Review

Diagnosis and Treatment of *Clostridium difficile* in Adults
A Systematic Review

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IMPORTANCE Since 2000, the incidence and severity of *Clostridium difficile* infection (CDI) have increased.

OBJECTIVE To review current evidence regarding best practices for the diagnosis and treatment of CDI in adults (age ≥18 years).

EVIDENCE REVIEW Ovid MEDLINE and Cochrane databases were searched using keywords relevant to the diagnosis and treatment of CDI in adults. Articles published between January 1978 and October 31, 2014, were selected for inclusion based on targeted keyword searches, manual review of bibliographies, and whether the article was a guideline, systematic review, or meta-analysis published within the past 10 years. Of 4682 articles initially identified, 196 were selected for full review. Of these, the most pertinent 116 articles were included. Clinical trials, large observational studies, and more recently published articles were prioritized in the selection process.

FINDINGS Laboratory testing cannot distinguish between asymptomatic colonization and symptomatic infection with *C difficile*. Diagnostic approaches are complex due to the availability of multiple testing strategies. Multistep algorithms using polymerase chain reaction (PCR) for the toxin gene(s) or single-step PCR on liquid stool samples have the best test performance characteristics (for multistep: sensitivity was 0.68-1.00 and specificity was 0.92-1.00; and for single step: sensitivity was 0.86-0.92 and specificity was 0.94-0.97). Vancomycin and metronidazole are first-line therapies for most patients, although treatment failures have been associated with metronidazole in severe or complicated cases of CDI. Recent data demonstrate clinical success rates of 66.3% for metronidazole vs 78.5% for vancomycin for severe CDI. Newer therapies show promising results, including fidaxomicin (similar clinical cure rates to vancomycin, with lower recurrence rates for fidaxomicin, 15.4% vs vancomycin, 25.3%; $P = .005$) and fecal microbiota transplantation (response rates of 83%-94% for recurrent CDI).

CONCLUSIONS AND RELEVANCE Diagnostic testing for CDI should be performed only in symptomatic patients. Treatment strategies should be based on disease severity, history of prior CDI, and the individual patient's risk of recurrence. Vancomycin is the treatment of choice for severe or complicated CDI, with or without adjunctive therapies. Metronidazole is appropriate for mild disease. Fidaxomicin is a therapeutic option for patients with recurrent CDI or a high risk of recurrence. Fecal microbiota transplantation is associated with symptom resolution of recurrent CDI but its role in primary and severe CDI is not established.

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Clostridium difficile was first identified as the major infectious cause of antibiotic-associated diarrhea in 1978.[1] However, since the emergence of the epidemic BI/NAP1/027 strain of *C difficile* in 2000,[2] *C difficile* infections (CDIs) have increased in prevalence and become less responsive to treatment.[2-4]

In the United States, the number of CDI hospital discharge diagnoses more than doubled from 2001 (≈148 900 discharges) to 2005 (≈301 200 discharges).[5] The incidence of CDI has increased from 4.5 per 1000 adult discharges in 2001 to 8.2 per 1000 discharges in 2010.[6] Patients with CDI have higher health care costs: annual attributable costs exceed $1.5 billion in the United States.[7]

CDI requires both acquisition of *C difficile* and disruption of the gut microbiota. The exact mechanism by which *C difficile* causes symptomatic infection is unclear. The organism is not invasive, and toxin production is the key to pathogenesis (nontoxigenic strains of *C difficile* do not cause diarrhea) (**Figure 1**). The toxin disrupts epithelial integrity via microtubules and cell-cell tight junctions, resulting in release of inflammatory mediators such as IL-8.[8] These actions promote an inflammatory infiltrate in the colonic mucosa, fluid shifts leading to diarrhea, and epithelial necrosis. Antibiotics disrupt the microbiota, increasing CDI risk.[9] Other factors associated with CDI include older age, recent hospitalization, longer hospitalization, use of multiple antibiotics, longer antibiotic duration, proton pump inhibitors, chemotherapy, chronic kidney disease, and feeding tubes.[10-14] This review focuses on the diagnosis and treatment of CDI in adults, including new diagnostic and therapeutic modalities.

Methods

A literature search of the Ovid MEDLINE and Cochrane databases was conducted using search terms and synonyms for *Clostridium difficile* (eAppendix in the Supplement). We searched for studies of diagnostic testing and treatment of CDI published between January 1978 and October 31, 2014. Studies published in non-English languages and studies involving animals or children were excluded. We identified 4682 articles. Bibliographies of the retrieved studies and previous reviews were searched for other relevant studies. Meta-analyses, systematic reviews, and references cited in published clinical practice guidelines from the past 10 years were also reviewed. Initially, 196 articles were identified; of these, the most pertinent 116 articles were selected for inclusion. Clinical trials, large observational studies, and more recently published articles received priority in the selection process (eFigure in the Supplement). Eleven additional articles relevant to the topic but not selected are included in the supplemental materials (eTable in the Supplement).

