Practice Parameters for the Management of *Clostridium difficile* Infection

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It should be recognized that these guidelines should not be deemed inclusive of all proper methods of care or exclusive of methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of all the circumstances presented by the individual patient.

STATEMENT OF THE PROBLEM

Clostridium difficile is an anaerobic, gram-positive rod bacterium that may be a normal inhabitant of the human colon, or transmitted exogenously via ingestion.[1] Alterations in the bacterial component of the microbiome, most often due to the use of antibiotics, can lead to bacterial ecological changes that can select for both population growth of *C difficile* as well as the induction of pathogenic behavior. *C difficile* is the leading cause of infectious diarrhea in hospitals in the developed world, including up to 20% of reported antibiotic-associated diarrhea and nearly all incidences of pseudomembranous colitis.[2] Although the bacteria are present the stool of ~3% of healthy adults, up to 50% of those exposed to an in-patient facility are asymptomatic carriers. Higher rates have been cited in patients following a prolonged duration of exposure to antibiotics, and in those with severe underlying comorbid disease.[3–5] Infection can result in a wide range of presentations, from an asymptomatic carrier state or mild *C difficile* infection (CDI) to a severe and life-threatening condition (Table 1).[6] The prevalence and severity of CDI has dramatically increased since the early 2000s when a surge in morbidity and mortality rates occurred. *C difficile* infection most commonly involves the colon, where it is also commonly known as "pseudomembranous colitis" because of the common endoscopic finding of pseudomembranes covering the colonic mucosa. In rare circumstances, it may also involve the small bowel.[7,8] Globally, CDI is increasingly more prevalent and severe; this may be due to the emergence of certain strains (ie, ribotypes) of the bacteria, which can result in not only a life-threatening infection, but also a surgical emergency.[9] A number of studies have demonstrated an association between ribotype 027 and fulminant (heretofore referred as severe) CDI.[10] A wide variety of practice measures and collaborative efforts have been implemented to reverse this trend, with occasional reports of success.[11] Despite these efforts, reported cases of CDI increased 200% between 2000 and 2005, and have since continued to rise almost exponentially annually.[8] Given the growing incidence of CDI, the economic burden of prevention and treatment has surged,[11] and is increasingly important in the population of patients with colorectal diseases. This practice parameter will focus on the evaluation, management, and prevention of CDI.

METHODOLOGY

An organized search of Medline, PubMed, Embase, and the Cochrane Database of Collected Reviews was performed through July 2014. Key-word combinations included

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Table 1. Terminology associated with *Clostridium 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/carriage	Patient is colonized with *C difficile* without signs or symptoms of CDI
CDI	Presence of diarrhea characterized by >3 watery stools per day Other symptoms can include fever, abdominal pain, cramping, nausea, and loss of appetite Typically presents in high-risk patients (elderly, immunocompromised, nursing home residents, or severe underlying disease) with exposure to antibiotics
Pseudomembranous colitis	Presence of plaque formations on colon membranes Considered pathognomonic for CDI in the appropriate clinical setting
Toxic colitis	Extreme inflammation and distention of the colon often resulting from a severe episode of colitis Symptoms include abdominal distension and pain, fever, dehydration, sepsis

CDI = *Clostridium difficile* infection.
Adapted from Hansen G, Blatt S, Brecher SM, Dubberke E, Dorsett P. Clostridium difficile: navigating the testing options for diagnosis. American Association for Clinical Chemistry. *Clinical Laboratory News*. 2010;36.[6]

"*Clostridium difficile*," "Clostridia," "colitis," "pseudomembranous colitis," "antibiotic-associated," "diarrhea," "cdiff," "vancomycin," "flagyl," "metronidazole," "rifaximin," "antibiotics," "colectomy," "ileostomy," "lavage," "toxin," "toxin binding," "anion-exchange," "fecal transplant," "probiotics," "transmission," "recurrence," "recalcitrant," "treatment," "length of therapy," "perforation," "fulminant," and "megacolon." Directed searches of the embedded references from the primary articles were also performed in selected circumstances. Although not intending to be exclusionary, the authors primarily focused on English language articles and studies in adults. Recommendations were formulated by the primary authors and reviewed by the entire Clinical Practice Guidelines Committee. The final grade of recommendation was performed by using the GRADE system (Table 2).[12]

EVALUATION

1. **In a patient in whom CDI is suspected, a disease-specific history should be performed, emphasizing symptoms, risk factors, underlying comorbidities, and signs of advanced disease. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

