The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of *Clostridioides difficile* Infection

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The American Society of Colon and Rectal Surgeons (ASCRS) is dedicated to ensuring high-quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The Clinical Practice Guidelines Committee is composed of society members who are chosen because they have demonstrated expertise in the specialty of colon and rectal surgery. This committee was created to lead international efforts in defining quality care for conditions related to the colon, rectum, and anus and develop clinical practice guidelines based on the best available evidence. Although not proscriptive, these guidelines provide information on which decisions can be made and do not dictate a specific form of treatment. These guidelines are intended for the use of all practitioners, health care workers, and patients who desire information about the management of the conditions addressed by the topics covered in these guidelines.

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These guidelines should not be deemed inclusive of all proper methods of care nor exclusive of methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician considering all the circumstances presented by the individual patient.

STATEMENT OF THE PROBLEM

Clostridioides difficile, formerly known as *Clostridium difficile*, is an anaerobic, gram-positive, bacillus bacterium that can be a normal inhabitant of the human colon and is most commonly transmitted via a fecal-oral route.[1] Alterations in the bacterial component of the microbiota, most often due to the use of antibiotics, can lead to ecological changes that select for both population growth of *C difficile* as well as the induction of pathogenic behavior.[2,3] Although the number of patients with *C difficile* infection (CDI) in the United States appears relatively stable over the past decade (estimated 476,400 cases in 2011 associated with 29,000 deaths and 462,100 cases in 2017 associated with an estimated 20,500 deaths), the prevalence of the disease remains high.[3–5] Although the bacterium is present in the stool of approximately 3% of healthy adults, up to 50% of those exposed to an inpatient facility may be asymptomatic carriers.[5–8] Higher rates of CDI have been reported in patients after exposure to a prolonged duration of antibiotics including perioperative antibiotics and in patients with underlying comorbid conditions such as IBD or immunosuppression.[9–15]

TABLE 1. Terminology associated with *Clostridioides difficile*

Term	Definition
Antibiotic-associated diarrhea	Diarrhea in an individual who is currently taking or has recently taken antibiotics (not necessarily from *C difficile*, although *C difficile* is a cause of this type of diarrhea) Symptoms include watery diarrhea and abdominal cramping
Asymptomatic colonization/carrier	Patients colonized with *C difficile* without signs or symptoms of CDI
C difficile infection (CDI)	Presence of diarrhea characterized by >3 watery stools per day in the setting of positive *C difficile* testing Other symptoms can include fever, abdominal pain, cramping, nausea, and loss of appetite Higher-risk patients include elderly or immunocompromised patients, nursing home residents, and patients with severe underlying comorbidities who have been exposed to antibiotics
Pseudomembranous colitis	Presence of plaque formations on colon mucosa Considered pathognomonic for CDI in the appropriate clinical setting
Mild/nonsevere infection	CDI with leukocyte count $<15 \times 10^3$/μL and creatinine <1.5 mg/dL
Severe infection	CDI with leukocyte count $>15 \times 10^3$/μL or renal failure with creatinine >1.5 mg/dL
Severe-complicated/fulminant disease	CDI with hypotension, sepsis, shock, ileus, or megacolon or requiring intensive care unit care
Toxic colitis	CDI with extreme inflammation and dilation of the colon resulting from severe colitis Can present with abdominal distension and pain, fever, dehydration, sepsis
Recurrent CDI	Recurrence of symptoms with a positive stool test within 8 weeks after the completion of a course of CDI therapy with resolution of symptoms
Refractory CDI	More than 3 loose/watery stools per day with positive stool toxin assay despite appropriate therapy

CDI = *Clostridioides difficile* infection.

Clinical manifestations of *C difficile* can range from an asymptomatic carrier state to mild CDI to severe, fulminant, life-threatening infection. Although descriptions of presentation and severity of disease vary in the literature, commonly used definitions are included in Table 1.[16–19] *C difficile* infection most commonly involves the colon, where it can manifest with pseudomembranes covering the colonic mucosa ("pseudomembranous colitis"). In rare circumstances, CDI may also involve the small bowel.[20,21] In the early 2000s, predominantly in North America, but also in Europe, there was an increased incidence of more severe CDI due to the emergence of certain bacterial strains (ie, ribotypes) like the BI/NAP1/027/toxinotype III strain, which is associated with a life-threatening infection.[22–25] Although rates of infection with this "hypervirulent" strain recently decreased in North America, rates remain significant globally.[26,27]

A variety of practice measures and collaborative efforts have been implemented to reduce the rate of CDI and have had moderate success.[18,19,28–32] The combination of antibiotic stewardship programs and improved diagnosis and treatment have decreased the incidence and mortality rates of CDI; however, CDI continues to be a source of morbidity and mortality due in part to a rise in recurrent and resistant infections.[33–37] The relatively high incidence of CDI and the significant economic burden of certain infection control measures, such as "deep cleaning" of hospital rooms, requires a careful balance between prevention and cost.[21,38–41] Although several guidelines have been published on this subject, CDI presents a unique challenge in colon and rectal surgery.[17,18,20,42,43] This clinical practice guideline focuses on the evaluation, management, and prevention of CDI.

METHODOLOGY

These guidelines were developed on the platform of the previously published *Practice Parameters for the Management of Clostridium difficile Infection* published in 2015.[42] An organized, systematic search of MEDLINE, PubMed, EMBASE, Web of Science, and the Cochrane Database of Collected Reviews was performed between September 1, 2014 and September 20, 2020. Key word combinations included "*Clostridium difficile,*" "*Clostridioides difficile,*" "Clostridia," "colitis," "pseudomembranous colitis," "antibiotic-associated," "diarrhea," "cdiff," "vancomycin," "flagyl," "metronidazole," "rifaximin," "antibiotics," "colectomy," "ileostomy," "lavage," "toxin," "toxin binding," "fecal transplant," "probiotics," "transmission," "recurrence," "recalcitrant," "treatment," "length of therapy," "perforation," "fulminant," "prophylaxis," "prevention," and "megacolon." Although the search was not limited by language, only abstracts and reports with human subjects were included. Emphasis was placed on prospective trials, meta-analyses, systematic reviews, and practice guidelines. Peer-reviewed observational studies and retrospective studies were included when higher-quality evidence was insufficient. Directed searches using embedded references from primary articles were performed in selected circumstances. In brief, 8651 titles were identified after excluding duplicates, and these abstracts were screened. Overall, 8014 articles were excluded and a total of 637 full-text articles were evaluated of which 389 were excluded due to the availability of higher-level evidence, and a total of 248 were articles included in the final document (Fig. 1). The source material was evaluated for methodologic quality, the evidence base was examined, and a treatment guideline was formulated by the subcommittee