Diagnosing CDI

Laboratory testing alone cannot distinguish between asymptomatic colonization and clinical symptoms of infection. The diagnosis of CDI requires both of the following: presence of diarrhea (defined as ≥3 unformed stools in 24 hours) or radiographic evidence of ileus or toxic megacolon; and a positive stool test result for toxigenic *C difficile* or its toxins, or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis (**Box**).[15-17] The definitive gold standard for CDI is detection of toxigenic *C difficile* in stool along with colonic histopathology showing pseudomembranes in a patient with clinical symptoms.[18] Many laboratories will only test diarrheal stool for *C difficile*.[15,16,19-21]

In one study, 56% of patients who responded to treatment asymptomatically shed *C difficile* spores for as many as 6 weeks.[22,23] Thus a test of cure is not recommended.[15] Studies have documented chronic shedding and an increased prevalence of asymptomatic colonization in health care facilities, consistent with the hypothesis that long-term asymptomatic colonization occurs following CDI.[24,25] Recurrent symptoms can occur in association with a transient functional bowel disorder in as many as 35% of patients during the first 2 weeks following resolution of CDI. However, only approximately 4% of patients have symptoms more than 3 months after CDI due to a postinfectious irritable bowel syndrome.[26] The 2010 Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Clinical Practice Guidelines advise against treating asymptomatic carriage with *C difficile*[15]; thus, it is important to distinguish between symptoms due to recurrent CDI and transient functional bowel disorder or persistent irritable bowel syndrome. However, there are no validated approaches to distinguish between these conditions.

C difficile Testing

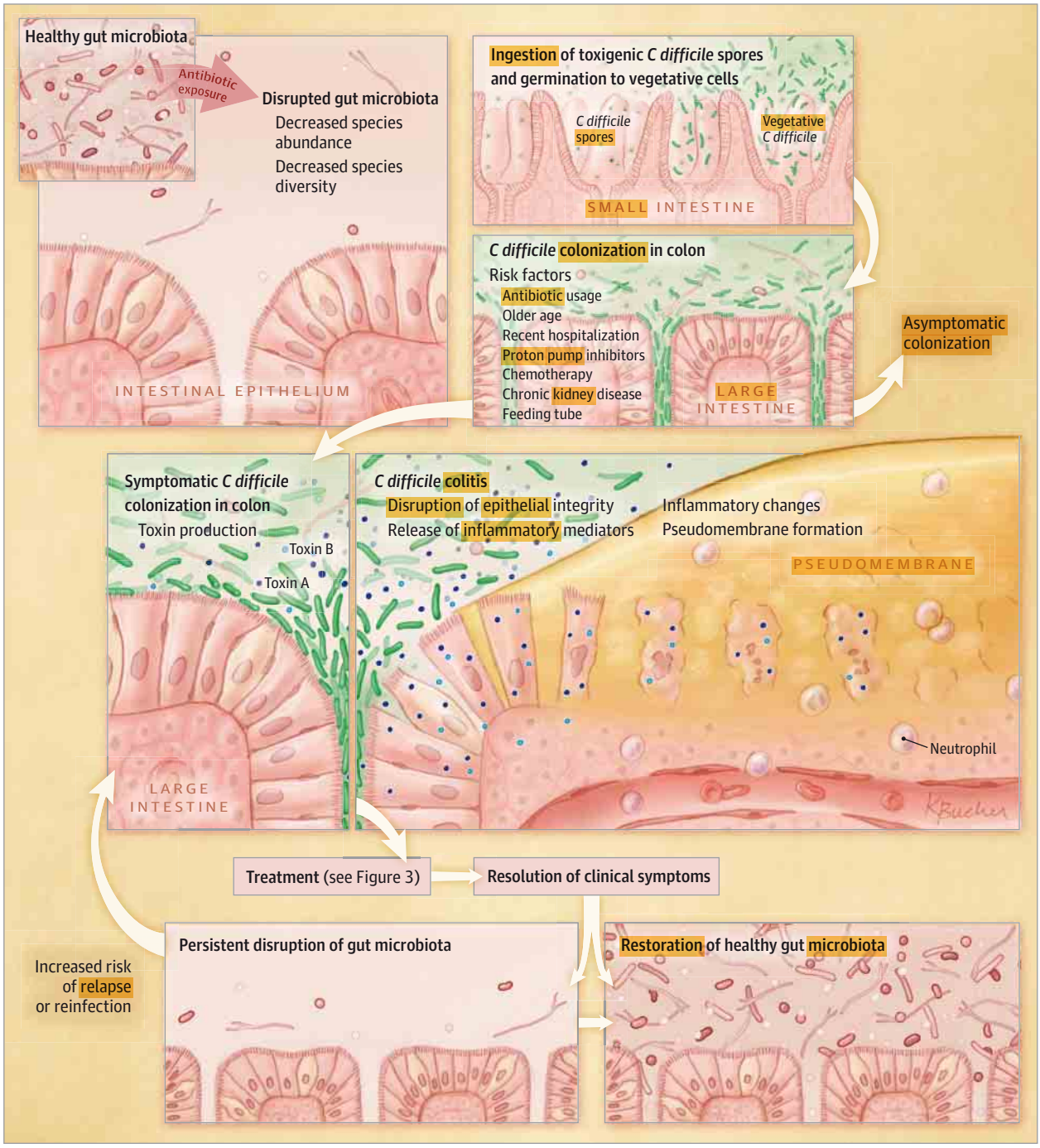
Organism Detection

The gold standard for detecting toxigenic *C difficile* in stool is toxigenic culture (**Table 1**).[19] Stool specimens are cultured anaerobically on special media[27] for 24 to 48 hours. After colony selection and confirmation of taxonomy (usually with an antigen-detection strategy with latex agglutination, enzyme immunoassay [EIA], or real-time polymerase chain reaction [PCR]),[27,28] isolates are incubated for 48 hours followed by testing using a cell cytotoxicity assay (CCA) (Table 1). The independent performance of this method is unclear because most studies compare other diagnostic modalities with toxigenic culture or CCA,[19] and there are differences in choice of media and sample pretreatment that can affect performance.