Gastrointestinal symptoms from CDI result from bacterial toxins that cause inflammation of and fluid secretion from the colonic mucosa.[13] *C difficile* infection can range in severity from simple diarrhea to moderately severe infection with abdominal pain, distension, watery stool, and leukocytosis. Severe infection can present as watery diarrhea with dehydration, toxic colitis, and sepsis that requires critical care and prompt surgical consultation.[14] The severe form of complicated CDI will develop in approximately 5% to 10% of patients with CDI and is associated with a correspondingly high mortality rate. Symptoms typically manifest 2 to 3 days following institution of antibiotic therapy for another disease process, but can be delayed for up to 2 to 3 months after discontinuation of antimicrobial therapy.[1]

The major risk factor for CDI is recent antibiotic use, with 1 report finding that 96% of symptomatic patients received antibiotics within 14 days of infection, and all affected patients were exposed to antibiotics within 3 months of CDI symptoms.[15] Although any antibiotic can result in a change in bacterial milieu, certain drugs such as penicillins, clindamycin, fluoroquinolones, and third-generation cephalosporins are more commonly associated with its development.[16] Other risk factors include advanced age, in-patient therapy, immunosuppression (eg, HIV, chemotherapy, malignancy), GI and emergency surgery, tube feeds, bowel preparation, malnutrition, IBD (especially ulcerative colitis), and comorbidities such as diabetes mellitus and renal failure.[17–20] Acid suppression with a proton pump inhibitor as well as antihistamine (ie, H2 blockers) therapy has also been associated with an increase in CDI, although a few studies have questioned this association.[21,22]

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

In general, CDI is difficult to diagnose on the basis of physical examination alone. A complete physical examination, supported by laboratory tests (complete blood count, renal, and liver function) should be performed to identify the presence of severe disease and associated sepsis. Digital rectal examination may be performed to exclude other pathology and determine sphincter tone, but it is not specific to the evaluation of CDI.

C difficile infection will almost always cause abdominal distention, abdominal pain, and diarrhea. Nonspecific findings on physical examination underscore the importance

Table 2. The GRADE system-grading recommendations

	Description	*Benefit vs risk and burdens*	*Methodological 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, methodological 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, methodological 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.[12] Used with permission.

of stool studies, as demonstrated in a previous prospective study that observed that CDI and non-CDI infectious colitides presented with similar incidences of abdominal pain, diarrhea, and blood per anum.[23]

Physical examination findings that differentiate CDI from other infectious colitides, IBD, or ischemic colitis are often unreliable. However, the identification of key historical information, such as recent sick contacts (ie, nursing home, sick companions, recent hospitalizations), travel history, antecedent use of antibiotics, and immunosuppression, may raise the index of suspicion for CDI.[24,25] Findings of localized or generalized peritonitis are a critically important finding, mandating admission to a monitored unit and urgent surgical consultation. Unfortunately, mortality rates of up to 80% have been reported in this scenario despite urgent surgery.[26] The development of multisystem organ failure is an ominous sign. Meta-analyses and multiinstitutional data have demonstrated this to be one of the strongest independent predictors of postoperative death following emergency colectomy for *C difficile* colitis.[27,28]

3. Endoscopic and radiologic evaluation may be performed to help determine the diagnosis and extent of disease. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Although CT scans, diagnostic colonoscopies, and sigmoidoscopies are often obtained when evaluating patients with CDI, their indication remains debatable, with a current absence of comparative studies delineating their proper roles. These studies and procedures largely remain an adjunct, chosen at the discretion of the physician and useful in particular circumstances, but without empiric evidence to require them for all CDI patients. They also lack validated predictive value in guiding medical therapy or the decision to operate. Endoscopy and CT imaging are most useful in evaluating patients with more severe forms

of CDI, in an effort to provide as much clinically relevant data as possible to help decide on the choice of therapy (medical vs surgical), although the weight that should be given to endoscopic and CT data is not clear.[29]

Colonoscopy and sigmoidoscopy are often performed to determine the extent of luminal disease (proctitis vs left-sided or pancolitis). However, the length of luminal disease has not been evaluated as an indicator of either the likelihood of the success of medical therapy or as an indicator of the need for surgical intervention. There is also a lack of data to suggest what impact the extent of pseudomembranous change has on the clinical course of the disease. The clinician should therefore avoid arbitrary and subjective evaluations of CDI severity based solely on endoscopic findings to the exclusion of other clinical data. Although *C difficile*–associated pancolitis (extending proximal to the splenic flexure) may suggest a more severe form of infection, unlike other colitides such as IBD, the finding of luminal disease alone is unlikely to provide useful information to guide patient care decisions or to direct the timing and extent of colectomy.