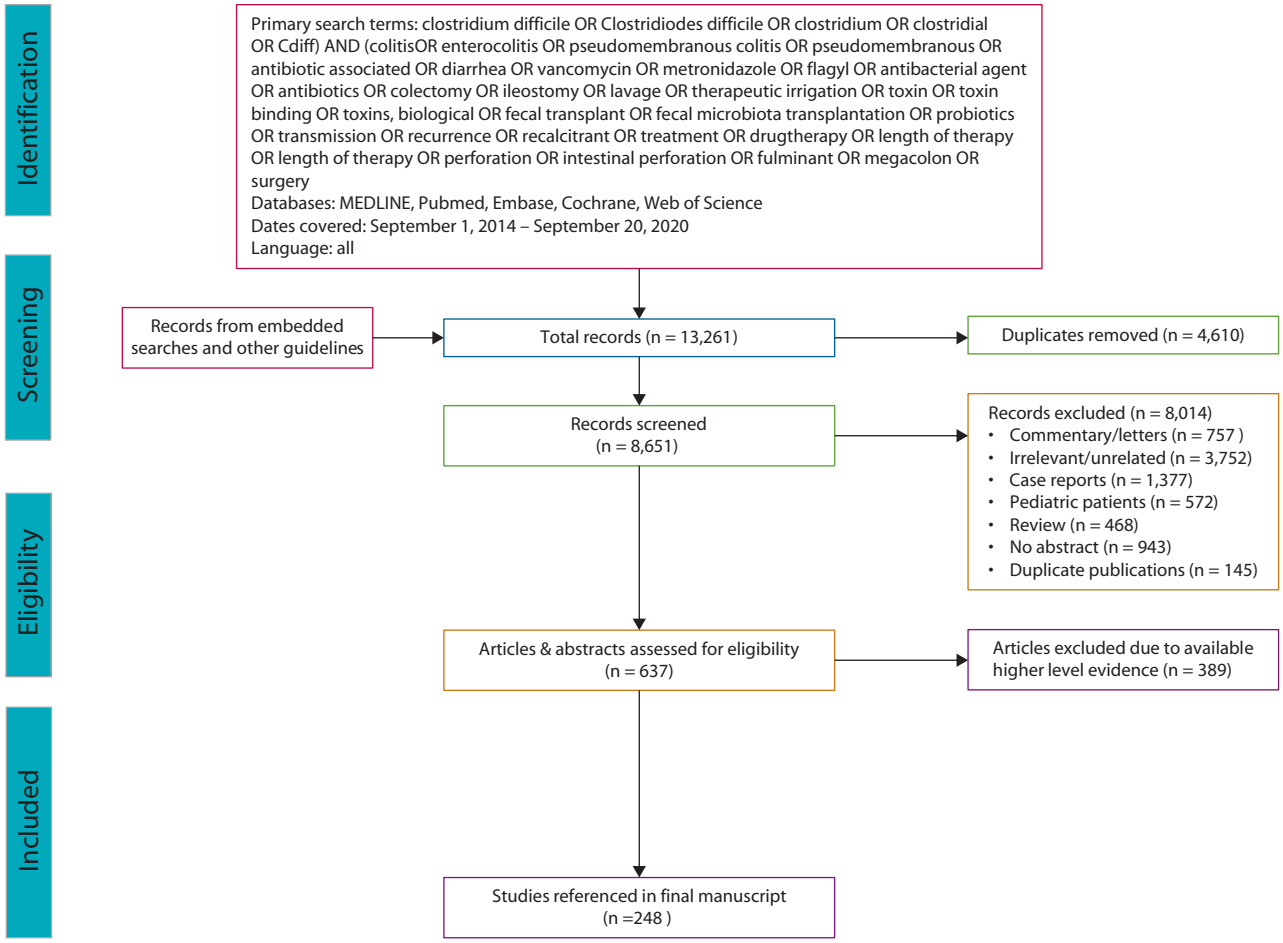

FIGURE 1. PRISMA literature search flow sheet.

for this guideline. The final grade of recommendation and level of evidence for each statement were determined using the Grades of Recommendation, Assessment, Development, and Evaluation system (Table 2).[44] When there was disagreement regarding the evidence or grade or treatment guidelines, consensus was obtained from the committee chair, vice chair, and 2 assigned reviewers. Members of the ASCRS Clinical Practice Guidelines Committee worked in joint production of these guidelines from inception to publication. Recommendations formulated by the subcommittee were reviewed by the entire Clinical Practice Guidelines Committee as well as by an invited gastroenterologist and an infectious disease specialist. The submission was peer-reviewed by *Diseases of the Colon & Rectum*, and the final recommendations were approved by the ASCRS Executive Council. In general, each ASCRS Clinical Practice Guideline is updated every 5 years. No funding was received for preparing this guideline, and the authors have declared no competing interests related to this material. This guideline conforms to the Appraisal of Guidelines for Research and Evaluation (AGREE) checklist.

Evaluation

1. **When CDI is suspected, a disease-specific history should be performed emphasizing risk factors, symptoms, underlying comorbidities, and signs of severe or fulminant disease. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.**

Symptoms related to CDI result from the release of bacterial toxins that cause inflammation of the colonic mucosa and fluid secretion resulting in diarrhea and typically manifest soon after starting antibiotic therapy for another disease process, but can be delayed for up to 3 months after discontinuation of antimicrobial therapy.[1,45] The strongest risk factor for developing CDI is recent antibiotic use (within 3 months), and increased duration of exposure and number of antibiotics used are associated with higher risk for developing CDI.[9,43,46–48] Although most antibiotics can change the colonic bacterial milieu leading to dysbiosis, drugs such as clindamycin, ampicillin, penicillin with beta-lactamase inhibitors, fluoroquinolones, and third-generation cephalosporins are more commonly associated with developing CDI.[46,49] Other risk factors for CDI

TABLE 2. The GRADE system: grading recommendations.

