotics for the prevention of *C. difficile* infection (CDI) in patients being treated with antibiotics (primary prevention) (conditional recommendation, moderate quality of evidence).
2. We recommend against probiotics for the prevention of CDI recurrence (secondary prevention) (strong recommendation, very low quality of evidence).
Diagnosis
3. CDI testing algorithms should include both a highly sensitive and a highly specific testing modality to help distinguish colonization from active infection (conditional recommendation, low quality of evidence).
Treatment
4. We recommend that oral vancomycin 125 mg 4 times daily for 10 d be used to treat an initial episode of nonsevere CDI (strong recommendation, low quality of evidence).
5. We recommend that oral fidaxomicin 200 mg twice daily for 10 d be used for an initial episode of nonsevere CDI (strong recommendation, moderate quality of evidence).
6. Oral metronidazole 500 mg 3 times daily for 10 d may be considered for treatment of an initial nonsevere CDI in low-risk patients (strong recommendation/ moderate quality of evidence).
7. As initial therapy for severe CDI, we recommend vancomycin 125 mg 4 times a day for 10 d (strong recommendation, low quality of evidence).
8. As initial therapy for severe CDI, we recommend fidaxomicin 200 mg twice daily or 10 d (conditional recommendation, very low quality of evidence).
9. Patients with fulminant CDI should receive medical therapy that includes adequate volume resuscitation and treatment with 500 mg of oral vancomycin every 6 hr daily (strong recommendation, very low quality of evidence) for the first 48–72 hr. Combination therapy with parenteral metronidazole 500 mg every 8 hr can be considered (conditional recommendation, very low quality of evidence).
10. For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hr) may be beneficial (conditional recommendation, very low quality of evidence).
11. We suggest fecal microbiota transplantation (FMT) be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly, when patients are deemed poor surgical candidates (strong recommendation, low quality of evidence).
12. We suggest tapering/pulsed dose vancomycin for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole (strong recommendation, very low quality of evidence).
13: We recommend fidaxomicin for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole (conditional recommendation, moderate quality of evidence).
Prevention of recurrence
14. We recommend patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences (strong recommendation, moderate quality of evidence).
15. We recommend FMT be delivered through colonoscopy (strong recommendation, moderate quality of evidence) or capsules (strong recommendation, moderate quality of evidence) for treatment of rCDI; we suggest delivery by enema if other methods are unavailable (conditional recommendation, low quality of evidence).
16. We suggest repeat FMT for patients experiencing a recurrence of CDI within 8 wk of an initial FMT (conditional recommendation, very low quality of evidence).
17. For patients with rCDI who are not candidates for FMT, who relapsed after FMT, or who require ongoing or frequent courses of antibiotics, suppressive oral vancomycin may be used to prevent further recurrences (conditional recommendation, very low quality of evidence).
18. Oral vancomycin prophylaxis may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence (conditional recommendation, low quality of evidence).
19. We suggest bezlotoxumab be considered for prevention of CDI recurrence in patients who are at high risk of recurrence (conditional recommendation, moderate quality of evidence).
20. We suggest against discontinuation of antisecretory therapy in patients with CDI, provided there is an appropriate indication for their use (strong recommendation, very low quality of evidence).
Special populations
21. We recommend *C. difficile* testing in patients with inflammatory bowel disease (IBD) presenting with an acute flare associated with diarrhea (strong recommendation, low quality of evidence).
22. We suggest vancomycin 125 mg p.o. 4 times a day for a minimum of 14 d in patients with IBD and CDI (strong recommendation, very low quality of evidence).
23. FMT should be considered for recurrent CDI in patients with IBD (strong recommendation, very low quality of evidence).

support specific indications (22). Quality control is often suboptimal with inconsistencies and deviations from the information provided on the product label; frequently misidentified, misclassified, or nonviable strains, contaminated products, or diminished functional properties are found (23,24). The belief that probiotics "cannot hurt," has been challenged by case reports

Table 3. Summary of key concept statements for the management of *Clostridium difficile*

Diagnosis and classification
1. Only individuals with symptoms suggestive of active *C. difficile* infection (CDI) should be tested (3 or more unformed stools in 24 hr)
2. We recommend the following criteria, which are predictive of unfavorable outcomes, be used to classify severe CDI at the time of diagnosis: white blood cell ≥15,000 cells/mm^3 or serum creatinine >1.5 mg/dL
3. We recommend defining fulminant infection as patients meeting criteria for severe CDI plus presence of hypotension or shock or ileus or megacolon
Treatment
4. We suggest that for patients who require surgical intervention, either a total colectomy with an end ileostomy and a stapled rectal stump or a diverting loop ileostomy with colonic lavage and intraluminal vancomycin, be used depending on clinical circumstances, the patient's estimated tolerance to surgery, and the surgeon's best judgement
Special populations
5. Immunosuppressive inflammatory bowel disease therapy should not be held during anti-CDI therapy in the setting of disease flare and escalation of therapy may be considered if there is no symptomatic improvement with treatment of CDI
6. We recommend using vancomycin to treat pregnant and peripartum patients with CDI
7. We recommend using vancomycin to treat breastfeeding patients with CDI
8. We suggest vancomycin or fidaxomicin be used first line for treatment of CDI in patients who are immunocompromised

of bloodstream infections with probiotic organisms in critically ill patients, leading to the recommendation that they be used with caution in immunocompromised patients and those with structural heart disease or central venous catheters (25). More recently, microbiome analyses have shown that they may actually impede normal recolonization of the colon after antibiotic courses (26).

Probiotics are widely recommended by physicians to prevent CDI in patients being treated with antibiotics (primary prevention) or in patients being treated for CDI to prevent further recurrences (secondary prevention) (27). Costs range from $30 to $100 per month for the most commonly recommended formulations that are frequently taken for extended periods and typically not covered by insurance (28,29). Given these costs, the desire to provide reliable health information to our patients and the potential for harm, it is important to critically appraise the data supporting use of probiotics for prevention of CDI. Evidence to support probiotics for this indication comes mainly from meta-analyses that pool data from small trials of different probiotic formulations and methodologies. There is a paucity of high-quality clinical trial data of probiotics in CDI, and most studies are underpowered, with CDI as a secondary outcome in studies performed to assess prevention of antibiotic-associated diarrhea (AAD). We determined that there is insufficient evidence to recommend any probiotic for the primary prevention or secondary prevention of CDI in most patients. The most important studies examining the efficacy of probiotics in CDI are detailed further.

Primary prevention. The PLACIDE trial is the largest double-blind clinical primary prevention trial to date (30). The study enrolled nearly 3,000 elderly inpatients who were receiving antibiotics for other indications and randomized them to treatment with a multistrain preparation composed of bifidobacteria and *Lactobacillus acidophilus* strains (n = 1,493) or placebo (n = 1,488) for 21 days. Primary outcomes in this study were AAD or CDI. Either (AAD or CDI) occurred in 159 (10.8%) participants in the probiotic group and 153 (10.4%) participants in the placebo group (relative risk [RR] 1.04; 95% confidence interval [CI] 0.84–1.28; $P = 0.71$). CDI was uncommon and occurred in 12 (0.8%) participants in the probiotic group and 17 (1.2%) in the placebo group, leading the authors to conclude that probiotics were of no benefit in prevention of AAD or CDI. The main limitation of PLACIDE was the low rate of CDI in the patient population, resulting in a study that was possibly underpowered to show benefits of probiotics. Nevertheless, a meta-analysis looking at the efficacy of probiotics for prevention of CDI in the hospitalized elderly population, which included results from PLACIDE and 4 other randomized controlled trials (RCTs), also concluded nonsignificant effects of probiotics in this population (31).

The 2017 Cochrane review of probiotics for the primary prevention of CDI in adults and children being treated with antibiotics analyzed 31 studies, enrolling a total of 8,672 participants (32). Most of these studies (n = 27) were deemed to be of high or unclear risk of bias, and more than half had missing data. The authors concluded a modest benefit of probiotics (number needed to benefit = 42). In *post hoc* subgroup analysis, the benefits of probiotics only held up in trials enrolling participants with baseline CDI risk >5%. The conclusions of this Cochran review have been criticized as misleading, in that only 4 of the 31 trials showed benefits, and small, poorly controlled studies were included (22). Results were heavily influenced by 5 studies with CDI baseline risk >15%, far above that seen in any hospital setting in the world, raising important questions of the external validity.

A meta-analysis by McFarland et al. looked specifically at trials of a particular probiotic combination comprising 3 lactobacilli strains (*Lactobacillus acidophilus*, *Lactobacillus casei*, and *Lactobacillus rhamnosus*; Bio-K+) with *in vitro* activity against *C. difficile* (33). Of the 3 RCTs, only one showed efficacy of this mixture for primary prevention of CDI. This was a Chinese trial of elderly patients being treated with antibiotics in which the background incidence of CDI was extremely high (nearly 24%) (34), a rate uncommon in most healthcare settings. More recently, a meta-analysis of 19 RCTs concluded that probiotics were helpful at prevention of CDI in hospitalized patients if given closer to start of antibiotics, with a 70% lower risk if probiotics were started within 2 days but falling to a 30% risk reduction if

probiotics were started after 2 days of antibiotic therapy (35). It is notable that these studies had extensive exclusion criteria including patients who were immunocompromised, undergoing cancer treatments, in an intensive care unit (ICU), or who had preexisting gastrointestinal (GI) conditions.

Secondary prevention. The PICO trial, published in 2017, randomized 33 patients with an initial mild-to-moderate CDI to 28 days of a 4-strain probiotics or placebo in addition to anti-CDI therapy and showed no difference in the rate of CDI recurrence (36). *Saccharomyces boulardii* is yeast that grows on lychee fruit and produces a protease that inactivates the receptor site for *C. difficile* toxin A, lending biologic plausibility to its use in CDI. Results from a multicenter double-blind RCT published in 1994 showed decreased CDI recurrence in patients treated with *S. boulardii* in addition to either metronidazole or vancomycin in those who had already experienced a recurrent episode (RR 0.43, 34.6% with *S. boulardii* vs 64.7% with placebo) (37). There was no benefit over placebo in patients who were being treated for an initial CDI. The authors' follow-up study, published in 2000, enrolled 168 patients with recurrent CDI who were treated with a 28-day course of *S. boulardii* or placebo in addition to anti-CDI therapy (38). The benefits in this study were limited to the subgroup that was treated with high-dose vancomycin and *S. boulardii* (16.7% recurrence vs 50% with placebo). The study was small, with 32 patients in the high-dose vancomycin group; thus, no firm conclusions could be drawn. Unfortunately, a planned larger trial was never conducted, and the benefits of *S. boulardii* for secondary prevention remain uncertain. A Cochrane review of probiotics for treatment of CDI, which included 4 studies, concluded that there is insufficient evidence to support a role for probiotics in treatment of CDI (39).

DIAGNOSIS OF CDI

Key concept

1. Only individuals with symptoms suggestive of active CDI should be tested (3 or more unformed stools in 24 hours).

Recommendation

3. CDI testing algorithms should include both a highly sensitive and a highly specific testing modality to help distinguish colonization from active infection (conditional recommendation, low quality of evidence).

