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

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Abstract

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

Objective: We reviewed 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. 4682 articles were initially identified; 196 were selected for full review. The most clinically pertinent 116 articles were included.

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 (multistep: sensitivity 0.68 to 1.00 / specificity 0.92 to 1.00; single step: sensitivity

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AUTHOR CONTRIBUTIONS

Dr. Malani had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis.
Study concept and design: Bagdasarian, Rao, Malani
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0.86–0.92 / specificity 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 demonstrates clinical success rates of 66.3% for metronidazole versus 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 = 0.005) 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 other adjunctive therapies. Metronidazole is appropriate for mild disease. Fidaxomicin is a therapeutic option for those 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.

Keywords

Clostridium difficile; diarrhea; infection

INTRODUCTION

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 (CDI) 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]. CDI incidence has increased from 4.5/ 1000 adult discharges in 2001 to 8.2/1000 discharges in 2010 [6]. Patients with CDI have higher healthcare costs than patients without CDI. Annual attributable costs exceed $1.5 billion in the U.S.[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. *C. difficile* is not invasive and toxin production is the key to pathogenesis (non-toxigenic strains of *C. difficile* do not cause diarrhea). The toxin disrupts epithelial integrity via microtubules and cell-cell tight junctions, resulting in cytokine release such as IL-8[8]. These actions promote an inflammatory infiltrate in the colonic mucosa, fluid shifts leading to diarrhea, and epithelial necrosis. Antibiotics alter normal microbiota, increasing CDI risk[9]. Other factors associated with CDI include older age, recent hospitalization, longer hospitalization duration, receipt of multiple antibiotics, longer antibiotic use 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* (Appendix A). We searched for studies of diagnostic testing and treatment of CDI published between Jan 1978 to October 31, 2014. Studies published in non-English languages and studies involving animals or children were excluded. We identified 4,682 articles. Bibliographies of the retrieved studies and previous reviews were searched for other relevant studies. 196 articles were initially identified and were reduced to the most clinically relevant 116 (Appendix B). Meta-analyses, systematic reviews, and references cited in published clinical practice guidelines from the past 10 years were also reviewed.

Diagnosing *C. difficile* Infection: Who Should Be Tested

Laboratory testing alone cannot distinguish between asymptomatic colonization and clinical symptoms of infection. The diagnosis of CDI requires: 1) presence of diarrhea, defined as three or more unformed stools in 24-hours, and 2) positive stool test for toxigenic *C. difficile* or its toxins, or colonoscopic/histopathologic findings demonstrating pseudomembranous colitis[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 up to six 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 healthcare facilities, consistent with the hypothesis that long-term asymptomatic colonization following CDI occurs[24,25]. Recurrent symptoms can occur in association with a transient functional bowel disorder in up to 35% of patients during the first two weeks following resolution of CDI. However, only 4.3% of patients have symptoms more than three months after the infection due to a post-infectious irritable bowel syndrome.[26] The 2010 Society for Healthcare Epidemiology of America and Infectious Disease 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, presently 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 (TC)(Table 1).[19] Stool specimens are cultured anaerobically on special media[27] for 24–48 hours. After colony selection and confirmation of taxonomy (usually with an antigen detection strategy with latex agglutination or enzyme immunoassay (EIA) or real-time 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, since most studies compare other diagnostic modalities to TC or CCA,[19] and there are differences in choice of media and sample pretreatment.

Although a reference standard, TC is time-intensive, 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 non-toxigenic strains of *C. difficile* and data on asymptomatic colonization suggest up to 46% of *C. difficile* isolates are non-toxigenic[31], GDH testing must be paired with a test that detects toxin.

Nucleic acid amplification testing (NAAT), including RT-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 in the >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]

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 TC. 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 picograms of toxin and is highly sensitive (0.94–1) and specific (0.99), especially if combined with antiserum.[27,35] The main disadvantage is turnaround time 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 one test and the probability of a second or third test becoming positive after 2 previous negative test(s) was <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 1; 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 one gold standard comparator (Appendix C). In general, multistep algorithms using NAAT had excellent sensitivity (0.68–1) and specificity (0.92–1), 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) (Appendix C).

Treating *C. difficile* Infection (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[15,16].