	Description	*Benefit versus risk and burdens*	*Methodologic quality of supporting evidence*	*Implications*
1A	Strong recommendation, High-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, Moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, Low- or very-low quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, High-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendations, Moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C	Weak recommendation, Low- or very-low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; RCT = randomized controlled trial.
Adapted from Guyatt G, Gutermen D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. Chest. 2006;129:174–181. Used with permission.

include having contact with a health care facility whether as an inpatient or an outpatient.

Historically, CDI was considered a nosocomial infection solely due to hospitalization or living in an extended care facility; however, an increasing proportion of CDI has been recognized as community acquired, which may be divided into community associated and community-onset health care facility associated.[50–52] Risk factors for community-acquired CDI are not well defined, but appear to be similar to nosocomial CDI and include environmental and antibiotic exposures as reviewed above.[50] Other notable risk factors include advanced age, female sex, immunosuppression, IBD (especially ulcerative colitis), and medical comorbidities (eg, congestive heart failure, diabetes, renal failure, and liver disease).[11,43,46,50–64] Emergency hospitalization and surgery, especially GI surgery, malnutrition, tube feeding, acid suppression with proton pump inhibitors, and bowel preparation are also considered potential risk factors for developing CDI.[46,65,66]

The clinical presentation of CDI ranges from mild diarrhea to fulminant colitis associated with a systemic inflammatory response that develops in less than 10% of patients and may be associated with abdominal pain or distension, severe diarrhea, ileus, dehydration, organ failure, or sepsis.[63,67] *C difficile* diarrhea is characterized by otherwise unexplained watery stools 3 or more times a day without intervening constipation or formed bowel movements. In general, patients who do not exhibit these kinds of bowel symptoms should not be tested for CDI. This recommendation notwithstanding, patients with a concern for fulminant disease who present with an ileus or megacolon and patients with an unexplained significant leukocytosis may benefit from a *C difficile* evaluation.[18,19] Although *C difficile* most commonly causes colitis, a few reports describe its pathogenicity in the small bowel, as well.[20,21,68] In almost all of these cases, clinically significant disease was identified in patients with an ileostomy and was associated with patients with a history of IBD, a prolonged antibiotic course, or recent surgery or a prior episode of CDI.[69]

Whether or not bowel preparation increases the risk for CDI remains controversial. Recent analyses of randomized, controlled trials and national data sets suggest a protective effect from oral antibiotic bowel preparation.[70–72] A recent retrospective review of 24,000 patients from the National Surgical Quality Improvement Program showed that combined bowel preparation (ie, including mechanical and antibiotic components) significantly decreased rates of CDI, in comparison with patients who received mechanical bowel preparation alone (OR, 0.58; $p < 0.001$).[73] Similar results were reported by Kim et al[74] in a propensity-matched analysis of 957 paired patients who differed only according to the bowel preparation received (combined preparation versus no preparation). In this Michigan Surgical Quality Collaborative–Colectomy Best Practices Project study, patients receiving combined

bowel preparation had significantly lower rates of CDI than patients who did not receive a bowel preparation (0.5% versus 1.8%, $p = 0.01$).[74] However, a trial of 310 patients with colon cancer who were randomly assigned to mechanical bowel preparation with or without oral antibiotics found no difference in the rates of CDI between the groups.[75] In addition, a recent meta-analysis of 4 randomized, controlled trials demonstrated an increased risk of CDI related to the use of oral antibiotics during bowel preparation (OR, 4.46; 95% CI, 0.96–20.66), but the absolute incidence of CDI was extremely low (only 11 events among 2753 patients), limiting the clinical relevance of these findings.[71] This study concluded that the incidence of CDI after colorectal surgery is low regardless of the bowel preparation used and, given the demonstrated benefits of bowel preparation related to a reduction in infectious risk profiles, the concern regarding CDI is not sufficient enough to warrant omitting bowel preparation in these patients.[72]

2. Patients should be evaluated to determine the severity of CDI and for the presence of peritonitis or multisystem organ failure. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

In general, it is difficult to classify CDI severity on the basis of history and physical examination alone. Clinical assessment and laboratory testing (complete blood count and renal and liver function) are typically performed to evaluate the patient and to help identify potential organ failure and associated sepsis.[12,76,77] A significant leukocytosis typically raises the suspicion for CDI but is not considered pathognomonic.[76,77]

The stratification of the severity of CDI as mild/nonsevere, severe, or severe-complicated/fulminant is loosely defined and is based on data and expert opinion (Table 1).[19] Diarrhea, leukocytosis (but less than $15 \times 10^3/\mu L$), and abdominal pain with positive testing for *C difficile* in the absence of hypotension or organ failure such as kidney injury is typically defined as mild disease, whereas severe CDI typically includes an elevated creatinine or leukocytosis over $15 \times 10^3/\mu L$. In severe-complicated or fulminant CDI, patients may develop peritonitis, worsening abdominal pain and distension, sepsis, otherwise unexplained clinical deterioration, ileus or megacolon, and/or organ failure.[18,78] The typically nonspecific physical examination findings of CDI, similar to non-CDI causes of colitis, underscore the importance of prompt evaluation with stool studies to expedite the diagnosis of CDI because mortality rates from severe CDI can reach 14% or higher.[34,79] Multisystem organ failure is one of the strongest independent predictors of postoperative mortality following emergency colectomy for *C difficile* colitis.[80,81] Early synthesis of key historical information, recognition of a suggestive clinical presentation, frequent clinical reevaluation, and confirmatory stool studies can diagnose CDI, facilitate appropriate therapy, and, potentially, avoid severe sepsis and its associated worse outcomes.

3. The diagnosis of CDI should include laboratory stool testing, and 2-step testing should be utilized to increase accuracy. Grade of recommendation: Strong recommendation based on high-quality evidence, 1A.