Although it is a reference standard, toxigenic culture is time intensive and requires specialized equipment and trained personnel. Diagnostic delays have implications for treatment decisions and infection control.[29,30] Rapid testing overcomes these limitations. One method focuses on detecting a product of *C difficile*, glutamate dehydrogenase (GDH), usually performed via EIA. Studies examining the performance characteristics of GDH EIA show substantial variability (**Table 2**). Because GDH is present in both toxigenic and nontoxigenic strains of *C difficile* and data on asymptomatic colonization suggest as many as 46% of *C difficile* isolates are nontoxigenic,[31] GDH testing must be paired with a test that detects toxin.

Nucleic acid amplification testing (NAAT), including rapid testing PCR and loop-mediated isothermal amplification (LAMP), can detect the *tcdA*/*tcdB* genes (regulate toxin A/B production) or the *tcdC* gene (a negative regulator of toxin A and B production) and identify the presence of toxigenic *C difficile* in a single step (Table 1).[19,21,32,33] NAAT testing shows sensitivity and specificity of greater than 0.90 range (Table 2). However, this higher sensitivity also identifies toxigenic *C difficile* in asymptomatic patients. This underscores the importance of only testing symptomatic patients, leading some experts to argue against NAAT-based testing alone.[16,19,34]

Figure 1. Steps in the Pathogenesis of *Clostridium difficile* Infection and Possible Treatment Outcomes



Toxin Detection

The gold standard for detecting toxins A and/or B is CCA,[27] which is performed directly on stool or as part of toxigenic culture. Filtrates of stool suspensions or culture supernatants are inoculated into a cell culture and assessed for cytopathic effect after 24 or 48 hours.[27] This test identifies as little as 3 pg of toxin and is highly sensitive (0.94-1.0) and specific (0.99), especially if combined with antiserum.[27,35] The main disadvantages are the time required for test completion and complexity.

Sensitivity and specificity of EIA for toxin A and/or B are variable (Table 2). Repeat testing does not improve sensitivity. A recent systematic review found that 91% of positive EIA results occur after 1 test and the probability of a second or third test becoming positive after 2 previous negative results was less than 2.5%.[36]

Multistep Algorithms for Diagnosis of CDI

Given the suboptimal sensitivity of some toxin EIA kits combined with increased detection of asymptomatic colonization with single-step

algorithms (NAAT), many experts and some guidelines have advocated approaches that use multiple tests (multistep algorithms) for rapid diagnosis.[15,16,19,34] One example is shown in **Figure 2**, with one center reporting a sensitivity of 0.91, specificity of 0.98, and negative predictive value of 0.99.[37]

We reviewed studies using rapid testing algorithms with at least 1 gold standard comparator (eTable in the Supplement). In general, multistep algorithms using NAAT had excellent sensitivity (0.68-1.0) and specificity (0.92-1.0), but algorithms using only GDH or toxin EIA testing performed worse with greater variability. A large multicenter study by Planche et al[38] reported that a GDH/NAAT-based algorithm yielded the highest sensitivity (0.91-0.98) and specificity (0.96-0.98) (eTable in the Supplement).

Treating CDI

Since 2000, CDI treatment failures and recurrences have increased.[2-4] Treatment failures are likely related to a complex interplay of host factors, bacterial pathogenicity, and the ability to deliver therapeutic levels of drug to the colon. Strains with higher minimum inhibitory concentrations to metronidazole have been described and may contribute to treatment failures.[39] Guidelines recommend that CDI should be treated according to disease severity and risk of recurrence or complications (Box).[15,16]

Markers of Disease Severity

Clinical manifestations of CDI ranges from mild diarrhea to life-threatening illness. Prediction rules have been developed to predict recurrences, complications, and mortality.[40] Many of these studies had small sample sizes, with significant heterogeneity.[40] One prospective study of 746 patients with CDI proposed the following scoring system to predict risk of fulminant CDI: age older than 70 years (2 points), white blood cell (WBC) count of at least 20 000 cells/mL or 2000/mL or less (1 point), cardiorespiratory failure (7 points), and diffuse abdominal tenderness (6 points). High-risk patients had a score of 6 or greater.[41] Another scoring system study used age, ongoing treatment with systemic antibiotics, leukocyte count, albumin, and serum creatinine to predict response to vancomycin or fidaxomicin.[42]

The 2010 Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Clinical Practice Guidelines categorize mild CDI as a WBC count of less than 15 × 10^9/L and serum creatinine of less than 1.5 times premorbid level; severe CDI as a WBC count of at least 15 × 10^9/L or serum creatinine of at least 1.5 times premorbid level; and severe, complicated CDI as hypotension or shock, ileus, or megacolon.[15] Guidelines from the European Society of Clinical Microbiology and Infectious Diseases define severe CDI as an episode of CDI with a complicated disease course or 1 or more signs or symptoms of severe colitis, with significant systemic toxin effects and shock, resulting in intensive care unit (ICU) admission, colectomy, or death. Predictive findings included a WBC count of greater than 15 × 10^9/L, serum albumin of less than 3 g/dL (to convert to g/L, miltiply by 10), and an increase in serum creatinine level of at least 1.5 times premorbid level.[16] The term *fulminant* is sometimes used to describe severe, complicated CDI[42-44] (**Table 3**).