Summary of evidence. There are little data to determine the optimum threshold for testing for *C. difficile* because reports of diarrhea are often subjective and confounded by other illnesses or medications. Although the recommended threshold for stools to justify testing for CDI has recently decreased from previous recommendations of 5–6 unformed stools per 24 hours to a more liberal ≥3 over 24 hours, there is still potential to miss true infections if a strict definition is required for testing. The 2013 ACG guidelines on CDI (1) recommended to only test patients "with diarrhea" without further definition. They also recommended that rectal swabs for polymerase chain reaction (PCR) may be useful for patients with an ileus, which we agree remains reasonable in this scenario (40). The 2017 IDSA/SHEA guidelines recommend testing patients with "unexplained and new-onset" diarrhea with ≥3 unformed stools in 24 hours (3). We agree with this recommendation, although recognize exceptions where epidemiologic determination of *C. difficile* prevalence, for example, on admission to oncology or transplantation units, may assist with infection control purposes. This can also serve to document colonization present on admission rather than hospital-acquired infections. Nevertheless, testing patients with formed stool is rarely clinically indicated.

Colonization with *C. difficile*, defined as detection of the organism in the absence of symptoms, is common (41), particularly in hospitalized patients and residents of long-term care facilities, and therefore, the diagnosis of CDI is not always straightforward. No single test can replace clinical acumen in determining whether a patient is experiencing a symptomatic infection (Table 4). All testing modalities are valid only for testing unformed stool (4). Although highly sensitive, the gold standards for detecting infection, toxigenic stool culture or cell cytotoxicity neutralization assays for *C. difficile*, are impractical for use outside of research settings. Enzyme immunoassays (EIAs) tests detect toxins A and B produced by the organism, providing rapid results with high specificity; however, sensitivity can be impacted by specimen handling (42). Ultrasensitive toxin assays are not yet available for widespread clinical use, but the more recently marketed ones have demonstrated increased diagnostic accuracy (43). With sensitivity comparable with toxigenic culture, nucleic acid amplification testing (NAAT), such as PCR and loop-mediated isothermal amplification, detects the presence of the gene encoding toxin, confirming the presence of a toxigenic strain but not whether the toxin is being elaborated by the organism in the infected individual (44). Glutamate dehydrogenase (GDH) is an enzyme produced in large amounts by both toxigenic and nontoxigenic strains of *C. difficile* and other clostridial species. The test detecting GDH antigen is extremely sensitive and functions well as a screening tool, with a high negative predictive value (45). Positive GDH tests require confirmation of a toxigenic strain with either NAAT or EIA, and false negatives do occasionally occur; so, further testing is warranted when clinical suspicion is high (46).

NAAT was rapidly adopted by clinical laboratories, and published evidence indicates that it can be used alone when stool is unformed and when there is close attention to clinical symptoms (47). The problem with this approach is that asymptomatic, colonized patients test positive by NAAT, and alternative etiologies for diarrheal symptoms in colonized patients are common. CDI rates in hospitalized patients increased significantly after implementation of NAAT, and asymptomatic carriers may approach or exceed the number of patients with CDI in some settings (41,48). CDI-related complications are rare in NAAT-positive, toxin EIA-negative patients, who, even when untreated, may have clinical courses similar to those without CDI (49). Because no single test is suitable to be used as a stand-alone test, use of a 2-step testing algorithm, as recommended by European guidelines, is our preferred testing method for optimal diagnostic accuracy (4,46,50) (Figure 1). In this approach, stool is first tested using a highly sensitive NAAT or GDH test, and the second test is the more specific toxin EIA. If both are positive, the diagnosis of CDI can be made reliably. If both are negative, CDI is unlikely. Discordant results when NAAT or GDH is positive and toxin EIA is negative require clinical evaluation and consideration of the possibility of colonization or that the patient has CDI but toxin levels are below the limits of detection. Because no test is perfect, the diagnosis and decision to treat is a clinical one. Treatment should not be withheld when there is high clinical suspicion based on laboratory testing alone.

Clinicians should be aware that alternative causes of diarrhea may be causing symptoms in colonized patients (i.e., symptomatic colonization). Clinical clues suggestive of a non-CDI diagnosis include lack of response to vancomycin in nonsevere cases; atypical

Table 4. CDI testing modalities

Test	Sensitivity (%)	Specificity (%)	Positive predictive value (%)[a]	Negative predictive value (%)[a]	Distinguishes colonization from active infection	Other considerations
Toxigenic culture (47)	94	99	—	—	No	Detects toxin producing *C. difficile* strains in culture. Not used clinically.
CCNA (12,47)	93	98	—	—	Yes	Demonstrates presence of free toxin B. Not used clinically.
GDH (4,45)	94–96	90–96	34–38	100	No	Does not distinguish nontoxigenic from toxigenic strains.
NAAT (PCR or LAMP) (4,44)	95–96	94–98	46	100	No	Detects gene for toxin B
EIA for toxins A and B (4)	57–83	99	69–81	99	Yes	Detects presence of free toxin

CCNA, cell cytotoxicity neutralization assay; CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; LAMP, loop-mediated isothermal amplification assay; NAAT, nucleic acid amplification testing; PCR, polymerase chain reaction.
[a]Assuming *C. difficile* infection prevalence of 5%.

course, including a long history of chronic diarrhea leading up to testing, intermittent or nonprogressive symptoms in the absence of treatment, and history of alternating constipation; and symptoms more suggestive of postinfection irritable bowel syndrome (IBS) in a patient after treatment of CDI (51,52). One study showed persistent shedding of *C. difficile* in 56% of patients who had resolution of diarrhea as long as 4 weeks after completing treatment (53), which is why routine testing for cure in asymptomatic patients after treatment of CDI is not recommended. New-onset postinfection IBS is common after CDI, occurring in as many as 25% of patients, and is most frequently the mixed or diarrheal subtypes (54). In a retrospective cohort study of active-duty US military personnel, the risk of incident IBS after CDI was shown to be 6 times greater than those who did not have a CDI diagnosis over the same period (RR 6.1; 95% CI 2.9–12.9) (55). The persistence of shedding or colonization can present challenges in evaluating these patients. In cases of diagnostic uncertainty, expanded diarrhea workup including colonic biopsy to assess for alternate etiology of symptoms, such as microscopic colitis or IBD, may be clinically useful. If the colon is normal endoscopically and histologically, *C. difficile* is unlikely to be the source of diarrheal symptoms.

CLASSIFICATION OF CDI

Key concepts

2. We recommend the following criteria, which are predictive of unfavorable outcomes, be used to classify severe *C. difficile* infection at the time of diagnosis: white blood cell (WBC) ≥15,000 cells/mm^3 or serum creatinine >1.5 mg/dL.
3. We recommend defining fulminant infection as patients meeting criteria for severe *C. difficile* infection plus presence of hypotension or shock or ileus or megacolon.

Summary of evidence. Over the past decade, numerous clinical prediction rules (CPRs) have been developed to prognosticate unfavorable outcomes of CDI at the bedside, aiming to foretell treatment failure (56,57), colectomy, and mortality (58–65). The spectrum of CPRs ranges from few variables (57,61,65) to complex-weighted multivariable scoring systems (58–60,64), developed in a single-center cohort (62,63), randomized trial population (56,57), or in a large national database (60). CPRs include a combination of various demographic (age), clinical (ICU stay, hypotension, abdominal tenderness, ileus, delirium, immunosuppression, narcotic, proton pump inhibitor (PPI) or systemic antibiotic use, liver disease, diabetes, and malignancy) and laboratory variables (serum WBC, albumin, creatinine, blood urea nitrogen, and C-reactive protein concentration). Despite performing well in internal validation, most of the tested CPRs for poor outcomes of CDI had suboptimal discriminatory function with area under the receiver operating characteristics curve values between 0.63 and 0.74 (66,67).

Noting such limitations with CPR, the simplest and most widely known prediction rule was introduced by the 2010 IDSA guidelines (68). Their proposed criteria for severe CDI were leukocytosis (WBC >15,000 cells/L) or elevation of serum creatinine 1.5× above baseline. A *post hoc* analysis of 2 RCTs comprising 1,105 patients found that leukocytosis (risk ratio 2.29; 95% CI 1.63–3.21) and renal failure (risk ratio 2.52; 95% CI 1.82–3.50) measured at the time of CDI diagnosis predicted treatment failure to vancomycin and fidaxomicin (57). The authors noted that baseline creatinine was often unavailable at the time of CDI diagnoses. Therefore, the updated IDSA guidelines published in 2018 suggested a serum creatinine of >1.5 mg/dL, whereas acknowledging that it will not be helpful among patients with renal disorders (3). To distinguish those with fulminant disease, the IDSA 2018 guidelines suggested the use of the criteria shock, hypotension ileus, or megacolon based on expert consensus. Although no single study evaluated these together as composite criteria, many reported strong correlations between hypotension with or without vasopressor use, shock, ileus, megacolon, and the likelihood of needing colectomy, increased postsurgical mortality, or death (59,62,69,70).

Validation of the 2010 and 2018 IDSA guidelines was recently performed using the VA healthcare system database, in >80,000 episodes of CDI capturing both inpatient and outpatient diagnoses, hospital and ICU admissions, colectomies, and 30-day all-cause mortality (66). Sensitivity ranged from 0.48 for ambulatory setting using the 2010 IDSA criteria to 0.73 for hospital setting using 2018 IDSA criteria. Area under the curve statistics were suboptimal and similar (0.60 for ambulatory and 0.57 for hospital setting) for both versions, but negative predictive values were >0.80, suggesting that

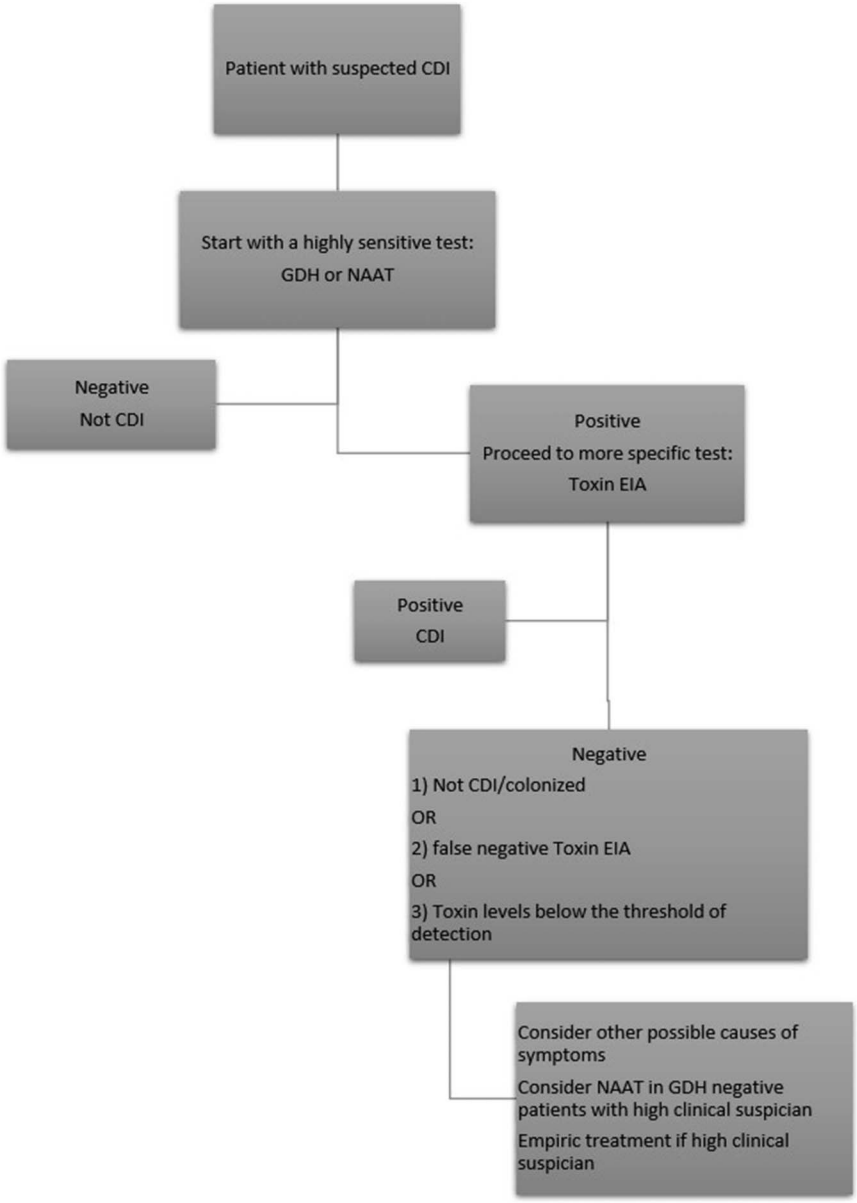

Figure 1. Proposed CDI testing algorithm. CDI, *Clostridioides difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification testing.

the severity criteria may be more appropriate to identify low risk patients unlikely to experience poor outcomes than to identify patients at high risk. The study was unable to separate patients with ileus and megacolon and, thus, was not able to validate criteria proposed for fulminant infection. Despite its less-than-perfect discriminatory function, the IDSA 2018 severity classification is by far the simplest among all other published CPRs, and the most likely to be applied broadly given the availability of the suggested laboratory parameters in most patients at the time of CDI diagnosis. Therefore, we recommend IDSA 2018 severity criteria in clinical practice until better CPRs are developed.