Laboratory stool testing is the most accurate way to diagnose CDI. More than 30% of antibiotic-associated diarrhea is secondary to CDI, highlighting the importance of obtaining stool assays to evaluate for CDI.[82] The goal of laboratory assessment is to diagnose CDI in a timely and accurate manner to facilitate treatment and containment and to institute isolation and contact precautions.[83]

Several different laboratory assays are currently available to diagnose CDI. Regardless of the specific study used, laboratory protocols recommend that only watery or loose stool samples (not swabs or formed stool) be sent, because patients with formed stool are unlikely to have CDI and laboratories can improve their false-positive rate, positive predictive value, and assay specificity by rejecting specimens that do not take the shape of the specimen container (ie, are not loose or soft).[18] Because no single test has a high enough sensitivity and specificity to reliably distinguish between an asymptomatic carrier and symptomatic CDI, 2-step testing is typically preferred using 2 enzyme immunoassays highly sensitive for glutamate dehydrogenase (GDH) and highly specific for *C difficile* toxins (ie, antigen recognition).[18,77,84–89] These assays are inexpensive and rapid, in general, and achieve a specificity and sensitivity of greater than 90%.[35,85,90] An alternative to GDH-based testing, nucleic acid amplification testing (NAAT), targets chromosomal toxin genes and, in the past, these tests were expensive and time consuming; however, many facilities have adopted these as their primary testing modality.[91–94] In practice, a positive initial screening using highly sensitive GDH or NAAT testing is usually followed by a highly specific test for *C difficile* toxin. An alternative diagnostic algorithm simultaneously performs both tests to expedite diagnosis but is associated with higher costs.[85,91] In places where 2-step testing or toxin-based testing is not available, NAAT alone may be used, but the results should be interpreted in the context of risk factors and symptoms suggestive of CDI.[19]

Stool culture, although highly sensitive, does not differentiate between active infection and the presence of several nontoxigenic, nonpathologic strains of *Clostridioides* that may grow in culture. Because stool cultures are also time consuming, they are impractical for clinical use in general.[77,95]

Although stool testing is most appropriate when evaluating patients with a suspicion of having CDI, high rates of asymptomatic chronic colonization (up to 50% of patients in hospitals and long-term care facilities) have prompted calls for screening policies; however, these initiatives have

not been well-supported by the evidence.[5,6] Meanwhile, selective testing may be considered for higher-risk patients with a diarrheal illness but without a high suspicion for CDI who have had recent exposure to antibiotics or have IBD, renal failure, vascular disease, or a transplant, or who reside in a long-term care facility.[96–98]

4. Routine endoscopic evaluation to diagnose or determine the extent of CDI is not recommended. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

Adjunctive endoscopic evaluation may be performed when managing patients with CDI, but the absence of comparative and predictive studies limits the utility of endoscopy under these circumstances. Endoscopy also lacks a validated predictive value in guiding medical or surgical therapy or providing prognostic information.[99,100] Given the rapid, sensitive, and specific stool assays used to diagnose CDI, the role of endoscopy in this setting is usually limited to potentially providing information when concomitant conditions confound the diagnosis or when unique circumstances require a more urgent diagnosis.[101]

Diagnostic lower endoscopy with biopsies may distinguish CDI from other types of colitides, such as cytomegalovirus, graft-versus-host disease, IBD, and ischemic colitis.[99] Although pancolitis in the setting of CDI (ie, extending proximal to the splenic flexure) may suggest a more severe infection, the anatomic extent of luminal disease alone is unlikely to guide patient management or influence the decision for and timing of colectomy. In addition, pseudomembranes, often considered pathognomonic for CDI, are actually found in only approximately 45% to 55% of laboratory-proven cases of CDI and offer little additional diagnostic or prognostic value.[99,100,102] In terms of the prevalence of pseudomembranes in the setting of CDI, the studies describing pseudomembranes are mainly retrospective and include only a fraction of patients with CDI who have undergone endoscopy, suggesting that the actual incidence of pseudomembranes would be lower than reported in these studies. The likelihood of finding pseudomembranes in patients with CDI who are immunosuppressed or have IBD is even lower.[100,102] Therefore, routine endoscopic evaluation in the setting of CDI is not recommended because of the risk of complications like perforation and the limited clinical utility.

5. Radiologic evaluation has limited utility in the setting of CDI. Grade of recommendation: Weak recommendation based on low-quality evidence, 2C.

In general, radiographic investigation has limited utility when managing patients with CDI. Although CT scans of the abdomen and pelvis, often obtained as part of the evaluation of an acute abdominal process, are highly specific for perforation, the predictive value of other CT findings in the setting of CDI is less clear. Cross-sectional imaging in patients with CDI can demonstrate colonic wall thickening and an abnormal haustral pattern or an "accordion sign" (hyperemic enhancing mucosa stretched over markedly thickened submucosal folds with contrast trapped between edematous haustral folds); however, these findings are nonspecific.[103–106] Computed tomography scans from patients with CDI may also demonstrate ascites, pericolic fat stranding, or prominent intravenous contrast enhancement of the layers of the colonic wall and even portal venous gas or pneumatosis.[107]

The ability for CT scanning to predict the need for surgical intervention is poor (sensitivity 52%–85% and specificity 48%–92%).[108] Older studies suggest that CT findings correlate poorly with the clinical severity of disease.[104] In fact, about 40% of patients with CDI have a normal CT scan without radiographic evidence of colitis.[104,109] A retrospective review of 176 hospitalized patients with CDI found that abnormal wall thickening, pancolitis, and bowel dilation demonstrated on CT imaging were associated with the need for colectomy, whereas wall thickening was an independent predictor of 30-day mortality; however, these findings had a low predictive value of 50%.[110]

Medical Management

6. Infection control measures should be implemented for hospitalized patients with CDI. Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Within the colon in the setting of dysbiosis and altered bile acid metabolism, *C difficile* exists in its vegetative (ie, functioning) form that is susceptible to antimicrobial agents. Outside the colon, however, *C difficile* survives in a spore form that is highly resistant to heat, acid, chemicals, and antibiotics.[96,111] In a hospital setting, *C difficile* can readily spread from fomites like clothing or equipment[28,112–114] and contamination can also occur by simple contact with intact skin of infected patients.[28,96,112–115] Disease containment and prevention of transmission rely on patient isolation, the use of personal protective equipment, and hand washing with soap and water to physically remove spores from the surface of contaminated hands after patient encounters.[114,115] Alcohol hand rubs, commonly used in health care settings, do not kill spores and therefore should not be used as a single agent for decontamination purposes under these circumstances.[116,117] Rather, combining contact precautions and hand washing with soap and water is recommended to prevent transmission of CDI in hospital and long-term care facilities. Daily and terminal (ie, after patients are discharged) decontamination of patients' rooms can also prevent transmission of CDI.[28,118–120] Other methods of potential *C difficile* containment or decontamination including ultraviolet light-emitting devices, chlorhexidine washings, and changes in hospital architectural designs are not well-supported by evidence.[121–126]