The primary benefit of a diagnostic lower endoscopy for the CDI patient is to distinguish it from other types of colitides, such as cytomegalovirus, graft-versus-host disease, IBD, and ischemic colitis.[30] However, colonoscopy introduces the risk of endoscopic perforation, and, although probably low, the incidence of colonoscopic perforation in CDI has not been quantified. With the development of rapid, sensitive, and specific polymerase chain reaction (PCR)-based stool assays to diagnose CDI, the diagnostic role of endoscopy is limited, although it may provide valuable information when concomitant conditions confound the diagnosis or more urgent results are needed.[31] Pseudomembranes, often considered the hallmark of the disease, are present in only approximately 45% to 55% of laboratory-proven CDI,[14] and are present at even lower rates in patients with concomitant immunosuppression[32] or IBD.[33] Biopsy essentially has no impact, more often demonstrating a nonspecific colitis than pseudomembranous colitis in small series, and cannot be promoted.[30]

Radiology has limited usefulness in the specific diagnosis of *C difficile* colitis, although CT scans of the abdomen and pelvis are often obtained as part of the evaluation for acute abdominal pain. There are no current data to suggest that patients with CDI have characteristic CT findings, although CT will commonly demonstrate colonic wall thickening, nodular haustral thickening, or an "accordion pattern."[34–36] In addition to these findings, fulminant forms of CDI will frequently show ascites, fat stranding, and a prominent intravenous contrast enhancement of the layers of the colonic wall. Mesenteric venous gas, pneumatosis, and pneumoperitoneum are less common and signify severe life-threatening disease.[37] Unfortunately, CT sensitivities and specificities are reported at 52% to 85% and 48% to 92%.[38] There are older data to suggest that CT findings correlate poorly with the clinical severity of disease.[34] Such imaging may provide information regarding the extent of colonic involvement, with the rectum and sigmoid colon mostly commonly involved (>70%).[39] A remarkably large percentage (~40%) of CDI patients will have a normal CT scan with no radiographic evidence of colitis.[34,39]

The predictive value of radiographic findings for the failure of medical therapy, need for surgery, and disease-related mortality have not been evaluated. Computed tomography results can only provide another mode of assessing the CDI patient, establishing a general sense of disease severity

4. Diagnosis of CDI typically includes laboratory testing. Grade of Recommendation: Strong recommendation based on high-quality evidence, 1A.

Approximately 30% of antibiotic-associated diarrhea is secondary to *C difficile,* highlighting the importance of obtaining stool assays to establish or disregard CDI.[40] Several different laboratory tests are currently available to detect *C difficile,* but watery or loose stool samples (not swabs) must be sent. Unfortunately, there are multiple limitations (ie, increased false positives and false negatives) to single tests for CDI detection.[41] Because of this, the US Department of Health in 2011 advised that a 2-stage test approach should be used to improve the diagnostic accuracy of CDI.[42] Although several test combinations are currently used, in general, culture positivity is a marker for the *presence* of the bacterium, whereas the presence of the *toxin* more often signifies clinically relevant intestinal disease.

The method of detection is clinically important, because sensitivities vary between culture and antibody testing. Cell cytotoxicity assays, which test for cytopathy caused by toxins A and B, have reported sensitivities between 60% and 100%.[43] In contrast, stool culture is highly sensitive, but does not differentiate between active infection and the presence of *Clostridium* spp. bacteria; several nontoxigenic, nonpathologic strains may grow in culture. Therefore, culture is commonly used in conjunction with toxin detection.[44,45]

Antigen recognition using enzyme immunoassay testing for toxins A and B is inexpensive and rapid, leading to increased use. However, its low sensitivity (39%–76%)[46] despite adequate specificity has made this test less suitable when used alone.[47,48] Glutamate dehydrogenase (GDH) is another enzyme that has been shown to be highly sensitive but nonspecific for CDI.[49] Two-step testing, involving enzyme immunoassay to detect GDH as an initial screening step, followed by cell cytotoxicity or toxigenic culture for GDH-positive samples, is 1 method used to overcome the limitations of other methods. Reported sensitivities, specificities, negative predictive value, and positive predictive values are 91.57%, 98.07%, 99.03%, and 84.44%.[46,50] Meta-

analysis of 21 studies confirmed a specificity and sensitivity >90% with the use of GDH, and recommended its use in a dual testing algorithm.[49,51–53] Drawbacks to the 2-step approach include the lack of widespread availability of both tests at single centers and the 48 to 96 hours needed for results.