Low serum albumin concentration is a well-described phenomenon in patients with severe CDI and a predictor of poor outcome as suggested by several guidelines (1,5,71): a result of protein-losing colopathy (72,73) and a host defense mechanism that secretes albumin into the gut lumen to bind toxin A or B to promote proteolytic cleavage external to gut epithelium, thereby preventing cytotoxic effects in the mucosa (74). High fecal calprotectin (>2,000 μg/g) (75) and peripheral eosinopenia or undetectable eosinophil count have also been reported as a potential biomarkers of severe disease and poor outcomes (65). Fever >38.5 °C was reported as a strong predictor of poor outcome but occurs rarely, only in about 1% of patients with severe CDI (57). Infection with the hypervirulent NAP/027/BI *C. difficile* strain predicts significantly higher rate of severe CDI, increased colectomy, and mortality (76). For clinicians performing colonoscopies, the presence of pseudomembrane might be a useful marker of severe disease (77–80). In studies evaluating the effectiveness of FMT for severe CDI, pseudomembrane was associated with treatment failure, predicting need for multiple FMTs (77,79,81). Abdominal tenderness was a criterion

for severe disease in the previous ACG guidelines (1), although this measure is subjective and not included in this study as a part of the severity classification, whereas it may be useful in assessment of the overall clinical picture.

TREATMENT OF CDI

Non-severe CDI

Recommendations

4. We recommend that oral vancomycin 125 mg 4 times daily for 10 days be used to treat an initial episode of nonsevere CDI (strong recommendation, low quality of evidence).
5. We recommend that oral fidaxomicin 200 mg twice daily for 10 days be used for an initial episode of nonsevere CDI (strong recommendation, moderate quality of evidence).
6. Oral metronidazole 500 mg 3 times daily for 10 days may be considered for treatment of an initial nonsevere CDI in low-risk patients (strong recommendation/moderate quality of evidence).

Summary of evidence. The previous ACG Practice Guideline (1) recommended oral metronidazole for mild-to-moderate CDI and vancomycin for severe CDI. Fidaxomicin was mentioned but not yet advised because of increased cost and evolving data. The recent IDSA/SHEA guidelines published in 2018 (3) recommended either vancomycin or fidaxomicin in nonsevere CDI but advised that metronidazole may be considered in settings where "access is limited" to vancomycin or fidaxomicin. We agree that there are now ample data supporting the efficacy of vancomycin and fidaxomicin as primary treatment in nonsevere disease. Fidaxomicin has been demonstrated to be generally equivalent to vancomycin in this population for cure (82), with data demonstrating decreased recurrence rates (83,84). A number of industry-led cost-effectiveness analyses have reported that increased initial acquisition costs may be offset by lower recurrence costs, leading to near equivalence with vancomycin (85,86).

There are now a number of industry-sponsored studies comparing fidaxomicin with vancomycin. In a double-blind RCT, fidaxomicin at 200 mg twice daily for 10 days was found to be noninferior to vancomycin at 125 mg 4 times daily dose for 10 days in the treatment of CDI (82). In the modified intention-to-treat analysis, cures rates with fidaxomicin (82.1%) were similar to vancomycin (88.6%). The rate of recurrence within 30 days, however, was significantly lower with fidaxomicin (13.0% vs 26.6%, $P = 0.02$). A subsequent double-blind, noninferiority RCT with the same protocol yielded similar results, demonstrating no significant difference in clinical cure (76.2% vs 70.5%, $P = 0.473$), but lower recurrence rates with fidaxomicin (8.3% vs 32.6%, $P < 0.05$) (87,88). A recent Japanese study of inpatients with an initial episode of CDI demonstrated statistically equal global cure rates between fidaxomicin (67.3%) and vancomycin (67.3% vs 65.7%, 95% CI −11.3 to 13.7) (89). An open-label European trial reported superior outcomes in older inpatients with CDI with an extended-pulsed fidaxomicin regimen compared with a shorter duration 10-day vancomycin treatment (90). Unfortunately, there was no arm with an extended-pulsed vancomycin regimen, making a direct comparison unavailable. Finally, a retrospective, multicenter, propensity score-matched analysis of the Veteran Administration's national database found no statistically significant difference in the combined outcome of clinical failure or recurrence between 213 fidaxomicin treatment courses (31.9%) and 639 vancomycin treatment courses (25.5%) (91). The 30-day (10.8% vs 11.7%), 90-day (22.5% vs 21.9%), and 180-day mortality rates (29.1% vs 29.1%) were also similar between the 2 treatment groups.

Metronidazole's role in patients with first occurrence and nonsevere disease remains controversial. The largest randomized head-to-head comparison of metronidazole and vancomycin to date was published in 2014 (92) and reported no statistical difference between metronidazole and vancomycin for nonsevere disease, although a nonsignificant trend in favor of vancomycin was described. The most recent and rigorous review is the Cochrane 2017 publication that reviewed 22 trials, mostly consisting of patients with nonsevere disease and found vancomycin to be overall more effective than metronidazole for achieving symptomatic cure (79% vs 72%) and fidaxomicin to be more effective than vancomycin (71% vs 61%) (93). The authors concluded that "moderate quality evidence suggests that vancomycin is superior to metronidazole and fidaxomicin is superior to vancomycin. The differences in effectiveness between these antibiotics were not large and the advantage of metronidazole is its far lower cost compared to the other 2 antibiotics." Finally, a recent effectiveness analysis of a cohort of US veterans aged 65 years or younger with a first episode of mild CDI reported no difference between metronidazole compared with vancomycin regarding risk of 30-day all-cause mortality or CDI recurrence (94). However, in the same study, in older patients or those with hospital admission for CDI, severe underlying comorbidities, or hypoalbuminemia, metronidazole was inferior (94).

Given the above-reported data, we believe that all 3 agents have a role in first-line treatment of initial nonsevere CDI. Vancomycin or fidaxomicin are appropriate initial treatments for most patients. Although vancomycin is less expensive, lower recurrence rates of fidaxomicin imply overall similar cost-effectiveness for both agents. For lower-risk patients (younger outpatients with minimal comorbidities), particularly in cost-sensitive environments, metronidazole is an appropriate alternative.

There have been other agents with suggested efficacy in *C. difficile* treatment, particularly rifaximin. Rifaximin as a follow-on treatment was supported by a randomized trial published in 2011 at a dose of 400 mg t.i.d. for 20 days after standard CDI therapy in which recurrent CDI rates decreased from 31% to 15%, although this was not statistically significant because of small sample size (95). Another randomized trial reported on 130 patients treated with rifaximin 400 mg t.i.d. for 14 days and then 200 mg t.i.d. for an additional 14 days. This study demonstrated a numerical reduction in recurrence from 30% to 16% ($P = 0.06$) but the difference was also nonsignificant (96). Finally, a recent systematic review evaluated an additional 6 nonrandomized trials and concluded that rifaximin has a potential role but expressed concerns about 30%–50% resistance rates and suggested further randomized trials, including cost-benefit analyses (97). We agree with this assessment and do not currently recommend its routine use. Tigecycline, a broad-spectrum oral antibiotic, demonstrated some early efficacy in open-label trials, although a phase 2 trial was discontinued because of slow enrollment. A recent review of 10 reports and meta-analysis of 4 reported clinical cure in 79% and suggested further studies, which we agree with but do not recommend its use currently (98). A number of novel agents such as cadazolid and surotomycin and existing drugs such as teicoplanin and nitazoxanide have been studied for their efficacy in

CDI. A recent Cochrane review concluded that the use of these agents is not currently supported by the evidence, and the authors of this guideline agree with that assessment (93).

Symptomatic treatment with antimotility agents, such as loperamide, has fallen out of favor because of theoretical concerns that bacterial toxins would be retained in the colon and would increase the risk of toxic megacolon. Indeed, review of the literature indicated that patients who experienced complications or died were given antimotility agents alone initially, without an appropriate antibiotic (99). However, a study of patients with mild-to-moderate CDI who received metronidazole or vancomycin coadministered with the antimotility agent experienced no complications, although addition of the antimotility agent did not decrease duration of symptoms (100). Based on these data, antimotility agents should be avoided in untreated CDI and in patients with fulminant infection. However, once patients have initiated anti-CDI therapy, they can be used safely on an as-needed basis. Cholestyramine or other bile acid–binding agents are sometimes given with anti-CDI therapy with the belief that they bind toxins or may help hasten resolution of diarrheal symptoms. However, there is a paucity of evidence to support these claims, and administration together with vancomycin is contraindicated because of drug–drug interactions, specifically the potential to bind antibiotics (101). Therefore, they should not be used as monotherapy or concurrently with anti-CDI therapy. The addition of psyllium husk as a bulking agent may help diarrheal symptoms when given during the recovery phase, and animal studies have shown benefits of dietary fiber in promoting beneficial gut microflora and reducing *C. difficile* burden (102–104) and regulation of intestinal barrier function and inflammation (105). Furthermore, fiber is beneficial for post-infection IBS symptoms (106), which are common after CDI (54).

Severe CDI

Recommendations

7. As initial therapy for severe CDI, we recommend vancomycin 125 mg 4 times a day for 10 days (strong recommendation, low quality of evidence).
8. As initial therapy for severe CDI, we recommend fidaxomicin 200 mg twice daily or 10 days (conditional recommendation, very low quality of evidence).