Markers of Disease Severity—Clinical manifestations of *C. difficile* infections (CDI) range 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 risk scoring system to predict risk of fulminant CDI: age >70 years (2 points), WBC ≥20,000 cells/mL or ≤2,000/mL (1 point), cardiorespiratory failure (7 points), and diffuse abdominal tenderness (6 points). High risk patients had a score ≥6[41]. Another scoring system study used age, treatment with systemic antibiotics, leukocyte count, albumin, serum creatinine to predict response to vancomycin or fidaxomicin[42].

The 2010 Society for Healthcare Epidemiology of America and Infectious Disease Society of America Clinical Practice Guidelines categorize mild CDI as WBC < 15 X 10^9/L and serum creatinine < 1.5 times premorbid level; severe CDI as WBC ≥ 15 X 10^9/L, or serum creatinine ≥ 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 one or more signs or symptoms of severe colitis, with significant systemic toxin effects and shock, resulting in intensive care unit admission, colectomy or death. Key findings included WBC >15 X 10^9/L, serum albumin <30 g/L and an increase in serum creatinine level ≥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[45–4925]. Asymptomatic fecal shedding of *C. difficile* may be transient and 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 studied 618 non-colonized patients and 192 asymptomatic carriers with two or more weekly follow up rectal swabs and reported that 3.6% of the non-colonized patients and only 1% of the asymptomatic carriers developed symptomatic CDI [31].

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 2.12–42 for clindamycin, and 3.84–26 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 evaluated 908 patients with CDI from 1982–1991and found that 15% had symptom resolution without antibiotic therapy[56]. 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 versus 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% to 26%), and the 60-day probability of recurrence increased (21% to 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 conducted a randomized trial evaluating response to metronidazole versus 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 (76% vs. 97%)[63]. A systematic review from 2001–2010 reported higher treatment failures with metronidazole than vancomycin (22.4% vs. 14.2%; P = 0.002), while recurrence rate were similar (27.1% vs. 24.0%; P = 0.26). 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>60 years, fever, hypoalbuminemia, peripheral leukocytosis, ICU stay and abnormal abdominal CT imaging [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 side 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 2 provides a possible approach for CDI treatment according to disease severity. However, the approach in Figure 2 has not been validated [71–73,74,75].

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 500mg orally, three times daily for 10–14 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]. Vancomycin 125 mg orally four times daily for 10–14 days is non-inferior 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 oral and/or rectal vancomycin. However, there are no randomized trials supporting this practice[15,16]. Treatment failures have occurred in patients with ileus administered IV metronidazole monotherapy[56,77].

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 *C. difficile* Infection—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].

Guidelines recommend oral metronidazole or vancomycin for the first recurrence of mild-moderate CDI[15,16]. Vancomycin is recommended therapy for any subsequent recurrences. Pulsed or tapering courses are often employed [84]. Randomized trials are lacking but case series and case reports support this practice[23,84,85]. McFarland et al enrolled 163 patients with recurrent CDI, with an overall subsequent recurrence rate of 44.8%; while tapering and pulsed courses of vancomycin resulted in fewer recurrences (31%, p=0.01 and 14.3%, p=0.02 respectively), although the number of patients was small (29 and 7 respectively) [23].

Fidaxomicin was approved for treating CDI in 2011. Randomized studies demonstrated similar cure rates between fidaxomicin and oral vancomycin[74,86]. In a double-blinded randomized trial, Cornely et al reported that 221/252 (87.7%) of patients receiving fidaxomicin for CDI achieved clinical cure, versus 223/257 (86.8%) of patients receiving vancomycin. These results achieved criteria for non-inferiority between fidaxomicin and vancomycin[74]. Louie et al reported clinical cure rates with fidaxomicin that were noninferior to vancomycin (88.2% versus 85.8%) in 629 patients, with fewer recurrences with fidaxomicin (15.4% vs. 25.3%, P = 0.005) [86].

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 its use 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 side 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, with the instillation of donor stool into the gastrointestinal tract of an infected patient. 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/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 a 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 one or two treatments with fecal microbiota transplantation, versus 31% in those receiving 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 two patients with recurrent CDI who had failed repeated courses of antibiotics and resulted in symptom resolution[99]. A 1989 study used a rectal administration of ten facultatively aerobic and anaerobic bacteria to successfully treat five 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 one or two treatment courses[101]. Pre-screened, filtered, and frozen donor stool for fecal microbiota transplantation is also available[102] However, the FDA 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 U.S.[59]. Case reports suggest efficacy of tigecycline for severe or recurrent CDI [104], however the role of tigecycline for CDI remains unclear. Phase III trials are ongoing for 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[45,82]. A *C. difficile* vaccine is in development for both primary and recurrent CDI [105)[106,107].