Nucleic acid amplification tests target chromosomal toxin genes (usually the toxin B gene *tcdB* or regulatory gene *tcd*C) are increasingly being adopted for diagnosis of CDI.[54] Population-based data have demonstrated increases in the incidence of these toxin genes to 43% to 67%, along with to 2- to 3-fold increases in enzyme immunoassay negative detection rates.[55] This has led several authors to recommend the routine use of nucleic acid amplification tests.[56] Polymerase chain reaction testing, which provides improved sensitivities and specificities, has the additional benefit of being more rapid.[57] In fact, the institution of PCR testing for CDI, although more expensive, has resulted in decreased days of patient isolation, tests ordered, and empiric antibiotic treatment.[58,59]

At present, the most commonly recommended strategy is a 2-step process: initial screening using a GDH assay followed by confirmation of a positive sample with cytogenic or toxigenic culture. Nucleic acid amplification tests, either as stand-alone or in combination with other testing, are gaining support to replace this 2-step because isothermic PCR testing is now available in kit form.

MEDICAL TREATMENT

1. **Infection control measures should be implemented for hospitalized patients with *C difficile* colitis. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

Within the colon, *C difficile* exists in its functioning vegetative form and is susceptible to antimicrobial agents. Outside the colon, however, *C difficile* survives in its spore form and is highly resistant to heat, acid, chemicals, and antibiotics. In a hospital, *C difficile* can be rapidly spread from the hands, clothing, and equipment used by health care workers.[1,60–63] Contamination can also occur by simple contact with intact areas of the skin of hospitalized patients.[1,62,64–66] Disease containment therefore relies on isolation, protective equipment, and hand washing with soap and water to physically remove spores from the surface of contaminated hands after each patient encounter.[67] Alcohol hand rubs are commonly used and can be used in conjunction with gloves for avoidance of contamination, as well as soap and water every few hand-cleansing sessions. However, for any potential contamination, alcohol hand rubs are insufficient, because they do not kill spores and therefore should not be used alone to decontaminate hands.[67–69] In addition to diligent hand hygiene with warm water and scrubbing, when providing care for patients with *C difficile*-associated diarrhea, contact precautions, including the routine use of gloves, can help decrease the risk of iatrogenic spread.[70] Similar quality control measures, including attention to proper hand-washing hygiene and cleaning of potentially contaminated surfaces, should be instituted for infected patients in the outpatient environment. In the hospital, patient isolation and donning of protective gowns have also been advocated, but evidence supporting the efficacy of this procedure is lacking.[45] A systematic review evaluating the impact of hospital architectural design demonstrated no change in the rates of nosocomial spread in 5 of the 8 included studies.[71] If multiple occupants are required in 1 room, every effort should be made to allow for separate commodes.

When diarrhea ceases, patients are no longer considered "contagious" and contact precautions can be discontinued, although this practice is somewhat controversial and varies from institution to institution. Appropriate cleaning of rooms vacated by patients and equipment used on patients with *C difficile* is required. Sodium hypochlorite solutions have proven efficacy in decontaminating surfaces.[72,73]

Identification of asymptomatic chronic colonization with *C difficile* occurs in ~8% to 20% of patients admitted to the hospital,[74,75] and up to 50% (2.1%–51%) of patients in rehabilitation and long-term care facilities.[76–80] This rate increases with factors such as recent hospitalization, recent antibiotic use, renal failure requiring dialysis, transplantation, vascular disease, and steroid use.[75] However, identification of these patients through targeted or routine widespread screening is controversial, and not currently widely recommended. Proponents cite the need to identify and treat the potential reservoir of asymptomatic carriers before spread.[81] Although some evidence suggests that this is possible with vancomycin, other reports have found no significant impact on the spread of *C difficile* and note a high rate of recurrent infection at relatively short follow-up intervals.[82–84]

2. **Once CDI is diagnosed, the associated antibiotics should be stopped as soon as possible, as clinically indicated. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

A frequent precursor to *C difficile* proliferation is an alteration of the normal GI flora, commonly the result of antibiotic use. The most commonly associated antibiotics include clindamycin, penicillins, cephalosporins, and fluoroquinolones.[85] Both the length of exposure to the antibiotic and the number of antibiotics affect the rate of CDI.[86] The recommendation to stop the inciting antibiotic(s) once CDI is established is almost universal. Despite this, nothing other than expert opinion exists to clarify either the impact or the timing on the course of the disease.[45,87,88] Educating

hospital staff about the onset of symptoms associated with CDI has been shown to reduce the time for fecal sampling and the institution of therapy by several days.[89,90] Despite the absence of clinical trials, there is likely a limited downside to stopping the potential antibiotic immediately upon the diagnosis, and this should be considered as a first-line step. In certain cases, however, the patient may either have a known infection or is clinically unstable or deteriorating (ie, sepsis), which warrants continuation of the antibiotic regimen. Further data are needed to elucidate the impact of stopping antibiotics immediately upon suspicion but before a confirmed diagnosis of CDI. Until this is further clarified, the decision to discontinue the possible offending antibiotic should be individualized based on the clinical state of the patient and provider judgment.