Asymptomatic Carriers

Asymptomatic carriage of *C difficile* affects 10% to 52% of defined populations.[25,45-49] Asymptomatic fecal shedding of *C difficile* may be transient; one study showed that vancomycin therapy may temporarily interrupt shedding but increased the risk of *C difficile* carriage following therapy completion.[50] Asymptomatic colonization does not increase the risk of symptomatic CDI and may protect against later development of symptomatic disease.[31,47,51] Shim et al[31] studied 618 noncolonized patients and 192 asymptomatic carriers with 2 or more weekly follow-up rectal swabs and reported that 3.6% of the noncolonized patients and only 1% of the asymptomatic carriers developed symptomatic CDI.

Box. Key Messages Regarding Diagnosis and Treatment of *Clostridium difficile* Infection in Adults

Diagnosis

Clostridium difficile infection (CDI) requires presence of diarrhea (≥3 unformed stools in 24 hours) or radiographic evidence of ileus or toxic megacolon; and a positive stool test result for toxigenic *C difficile* or its toxins, or colonoscopic or histopathologic evidence of pseudomembranous colitis.

Laboratory testing cannot distinguish between colonization and infection.

CDI testing should be performed only in symptomatic patients.

Diagnostic testing strategies for CDI vary. Multistep approaches using polymerase chain reaction (PCR) for the toxin gene(s) or single-step PCR on liquid stool samples have the highest sensitivity and specificity.

Test of cure is not recommended after CDI treatment.

Treatment

CDI should be treated according to disease severity and risk of recurrence or complications.

Vancomycin and metronidazole are first-line therapy.

Vancomycin is preferred for severe or complicated disease.

Recurrent CDI is more common in older patients and those with concomitant antibiotic use, presence of comorbidities, concomitant use of proton pump inhibitors, and worse initial disease severity.

Oral metronidazole or vancomycin are recommended for the first recurrence of mild to moderate CDI.

Vancomycin is recommended for patients with 2 or more recurrences.

Fidaxomicin may be considered for recurrent CDI or where risk of recurrence is high.

Fecal microbiota transplantation is associated with symptom resolution in recurrent CDI, but its role in primary and severe CDI is not established.

Withdrawing Precipitating Antibiotics

The human gut microbiota protects against pathogen overgrowth, including *C difficile*. Any antibiotic can disrupt microbiota, although penicillins, cephalosporins, and clindamycin are particularly associated with risk of CDI.[52-54] A systematic review on antibiotic use and CDI risk reported odds ratios ranging from 2.12 to 42 for clindamycin and 3.84 to 26 for third-generation cephalosporins,[53] while a more recent meta-analysis found an odds ratio of 3.2 for third-generation cephalosporins and 2.86 for clindamycin.[52] Fluoroquinolones are associated with increased risk of the BI/NAP1/027 strain.[12]

Historically, antibiotic withdrawal was sometimes a stand-alone treatment.[55] Olson et al[56] evaluated 908 patients with CDI from 1982-1991 and found that 15% had symptom resolution without antibiotic therapy. Whether antibiotic withdrawal remains effective for mild CDI is unclear, although some evidence exists to support this approach in

combination with standard *C difficile* therapy.[57] Failure to stop offending antibiotics is associated with CDI recurrence.[58]

Metronidazole vs Vancomycin

Metronidazole and vancomycin have been primary therapies for CDI since the 1980s. Early studies suggested that oral metronidazole and oral vancomycin had equivalent efficacy, with similar tolerability and relapse rates.[56,59,60] Newer data suggest higher treatment failure rates when metronidazole is used in severe or complicated CDI.[3,61-64]

A large retrospective study found that oral metronidazole treatment failures increased (10%-26%) and the 60-day probability of recurrence increased (21%-47%) before vs after emergence of BI/NAP1/027.[4] Other studies have not demonstrated increased metronidazole failures after BI/NAP1/027 emergence.[65,66]

Zar et al[63] conducted a randomized trial evaluating response to metronidazole vs vancomycin in 150 patients stratified by CDI severity. Among patients with mild CDI, cure rates for metronidazole and vancomycin were not different (90% vs 98%, respectively). However, among patients with severe CDI, cure rates were better for vancomycin (97%) vs metronidazole (76%). A systematic review from 2001-2010 reported higher treatment failures with metronidazole than vancomycin (22.4% vs 14.2%; $P = .002$), while recurrence rates were similar (27.1% vs 24.0%; $P = .26$). Metronidazole treatment failures were more frequent in North America than Europe.[3] A large clinical trial comparing tolevamer, a toxin-binding polymer, with vancomycin and metronidazole found that while tolevemer was inferior to both metronidazole and vancomycin, metronidazole was inferior to vancomycin (success rates of 44.2%, 72.7%, and 81.1%, respectively). These differences were more pronounced in severe CDI (66.3% for metronidazole,78.5% for vancomycin).[64]

Factors associated with metronidazole failures include age older than 60 years, fever, hypoalbuminemia, peripheral leukocytosis, ICU stay, and abnormal abdominal computed tomography (CT) imaging findings.[61-63] Patients with hematologic malignancies and CDI respond more poorly to metronidazole and vancomycin (53.7% and 50%, respectively).[67]

Patients receiving metronidazole have a longer time to symptomatic improvement than patients receiving vancomycin.[60,68] A retrospective study of 102 patients after emergence of the BI/NAP1/027 strain found that only 71% of patients responded to metronidazole within 6 days. The overall response rate was 91% and failures were associated with higher severity of illness.[62]

Oral vancomycin is typically well tolerated. However both oral and rectal administration of vancomycin may rarely be systemically absorbed.[69] Metronidazole is associated with gastrointestinal

Table 1. Diagnostic Tests for Toxigenic *Clostridium difficile*[a]