Summary of evidence. Vancomycin has been the standard therapy for severe CDI, with the recent addition of fidaxomicin to the armamentarium. In a network meta-analysis comparing 13 agents across 24 trials comprising 5,361 patients, vancomycin was rated the best option for achieving primary cure of severe infection, although fidaxomicin had higher sustained cure (i.e., fewer recurrences) (107). Cost-effectiveness analysis favored vancomycin over fidaxomicin for initial episodes of severe CDI, based on combined analysis from 3 RCTs (108). Regarding the optimal dosage, a small RCT of 46 hospitalized patients with *C. difficile* colitis found no difference in cure rates, time to response, or recurrence rates between 125 and 500 mg of oral vancomycin given 4 times daily for 10 days (109). In agreement with these findings, a single-center experience on patients with severe CDI (n = 78) found no difference in cure rate (60% vs 64%) at day 10, time to cure, complications, or mortality rates on low-dose (≤500 mg daily) vs high-dose (>500 mg daily) oral vancomycin; although there was a trend toward decreased rate of recurrence (12% vs 2%; $P = 0.09$) in the high-dose group (110). Although fecal concentrations of vancomycin inversely correlate with stool frequency, only 125 mg 4 times daily dosing in patients with severe CDI consistently achieved stool drug levels ≥1,000-fold higher than the minimal *in vitro* inhibitory concentration needed against *C. difficile* (1.2 μg/L) (111). Higher doses of vancomycin are unlikely to be more beneficial; thus, we do not recommend their routine use. If a patient is not responding to standard dosing, we suggest assessing for alternative causes of diarrhea.

In patients with severe disease, fidaxomicin was noninferior to vancomycin in achieving clinical cure at the end of therapy and associated with decreased risk of recurrence in a phase 3 clinical trial (82). This and other clinical trials of fidaxomicin have excluded patients with fulminant CDI and life-threatening illness, so evidence to support its use in these populations is limited. One retrospective study of critically ill patients treated with fidaxomicin showed the response to therapy was similar to that seen in the general medical wards, although only 36 patients in this series had a diagnosis of severe or fulminant CDI, with one-third of them experiencing treatment failure (112). A more recent retrospective chart review consisting of 213 fidaxomicin and 639 oral vancomycin courses showed no statistically significant difference for the primary outcome of combined clinical failure or recurrence (68/213 [31.9%] vs 163/639 [25.5%], respectively, $P = 0.071$). Furthermore, there were no differences in mortality between the 2 treatment groups at either 30 or 180 days (91). Nearly all studies have used the 10-day treatment courses for both vancomycin and fidaxomicin, which seems sufficient for most patients.

Metronidazole should not be used for the treatment of severe CDI because it was shown to be inferior to vancomycin in multiple RCTs and cohort studies (92,113). A retrospective study of patients with severe CDI demonstrated that patients who received vancomycin only after failing metronidazole (≥48 hours) compared with those who received vancomycin at time of diagnosis had longer hospital stays, higher rates of acute kidney injury, and lower rates of cure (113,114) A large propensity-matched cohort study of 3,130 patients with severe CDI found that vancomycin compared with metronidazole reduced the 30-day all-cause mortality from 19.8% to 15.3% ($P = 0.01$) (115).

Management of Fulminant CDI

Medical therapy

Recommendations

9. Patients with fulminant CDI should receive medical therapy that includes adequate volume resuscitation and treatment with 500 mg of oral vancomycin every 6 hours daily (strong recommendation, very low quality of evidence) for the first 48–72 hours. Combination therapy with parenteral metronidazole 500 mg every 8 hours can be considered (conditional recommendation, very low quality of evidence).
10. For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hours) may be beneficial (conditional recommendation, very low quality of evidence).

Summary of evidence. We recommend a multidisciplinary medical team including critical care, gastroenterology, and/or infectious diseases with early involvement of surgeons in the

monitoring and care of these critically ill patients. Supportive measures based on expert opinion include volume resuscitation, with close attention to renal function and urine output and a low threshold for cross-sectional imaging to assess severity of colitis and rule out megacolon or perforation.

In cases of fulminant CDI, a higher dose of oral vancomycin at 500 mg every 6 hours is recommended by multiple society guidelines (1,3). Given lack of clinical trial data, this recommendation is entirely based on expert opinion. Direct comparison of low-dose (<500 mg/d) and high-dose (>500 mg/d) vancomycin therapies failed to demonstrate significant differences in rates of cure, time to cure, mortality, or complication rates in severe infection (109,110), and even patients with profuse diarrhea seem to achieve sufficiently high fecal levels of vancomycin against *C. difficile* on a regimen of 125 mg 4 times a day (111). Studies justifying high dosages of vancomycin are certainly needed, but until we have more data to be consistent with other treatment guidelines and given the high mortality rate in fulminant disease, we believe that it is reasonable to treat fulminant CDI with the higher dose for the first 48–72 hours. Thereafter, in the case of clinical improvement, the dose should be decreased to 125 mg every 6 hours and continued for an additional 10 days. If no response is observed in the clinical course after 48–72 hours on high-dose vancomycin, the therapy should be reevaluated by the multidisciplinary team and an alternative treatment approach should be considered.

In patients with ileus, the addition of vancomycin enemas (500 mg in 100 mL saline) is also recommended by multiple guidelines based on assumptive improvement in colonic drug delivery (1,3). The actual clinical benefit is questionable. A retrospective case–control study of patients with fulminant CDI in the ICU failed to show advantage from adjunctive vancomycin enemas regarding mortality (45.8% enemas vs 41.7% control, $P = 0.73$) and need for colectomy (16.7% in both groups) (116). We agree with the theoretical advantage in drug delivery by enema in the setting of ileus: when orally administered, medications may not pass beyond the upper GI tract.

Although vancomycin monotherapy is superior to metronidazole in severe CDI, guidelines recommend addition of intravenous metronidazole to oral vancomycin in patients with fulminant disease (1,3). This recommendation is based on a single-center retrospective study, where patients with fulminant CDI in the ICU who received vancomycin plus metronidazole had lower rates of mortality compared with vancomycin monotherapy (15.9% vs 36.4%, $P = 0.03$) (117). A more recent, multicenter, retrospective study of 526 patients, however, found no benefit associated with addition of intravenous metronidazole regarding colectomy, death, or recurrence rate (118). Nevertheless, addition of intravenous metronidazole might be helpful in cases of paralytic ileus because transit of oral vancomycin may be impaired, whereas therapeutic concentrations of intravenously administered metronidazole in the inflamed colon are more likely to be achieved.

Although fidaxomicin was shown to be noninferior to vancomycin in the treatment of severe CDI, there are no data supporting its use in fulminant CDI. Case reports (119,120) have suggested that adjunctive intravenous immunoglobulin might be useful for patients with refractory fulminant CDI, but a larger cohort study of 79 patients of whom 18 received intravenous immunoglobulin showed no benefit in clinical outcomes including mortality, colectomy, and length of stay (121). In a retrospective cohort of 36 patients, bedside colonic lavage with 8 L of polyethylene glycol 3350 electrolyte solution over 48 hours through nasojejunal tube reduced in-hospital mortality compared with colectomy (26% vs 41%, $P = 0.35$) (122). We do not recommend routine use of these agents in patients with fulminant CDI.

Surgical therapy

Key concept

4. We suggest that for patients who require surgical intervention, that either a total colectomy with an end ileostomy and a stapled rectal stump or a diverting loop ileostomy with colonic lavage and intraluminal vancomycin be used depending on clinical circumstances, the patient's estimated tolerance to surgery, and the surgeon's best judgment.

Summary of evidence. Traditionally, surgical intervention for fulminant CDI has involved a total colectomy with the construction of an end ileostomy and a stapled rectal stump. This surgery, although of significant magnitude, removes most of the infected large intestine, avoids anastomosis in a patient in physiologic extremis, and, technically, provides a postoperative anatomy that would potentially allow for an eventual closure of the patient's stoma. Two systematic reviews have evaluated the role of colectomy in the setting of fulminant CDI. A meta-analysis of 31 studies by Bhangu et al. (123) compared survivors and nonsurvivors after either a total colectomy or a partial colectomy. Postoperative mortality was higher after total colectomy among patients experiencing preoperative acute renal failure, the need for vasopressors, and respiratory failure requiring mechanical ventilation. Furthermore, attempts at performing partial colectomies were associated with a 16% reoperation rate due to persistent sepsis requiring the resection of additional colon. Stewart et al. (124) compared the survival benefit of a total colectomy with an end ileostomy with ongoing medical therapy for fulminant CDI. Based on a study population of 510 patients, an odds ratio (OR) for mortality of 0.7 (CI 0.49–0.99) was associated with patients undergoing a total colectomy when compared with continued medical therapy. These reviews suggest that at least in certain instances, a total colectomy provides a survival benefit compared with ongoing medical therapy that has failed to improve the overall condition of a patient with fulminant CDI and partial colectomies should be avoided.

Given that total colectomy is viewed by many surgeons as too physiologically demanding for many patients, with significant long-term consequences that include a permanent stoma, the need for an effective but less drastic surgical intervention has been ongoing. In 2011, Neal et al. (125) provided the first report of a new surgical approach involving the construction of a diverting loop ileostomy, with intraoperative antegrade colonic irrigation using 8 L of PEG administered through the distal limb of the ileostomy, with 10 days of postoperative intraluminal vancomycin also administered through the ileostomy. Forty-two patients underwent the construction of a loop ileostomy, with 35 (83%) undergoing a laparoscopic procedure. Each of the diverted patients experienced resolution of their leukocytosis and their clinical symptoms of CDI. Furthermore, compared with a historical control group of patients who underwent a total colectomy, mortality rates among patients with a loop ileostomy were significantly lower (19% vs 50%, $P = 0.006$).

In 2017, a retrospective study using data from 10 centers was published, which compared clinical outcomes between patients with CDI who underwent either diversion with a loop ileostomy vs a total colectomy (126). The preoperative laboratory test results, antibiotic exposures, and the incidence of preoperative organ failure were comparable between these 2 surgical cohorts. After surgery, length of ICU and hospital stay, reoperation rates, and the incidence of all complications were comparable between the 2 groups. Patients undergoing the construction of a diverting ileostomy demonstrated significantly lower volumes of intraoperative blood loss, whereas fluid and vasopressor requirements during the first 24 hours after surgery did not favor either surgical approach. There was no difference between the 2 cohorts regarding the development of postoperative complications such as pneumonias, sepsis, bladder infections, renal failure, or deep vein thromboses, or was there a difference in unadjusted overall mortality rates. When adjusted for preoperative patient variables, the authors observed significantly lower mortality among patients undergoing the creation of a loop ileostomy (17.2% vs 39.7%, $P = 0.002$).

The limited data available, including from surgical registries (127), suggest that diversion is not associated with a clear survival advantage compared with patients undergoing a total colectomy. In addition to avoiding surgical intervention that is approached too late in the course of CDI because this is associated with increased postoperative mortality (70,128,129), it will be equally important that surgical intervention not occur too early under the auspices that diversion is a low-magnitude surgery that represents a low-risk intervention. In keeping with published surgical society guidelines, for fulminant CDI, surgeons may select either total colectomy or diversion without colectomy based on their best judgment (71,130). Institutions would benefit from reviewing their experience with diversion to ensure that mortality or recurrent CDI rates are not higher than what has been previously described in the literature for total colectomy.

Fecal microbiota transplantation for severe and fulminant CDI

Recommendation

11. We suggest FMT be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, in particular, when patients are deemed poor surgical candidates (strong recommendation, low quality of evidence).