3. Metronidazole and vancomycin are acceptable first-line agents for an initial bout of CDI, with selection normally based on disease severity. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Medical management including early diagnosis, fluid resuscitation, electrolyte replacement, and antibiotic administration may be effective in limiting the severity, duration, and associated complications of CDI. Although various antibiotics have demonstrated efficacy in combating *C difficile*, metronidazole and vancomycin have remained the mainstays of primary therapy.[91,92] In part, this is secondary to the higher rates of persistent and recurrent disease associated with other antibiotics like bacitracin, rifampin, and fusidic acid.[93–98] Despite not having an US Food and Drug Administration indication for CDI, metronidazole has been used as a primary therapeutic agent to limit the spread of vancomycin resistance.[99] Adult dosing recommendations vary for both metronidazole (200–500 mg orally 4 times a day or 500–750 mg orally 3 times a day) and vancomycin (125–500 mg 4 times a day).[91,100] Some authors recommend the stratification of antibiotic use by the severity of disease, with mild to moderate illness treated initially with metronidazole, reserving vancomycin for severe/complicated disease, defined by a leukocytosis (>15,000 cells/μL) or an elevated serum creatinine (>1.5 mg/dL).[45,101,102] Additional risk factors to identify severe disease and increased mortality risk include leukopenia (<4000 cells/μL), bandemia (>10% bands), cardiorespiratory failure, shock, megacolon, and perforation.[103–106] When used in mild- to moderate-severity disease, metronidazole has reported cure rates of 40% to 75% and recurrence rates of 14% to 25%.[107] Unlike vancomycin, metronidazole may be given by using both oral (preferred) and intravenous routes, the latter being particularly beneficial in patients with CDI associated with an ileus.

Despite its recommendations for use in more severe disease, vancomycin has similar efficacy in comparison with metronidazole, in the limited data available with severe CDI subgroup analyses.[108] Small retrospective studies, however, have reported better cure rates for severe disease in 97% to 100% of patients.[107,109] In addition to the oral route, vancomycin enemas have also been used as an adjunctive treatment for primary therapy, with reported success rates up to 70% to 89%.[110,111] A 2011 Cochrane review evaluated 15 studies that included 1152 patients with *C difficile*–associated diarrhea.[105] Of note, patients with "severe" infection were often excluded from the primary studies, limiting widespread recommendations. The authors found no statistically significant difference in efficacy between vancomycin and metronidazole, as well as either antibiotic in comparison with fusidic acid, nitazoxanide, or rifaximin. Because of the high risk of bias in this analysis, the authors were unable to identify a single agent or regimen of choice. The conclusions were consistent with other systematic reviews that were unable to recommend a superior antibiotic for the initial cure of CDI.[108]

Although more recent evidence has demonstrated decreased recurrence with fidaxomicin, an oral macrocyclic antibiotic with targeted activity against *C difficile*, initial cure rates are similar and have not led to widespread recommendations for it to replace either metronidazole or vancomycin as a first-line agent.[112–116] At present, its use is largely limited to infectious disease specialists. With emerging strains such as ribotype 027 that are more highly virulent, along with the developing resistance patterns,[117,118] the recommended initial antibiotic of choice may change in the future.

The recommended duration of medical treatment for CDI is 10 to 14 days. Limited data have demonstrated >90% resolution of diarrhea for patients who complete a 10-day course with either antibiotic.[119] Symptomatic resolution of diarrhea may be earlier with metronidazole,[120] although a full treatment course is still recommended. Repeat stool assays are typically unnecessary if there is clinical response.[121,122] All patients with a history of CDI should have an annotation in their chart of the associated antibiotic to attempt to avoid its use.

4. Probiotics may be useful in the prevention and treatment of *C difficile*-associated diarrhea. Grade of Recommendation: Weak recommendation based on high-quality evidence, 2A.