Tests by Type and Method	Target(s)	Characteristics
Gold standards		
Toxigenic culture	Toxigenic *C difficile*	Reference standard Difficult to perform Time consuming (24-48 h)
Cell cytotoxicity assay	Toxins A or B[b]	Reference standard Highly sensitive for toxin compared with EIA Difficult to perform Time consuming (24-48 h)
Rapid diagnostic tests		
EIA	GDH	GDH alone insufficient for diagnosis (must be paired with a test for toxin) Rapid Variable sensitivity and specificity
EIA	Toxins A or B[b]	Rapid Variable sensitivity and specificity
NAAT		Rapid but more expensive than EIA Highly sensitive and specific for presence of toxigenic *C difficile* May increase detection of colonization and not true CDI
RT-PCR	*tcdB* or *tcdC* genes	*tcdA*-negative/*tcdB*-positive strains can cause disease
LAMP	*tcdA* or *tcdB* genes	*tcdA*-positive/*tcdB*-negative not well described in human disease Caution required in interpreting negative results based on *tcdA* testing alone by LAMP

Abbreviations: CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; LAMP, loop-mediated isothermal amplification; NAAT, nucleic acid amplification testing; RT-PCR, real-time polymerase chain reaction.

[a] Refer to the text or Table 2 and eTable for sensitivity and specificity of the diagnostic tests.

[b] *C difficile* can produce toxin A and/or toxin B. Although toxins A and B both play a role in clinical disease, it is not known if strains producing only toxin A are associated with symptomatic infection in humans.

Table 2. Systematic Reviews and Meta-analyses Examining the Performance Characteristics of Rapid Diagnostic Tests for *Clostridium difficile* Infection

Source by Test	No. of Included Studies	Sensitivity	Specificity
Organism			
GDH EIA			
Crobach et al,[19] 2009	11	Mean (range), 0.88 (0.6-0.97)[a]	Mean (range), 0.89 (0.75-0.97)[a]
Shetty et al,[110] 2011	13	Mean (range), 0.92 (0.8-1)[a]	Mean (range), 0.93 (0.83-1)[a]
NAAT			
Crobach et al,[19] 2009	4	Mean (range), 0.91 (0.86-1)[a]	Mean (range), 0.96 (0.94-1)[a]
Deshpande et al,[111] 2011	19	Pooled (95% CI), 0.9 (0.88-0.91)[a]	Pooled (95% CI), 0.96 (0.96-0.97)[a]
O'Horo et al,[112] 2012	25[b]	Pooled (95% CI), 0.92 (0.91-0.94)[c]	Pooled (95% CI), 0.94 (0.94-0.95)[c]
O'Horo et al,[112] 2012		Pooled (95% CI), 0.87 (0.84-0.9)[d]	Pooled (95% CI), 0.97 (0.97-0.98)[d]
Toxin			
Toxin A/B EIA			
Crobach et al,[19] 2009	60	Mean (range), 0.73 (0.32-0.99)[a]	Mean (range), 0.98 (0.65-1)[a]
Planche et al,[113] 2008	18	Mean (range), 0.87 (0.69-0.99)[a]	Mean (range), 0.97 (0.92-1)[a]

Abbreviations: EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification testing.

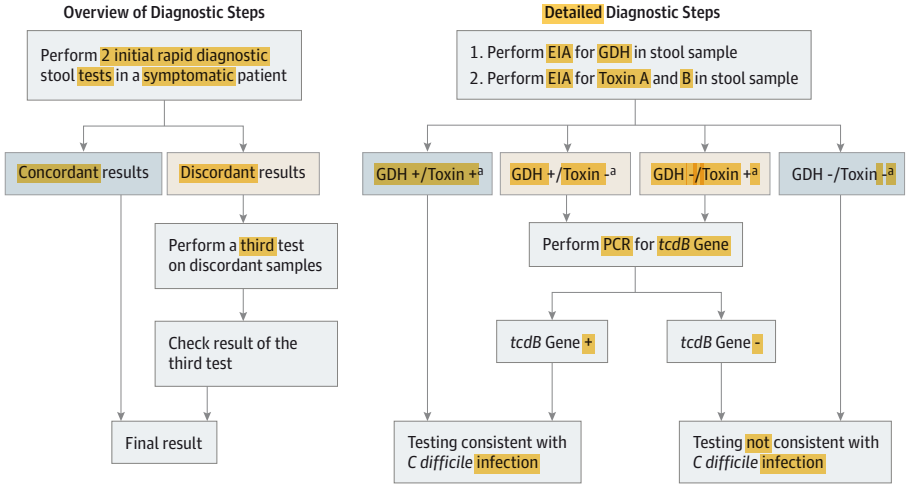
[a] Comparisons were with toxigenic culture plus cell cytotoxicity assay or another mixed reference standard.

[b] Of the 25 studies by O'Horo et al, comparisons were with toxigenic culture for 14 studies, cell cytotoxicity assay for 16 studies, and both were used for 5 studies.

[c] Comparisons were with toxigenic culture.

[d] Comparisons were with cell cytotoxicity assay.

Figure 2. Sample Multistep Algorithm for Rapid Diagnosis of *Clostridium difficile* Infection



Abbreviations: EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; PCR, polymerase chain reaction.