The duration for maintaining contact precautions and whether to isolate patients suspected of possibly having CDI before obtaining diagnostic confirmation remain controversial topics, and policies vary between institutions. In general, lifting isolation precautions for patients undergoing CDI treatment 48 hours after cessation of diarrhea may be considered.[127]

7. Implementing an evidence-based antibiotic stewardship program can decrease rates of CDI. Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Antibiotic use is the main risk factor for developing CDI, and the overuse and inappropriate use of antibiotics, in particular, have been well documented to increase the risk of CDI.[31,111,128–131] Multiple intervention bundles have been implemented in the United States and internationally with the primary goal of promoting appropriate antibiotic use and limiting duration of treatment in an effort to improve antibiotic-related outcomes.[132–135] Although antibiotic stewardship programs vary between hospitals, most include defined prescribing parameters determined by infectious disease specialists and have resulted in significant decreases in overall antibiotic use.[29,30,111,136,137]

A Cochrane review by Davey et al[31] of 221 studies found that compliance with antibiotic-prescribing practices in hospitalized patients reduced the duration of CDI treatment by 1.95 days (95% CI, 1.67–2.22) and reduced CDI rates up to 48.6% (interquartile range, –80.7% to –19.2%). Stewardship bundles typically include recommendations to stop associated antibiotics once CDI has been diagnosed, as clinically indicated, and extend the use of anti-*C difficile* treatment beyond the duration of other antibiotics for 5 to 14 days.[30,97,113]

In terms of other potential ways to reduce CDI rates, vaccines have been considered, although they remain investigational. Recently, a phase 3 multicenter trial evaluated the efficacy of a *Clostridiodes* toxoid vaccine, but the study was terminated prematurely because a data analysis demonstrated that the vaccine lacked clinical efficacy.[138]

8. Oral vancomycin or fidaxomicin is considered first-line treatment for an initial CDI, whereas metronidazole alone is no longer considered appropriate first-line treatment. Grade of recommendation: Strong recommendation based on high-quality evidence, 1A.

Although various antibiotics have demonstrated efficacy for treating mild-moderate or severe CDI, oral vancomycin or fidaxomicin is considered first-line therapy (Table 3).[18,19,139] Fidaxomicin, a narrow-spectrum, oral macrocyclic antibiotic, has been shown to have fewer CDI recurrences and higher success rates treating CDI than vancomycin; however, higher costs have prevented the widespread use of this drug as a first-line therapy.[140,141] When instituting antibiotic therapy to treat *C difficile*, it is important to also discontinue the inciting antibiotics associated with the *C difficile* episode as soon as possible (clinical circumstances permitting), because continuing these antibiotics can increase the risk of CDI recurrence.[20] For nonfulminant CDI, the recommended oral vancomycin dose is 125 mg 4 times a day and the recommended fidaxomicin dose is 200 mg twice a day; a 10-day course of either medication resolves CDI diarrhea in >90% of patients.[142,143]

Previous guidelines, including the 2015 ASCRS Clinical Practice Parameters, recommended using metronidazole or oral vancomycin as first-line treatment stratified by the severity of disease, with metronidazole used for more mild disease and vancomycin for more severe disease.[42,144] Although a number of studies still show reasonable success with metronidazole treatment for younger patients (≤65 years old) with initial, mild disease, there has been a rise in *C difficile* metronidazole resistance over the past 20 years. In addition to its overall lower efficacy, metronidazole currently has a higher risk of CDI treatment failure, including death and recurrence, compared with vancomycin.[145–149] Combination therapy with both vancomycin and metronidazole is associated with a higher rate of adverse events compared with monotherapy and is not typically recommended unless patients have severe-complicated or fulminant CDI.[142] Further supporting the change in the recommended antibiotic therapy, a Cochrane review by Nelson et al[150] of 22 studies including 3215 patients showed that vancomycin was more effective in achieving a cure (79%) than metronidazole (72%; relative risk (RR), 0.90; 95% CI, 0.84–0.97). A meta-analysis by Di et al[139] also showed that metronidazole was inferior to vancomycin in both initial cure rate (RR, 0.91; 95% CI, 0.84–0.98; $p = 0.02$) and sustained cure rate (RR, 0.88; 95% CI, 0.82–0.96; $p = 0.003$) and that the inferiority of metronidazole was even more pronounced in patients with moderate to severe disease.[151]

Vancomycin slurry delivery via retention enema can be considered as an adjunct treatment for patients with adynamic ileus or otherwise severe-complicated or fulminant CDI. Akamine et al[152] retrospectively compared 26 patients with moderate to severe CDI treated with oral vancomycin and vancomycin enemas with 101 patients who received oral vancomycin alone. In this study, the group that received vancomycin enemas experienced more complications but had similar overall mortality compared with the standard therapy group, although the enema group had more severe disease and had higher rates of toxic megacolon, intensive care unit admission, and colectomy. Meanwhile, Malamood et al[153] reported a case-controlled study comparing 24 patients who received vancomycin enemas in addition to standard therapy with 48 patients who received standard treatment alone and showed no differences in outcomes. A systematic review by Fawley and Napolitano[154] suggested that the efficacy of

TABLE 3. Treatment recommendations for initial and recurrent *C difficile* infection