Summary of evidence. There is convincing evidence to suggest that FMT should be considered for the treatment of severe and fulminant CDI unresponsive to standard medical therapy. Although a single FMT resulted in cure in 66%–91% patients in case reports (131,132), for many patients with severe and fulminant presentation, multiple FMTs in short succession proved necessary for lasting cure. These observations have led to the development of sequential FMT protocols. Fischer et al. described a pseudomembrane-driven FMT protocol with selective use of oral vancomycin that had high rates of success in severe and fulminant CDI refractory compared with standard therapy (133). In this protocol, patients with severe or fulminant infection who fail to respond to 5 days of vancomycin ± intravenous metronidazole therapy undergo FMT using colonoscopy. If pseudomembrane is present, oral vancomycin is restarted within 24–48 hours, and subsequent FMT(s) is delivered at 3- to 5-day intervals until complete resolution of pseudomembrane is achieved. In a retrospective analysis of 57 patients using this protocol, 100% of patients with severe CDI and 87% of patients with fulminant CDI were cured during the same hospital admission (78). In an open-label randomized trial by Ianiro et al. (80), a similar, pseudomembrane-driven FMT protocol in combination with a 14-day vancomycin treatment was compared with a single FMT infusion followed by a 14-day vancomycin course. The overall success was 75% for a single FMT–vancomycin group and 100% for multiple FMT–vancomycin group ($P = 0.01$), the latter containing 57% cases with fulminant infection. No serious adverse events were noted with the use of either protocol.

Beyond improved cure rates, FMT may result in decreased rates of CDI-related colectomy and sepsis and may offer survival benefit in this critically ill patient population. In a single-center study, although the number of patients hospitalized for CDI and related colectomy rates increased steadily from 54 to 268 between 2010 and 2014, introduction of inpatient FMT in 2013 led to a significant decline in the number of CDI-related colectomies (zero) (134). A single-center retrospective cohort study also reported dramatically decreased CDI-related colectomy and mortality in severe and fulminant CDI with FMT compared with standard medical therapy, particularly in patients with symptoms refractory to maximal anti-CDI therapy, in whom mortality was reduced from 43.2% before the establishment of an FMT program to 12.1% (135). In a French retrospective cohort study of hospitalized patients with severe CDI, early FMT given within 2–4 days of diagnosis in combination with standard therapy decreased the 90-day mortality rate from 42.2% to 12.1% ($P < 0.0001$) (136). No patients in this cohort underwent surgery, and the authors concluded that the number needed to treat with FMT would be only 2 to save 1 life. A retrospective, matched cohort study of 48 patients with severe or fulminant CDI requiring intensive unit care showed 77% decrease in OR of with a number of needed to treat of 3 to prevent 1 death. Taken together, we now believe that there are ample data demonstrating the safety and efficacy of FMT in patients with severe or fulminant CDI.

Importantly, most patients described in these studies required multiple or sequential FMTs in combination with anti-CDI antibiotics such as vancomycin or fidaxomicin. FMT can be safely administered through careful colonoscopy even in patients with toxic megacolon with gentle CO_2 insufflation and careful advancement of the scope beyond the splenic flexure. FMT should be repeated every 3–5 days until resolution of pseudomembrane. Concomitantly, administration of oral vancomycin (125 mg every 6 hours) or fidaxomicin (200 mg every 12 hours) should be continued as long as pseudomembrane is present. When a complete resolution of pseudomembrane is ascertained by colonoscopy, a final FMT should be delivered completing the sequential therapy. If clinical symptom improvement allows for hospital discharge before complete resolution of pseudomembrane is achieved, oral vancomycin or fidaxomicin should be continued for a minimum of 5 days, followed by a final FMT as an outpatient (78,80). The availability of screened and frozen donor stool-derived microbiota from stool banks has facilitated more prompt treatment of such patients. Clinical response after FMT can be gauged by stool form and frequency, presence of pseudomembrane, and monitoring leukocytosis and C-reactive protein levels. Although FMT and colectomy should both be considered when the patient fails to respond to maximum standard therapy, there is currently no standard set of criteria to determine when colectomy should be performed. Therefore, patients should be monitored closely because their clinical course

rapidly evolves. Optimally, FMT should be considered for those with severe and fulminant CDI after 48–72 hours of maximum medical therapy because it is a significantly less invasive without the risks associated with surgery and the burden of postoperative recovery. Surgical intervention, however, is still a standard treatment modality for refractory severe and fulminant CDI, particularly in cases of colonic toxic megacolon, ischemia, or perforation.

Treatment of Recurrent CDI

Recommendations

12. We suggest tapering/pulsed-dose vancomycin for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole (strong recommendation, very low quality of evidence).
13. We recommend fidaxomicin for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole (strong recommendation, moderate quality of evidence).

Summary of evidence. The rCDI is generally defined as the recurrence of diarrhea and a confirmatory positive test (NAAT or EIA) within 8 weeks after treatment of an initial episode of CDI. Approximately 20% of patients will experience an initial recurrence, and rates of further recurrences continue to go up significantly after each one (137). Another course of antibiotics is generally required for the treatment of a first recurrence of CDI, and the choice of treatment is dependent on what was used to treat the initial episode. Outcomes of interest in this patient population are sustained symptomatic cure defined as initial resolution of the diarrhea and no evidence of recurrence of diarrhea due to CDI. Bacteriologic cure has also been reported in trials, defined as a confirmed negative stool test and no recurrence of diarrhea. The time to recurrence assessed varied among studies as well, but the window of recurrence is generally considered between 8 and 12 weeks (138).

For sustained clinical cure with no recurrence in patients with rCDI, existing data from industry-funded studies slightly favor fidaxomicin. Two phase 3 randomized, double-blind trials were conducted comparing fidaxomicin with vancomycin for the treatment of CDI (82,87). In both, patients with CDI were randomized to receive fidaxomicin 200 mg twice daily or vancomycin 125 mg 4 times daily for 10 days. Overall, 1,164 subjects were enrolled, of which 128 patients in the per-protocol population had a recent episode of CDI before the CDI diagnosis at study enrollment. In the analysis of this subgroup, fidaxomicin was similar to vancomycin in achieving a clinical response at the end of the therapy but superior in preventing a second recurrence within 28 days (35.5% of patients treated with vancomycin and 19.7% of patients treated with fidaxomicin, $P = 0.045$) (83). Another study reporting treatment outcomes at 3 referral centers showed greater benefits when fidaxomicin was used earlier in the treatment course; recurrence after fidaxomicin was 23% in patients with 1 previous episode and 29% after 2 or more previous CDI episodes ($P = 0.005$) (139). Treatment with extended-pulsed regimens of fidaxomicin was superior to standard course of vancomycin in a randomized, open-label study of patients aged 60 years and older. In this, 124 (70%) of 177 patients in the modified full analysis set receiving extended-pulsed fidaxomicin achieved sustained clinical cure 30 days after the end of the treatment, compared with 106 (59%) of 179 patients receiving vancomycin (difference 11% [95% CI 1.0–20.7], $P = 0.030$; OR 1.62 [95% CI 1.04–2.54]). Notably, patients with multiple previous rCDI were excluded from this study (90). Head-to-head trials of fidaxomicin vs pulsed/tapering vancomycin for prevention of rCDI have not been performed.

There are limited data on extended or pulsed vancomycin tapers, and no randomized trials specifically assessing this therapy (140). However, data collected from the placebo arm of a trial in which patients with rCDI were randomized to receive either an investigational therapy or placebo in conjunction with varying doses of vancomycin or metronidazole suggested that longer tapered courses and pulse dosing of vancomycin may be more effective than a standard course of vancomycin (137). In addition, this study provided comparisons of vancomycin with metronidazole. Vancomycin was more effective at clearing *C. difficile* detected by culture or toxin by the end of therapy than metronidazole (89% vs 59%, respectively; $P = 0.001$) (137). Given this and the overall higher failure rates of metronidazole in primary CDI, it can be reasoned that metronidazole should not be used to treat rCDI. Furthermore, metronidazole treatment should be limited to 1 course because of cases of neurotoxicity with prolonged or repeated use (141).

PREVENTION OF CDI RECURRENCE

FMT for recurrent CDI

Recommendations

14. We recommend patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences (strong recommendation, moderate quality of evidence).
15. We recommend FMT be delivered through colonoscopy (strong recommendation, moderate quality of evidence) or capsules (strong recommendation, moderate quality of evidence) for treatment of rCDI; we suggest delivery by enema if other methods are unavailable (conditional recommendation, low quality of evidence).
16. We suggest repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT (conditional recommendation, very low quality of evidence).

Summary of evidence. FMT has emerged as a safe and effective therapy for rCDI, which most studies have defined as 3 or more confirmed episodes, although some trials have performed FMT after a second episode. The efficacy of FMT after standard-of-care antibiotics for preventing rCDI has been well described in numerous case series and RCTs. The first RCT evaluating the efficacy of FMT in rCDI was published in 2013. In this study, FMT was administered by nasoduodenal tube infusion after a short course of vancomycin and yielded a cure rate of 81% for single administration compared with standard-of-care vancomycin (31%) (142). Other trials have compared FMT with placebo (143), vancomycin (79), and fidaxomicin (143), all yielding similar results. The first double-blind placebo-controlled trial was published by Kelly et al. In this study (143), 46 patients who had 3 or more recurrences of CDI and had received at least a standard course of vancomycin for their most recent CDI episode were enrolled and randomized to receive donor stool (heterologous) or their own stool (autologous) administered by colonoscopy. In the intention-to-treat analysis, 20 of 22 patients (90.9%) in the donor

FMT group achieved clinical cure compared with 15 of 24 (62.5%) in the autologous FMT group ($P = 0.042$). Resolution after autologous FMT differed by site (9 of 10 vs 6 of 14 [$P = 0.033$]), which was possibly related to enrollment of colonized patients and longer courses of vancomycin pre-FMT at the site with a high placebo response. Meta-analysis of RCTs confirmed the efficacy of FMT with a number needed to treat of 3 (144). Quaraishi et al. performed a more recent meta-analysis that considered 37 studies including numerous case series and 7 RCTs (n = 1,973), with a mean pooled overall response for FMT in recurrent and refractory CDI of 92%. Among 34 studies that presented data on the efficacy of a single FMT, the pooled response rate was 84%. This meta-analysis showed that lower administration (92%–97%) was more effective than upper modalities (82%–94%, $P = 0.02$) (145).

There have been 2 negative FMT trials. Hota et al. performed a small open-label RCT comparing 14 days of oral vancomycin followed by a single FMT by enema with a 6-week oral vancomycin taper in adult patients with rCDI (146). Nine of the 16 (56.2%) patients who received FMT compared with 5 of 12 (41.7%) in the vancomycin taper group experienced recurrence, differences that were not clinically significant. The PUNCH-CD 2 trial compared 1 or 2 enema doses of the donor stool product, RBX2660, with placebo for prevention of rCDI in patients who had completed a standard course of vancomycin. The *a priori* primary end point of decreased recurrence after 2 FMTs was not met because cure with the 2-dose regimen (61%) was not statistically different from placebo (45%) (147). Notably, similarly low cure rates with a single-dose enema in a large clinical trial that compared fresh with frozen FMT by enema were seen (148); efficacy in this study improved with multiple FMTs. These negative results may reflect the lower efficacy seen with FMT delivered through enema, discussed further.