[a] Toxin-positive (+) indicates presence of either Toxin A or Toxin B when a combined test is performed, as in this example. Toxin-negative (–) indicates that neither Toxin A nor B is present. Adapted under Creative Commons License.[116]

adverse effects, a disulfiram-like reaction when ingested with alcohol, and peripheral neuropathy with prolonged therapy.[70]

Treatment by Disease Severity

Table 3 lists definitions of CDI severity, definitions for recurrent disease, and factors associated with recurrence.[15,16,20] **Figure 3** provides a possible approach for CDI treatment according to disease severity. However, the approach in Figure 3 has not been validated.[71-75]

Treating Mild to Moderate CDI

For mild to moderate CDI, oral metronidazole remains the preferred therapy, in part because of its low cost.[15,16,63] The standard dose is 500 mg orally, 3 times daily for 10 to 14 days. For patients unable to take oral medications, metronidazole can be administered intravenously at the same dose, although metronidazole is not recommended as monotherapy when administered intravenously.[15,16] Based on a recent study[64] that showed a lower clinical success rate for metronidazole vs vancomycin, it may be reasonable to consider vancomycin for mild to moderate CDI.

Treating Severe or Complicated CDI

Vancomycin is the preferred therapy for severe or complicated CDI.[15,16,63] Taking vancomycin 125 mg orally, 4 times daily for 10 to 14 days, is noninferior to higher doses in the absence of complicated infection.[22] However, expert opinion often favors higher doses in severe or complicated disease.[15,16]

Vancomycin may also be administered rectally in the setting of ileus, as an adjunctive therapy, although evidence is limited to case reports.[15,76,77] Rectally administered vancomycin is not typically used alone because rectally administered vancomycin may not reach the entire affected area.[78] Intravenous metronidazole achieves detectable levels throughout the colon[79] and may be an adjunctive therapy for ileus or severe/complicated CDI, typically with vancomycin when administered orally, rectally, or by both methods. However, there are no randomized trials supporting this practice.[15,16] Treatment failures have occurred in patients with ileus administered intravenous metronidazole monotherapy.[56,77]

Table 3. CDI Classification Based on Disease Severity

CDI Disease Category	Clinical and Laboratory Signs	Associated Risk Factors
Mild to moderate	Diarrhea without systemic signs of infection, white blood cell count <15 000 cells /mL, and serum creatinine <1.5 times baseline[15]	Antibiotic use, previous hospitalization, longer duration of hospitalization, use of proton pump inhibitors, receipt of chemotherapy, chronic kidney disease, and presence of a feeding tube[10-14]
Severe	Systemic signs of infection, and/or white blood cell count ≥15 000 cells/mL, or serum creatinine ≥1.5 times the premorbid level[15]	Advanced age, infection with BI/NAP1/027 strain[114,115]
Severe, complicated	Systemic signs of infection including hypotension, ileus, or megacolon[15]	See above,[a] plus recent surgery, history of inflammatory bowel disease, and intravenous immunoglobulin treatment[43]
Recurrent	Recurrence within 8 weeks of successfully completing treatment for CDI[16,20]	Patient age ≥65 y, concomitant antibiotic use, presence of significant comorbidities, concomitant use of proton pump inhibitors, and increased initial disease severity[16]

Abbreviation: CDI, *Clostridium difficile* infection.

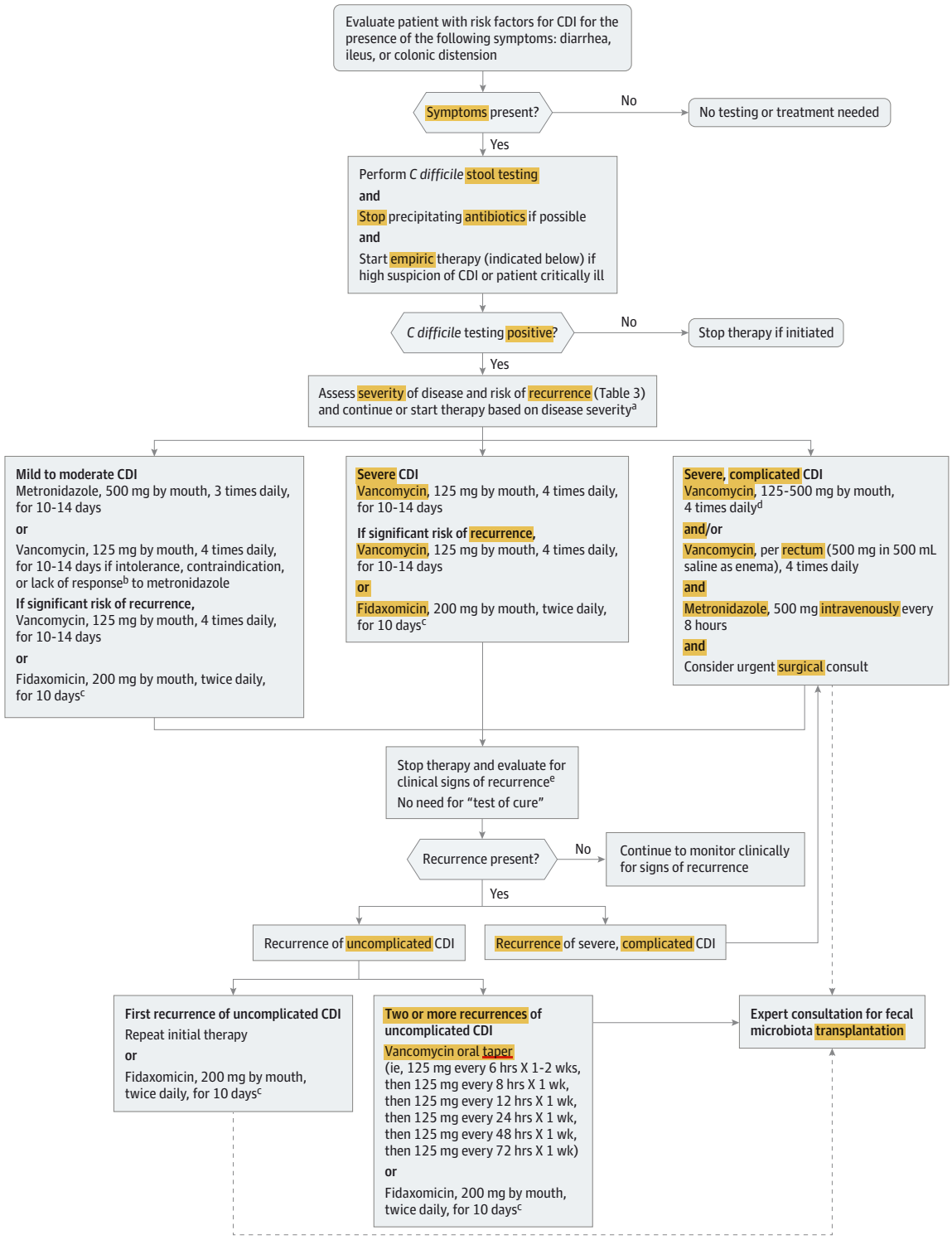
[a] Also includes associated risk factors for mild to moderate and severe CDI disease categories.