Episode	*Severity*	*Treatment recommendation*
Initial		
	Mild-moderate	• Vancomycin 125 mg 4 times a day or fidaxomicin 200 mg twice a day for 10 days
	Severe	• Bezlotoxumab 10 mg/kg infusion as an adjunct treatment for high-risk patients
	Severe-complicated or fulminant	• Vancomycin 500 mg 4 times a day orally and metronidazole 500 mg intravenously 3 times a day • For patients with ileus, consider adding vancomycin per rectum • Early surgery consult
Second		
	Mild-moderate	• If metronidazole was used initially, then vancomycin 125 mg 4 times a day for 10 days
	Severe	• If vancomycin for 10 days was used initially, then fidaxomicin 200 mg twice daily for 10 days or prolonged vancomycin with taper and pulse • If fidaxomicin was used initially, use prolonged vancomycin with taper and pulse • Bezlotoxumab 10 mg/kg infusion as an adjunct treatment for high-risk patients
	Severe-complicated or fulminant	• Vancomycin 500 mg 4 times a day orally and metronidazole 500 mg intravenously 3 times a day • For patients with ileus, consider adding vancomycin per rectum • Early surgery consult
Third or subsequent		
	Mild-moderate	• If FMT is available, then 10-day course of vancomycin followed by FMT
	Severe	• Bezlotoxumab 10 mg/kg infusion as an adjunct treatment for high-risk patients • If FMT is not available, then prolonged vancomycin with taper and pulse or fidaxomicin or rifaximin
	Severe-complicated or fulminant	• Vancomycin 500 mg 4 times a day orally and metronidazole 500 mg intravenously 3 times a day for patients with ileus, consider adding vancomycin per rectum • Early surgery consult

FMT = fecal microbiota transplantation.

vancomycin enema therapy is dose and volume dependent and recommended using a slurry of 500 mg in 500 mL every 6 hours.

Although a few case reports describe administering vancomycin through a mucus fistula to reach defunctionalized colon, these reports include relatively few patients, lack adequate controls, and do not adequately evaluate this approach.[155] Instilling vancomycin antegrade through a loop ileostomy is described in recommendation #12. Finally, prophylactic use of antibiotics to prevent CDI lacks sufficient supporting data, although some studies evaluating high-risk patients suggest possible benefit.[156–159]

9. Probiotics may be useful in preventing CDI, but not in treating CDI. Grade of recommendation: Weak recommendation based on high-quality evidence, 2A.

Probiotics consist of live organisms that, theoretically, can adjust the colonic bacterial milieu and restore an otherwise altered GI flora that predisposes to the development of CDI. Probiotics are typically safe and well tolerated, but the data regarding the utility of probiotics in the primary treatment and prevention of CDI are mixed. Early, large, randomized, controlled trials and systematic reviews studying probiotics demonstrated no significant benefit in terms of CDI treatment or prevention.[155,160–164] More recent meta-analyses, however, show some preventative but not therapeutic benefit from probiotics. A meta-analysis of 20 trials with almost 4000 patients demonstrated a reduced incidence of CDI associated with the use of probiotics (RR, 0.34; 95% CI, 0.24–0.49).[165,166] Another meta-analysis of 26 randomized, controlled trials including 7957 patients demonstrated that probiotics significantly decreased the development of *C difficile* diarrhea by 60.5%.[167] However, the trials included in this study were heterogeneous and reported different enrollment criteria, probiotic administration regimens, and follow-up periods. An analysis including 16 Cochrane reviews that evaluated the potential preventative effects of different probiotics reported a decreased incidence of antibiotic-associated diarrhea and CDI related to probiotic use, but, given the low quality of the evidence, the authors suggested that further trials should be conducted.[168]

Several reports evaluating specific strains or combinations of probiotics including *Lactobacillus acidophilus CL1285*, *Lactobacillus casei LBC80R*, and *Saccharomyces boulardii* reached conflicting conclusions and do not support a particular probiotic regimen.[164,169,170] Despite extensive analyses regarding probiotics, questions regarding efficacy, the optimal agent(s), length of therapy, and dosing remain unanswered. The potential role of probiotics in recurrent or recalcitrant CDI is discussed in recommendation #15.

Surgical Therapy

10. Surgery for *C difficile* colitis should typically be reserved for patients with colonic perforation or severe colitis who do not improve with medical therapy. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

Although the incidence of and mortality from CDI have been improving over time, surgery remains an important

part of the treatment algorithm, because approximately 1% of all patients with CDI and about 30% of patients with severe-complicated or fulminant disease require surgery.[17,63,171] In general, the most obvious indication for operation in the setting of CDI is in rare cases of colonic perforation; otherwise, the decision to proceed with surgery is difficult to standardize because there is no clear algorithm to determine which patients will ultimately respond to medical management and avoid surgery.

Retrospective studies have identified clinical factors that can potentially predict patients who are more likely to need surgery, including patients with electrolyte derangements, age greater then 60 years, peripheral vascular disease, or congestive heart failure.[63,80] Although there is no high-level evidence regarding the optimal timing of surgical intervention, it appears that colectomy earlier in the course of fulminant disease is beneficial.[17,32,80,172–175] Under the circumstances, these complex patients may have multisystem organ failure, coagulopathy, vasopressor requirements, and sepsis.[80,172,173,175]

In practice, it is helpful to recognize that IBD is a significant risk factor for developing CDI and for requiring surgery.[11,63] Steroids and immunomodulators, frequently used to treat these patients, have been shown to be independent risk factors for worse outcomes in patients with IBD and CDI.[176] Moreover, in a meta-analysis by Chen et al,[177] patients with ulcerative colitis had almost double the odds of needing a colectomy in the setting of CDI (OR, 1.90; 95% CI, 1.23–2.93).