Probiotics consist of live organisms that, in theory, combat the altered GI flora that leads to the development of CDI. Several authors have evaluated the use of probiotics for both the primary treatment as well as the prevention of CDI.[123] Early randomized controlled trials and systematic reviews demonstrated no improvement in either setting.[124,125] In part, this was felt to be secondary to the high risk of bias involved in the trials owing to factors from the varying species used, different regimens used, wide-rang-

ing inclusion criteria, and degree of disease severity .[126] Although data are still sparse regarding a definitive role in the primary treatment of CDI,[127,128] subsequent meta-analysis of 20 trials with almost 4000 patients have shown a reduced incidence in *C difficile*-associated diarrhea with the use of probiotics (relative risk [RR] 0.34; 95% CI 0.24–0.49).[129] The same group published a recent Cochrane review encompassing 31 studies and 4213 patients evaluating both the prevention of *C difficile*-associated diarrhea as well as CDI as a secondary outcome.[130] The incidence of *diarrhea* was significantly lower in the probiotic group (2.0% vs 5.5% control group; RR 0.36; 95% CI 0.26–0.51), but the overall incidence of CDI was similar in the 2 groups (probiotics 12.6% vs 12.7% control; RR 0.89; 95% CI 0.64–1.24). In addition, probiotics reduced the risk of adverse events by 20% (RR 0.80; 95% CI 0.68–0.95). Other meta-analyses suggest that only specific probiotic strains such as *Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, and *Saccharomyces boulardii* are effective in the prevention of CDI.[131,132] Unfortunately, despite this extensive analysis, the issues regarding optimal agent, length of therapy, and dosing remain.

SURGICAL THERAPY

1. **Surgery for *C difficile* colitis should typically be reserved for patients with severe colitis that fails to improve with medical therapy, for generalized peritonitis, or for rare cases of colonic perforation. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

Although CDI is an increasing community and nosocomial problem,[45] only ~1% (range, 0.2%–7.6%) of all patients with CDI and ~30% (range, 2.2%–86%) with "severe" disease require emergency surgery.[27,133,134] The decision to operate, outside of colonic perforation, can be difficult to standardize, because there is no evidence that allows us to predict which patients with severe colitis will not respond to further medical management. Retrospective studies have identified clinical factors associated with severe CDI, but these are not proven indicators of the inevitable failure of further medical therapy. Only 2 systematic reviews have compared emergent total colectomy with the construction of an end ileostomy with ongoing medical therapy.[27,135] Despite limitations in study design, both reviews demonstrated improved odds of survival with surgery.

There is no high-grade evidence regarding the optimal timing of surgical intervention, but it appears that surgical consultation early in the course of disease may be beneficial.[136,137] Owing to the increased potential for worsening disease and outcomes, consideration should also be given to early surgical consultation in CDI patients with underlying IBD,[8,138,139] recent surgery, prior treatment with intravenous immunoglobulin,[140,141] vasopressor requirement, or signs of impending sepsis.[142] For patients meeting any of these criteria, early surgical intervention may reduce morbidity and mortality. Perforation in patients with toxic *C difficile* colitis is associated with a high mortality rate.[143] Unfortunately, it is often difficult to predict the clinical course of the disease process and the optimal time to intervene before perforation, and signs of impending perforation can sometimes be masked by ongoing medical therapy.[144] The development of multisystem organ failure in the setting of severe *C difficile* colitis is an ominous sign, with several series demonstrating it to be an independent and strong predictor of death.[103,145,146]

2. **Subtotal colectomy with ileostomy is typically the operative procedure of choice for *C difficile* colitis. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

Because the major indication for operative intervention in *C difficile* colitis is severe colitis with complicated sepsis, the conventional surgical intervention has typically been a total abdominal colectomy with an end ileostomy and a stapled rectal stump. In a systematic review, the most commonly performed operation for *C difficile* was total colectomy with end ileostomy (89%, 1247/1401 described operations),[27] with small series and case reports describing segmental colectomy in the setting of severe disease. There are only 2 systematic reviews on this topic, although both of these demonstrate a survival benefit for total colectomy in this setting.[27,135]

Retrospective studies comparing the extent of resection demonstrated, in general, lower mortality with total colectomy than with segmental resection (11%–56% total colectomy vs 14%–100% partial colectomy).[28,143,147–149] Details regarding the rationale for the decision to perform a segmental colectomy are limited, although they include what is typically described as a "deceptively" normal-appearing colon on gross examination intraoperatively.[149] For those undergoing partial resection, reoperation to resect further bowel (16%, 20/126 patients) was required. Postoperative 30-day morbidity is uniformly high, with complications in 57% to 100%.[27,28,103,143,145,146] It should be noted that it is unusual for CDI to reach severe levels that would require surgical intervention, and great caution should be exercised in choosing this option.