There have been few trials comparing the effectiveness of different delivery modalities. The choice of the most appropriate should be driven partly by the options available to the provider, the preferences of the patient, and the clinical circumstances. Kao et al. conducted a randomized clinical trial (n = 116) that compared FMT through frozen oral capsules vs frozen FMT material delivered through colonoscopy. In this study, capsule administration (96.2%) was noninferior to colonoscopy (96.2%) with no related serious adverse events (145). In another study that compared lyophilized FMT capsules vs FMT enema with frozen FMT material, capsules (84%) yielded similar efficacy to the enema treatment (88%, $P = 0.76$) (149). Endoscopic administration has the added benefit of being able to do a mucosal assessment and rule out other GI pathology. This modality is limited to those trained in endoscopy. The efficacy of orally administered capsules containing donor material varies between 74% and 96% in the published studies to date (150–155). Capsule administration did not result in increase in GI symptoms post-FMT compared with lower GI administration, alleviating theoretical concerns regarding inducing small bowel overgrowth with encapsulated delivery (156,157). Several meta-analyses have shown reduced efficacy when FMT delivery method was by enema compared with colonoscopic or capsule delivery (144,158). FMT through enema remains an option in certain populations, such as pediatric patients, where lower endoscopy may not be feasible or if there are no providers able to perform an endoscopy. In these circumstances, multiple FMTs may be necessary to achieve cure.

The safety profile of FMT seems acceptable. Minor transient symptoms have been reported in case series. These include bloating, cramps, abdominal pain, nausea, gas, diarrhea, irregular bowel movements, constipation, and low-grade fevers (145). Serious adverse events have rarely been reported, even among immunocompromised patients (149), although risk of infection is an important consideration. One recent report described 2 patients in whom extended-spectrum β-lactamase–producing *Escherichia coli* bacteremia occurred after they had undergone FMT using stool from the same donor; one of the patients died (159). Careful donor selection and screening can mitigate the risk of infection transmission (160,161). The methods used to administer FMT may present increased risk such as perforation, bleeding, and sedation-related complications when FMT is delivered by colonoscopy. Flexible sigmoidoscopy without sedation may eliminate sedation-related risks while permitting mucosal assessment. Fatal aspiration pneumonia has been reported with administration through nasoenteric tube because of regurgitation of donor stool (162). This risk is considerably higher if the material is delivered into the stomach or any prepyloric location. In addition, when surveyed patients noted they would prefer to not undergo an FMT through nasoenteric tube administration (163). We do not recommend nasoenteric administration of FMT in cases of severe or fulminant CDI, particularly when the patient is lying flat or may have an ileus.

FMT failure is defined as recurrence of diarrhea with a confirmatory test for *C. difficile*. A prospective cohort trial noted that among 167 patients who underwent FMT for rCDI, 16.7% experienced an FMT failure of whom most (86%) experienced failure within 4 weeks after FMT, and 14% developed rCDI between 4 and 8 weeks (164). Several risk factors of FMT failure have been identified (77,165). In 1 large multicenter cohort study, among 328 patients, the early FMT failure rate (within 1 month) was found to be 18.6%, and risks of failure included FMT for severe or fulminant CDI, inpatient status, and previous CDI-related hospitalization. A subgroup analysis of outpatients revealed that the only predictor of FMT failure was previous CDI-related hospitalization, which serves as a surrogate for history of severe disease (77). Ianiro et al. also noted similar findings and that patients with severe CDI were more likely to require multiple FMTs to achieve cure (166).

We recommend closely following up patients after FMT to assess response. Patients can be evaluated in the clinic or through telephone within a week of the procedure to assess for symptoms of recurrence or adverse events. Patients should be evaluated again for late failure between 4 and 8 weeks post-FMT. If FMT failure is confirmed, repeat FMT should be offered. In a large cohort study that assessed multiple FMT failures, less than 5% of patients failed a second FMT (81). Once an FMT failure is confirmed, anti-CDI antibiotics should be restarted to control symptoms before repeat FMT (142). Reasons for failure, such as treatment with concomitant non-CDI antibiotics, should be considered. Colonoscopic delivery is the preferred route for those who fail to achieve cure with FMT through enema or encapsulated formulations. For patients who do not want or cannot undergo repeat FMT, alternative treatment options include prolonged or indefinite treatment with vancomycin; this can usually be tapered down to a single daily dose.

OTHER PREVENTION STRATEGIES

Suppressive and prophylactic vancomycin

Recommendations

17. For patients with rCDI who are not candidates for FMT, who relapsed after FMT, or who require ongoing or frequent courses of antibiotics, long-term suppressive oral vancomycin may be used to prevent further recurrences (conditional recommendation, very low quality of evidence).
18. Oral vancomycin prophylaxis (OVP) may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence (conditional recommendation, low quality of evidence).

Summary of evidence. There are very limited data to recommend extended antimicrobial treatment beyond a typical course for rCDI or for antimicrobial prophylaxis. One small (n = 20) retrospective study looked into the use of long-term oral vancomycin to prevent further recurrence (167). Patients with rCDI who were not candidates for FMT, refused, or relapsed after FMT were treated with vancomycin, followed by long-term oral vancomycin at a dose of 125 mg once daily for a minimum of 8 weeks. Patients had a median age of 80 years and experienced a median of 4 episodes of CDI before long-term vancomycin. One case of CDI relapse occurred while on long-term vancomycin during 200 patient-months of follow-up. Among those who stopped long-term vancomycin, 31% relapsed within 6 weeks. No adverse events or instances of vancomycin-resistant enterococci (VRE) were observed while patients were on long-term vancomycin. Although this series is supportive of this approach, further research is necessary to confirm or refine these strategies. For chronic suppression, we suggest a dose of 125 mg once daily, which controls symptoms and prevents recurrence in most patients. Some patients continue to experience loose stools at this dose, and twice daily or 3 times daily dosing of vancomycin may be necessary in those cases.

Patients presenting with a previous CDI episode may subsequently require systemic antibiotics for other indications. Use of concurrent antibiotics during anti-CDI therapy has been associated with lower cure rates and increases the risk of CDI recurrence when administered during the 4-week period after completion of anti-CDI therapy (168). Patients who receive additional antibiotics during the 60-day follow-up after a nosocomial CDI are at nearly 5 times the risk of developing a subsequent recurrence, and when combined with age 65 years or older and history of severe CDI, the risk of recurrence after antibiotics is as high as 87% (169). Both vancomycin and metronidazole have been used to prevent CDI in patients who require courses of antibiotics. Data to support this practice are limited, and previous guidelines have not recommended it. Besides expense, there is a risk of promoting drug-resistant organisms, such as VRE, and these agents may further disrupt the gut microbiome, theoretically increasing risks of CDI recurrence.

Three retrospective cohort studies explored OVP accompanying systemic antibiotics to reduce the risk of relapse in patients with history of CDI. All were conducted at single centers, the largest of which looked at a cohort of 557 patients receiving antibiotics not targeting CDI within 30 days of a primary or recurrent CDI episode (170). OVP was provided to 227 patients, although dose and duration varied, and the mean duration of OVP was 7 days. Patients in this group were more likely to have recurrent disease and to have not received metronidazole for previous CDI episodes, suggesting that they were at higher risk of subsequent CDI than those who did not receive OVP. In patients with only a single previous CDI, OVP was not found to be effective at preventing another CDI, but in those with a history of recurrent CDI, 49 of 90 (54.5%) in the OVP group developed another CDI within 90 days after antibiotics vs 57 of 82 (69.5%) of those who did not receive OVP, resulting in a number needed to treat of 7 to prevent 1 CDI ($P < 0.0001$). A similar study of 71 patients also showed decreased recurrence of CDI in the OVP group compared with the control group (4% vs 27%, $P < 0.001$) (171). The third study included patients with a history of CDI and who received antibiotics not targeted at *C. difficile*, most commonly fluoroquinolones or carboxypenicillins/ureidopenicillins such as piperacillin. OVP decreased the risk of further recurrence in patients whose CDI itself was a recurrence (adjusted hazard ratio 0.47; 95% CI 0.32–0.69; $P < 0.0001$) when compared with patients who did not receive vancomycin prophylaxis. However, secondary analysis, looking only at toxin-positive relapses of CDI, occurred within 90 days in 9.8% (19 of 193 of vancomycin prophylaxis–exposed group) vs 9.3% (53 of 567 of the unexposed group) with an adjusted OR (aOR) 0.63; 95% CI 0.35–1.14 (172). Of interest, CDI relapses at 90 days were less frequent in exposed patients with only 1 previous episode of CDI (OR 0.42; 95% CI 0.19–0.93). There was a lack of benefit with OVP overall, but a benefit was observed in patients with only 1 previous CDI episode. The small, retrospective nonrandomized nature and varied doses or durations for OVP are major limitations to all these studies. Recently, Johnson et al. published results from their open-label RCT of low-dose oral vancomycin 125 mg given once daily compared with no prophylaxis in 100 patients at high risk of CDI (173). Eligible patients were age 60 years or older, with hospitalization in the past 30 days, who were rehospitalized and receiving high-risk systemic antibiotics. No patient in the OVP arm developed CDI during hospitalization, whereas 6 (12%) in the no-prophylaxis arm developed CDI during the current hospitalization ($P = 0.03$). Two patients who experienced hospital-onset CDI in the no-prophylaxis group also experienced recurrent CDI on the outpatient basis. No cases of CDI were observed in the OVP group during the posthospitalization evaluation period, although more than half of patients did not have posthospitalization follow-up.

Given the high incidence and poor outcomes among immunocompromised individuals, prevention of CDI in this population is of great interest. A retrospective study of allogeneic hematopoietic stem cell recipients found that oral vancomycin 125 mg twice daily was highly effective in preventing a primary CDI (174). There were no cases of CDI in patients who received prophylaxis (0/90, 0%), whereas 11 of 55 (20%) patients who did not receive prophylaxis developed CDI ($P < 0.001$). The utility of OVP for primary prevention was also demonstrated in a randomized, placebo-controlled trial of fidaxomicin for prophylaxis of CDI in 600 adults undergoing hematopoietic stem cell transplantation and taking broad-spectrum antimicrobials, which showed that the incidence of confirmed CDI was significantly lower in the group treated with once-daily fidaxomicin vs placebo through 60 days posttreatment (4.3% vs 10.7%, respectively) (175). Recent cohort studies conducted in patients postrenal transplantation and hematopoietic stem cell transplant recipients also showed OVP that dramatically reduced risk of rCDI when

used as secondary prophylaxis, with no cases of rCDI in the OVP group in 1 study (176) and a rate of rCDI that was significantly lower in the OVP group compared with the no-OVP group in the other (5% [1 of 21] vs 35% [10 of 29]; $P = 0.016$) (177).

Meta-analysis of 9 studies examining OVP for primary or secondary prevention found overall CDI recurrence was less likely in patients who received OVP compared with controls (OR 0.245; 95% CI 0.13–0.48) with considerable heterogeneity ($I^2 = 61\%$) (178). Meta-regression showed that total daily dose of OVP used showed a significant correlation with odds for CDI, with lower doses being more effective and explained 100% of the statistical heterogeneity between included studies. A pooled analysis of data provided by 3 studies showed no significant increase in VRE infection rate in the OVP group compared with that in the control group. Another recent meta-analysis showed OVP not to be effective for primary CDI prevention; however, in 10 observational studies comprising a total of 9,258 CDI patients evaluating OVP for secondary prevention, the rate of future CDI in patients on OVP was 13.3% (95/713) compared with 21.9% (1,875/8,545) in patients who did not receive OVP, a statistically significant decreased risk of future CDI (OR 0.34; 95% CI 0.20–0.59; $P < 0.00001$) (179). Considering these data, OVP may be considered in high-risk patients who have been recently treated for CDI and require subsequent treatment with systemic antibiotics. This high-risk group includes patients aged 65 years or older or with significant immunocompromise who were hospitalized for severe CDI within the past 3 months. When using OVP, we suggest using low-dose vancomycin 125 mg once daily, which is typically continued until 5 days after completion of systemic antibiotics. There is a strong need for larger, prospective clinical trials and additional studies of narrow-spectrum agents such as fidaxomicin for this indication. Analyses of the impact of OVP on the gut microbiome and risk of drug-resistant organisms will be important secondary end points.