11. Subtotal colectomy with end ileostomy is typically the operative procedure recommended for severe-complicated or fulminant *C difficile* colitis. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

The recommended procedure for severe-complicated or fulminant *C difficile* colitis is subtotal colectomy with colorectal stump closure and end ileostomy, because this option typically affords optimal source control in the critically ill patient.[81,176] Retrospective studies comparing the extent of resection demonstrate lower mortality after an extended (ie, total or subtotal) colectomy than after a segmental colectomy; however, these studies are limited by small sample sizes and retrospective designs.[178–182] In a systematic review and meta-analysis comparing surgical approaches in 1433 patients with CDI between 1986 and 2011, subtotal colectomy (described as removal of most of or the entire colon) with end ileostomy was the most commonly performed procedure (89%).[81] In this study, the decision to perform a segmental colectomy was typically due to a "deceptively" spared, normal-appearing colon on gross, intraoperative examination. However, because *C difficile* colitis is a mucosal-based disease, a reliable assessment of the extent and severity of disease cannot typically be made by assessing the serosal surface of the bowel. When subtotal colectomy with end ileostomy was not performed, reoperation to resect further colon was needed in 16% of patients (20 of 126) and carried significantly high mortality (47%). Despite these data supporting extended colectomy, segmental colectomy continues to be performed in the Unites States under these circumstances.[183] In terms of adjunctive therapy after surgery, the literature does not support a specific recommendation for continuing antibiotics after colectomy for CDI.[18]

Mortality rates following surgery for CDI are high and can range from 34% to 57%.[81,184–187] However, despite the high mortality associated with colectomy, several large, retrospective studies have reported improved survival for patients with *C difficile* colitis who underwent timely subtotal colectomy compared with medical management alone.[175,185,188,189] A recent systematic review of 510 patients with *C difficile* colitis also demonstrated a survival advantage (pooled adjusted OR, 0.70; 95% CI, 0.49–0.99) with subtotal abdominal colectomy compared with medical therapy.[190] The most frequently reported predictors of mortality after colectomy for CDI include patient characteristics like age or immunosuppression and preoperative clinical signs of end organ damage such as shock or kidney failure.[185,191–193] According to several mortality prediction tools that stratify candidates for subtotal colectomy in the setting of CDI, patients who are critically ill and in whom medical therapy has failed, but who have not sustained advanced organ failure, are more likely to survive after surgery.[174,194] Although evidence suggests that, when surgery is necessary, earlier intervention can reduce mortality, the recommendation for surgery and timing of colectomy are typically individualized and depend on the specific circumstances.[172,184,188] Meanwhile, long-term outcomes after subtotal colectomy for CDI remain poor with a mean survival of 18.1 months, a median survival of 3.2 months, and a low rate of restoring GI continuity (20%).[187,192]

12. A diverting loop ileostomy with antegrade colonic lavage may be an alternative to subtotal colectomy for the treatment of severe-complicated or fulminant CDI. Grade of recommendation: Weak recommendation based on low-quality evidence, 2C.

Whereas subtotal colectomy with end ileostomy remains the recommended surgical treatment for patients with medically refractory CDI, an alternative surgical approach utilizing a loop ileostomy and antegrade colonic antibiotic lavage has been described. Proponents of this method cite the historically high mortality in patients treated with colectomy for severe-complicated or fulminant *C difficile* colitis, as well as the potential morbidity from an end ileostomy that may likely be permanent. The prospect of colonic preservation under these circumstances makes the lavage approach particularly appealing. In general, this technique involves laparoscopic creation of a loop ileostomy followed by antegrade colonic lavage with warmed

polyethylene glycol solution via the ileostomy and then antegrade instillation of vancomycin as well as intravenous antibiotics.[78]

An early, prospective trial evaluating diversion and colonic lavage for CDI examined 42 patients with severe-complicated CDI who underwent colonic lavage and showed encouraging results with 19% mortality compared with 50% mortality in a matched, historical control group treated with subtotal colectomy.[78] At 6-month follow-up, 93% of the patients undergoing lavage never required a colectomy and 79% had their ileostomy closed compared with only 19% in the historical control group. A retrospective, multicenter study compared patients treated with ileostomy and colonic lavage or subtotal colectomy and found decreased adjusted mortality in the ileostomy group (n = 21) compared with the colectomy group (n = 77, 17% versus 40%; $p = 0.002$).[195] A smaller, retrospective study by Fashandi et al[196] compared 10 patients who underwent diversion with colonic lavage with 13 patients who underwent subtotal colectomy and found that lavage therapy allowed for colon preservation and restoration of intestinal continuity in most patients, but did not decrease mortality or the rate of recurrent CDI.

Larger-scale studies evaluating diversion and lavage therapy for CDI include an analysis of the American College of Surgeons National Surgical Quality Improvement Program database that compared 47 patients who underwent loop ileostomy with 410 patients who had total abdominal colectomy and found a lower complication rate in the ileostomy group (72% versus 87%; $p = 0.02$) but no survival benefit (mortality 36% and 31%).[197] Another retrospective cohort study from the National Inpatient Sample compared 613 patients who had a loop ileostomy with 2408 patients who underwent total abdominal colectomy and found no significant differences in outcomes including in-hospital mortality between the 2 groups.[198] A recent meta-analysis that included 733 patients with diverting loop ileostomy and 2950 patients with total abdominal colectomy found no differences in mortality and postoperative complications, although rates of stoma reversal were higher in the ileostomy group (OR, 12.55; 95% CI, 3.3–47.5; $p < 0.001$).[199]

Recurrent and Refractory CDI

13. A prolonged course of vancomycin, adding bezlotoxumab or using fidaxomicin, is an acceptable therapy for recurrent or refractory CDI in stable patients. Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Recurrent and refractory disease can complicate the management of patients with CDI. Recurrent infection typically occurs within 8 weeks of completing treatment for an index episode, and recurrence rates range from 12% to 64%; the risk of mortality from recurrent disease ranges from 8% to 53%.[34,200] Risk factors for CDI recurrence include age, antibiotic use after completing treatment for CDI, use of proton pump inhibitors, neutropenia, and infection with certain *C difficile* strains.[34,37,200–203] Although not universally accepted, several strategies are emerging for preventing recurrent CDI (Table 3).

For the first recurrence of CDI, the recommended antibiotic regimen depends on the therapy used for the initial episode and, in general, patients are not treated by simply repeating the same regimen. If a conventional 10- to 14-day course of vancomycin is used for the first episode, the first recurrence should typically be managed with a tapered and pulsed vancomycin regimen or a 10-day course of fidaxomicin.[18] Vancomycin tapered and pulsed regimens typically include a 10- to 14-day course of oral vancomycin at a dose of 125 mg 4 times per day followed by a tapering dose over 2 weeks followed by pulsed dosing with 125 mg once every 2 or 3 days for 2 to 8 weeks.[204,205] Alternatively, fidaxomicin may be used and, despite the cost of fidaxomicin, cost analyses support its use over other strategies.[18,206,207] If metronidazole is used for an initial episode, then the first recurrence can be managed with a 10- to 14-day course of vancomycin.