Single-institution retrospective studies have described high postoperative mortality rates, although the cause of postoperative mortality is often related to the patient's chronic comorbidities, and not to surgery. Both reviews by Bhangu et al and Stewart et al demonstrated lower cumulative mortality rates than many single-institution studies.[27,135] Independent predictors of postoperative mortality include shock with vasopressor requirement, mental status changes, length of treatment, respiratory failure, hypoal-

buminemia, delayed colectomy, multisystem organ failure, and preoperative acute renal failure.[27,28,145,146,150]

3. **Diverting loop ileostomy with colonic lavage may be an alternative to total abdominal colectomy for the treatment of severe *C difficile* colitis. Grade of Recommendation: Weak recommendation based on low-quality evidence, 2C.**

Proponents of this newer operative approach cite the historically high mortality (35%–80%) in patients treated with abdominal colectomy for severe *C difficile* colitis as well as the long-term morbidity of malabsorption and diarrhea with this anatomy. This alternative management protocol involves a laparoscopic evaluation of the colon to ensure viability, creation of a loop ileostomy, and intraoperative antegrade lavage of the colon with 8 liters of warmed polyethylene glycol solution. Patients then receive antegrade vancomycin enemas through the efferent limb of the ileostomy every 8 hours for 10 days as well as intravenous metronidazole for 10 days. A single study of 42 patients showed encouraging results with this approach (19% mortality vs 50% in historically matched controls treated with total abdominal colectomy).[151] At follow-up, 93% of the patients never required a colectomy, and 79% of patients had their ileostomy closed within 6 months, compared with 19% in the historical control group. Although intriguing, these results have not been replicated, and no clear evidence exists to suggest which patients may benefit from this approach. It is hoped that ongoing multi-institutional trials will hopefully clarify the role this procedure will play in the surgical management of patients with severe *C difficile* infection.[152]

RECURRENT AND RECALCITRANT CDI

1. **Adjunctive agents including toxin binders, probiotics, and/or other antibiotics may be considered in recurrent or recalcitrant CDI. Grade of Recommendation: Strong recommendation based on low-quality evidence, 2C.**

Although most patients with CDI are managed effectively with oral metronidazole or vancomycin, approximately 25% of treated patients will experience recurrent or recalcitrant disease.[153] For those that develop a single recurrence, up to 65% will develop an additional recurrence.[154] Recurrence is defined similarly to the initial infection, with 1) recurrent diarrhea (>3 unformed stools in ≤24 hours) and 2) a positive fecal sample for *C difficile* or its toxins, or colonoscopic/histopathologic evidence of pseudomembranous colitis.[45] Because *C difficile* toxin remains positive for periods of time after completion of treatment, the diagnosis of disease requires loose stools in addition to the positive assay. Recurrent disease can be from the original or a new *C difficile* strain. Risk factors for recurrence include advanced age, continued "other" antibiotic use, and prolonged hospital stay.[155] The underlying mechanism is likely either from a poor immune response to the *C difficile* toxin or persistent alterations in the colonic flora.[155]

Several additional options for recurrent disease exist, but they fall into the general categories of antibiotics, toxin-binding agents, bacterial therapy (ie, probiotics and fecal transplant), and immunoglobulins. In general, there is a lack of high-grade data on which to base recommendations, and most guidelines are founded on expert opinion. Both metronidazole and vancomycin have been shown to have similar efficacy in the setting of recurrent disease, even if used previously, and either may be considered as a first-line agent in this setting if previously effective.[156] In general, vancomycin should be used if the recurrence is clinically more severe.[45] Alternative agents include fecal bacteriotherapy, antibiotic "chasers" (ie, rifaximin), tapering of antibiotics with pulsed dosing of vancomycin, probiotics,[154] and intravenous immunoglobulin against *C difficile* toxin. Fidaxomicin has been approved recently, with some authors recommending it as a first-line agent in the setting of relapse or severe infection.[112,157] At present, its use is limited by its increased cost and lack of widespread data.[116] Head-to-head comparison of fidaxomicin with vancomycin for recurrent disease demonstrated similar efficacy, but lower overall repeated recurrence rates at 28 days with fidaxomicin.[158] The recommended dosing is fidaxomicin 200 mg orally twice daily for 10 days and may be considered for patients who previously received treatment with metronidazole or vancomycin, and those who are diagnosed with recurrent CDI from a non-NAP1/BI/027 strain.[113]

Other antimicrobial agents that may be useful include rifaximin and fusidic acid with clinical cure rates of 56% to 67% and 45% to 93%.[159–161] Teicoplanin, which is not currently available in the United States, has also demonstrated cure rates of more than 80%, but it is limited by its availability and cost.[105]

Toxin-binding agents such as cholestyramine and colestipol are often used as an adjunct, but have demonstrated some effectiveness in small reports for recalcitrant and multiply recurrent disease.[162,163] Although the effectiveness of probiotics alone for recurrent disease is inconclusive, there are small reports of their use (ie, *Saccharomyces boulardii*) with vancomycin and other combination therapy as an adjunctive treatment aimed to decrease recurrent disease.[45,164]