Bezlotoxumab

Recommendation

19. We suggest bezlotoxumab (BEZ) be considered for prevention of CDI recurrence in patients who are at high risk of recurrence (conditional recommendation, moderate quality of evidence).

Summary of evidence. Toxigenic strains of *C. difficile* produce 2 potent exotoxins: toxin A and toxin B, which are responsible for mucosal injury, acute inflammation (colitis), and diarrhea (68,180,181). Host immunity to these toxins may play an important role in the severity of symptoms or risk of recurrence, and higher levels of antitoxin antibodies have been correlated with protective effects against primary and recurrent CDI (182–184). BEZ is a human monoclonal antibody that binds to toxin B and prevents it from entering the GI cell layer, preventing colonic cell damage (185–187). After 9 clinical trials, BEZ was approved by the US FDA for the prevention of CDI recurrences in 2016 (181,183,185,188–190). The drug is administered as a single weight-based intravenous infusion during a course of anti-CDI treatment and has a half-life of 19 days. Neutralization of the toxin while the antibody remains in circulation may prevent symptoms in the event of *C. difficile* regrowth after completion of antibiotic therapy. The average wholesale drug cost is $4,560 per 1,000-mg vial (191), with additional costs related to administration an infusion. Considering the high cost of BEZ and the minimal benefits over placebo in patients at low risk of recurrent CDI, as detailed further, we recommend this drug be considered for patients in whom the observed benefits in clinical trials were greatest including those aged 65 years or older with at least one of the following additional risk factors: experiencing their second episode of CDI within the past 6 months, immunocompromised, or severe CDI.

MODIFY I and MODIFY II were multicenter, double-blind, placebo-controlled, phase 3 trials that evaluated the safety and efficacy of BEZ in adult patients receiving standard-of-care antibiotics for primary or recurrent CDI (183). Modified intention-to-treat analysis of a pooled data set from the 2,655 adult patients enrolled in these clinical trials revealed that sustained cure from recurrence of CDI at 12 weeks was significantly higher in the BEZ group (63.5% [496/781]) in comparison with the placebo group (53.7% [415/773]). The adjusted difference between BEZ and placebo group was 9.7 percentage points (95% CI 4.8–14.5; $P < 0.0001$), giving a number needed to treat of 10 to prevent 1 episode of recurrent CDI with BEZ. A *post hoc* analysis exploring the efficacy of BEZ for the subset of participants with an IBD diagnosis (n = 44) showed a trend for rCDI to recur less frequently in the BEZ group (192). However, given small sample sizes and inconclusive results of statistical analysis, there is insufficient evidence to recommend BEZ for patients with IBD in the absence of other risk factors listed earlier.

It is important to note that in *post hoc* analysis, BEZ did not show significant benefits over placebo in patients who did not have any risk factors for recurrence (20.9% [32/153] with BEZ vs 18.8% [29/154] with placebo) including patients younger than 65 years, with or without additional risk factors (193). Analysis of predefined subgroups of patients showed that the benefits of the drug were greatest for patients aged 65 years or older, for those experiencing a recurrent episode of CDI, in immunocompromised patients, and in severe CDI (183). The greatest absolute difference in the rate of recurrence between BEZ- and placebo-treated groups was observed in participants with both a history of CDI and severe CDI (−35.7% [95% CI −60.5% to −2.8%]) (193). The number needed to treat to prevent 1 recurrent CDI was only 6 for the subgroup of patients aged 65 years or older and for those with ≥1 CDI episode within the past 6 months. BEZ seemed equally effective in patients infected with the hypervirulent strain (NAP1/BI/027); CDI recurrence with BEZ occurred in (23.6% [21/89]) vs placebo group (34% [34/100]) (183). Cost-effectiveness models have shown that, compared with placebo, BEZ was cost-effective in preventing CDI recurrences, with an incremental cost effectiveness ratio (ICER) of $19,824 per quality-adjusted life-year (QALY) gained. Compared with placebo, BEZ was more cost-effective in the subgroups of patients aged 65 years or older (ICER of $15,298/QALY) and immunocompromised patients (ICER of $12,597/QALY) (194).

There are no absolute contraindications to use of BEZ, but caution is advised for use in patients with a history of congestive heart failure, given the higher incidence of heart failure in the active compared with the control group (2% vs 1%) observed in phase 3 clinical trials (195,196). Patients with congestive heart failure in the BEZ arm were more likely to report increased treatment-emergent adverse events (83.9% vs 70.2%), serious adverse events (53.4% vs 48%), and deaths (19.5% vs 12.5%) than placebo-treated patients (197). Death from cardiovascular diseases was also numerically higher in BEZ-treated patients (8 [14.3%] vs 4 [6.8%]). The mechanisms for these effects are not clear. Based on these data, we do not recommend use of BEZ in patients with a history of heart failure and that it be used with caution in patients with severe underlying cardiovascular comorbidities.

OTHER THERAPEUTIC CONSIDERATIONS

Recommendation

20. We suggest against discontinuation of antisecretory therapy in patients with CDI, provided there is an appropriate indication for their use (strong recommendation, very low quality of evidence).

Summary of evidence. PPIs are among the most commonly prescribed medications (198), and many patients who develop CDI are being treated concurrently with PPIs (199). Increased risk of primary and recurrent CDI has been reported with gastric acid suppression. A systematic review that included 16 observational studies, together reporting more than 7,000 patients showed an increased rate of CDI in patient with gastric acid suppression vs those without (OR 1.52; 95% CI 1.20–1.94); the increased risk persisted even with adjusting for potential confounders (200). In 2012, based on review of reports from its Adverse Event Reporting System, the US FDA issued a safety communication stating that the role of PPIs could not be definitively ruled out as posing a risk of CDI, although the agency conceded significant confounding factors such as advanced age, medical comorbidities, or use of broad-spectrum antibiotics could have predisposed these patients to develop CDI (201).

Observational data such as these need to be cautiously interpreted because patients treated with PPIs tend to have other comorbidities and may have more healthcare contacts that increase CDI risk. It is not possible to adjust for every confounding variable in retrospective analyses. Biologically plausible mechanisms for increased CDI risk include alterations in gut microbiota or loss of the protective effects of gastric acid, which would allow colonization with ingested organisms (202) Recently published results form a large prospective trial of more than 17,000 participants who were randomized to receive pantoprazole or placebo and followed up for an average of 3 years (203) found a statistically significant difference between the groups in rates of enteric infection (1.4% vs 1.0% in the placebo group, OR 1.33 95% CI 1.01–1.75). In this study, there were 9 CDI in the PPI group and 4 in the placebo group, although the difference was not statistically significant.

In summary, the effects of antisecretory therapy on CDI risk are extremely small in comparison with known CDI risk factors. Furthermore, discontinuing antisecretory therapy may leave patients at risk of harm by leaving acid-related upper GI disease untreated. Patients presenting with CDI should be assessed for the appropriateness of antisecretory therapy. In 1 study, more than half of patients with CDI did not have a valid indication for PPI use (199). When used for appropriate indications, the benefits of PPI are clear (204), and therapy should be continued.

CDI MANAGEMENT IN IBD PATIENTS

CDI diagnosis in IBD

Recommendation

21. We recommend *C. difficile* testing in patients with IBD presenting with an acute flare associated with diarrhea (strong recommendation, low quality of evidence).

Summary of evidence. A large population-based study from Manitoba showed that individuals with IBD have a 4.8-fold increased risk of developing CDI, are more likely to have community-onset CDI, are younger at the time of CDI diagnosis, and are more likely to have recurrent CDI (13% vs 7%) (205). The magnitude of risk of getting CDI is similar between individuals with ulcerative colitis (UC) and Crohn's disease. Risk factors of CDI in this population include exposure to corticosteroids, infliximab or adalimumab, previous hospitalizations, more frequent ambulatory care visits, shorter duration of IBD, and higher rate of comorbidities (205). In addition, patients with IBD and concurrent CDI are more likely to need escalation of IBD therapy and have higher rates of ER visits (206). When both ambulatory and hospitalized patients were considered, there was lower mortality after CDI among individuals with IBD than without IBD when (hazard ratio 0.65; 95% CI 0.44–0.96) (205). However, when patients with IBD are hospitalized with CDI, the mortality risk is about 4-fold higher than patients admitted for IBD alone (aOR 4.7, 95% CI 2.9–7.9) or *C. difficile* alone (aOR 2.2, 95% CI 1.4–3.4) (207). The higher mortality rate is even more pronounced in UC (OR 3.79, 95% CI 2.84–5.06) (208). A systemic review of 12 observational studies concluded that CDI increases the risk of colectomy in IBD long term (>3 months) but not short term (<3 months) (209).

Some argue that CDI is a marker of IBD severity, or conversely, that IBD is a predictor of difficult to treat, complicated CDI. It is notable, that patients with IBD tend to have pseudomembrane very rarely, if at all, on endoscopy, only mucopurulent exudate, which can make the diagnosis of CDI and assessment of severity difficult (210). Nevertheless, detection of CDI in an acute flare of IBD and administration of effective antimicrobial therapy often leads to favorable outcomes; therefore, testing is recommended in any patient with acute onset of or worsening IBD symptoms. As discussed previously, testing with a 2-step testing algorithm in this population is recommended because colonization by *C. difficile* (PCR+/toxin−) is common in IBD (211), so PCR-only testing methods may not be helpful.

Treatment of CDI in IBD

Recommendation

22. We suggest vancomycin 125 mg p.o. 4 times a day for a minimum of 14 days in patients with IBD and CDI (strong recommendation, very low quality of evidence).

Summary of evidence. To date, there are no published RCTs comparing treatments for CDI in adults with IBD. In a retrospective, single-center study of 114 patients with UC and patients with nonsevere CDI had fewer readmissions and shorter lengths of stay when treated with a vancomycin-containing regimen compared with those treated with metronidazole (30-day readmissions, 0% vs 31.0%, $P = 0.04$; length of stay, 6.38 days vs 13.62 days, $P = 0.02$) (212). Colectomy rate was also lower when CDI was treated with vancomycin compared with metronidazole (210). Longer duration of vancomycin therapy (21–42 days) compared with shorter duration (<21 days) reduced the rate of CDI recurrence from 11.7% to a 1.8% (OR 0.13, $P = 0.043$) in a single-center retrospective study (213). Decreasing the likelihood of recurrence of CDI is of particular interest in IBD. In a retrospective cohort of 503 patients with IBD, 33% were more likely to experience recurrent CDI compared with the general population (32% vs 24% $P < 0.01$) (214).

There are very limited data on fidaxomicin in IBD from small single-center studies, but it seems to be effective (81%–82% cure rates) and safe (139,215). No studies compared a standard 10-day course with a longer duration of fidaxomicin therapy in patients with IBD and CDI. Based on our clinical experience and extrapolation of the benefits gained from extended treatment courses of vancomycin and favorable safety, we recommend a longer than standard 10-day treatment course of vancomycin, with a minimum of 14 days of treatment.

IBD therapy considerations

Key concept

5. Immunosuppressive IBD therapy should not be held during anti-CDI therapy in the setting of disease flare, and escalation of therapy may be considered if there is no symptomatic improvement with treatment of CDI.