Prompt surgical evaluation should be obtained in patients with complicated CDI. Early intervention can reduce mortality.[80,81] Subtotal or total colectomy with end ileostomy is often performed when surgery is required, although there are newer colon-preserving techniques.[80,81]

Treating Recurrent CDI

Recurrent CDI is more common in older patients and in those with concomitant antibiotic use, presence of comorbidities, concomitant use of proton pump inhibitors, and worse initial disease severity.[11,16] Inadequate antibody response after an episode of CDI is associated with increased recurrence rates.[82,83]

Figure 3. Possible Approach for the Treatment of *Clostridium difficile* Infection



[a] Suggested approach for *Clostridium difficile* (CDI) treatment according to disease severity based on current guidelines, recent reviews and meta-analyses of fecal microbiota transplantation, and randomized controlled trials of fidaxomicin. This approach is not validated. There are no data supporting the use of fidaxomicin for complicated CDI.

[b] Treatment response is defined by clinical improvement in diarrhea or other signs of infection. Response may require 3 to 5 days after starting therapy, but therapy escalation can be considered sooner based on disease severity.

[c] Indicates that costs are substantially higher.

[d] Duration of therapy depends on treatment response.

[e] Consider postinfectious irritable bowel syndrome rather than recurrent CDI for mild symptoms.

References[15,16,71-73,75]

Guidelines recommend oral metronidazole or vancomycin for the first recurrence of mild to moderate CDI.[15,16] Vancomycin is recommended therapy for any subsequent recurrences. Pulsed or tapering courses are often used.[84] Randomized trials are lacking but case series and case reports support this practice.[23,84,85] McFarland et al[23] enrolled 163 patients with recurrent CDI with an overall subsequent recurrence rate of 44.8%; tapering and pulsed courses of vancomycin resulted in fewer recurrences (31%; $P = .01$ and 14.3%; $P = .02$, respectively), although the number of patients was small (29 and 7, respectively).

Fidaxomicin was approved for treating CDI in 2011. Randomized studies demonstrated similar cure rates between fidaxomicin and oral vancomycin.[74,86] In a double-blind randomized trial, Cornely et al[74] reported that 221 of 252 patients (87.7%) receiving fidaxomicin for CDI achieved clinical cure vs 223 of 257 (86.8%) receiving vancomycin. These results achieved criteria for noninferiority between fidaxomicin and vancomycin. Louie et al[86] reported clinical cure rates with fidaxomicin that were noninferior to vancomycin (88.2% vs 85.8%) in 629 patients, with fewer recurrences with fidaxomicin (15.4% vs 25.3%; $P = .005$).

When antibiotics cannot be discontinued because of ongoing infection, clinical cure rates for concomitant CDI are higher with fidaxomicin than with vancomycin.[58] Fidaxomicin may preserve the human gut microbiota better than alternative treatments.[75] Fidaxomicin is not considered first-line therapy for mild or uncomplicated disease because of its higher costs.[87] No data support use of fidaxomicin in complicated or fulminant disease.[16] Fidaxomicin may be used for recurrent CDI, for the treatment of an initial CDI episode, when there is a high risk of recurrence or when administered immediately after a course of vancomycin for patients with multiple CDI recurrences.[16,84,88]

Anecdotal evidence supports rifaximin as an adjunctive therapy for recurrent CDI, usually after a course of standard therapy for CDI.[89,90] Monotherapy should be avoided given the propensity for resistance.[89] Nitazoxinide is not a first-line therapy for an initial episode of CDI but may be used as an adjunctive therapy for recurrent CDI. However, data are limited.[15]

Probiotics and Fecal Microbiota Transplantation

Recurrent CDI can occur as relapse of infection or as reinfection with another strain. Preserving normal gut microbiota diversity may prevent or treat recurrences.[91]

Probiotics are live microorganisms that can restore normal gut microbiota. The role of probiotics in CDI treatment is poorly defined, although evidence suggests probiotics may prevent initial episodes as well as recurrence.[92-94] Probiotic-associated bacteremia and fungemia have been described, primarily in immunocompromised or critically ill patients.[95] However, probiotics are generally well tolerated without major adverse effects.[96] A recent case series suggested that daily administration of kefir, a probiotic made from fermented milk, with staggered, tapered doses of either vancomycin or metronidazole was beneficial for recurrent CDI.[97]