Pooled immunoglobulin neutralizes *C. difficile* toxins *in vitro* but there are limited data supporting intravenous immunoglobulin for recurrent CDI[108], although its role in severe CDI remains unclear. In a randomized, double-blind, placebo-controlled study, two neutralizing, human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1) combined with standard therapy resulted in a lower recurrent infection rate (7% vs. 25%) [109]. Phase III 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[110].

Discussion

Manifestations of *C. difficile* vary from asymptomatic colonization to fulminant disease. Laboratory testing does not distinguish between asymptomatic colonization versus CDI, therefore testing should be limited to symptomatic individuals[15]. Many testing strategies exist for CDI diagnosis. Many experts and some 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, however cost may be prohibitive. Data supporting the use of FMT for recurrent CDI are growing,[71–73,98] however the regulation and standardization of FMT is evolving. Studies are ongoing to develop synthetic stool for treating CDI[99] or capsules for administrating FMT[101].

Conclusion

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BOX: "Key messages regarding diagnosis and treatment of *Clostridium difficile* infection in adults.

DIAGNOSIS

- *Clostridium difficile* infection (CDI) requires diarrhea (three or more unformed stools in 24-hours), AND a positive stool test for toxigenic *C. difficile* or its toxins, or colonoscopic/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-moderate CDI.
- Vancomycin is recommended for patients with 2 or more recurrences.
- Fidaxomicin may be considered for recurrent CDI.
- Fecal microbiota transplantation is associated with symptom resolution in recurrent CDI.