2. **A prolonged course of oral antibiotics is acceptable therapy for recurrent or resistant disease in stable patients. Grade of Recommendation: Weak recommendation based on low-quality evidence, 2C.**

The typical length of antibiotic treatment for primary or recurrent CDI is 10 to 14 days.[45,67] At present, no prospective

data are available comparing the length of treatment with outcomes for either vancomycin or metronidazole; however, certain patients may be slow to respond to the initial course of therapy and may be considered for a longer duration of antibiotic regimen.[45,67,120] Despite its relative safety, there is some concern for neurotoxicity associated with the chronic use of metronidazole,[165] and care must be taken to prevent this from occurring. In addition, successful resolution of CDI (~67%) in patients with multiple recurrences has been described with a course of rifaximin immediately following a 2-week course of vancomycin.[160,166] Finally, tapering courses of vancomycin and pulsed dosing has been shown to result in fewer recurrences at a minimum of 2-month follow-up.[167]

3. **Patients with refractory CDI may be considered for fecal bacteriotherapy (intestinal microbiota transplantation) if conventional measures have failed. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.**

Patients with refractory CDI for whom conventional treatments have failed may also be considered for fecal transplantation.[168–171] Fecal transplantation is performed with fresh stool obtained from a healthy donor and homogenized with water. The most common method of transplantation presently is via direct infusion of the stool into the cecum via colonoscopy,[172–177] although it may be administered by nasogastric or nasoduodenal tube[168,178] or retention enema.[179] This technique may promote colonization resistance by restoring colonic microbial diversity. Most protocols require the patient to be off of antibiotics for at least 36 hours before the transplant, and donors must be negative for select infectious diseases and must not have received antibiotics for the previous 6 months.

The rates of eradication of diarrhea are reported as 83% to 92%[173,177,180] after a single treatment. Freedom from diarrhea is achieved in 70% to 100% of patients with long-term follow-up (3 months to 8 years).[173] To date, no studies have directly compared the methods of delivery. However, a pooled analysis of 182 patients from 12 studies comparing fecal transplant via colonoscopy with nasogastric tube demonstrated similar treatment success rates (93% colonoscopy vs 85% nasogastric tube; $p = 0.162$), although colonoscopy required a higher volume of stool.[181] There are also limited studies that directly compare this treatment with other treatment modalities. One open-label, randomized, controlled trial of 43 patients published in *The New England Journal of Medicine* compared vancomycin 500 mg 4 times a day for 4 or 5 days followed by bowel lavage and a donor-feces infusion via nasoduodenal tube (n = 16) with vancomycin 500 mg orally 4 times a day for 14 days (n = 13) and vancomycin 500 mg orally 4 times a day for 14 days with bowl lavage on day 4 or 5 (n = 13).[178] The study was halted after interim analysis because most patients in the 2 latter control groups had a relapse, whereas 81% of the donor-feces infusion group were cured after the first infusion. Of the 3 failures in the infusion group, 2 of the 3 were subsequently cured after a second infusion from a different donor for a total cure rate of 94%. This protocol was significantly superior to both the vancomycin alone (31%) and vancomycin with bowel lavage (23%; $p < 0.001$). Additional trials comparing its use with antibiotic therapy alone are also underway.[182]

A review of 115 patients (ages, 60–101 years) from 10 published studies demonstrated cure of CDI in 89.6% (mean, 5.9; range, 2 months to 5 years), demonstrating its effectiveness in the older population.[183] Although this practice appears to be relatively safe, currently it is recommended that conventional methods of treatment should be sequentially exhausted before considering fecal bacteriotherapy. Best practices for this treatment modality still need to be developed with regard to patient selection, donor selection, and fecal transplant protocol as further experience with this technique evolves. Limited long-term follow-up currently exists, with 1 multicenter retrospective review reporting primary and secondary cure rates of 91% and 93% at a mean follow-up of 17 months (range, 3–68 months).[180] Finally, for those patients with refractory disease despite maximal medical therapy or those patients with persistent disease following fecal transplant, a colectomy should be considered.

APPENDIX A

Contributing Members of the ASCRS Clinical Practice Guideline Committee

Janice Rafferty, Chair; Scott R. Steele, Co-chair; Patricia L. Roberts, Council Representative; W. Donald Buie, Advisor; George Chang; Dan Feingold; Dan Herzig; Scott Strong; Kirsten Wilkins; Marty Weiser; Samantha Hendron; Ian Paquette; David Rivadeneira; David Stewart; Genevieve Melton-Meaux.

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