Summary of evidence. Previous recommendations on holding immunosuppressive therapy in patients with IBD diagnosed with CDI were largely based on a European multicenter retrospective cohort study (216). In this, 12% of the 104 hospitalized patients with IBD and CDI who were treated with antibiotics and immunomodulators developed a severe adverse event including toxic megacolon, bowel perforation, shock, respiratory failure, death, or colectomy within 3 months of admission. No severe adverse events were documented in those patients with IBD treated with antibiotics alone. The use of more than 1 immunosuppressive agent (immunomodulator and systemic steroid) further increased the risk of having an adverse outcome independent of IBD severity at presentation. On the contrary, in a more recent multicenter cohort of 294 hospitalized patients with IBD and CDI, serum albumin below 3 g/dL was identified as an independent predictor of surgery and death, but the use of immunomodulators, systemic corticosteroids, or antitumor necrosis factor agents were not associated with these adverse outcomes (217).

One of the ongoing debates around management of CDI in IBD is sequential vs concomitant anti-CDI antibiotic and immunosuppressive therapy. Although immunosuppressive therapy may weaken the host's defense mechanisms against *C. difficile* and hinder elimination of the infection, it is crucial for the treatment of the underlying IBD. Distinguishing CDI in quiescent IBD from *C. difficile* colonization in active IBD is challenging. Patients with inactive IBD may develop CDI, which resolves with vancomycin, as in a patient without IBD. Alternatively, those whose IBD is inadequately controlled may develop CDI, perhaps as a consequence of the inflammation and disturbed microbiota, which then contributes to symptoms of disease flare. Often, endoscopic evaluation can help distinguish between these 2 scenarios. In the first case scenario, anti-CDI antibiotic therapy should be initiated and maintenance therapy for IBD continued. In the second case scenario, immunosuppressive therapy should be escalated to treat the flare because anti-CDI therapy alone is unlikely to change the outcome. Therefore, we recommend that when CDI is diagnosed, anti-*C. difficile* antimicrobial therapy is initiated while the maintenance IBD therapy is continued. If no improvement in clinical symptoms is observed after 3 days, immunosuppressive therapy should be optimized or escalated to address the underlying active IBD.

FMT for CDI in IBD

Recommendation

23. FMT should be considered for recurrent CDI in patients with IBD (strong recommendation, very low quality of evidence).

Summary of evidence. Patients with IBD are at higher risk of developing recurrent CDI. FMT has been shown to be beneficial in patients with IBD with a 79%–91% success rate in preventing CDI recurrence in numerous single-center and multicenter retrospective cohorts (149,218–221). Although FMT improved the clinical course in most patients, a few patients (7%–25%) in retrospective studies experienced worsening of IBD, some requiring escalation of immunosuppressive therapy, hospitalization, or colectomy (222). These studies were limited in that baseline IBD activity, IBD-directed therapies, and biomarkers were not always well documented. Only 1 prospective study to date reported 91% success rate in eradicating CDI measured by resolution of diarrhea and undetectable *C. difficile* toxin (223). In this study, patients were offered FMT after at least 1 CDI recurrence; overall, two-third of patients experienced improvement in their IBD symptoms, nearly one-third had unchanged IBD activity, and only 4% (n = 1) had worsening of IBD symptoms. These data support the notion that FMT is as safe and well tolerated in patients with IBD as those without.

OTHER SPECIAL POPULATIONS

Pregnancy and lactation

Key concepts

6. We recommend using vancomycin to treat pregnant and peripartum patients with CDI.
7. We recommend using vancomycin to treat breastfeeding patients with CDI.

Summary of the evidence. The diagnosis of CDI in peripartum women has increased over the past 15 years and the diagnosis is associated with significant maternal morbidity and mortality (224,225). Although not a reportable illness, more severe infections resulting in intensive care admission, colectomy, fetal loss, and death have been identified through passive surveillance and survey of infectious disease consultants (226). Early reports of 10 cases of peripartum disease were concerning in that 40% required hospitalization, 50% experienced relapse, and 1 died (224). A large retrospective cohort study found that deliveries complicated by CDI doubled between 1999 and 2013 and a diagnosis of CDI was associated with 57 times greater the risk of maternal death, 8 times the risk of venous thromboembolism, and 24 times the risk of prolonged hospital stay (227). An observational study of 31 pregnant patients showed that treatment change due to adverse events or nonresolution of symptoms on metronidazole was common, occurring in 50% of those so treated (228). This study also showed higher rates of preterm birth, gestational hypertension, and adverse neonatal outcomes compared with national data. Besides the emergence of the hypervirulent strain, the risk of CDI in pregnant women is strongly related to exposure to antibiotics and the hospital environment, particularly in the setting of cesarean section deliveries, and the immune changes associated with pregnancy (224,225).

Because of the higher risk of severe disease and poor outcomes, the frequent treatment failures observed with metronidazole, and minimal systemic absorption of oral vancomycin, we recommend it be used as first-line treatment in pregnant and peripartum

women with CDI. Furthermore, there are decades of clinical experience with the efficacy and safety of this drug in pregnant patients. No adequate or well-controlled studies of fidaxomicin have been conducted in pregnant women, although no evidence of fetal harm was observed when pregnant rabbits and rats were given intravenous fidaxomicin at doses approximately 66 and 200 times the human plasma exposure (229). Systemic absorption of fidaxomicin is minimal, although it should be reserved for vancomycin treatment failures until further data to support first-line use in pregnancy is available. Given procedural risks and lack of safety data, FMT should be avoided in pregnant patients with rCDI. These patients may be maintained on oral vancomycin and FMT performed postpartum.

Mothers being treated for CDI may continue to breastfeed and oral vancomycin is recommended. Vancomycin is not absorbed and, given its large molecular weight, would not be expected to enter breast milk and any drug that got into the breast milk would not be absorbed by the infant's gut (230). Fidaxomicin acts locally in the gut with minimal systemic absorption; pharmacokinetic properties suggest transfer into breast milk would be minimal. However, until more established data are available, it is recommended to use with caution in breastfeeding women (231). Numerous studies have shown no untoward effects with metronidazole; however, it is secreted in breast milk and the infant can be exposed to fairly high doses, up to 24% of the maternal dose. Although the daily dose received by the infant would be far below typical therapeutic doses, there are theoretical concerns around antibiotic exposure early in infancy and the effect on the developing gut microbiome.

Immunocompromised patients

Key concept

8. We suggest vancomycin or fidaxomicin be used first line for treatment of CDI in patients who are immunocompromised.

Summary of evidence. Immunocompromised individuals are at higher risk of acquiring CDI, having multiple recurrent CDI, and developing a complicated clinical course. This is due to a myriad of factors, including being more hospital experienced and the increased use of antibiotics for prophylaxis and treatment of opportunistic infections. They may also have times of prolonged neutropenia or immunosuppressive therapy that in parallel requires prolonged antibacterial therapy. The resultant intestinal disruption leads to increased risk of CDI. Overall, organ transplantation has the highest associated CDI risk, approximately 9-fold higher than average risk associated with hospitalization (232,233). Among solid organ transplant recipients, patients with multiple organ transplants have the highest prevalence of CDI at 12.7%, followed by lung 10.8%, liver 9.1%, intestine 8%, heart 5.2%, and kidney 4.7% (234). Among hematopoietic stem cell transplant recipients, the rates of CDI are nearly 2-fold higher compared with autologous transplant patients (9.3% vs 5.2%) with most of the cases occurring during the first 100 days of the posttransplantation period (235). Patients with end-stage renal disease and end-stage liver disease have a considerable elevated risk of CDI, approximately 2.5-fold higher for both initial and for recurrent infection (236,237). CDI significantly increases mortality, length of stay, readmission rates, and resulting healthcare costs in both populations (238,239). In addition, *C. difficile* remains the leading cause of diarrhea in patients living with human immunodeficiency virus in the antiretroviral therapy era, with a CD4 count $\leq$50 cells/mm^3 as an independent risk factor (240).

A *post hoc* analysis of 2 large randomized trials comparing fidaxomicin and vancomycin found that patients with cancer (n = 183) had a lower cure rate than patients without cancer (n = 922) (79% vs 87%). Patients with cancer tended to achieve a higher initial cure rate with fidaxomicin (85%) compared with vancomycin (74%) (P = 0.065) and lower likelihood of recurrence (OR 0.37; P = 0.018) (241). Subgroup analysis of the same 2 trials found that stages 3–4 chronic kidney disease was associated with lower likelihood of cure and greater chance of recurrence. Although initial cure rates were similar in the vancomycin or fidaxomicin groups, the rate of recurrence was higher after vancomycin treatment independent of renal function (242).

FMT, as previously discussed, is considered to be the best treatment option for multiply recurrent CDI. There has been concern that immunocompromised patients may be at higher risk of infectious complications after FMT, although this concern has not been corroborated by published studies to date. The first multicenter cohort study comprising 80 patients with various immunocompromising conditions found FMT to be effective, with 78% achieving cure after a single treatment, and safe with no treatment-related infectious complications reported (149). Accordingly, a study of 94 solid organ transplant recipients found no FMT-associated bacteremia but reported a lower cure after a single FMT at 58% (243). Notably, predictors of FMT failure were inpatient status, severe and fulminant CDI, presence of pseudomembranous colitis, and use of non-CDI antibiotics at the time of FMT. Three small case series of FMTs in hematopoietic stem cell transplant recipients (N = 18) reported cure rates around 80% with no significant complications relating to FMT (244–246). In a retrospective study, 63 patients with cirrhosis, 38.1% decompensated, received FMT for CDI with an overall 85.7% cure rate. There were only 3 SAEs possibly related to FMT, none of which involved infection, hepatic decompensation, or death (247). Rigorous donor screening is critical because infectious complications after FMT have been reported. Transmission of CMV and EBV is a unique concern in immunocompromised patients. Although most healthy adults are seropositive for both viruses, to date, no transmission attributable to FMT performed in healthcare facilities have been reported, even among immunocompromised individuals (161). Accordingly, the panel recommends that immunocompromised recipients should be tested for these viruses before undergoing FMT and, if seronegative, appropriate conversation about risk, benefits, and alternatives (including patient-selected donor use) should take place. Immunosuppressive therapies may hinder pseudomembrane formation; thus, reliance on the presence of pseudomembrane for CDI severity assessment to guide therapy in immunocompromised individuals might be misleading (248,249).

CONCLUSIONS

CDI will remain a common and challenging clinical problem. Infection control and antibiotic stewardship programs in hospital settings have been effective at reducing the CDI incidence, but community spread is a growing problem and efforts should be directed at prevention in this population. Understanding around the pathophysiology of the infection, including the relative roles of the gut microbiota and host immune factors, has increased, and

further research may identify new targets for prevention and treatment. Challenges around diagnosis will continue, and higher sensitivity toxin assays may prove helpful. Novel, narrow-spectrum antibiotics for CDI have lesser impact on gut microbial composition, which may translate to a reduced the risk of recurrence (250). FMT has emerged as an effective treatment, but questions remain about best methods of delivery, optimal donor screening, and long-term safety of the procedure. Defined microbiota consortia may enable a more targeted approach to treatment of the underlying dysbiosis that drives CDI, and formulations of microbiota may soon gain regulatory approval. If cost-effective and safe, these products may ultimately be used earlier in the clinical course, even after a first infection.

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CONFLICTS OF INTEREST

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