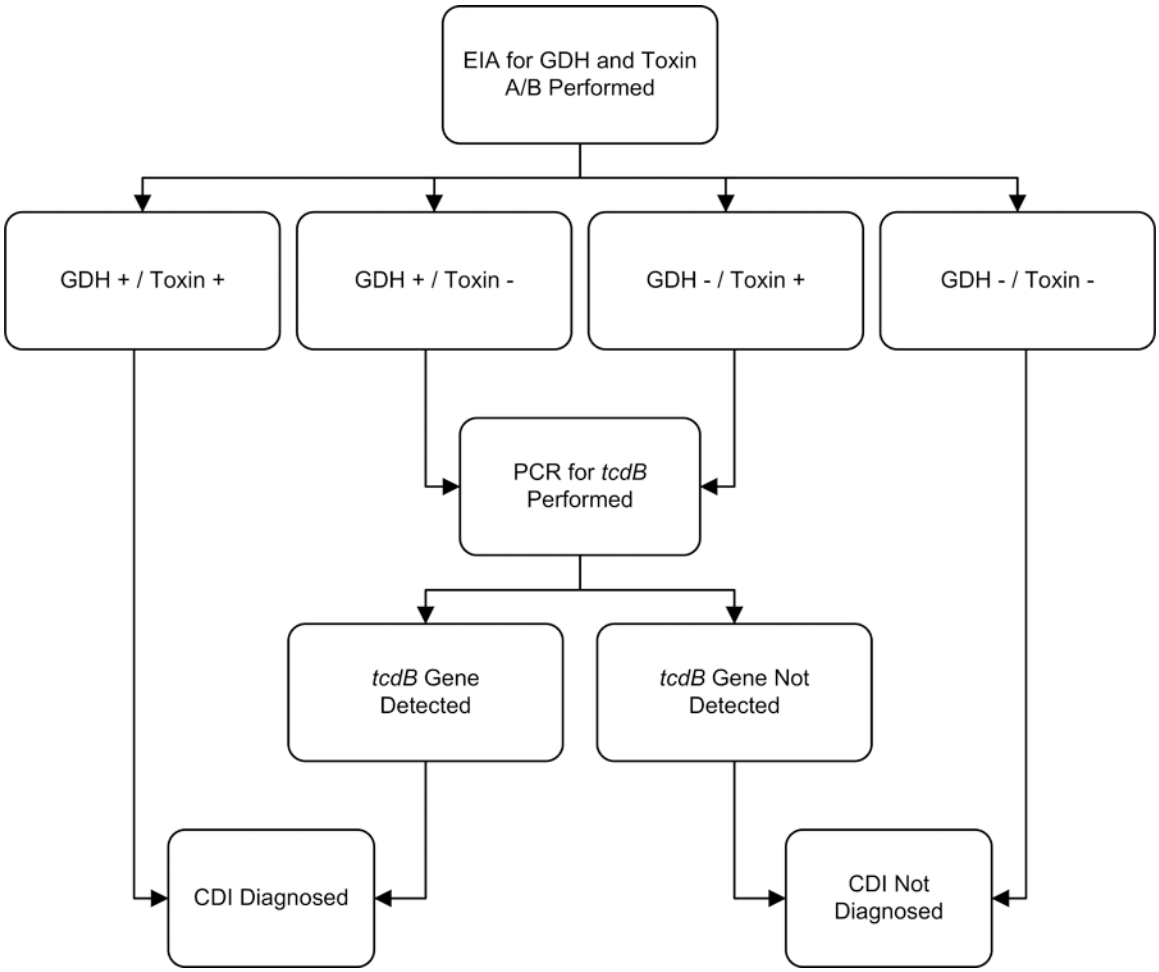

Figure 1. Sample multistep algorithm for the rapid diagnosis of *C. difficile* infection.

Abbreviations: CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; PCR, polymerase chain reaction.

Footnotes: Adapted under Creative Commons License from Rao K, Erb-Downward JR, Walk ST, et al. The Systemic Inflammatory Response to *Clostridium difficile* Infection. PLoS ONE. 2014;9(3):e92578.