Bezlotoxumab, a monoclonal antibody that binds exotoxin B, approved by the US Food and Drug Administration to be administered concurrently with treatment of CDI, can decrease the risk of recurrence in patients at higher risk due to advanced age, immunosuppression, IBD, or other comorbidities.[89,208,209] Two double-blind, randomized, placebo-controlled, phase 3 trials evaluated the efficacy of bezlotoxumab added to standard oral antibiotic regimens (including vancomycin and metronidazole) and demonstrated that treatment with bezlotoxumab significantly decreased rates of recurrent CDI compared with placebo (17% versus 28%, $p < 0.001$). Overall, a single intravenous dose of 10 mg/kg bezlotoxumab infused during an antibiotic course for CDI demonstrated a 40% relative risk reduction for recurrent CDI and a decrease in hospital length of stay.[210–212] However, the cost of bezlotoxumab may be prohibitive, limiting its use in these patients.[208]

14. Patients with recurrent or refractory CDI should typically be considered for fecal bacteriotherapy (eg, intestinal microbiota transplantation) if conventional measures, including appropriate antibiotic treatment, have failed. Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Patient with 3 or more CDI episodes can be managed with a vancomycin tapered and pulsed course or fidaxomicin followed by a microbiome-based therapy such as fecal microbiota transplantation (Table 3). Randomized, controlled trials, systematic reviews, and meta-analyses suggest that patients with recurrent or refractory CDI

in whom medical treatment has failed should be considered for fecal transplantation.[209,213–219] In general, conventional antibiotic treatment should be used for at least 2 recurrences (ie, 3 CDI episodes) before offering fecal microbiota transplantation.[18] In terms of the technical aspects involved, randomized, controlled trials have shown similar CDI cure rates after fecal transplants performed with fresh and frozen fecal samples.[220] Given the significant heterogeneity with which fecal transplants have been conducted clinically, standardized products for microbiome-based therapies have been commercialized.[221–223] Although a number of methods of administration have been described, including using a nasogastric tube or enema, the most common transplant delivery route is via colonoscopy; however, oral capsules were found to be noninferior to colonoscopic delivery for preventing recurrent infection.[224] Overall success rates for fecal transplantation, regardless of the delivery mode, are reported to be between 60% and 90% after a single treatment.[219,225–230]

Fecal transplantation has been studied in certain subpopulations and has been shown to be effective in elderly, immunocompromised, and critically ill patients and in patients with IBD or HIV.[231–245] For patients who develop recurrent CDI after undergoing an IPAA, fecal transplantation (administered into the pouch and afferent limb) has been an effective treatment.[231,246] Independent predictors of failure after single fecal infusion by colonoscopy in the setting of recurrent CDI include severe CDI and inadequate bowel preparation.[232] Further evaluation of this treatment modality is needed to optimize patient selection, donor selection, and technical details of the fecal transplant protocol. A relevant area of ongoing investigation regarding fecal transplantation is assessing this modality as a first-line therapy for initial CDI.[233] A small, randomized, controlled trial compared primary fecal transplant (n = 9) with metronidazole therapy (n = 11) and suggested that transplant may be an alternative to antibiotics in this setting.[234]

The efficacy of fecal transplantation in patients with severe CDI has not been extensively studied. Many case reports and small case series suggest that fecal bacteriotherapy may be safe and effective in decreasing the need for surgery in hospitalized patients unresponsive to other treatments (rescue fecal microbiota transplantation), but the evidence is limited.[235,236] There have been recent reports of fecal transplantation transmitting infectious agents, and prospective donors should be screened for colonization with multidrug-resistant organisms in addition to more typical infections. In June 2019, in response to 2 fecal transplant-related deaths in immunosuppressed patients, the US Food and Drug Administration issued a warning detailing the importance of obtaining proper patient consent, including a discussion regarding risks related to the therapy.[237,238]

15. Adjunctive agents including other antimicrobials, binding agents, and probiotics may be considered in addition to standard treatment in cases of recurrent or refractory CDI. Grade of recommendation: Weak recommendation based on low-quality evidence, 2C.

In situations where conventional antibiotic therapy for recurrent CDI fails, other antimicrobials can be considered. Rifaximin may be used to treat recurrent CDI and has a moderate success rate (53%–67%) in this setting.[239–241] However, because of the propensity of *C difficile* to develop resistance to rifaximin, this drug should typically be used in combination with other recommended agents.[241] Another antimicrobial option for refractory CDI, tigecycline, can successfully treat otherwise multidrug-resistant strains of *C difficile* (100 mg IV loading dose followed by 50 mg every 12 hours for 5–24 days). In a pooled analysis of 47 cases of refractory CDI treated with standard antibiotics together with adjunctive tigecycline, 7 patients (15%) died and 35 (77%) were cured.[242,243] Nitazoxanide, an antiparasitic drug, is another potential adjunctive therapy alternative for treating recurrent or refractory CDI.[244]

Toxin-binding agents such as cholestyramine and colestipol are also used as adjuncts for recurrent CDI with variable success.[244] Small, retrospective reports ascribe some efficacy for these polymers to bind and inactivate *C difficile* toxins; however, prospective studies have not demonstrated efficacy in improving symptoms or preventing recurrence.[244,245] Because binding agents can also bind oral vancomycin (based on in vitro studies), the administration of these medications should be staggered by a few hours.[244] Data regarding tolevamer, a large, nonbactericidal, soluble polymer developed to specifically bind *C difficile* toxins A and B, show it is inferior to vancomycin and metronidazole for treating CDI, but its potential efficacy as an adjunctive therapy is unknown.[247]

Finally, administering antimotility agents to patients with CDI has historically been discouraged because this therapy has been associated with poor outcomes; however, prospective data regarding this practice is not available.[18,27] Similarly, probiotics may be useful in treating recurrent or refractory disease, but the efficacy of probiotics under these circumstances remains unclear. When used in combination with appropriate medical therapy (especially oral vancomycin), probiotics were shown to decrease the risk of recurrent disease in a small, randomized, controlled trial (RR, 0.59; 95% CI, 0.35–0.98) but 3 other randomized, controlled trials did not demonstrate a benefit to adding probiotics under these circumstances.[165,248]

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