Fecal microbiota transplantation restores gut microbiota diversity via the instillation of donor stool into the gastrointestinal tract of a patient with CDI. This procedure has had good clinical response without reports of adverse events for refractory or recurrent CDI.[71-73] The first systematic review was published in 2011 and included 317 patients with recurrent CDI treated with fecal microbiota transplantation via enema, nasojejunal-tube or gastroscope, or colonoscopy. Clinical resolution occurred in 92% of patients (89% after a single treatment) without serious adverse effects.[73] A recent review of 536 patients reported an 87% clinical response rate.[72]

A randomized trial of fecal microbiota transplantation demonstrated symptom resolution in 94% of patients who received vancomycin for 5 days followed by either 1 or 2 treatments with fecal microbiota transplantation, vs 31% in patients who received vancomycin alone for 14 days and 23% for those receiving vancomycin for 14 days plus bowel lavage. This study was stopped early after interim analyses demonstrated superiority of fecal microbiota transplantation. Among 18 patients in the other treatment groups who received subsequent fecal microbiota transplantation, 83% had symptom resolution.[98]

In 2013, a stool substitute preparation made from purified fecal cultures from a single healthy donor was used to treat 2 patients with recurrent CDI who had not responded to repeated courses of antibiotics, and this approach resulted in symptom resolution.[99] A 1989 study used a rectal administration of 10 facultatively aerobic and anaerobic bacteria to successfully treat 5 patients with CDI.[100] A recent feasibility study used frozen fecal capsules, prepared from prescreened unrelated donors, to treat 20 patients with recurrent CDI, resulting in a 90% response rate after 1 or 2 treatment courses.[101] Prescreened, filtered, and frozen donor stool for fecal microbiota transplantation is also available.[102] However, the US Food and Drug Administration considers fecal microbiota transplantation investigational, requiring an Investigational New Drug application. There are also anecdotal reports supporting fecal microbiota transplantation for treating refractory or complicated CDI in the setting of ileus or megacolon.[103]

Other Therapies for the Treatment of CDI

Other Antibiotics

Teicoplanin was demonstrated to be noninferior to vancomycin, but teicoplanin is unavailable in the United States.[59] Case reports suggest efficacy of tigecycline for severe or recurrent CDI[104]; however, the role of tigecycline for CDI remains unclear. Phase 3 trials are ongoing for use of surotomycin and cadazolid.

Toxin Binders

Randomized trial data show that nonabsorbable anionic polymers, including colestipol and cholestyramine, are not effective for CDI. Tolevamer is an anionic polymer that binds *C difficile* toxins A and B. However recent data show that tolevamer is inferior to vancomycin and metronidazole for CDI.[64] Polymers can bind other agents such as vancomycin and should not be administered concomitantly with standard therapy.[15]

Immunotherapy

Serum antibody response to toxin A may protect against recurrent symptomatic CDI.[32,45] A *C difficile* vaccine is in development for both primary and recurrent CDI.[105,106]

Pooled immunoglobulin neutralizes *C difficile* toxins in vitro but there are limited data supporting intravenous immunoglobulin for recurrent CDI,[107] although its role in severe CDI remains unclear. In a randomized, double-blind, placebo-controlled study, 2 neutralizing, human monoclonal antibodies against *C difficile* toxins A (CDA1) and B (CDB1), combined with standard therapy, resulted in a lower recur-

rent infection rate (7% vs 25%).[108] Phase 3 trials are evaluating MK-3415 (human monoclonal antibody to *C difficile* toxin A), MK-6072 (human monoclonal antibody to *C difficile* toxin B), and MK-3415A (human monoclonal antibodies to *C difficile* toxins A and B) to prevent recurrent CDI in patients receiving other recommended therapies.[109]

Discussion

Manifestations of *C difficile* vary from asymptomatic colonization to fulminant disease. Laboratory testing does not distinguish between asymptomatic colonization vs CDI; therefore, testing should be limited to individuals who are symptomatic.[15] Many testing strategies exist for CDI diagnosis. Some experts and guidelines recommend multistep algorithms.[15,16,19,34]

Whether and how to treat *C difficile* should be based on disease severity and relapse risk. Oral vancomycin is recommended for severe, complicated, or recurrent CDI, while oral metronidazole is recommended for mild to moderate disease, although recommendations may change if further studies demonstrate that metronidazole is inferior to vancomycin.[15,16,64] Fidaxomicin may be used when risk of recurrence is high, but cost may be prohibitive. Data supporting the use of fecal microbiota transplantation for recurrent CDI are increasing[71-73,98]; however, the regulation and standardization of fecal microbiota transplantation is evolving. Studies are ongoing to develop synthetic stool for treating CDI[99] or capsules for administrating fecal microbiota transplantation .[101]

Conclusions

C difficile remains an important cause of morbidity and mortality. Treatment strategies should be based on disease severity and risk of recurrence. Fecal microbiota transplantation is associated with symptom resolution in recurrent CDI, and its role may be expanded in the future.

ARTICLE INFORMATION

Author Contributions: Dr Malani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bagdasarian, Rao, Malani.
Acquisition, analysis, or interpretation of data: Bagdasarian, Rao, Malani.
Drafting of the manuscript: Bagdasarian, Rao, Malani.
Critical revision of the manuscript for important intellectual content: Bagdasarian, Rao, Malani.
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