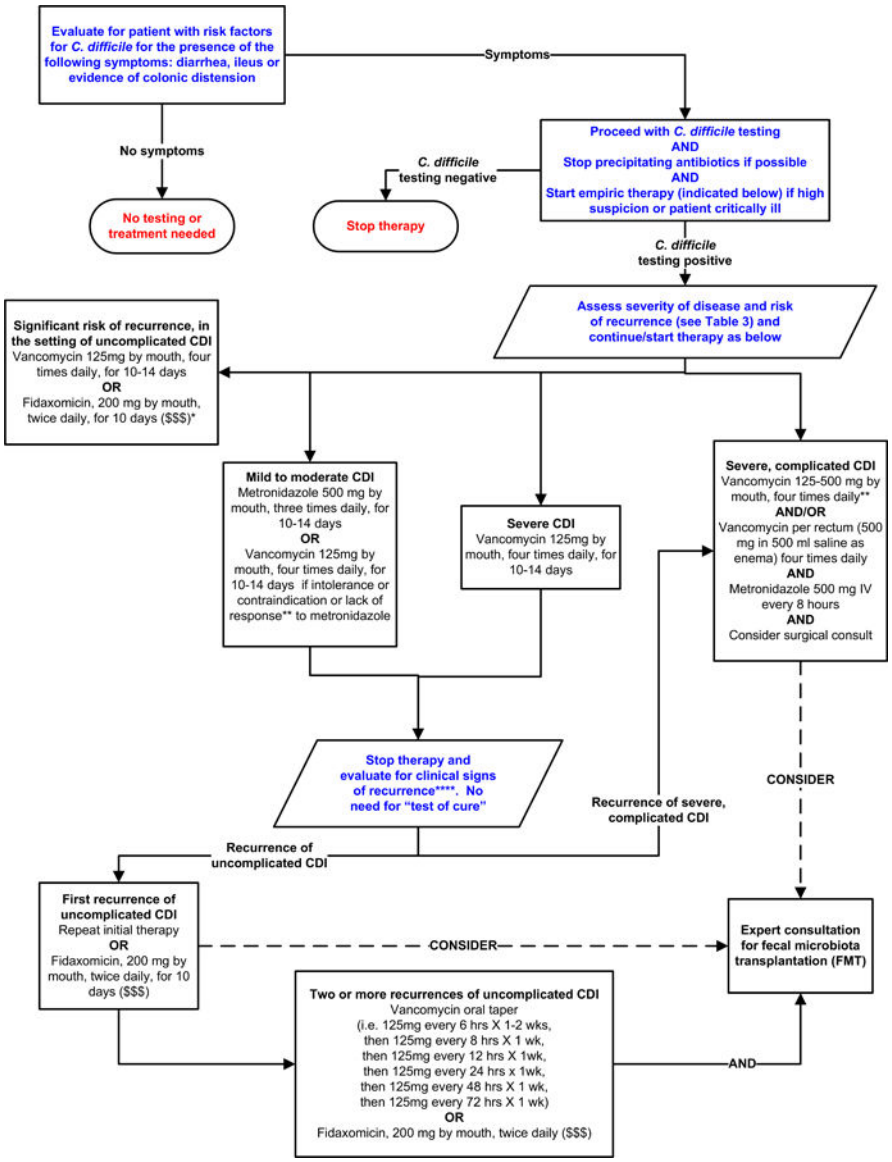

Figure 2. Possible Approach for the Treatment of *C. difficile* Infection (CDI).

Footnotes: *Suggested approach for CDI treatment according to disease severity based on current guidelines, recent reviews/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. **Treatment response is defined by clinical improvement in diarrhea or other signs of infection; response may require 3–5 days after starting therapy, but therapy escalation can be considered sooner based on disease severity. ***Duration of therapy depends on treatment response. ****Consider post-infectious irritable bowel syndrome rather than recurrent CDI for mild symptoms. "$ $ $" indicates that costs are substantially higher. References: [15,16,71–73,75]

Table 1.

Diagnostic tests for toxigenic *C. difficile*[a]

Testing Method	Target(s)	Notes
Gold Standard Tests		
Toxigenic Culture	Toxigenic *C. difficile*	• Reference standard
		• Difficult to perform
		• Time consuming (24–48 hours)
Cell Cytotoxicity Assay	Toxins A or B[b]	• Reference standard
		• Highly sensitive for toxin compared to EIA
		• Difficult to perform
		• Time consuming (24–48 hours)
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*$^-$ / *tcdB*$^+$ strains can cause disease
LAMP	*tcdA* or *tcdB* genes	• *tcdA*$^+$ / *tcdB*$^-$ 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 / Appendix C for sensitivity / specificity of the diagnostic tests

[b]*C. difficile* can produce toxin A and/or toxin B. Although 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

Test	Source	Number of Included Studies	Sensitivity	Specificity
Organism Detection				
GDH EIA	Crobach et al., 2009[19]	11	0.88 (0.6–0.97)[ae]	0.89 (0.75–0.97)[ae]
	Shetty et al., 2011[111]	13	0.92 (0.8–1)[ae]	0.93 (0.83–1)[ae]
NAAT	Crobach et al., 2009[19]	4	0.91 (0.86–1)[ae]	0.96 (0.94–1)[ae]
	Deshpande et al., 2011[112]	19	0.9 (0.88–0.91)[be]	0.96 (0.96–0.97)[be]
	O'Horo et al., 2012[113]	25	0.92 (0.91–0.94)[bc]	0.94 (0.94–0.95)[bc]
			0.87 (0.84–0.9)[bd]	0.97 (0.97–0.98)[bd]
Toxin Detection				
Toxin A/B EIA	Crobach et al., 2009[19]	60	0.73 (0.32–0.99)[ae]	0.98 (0.65–1)[ae]
	Planche et al., 2008[114]	18	0.87 (0.69–0.99)[ae]	0.97 (0.92–1)[ae]

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

[a]Mean (range)

[b]Pooled (95% confidence interval)

[c]Compared to TC

[d]Compared to CCA

[e]Compared to TC+CCA or another mixed reference standard

Table 3.

C. difficile Infection (CDI) Classification based on Disease Severity

Disease Category	Clinical and Laboratory Signs	Associated Risk Factors
Mild to moderate CDI	Diarrhea without systemic signs of infection, WBC< 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 CDI	Systemic signs of infection, and/or WBC ≥ 15,000 cells/mL, or serum creatinine ≥ 1.5 times the premorbid level [15]	Advanced age, infection with BI/NAP1/027 strain [115,116].
Severe, complicated CDI	Systemic signs of infection including hypotension, ileus, or megacolon [15]	See above, plus recent surgery, history of inflammatory bowel disease and intravenous immunoglobulin treatment[43]
Recurrent CDI	Recurrence within 8 weeks of successfully completing treatment for CDI [16,20]	Patient age ≥65 years, concomitant antibiotic use, presence of significant comorbidities, concomitant use of proton pump inhibitors, and increased initial disease severity [16]