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SUPPLEMENT

Navigating Changes in *Clostridioides difficile* Prevention and Treatment

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LEARNING OBJECTIVES

At the completion of this activity, participants should be able to:

1. Outline the updated *Clostridioides difficile* (*C. difficile*) guidelines.
2. Explain emerging evidence on the role of the microbiome in new and recurrent *C. difficile* infections.
3. Describe the mechanisms of action, safety, and efficacy data on newly approved and pipeline treatments for *C. difficile* management.
4. Identify which patients are appropriate for newly approved *C. difficile* treatments.
5. Review the comparative effectiveness research data for available *C. difficile* treatments.

Presented as an AMCP live webinar on July 15, 2020.

SUPPLEMENT SYNOPSIS

Clostridioides difficile (*C. difficile*, previously known as *Clostridium difficile*) infections are a major health care concern. The Centers for Disease Control and Prevention (CDC) estimates that *C. difficile* causes almost half a million illnesses in the United States yearly, and approximately 1 in 5 patients with a *C. difficile* infection (CDI) will experience 1 or more recurrent infections. There have been noteworthy advances in the development of CDI prevention and treatment, including a growth in the understanding of the role a patient's gut microbiome plays.

A qualitative review and evaluation of the literature on the cost-effectiveness of treatments for CDI in the U.S. setting was conducted and the summary provided herein. Due to the higher cost of newer agents, cost-effectiveness evaluations will continue to be critical in clinical decision making for CDI.

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Navigating changes in *Clostridioides difficile* prevention and treatment

Spencer H Durham, PharmD; Phuc Le, PhD, MPH; and Angela T Cassano, PharmD

ABSTRACT

Clostridioides difficile (*C. difficile*, previously known as *Clostridium difficile*) infections are a major health care concern. The Centers for Disease Control and Prevention (CDC) estimates that *C. difficile* causes almost half a million illnesses in the United States yearly, and approximately 1 in 5 patients with a *C. difficile* infection (CDI) will experience 1 or more recurrent infections. The incidence of infection has risen dramatically in recent years, and infection severity has increased due to the emergence of hypervirulent strains. There have been noteworthy advances in the development of CDI prevention and treatment, including a growth in the understanding of the role a patient's gut microbiome plays.

The 2017 Infectious Diseases Society of America (IDSA) guidelines made a significant change in treatment recommendations for first time CDI episodes by recommending the use of oral vancomycin or fidaxomicin in place of metronidazole as a first-line treatment. The guidelines also included detailed recommendations on the use of fecal microbiota transplant (FMT) in those patients who experience 3 or more recurrent CDI episodes.

A number of novel therapies for the treatment of CDI are in various stages of development. Treatments currently in phase 3 trials include the antibiotic ridinilazole, the microbiome products SER-109 and RBX2660, and a vaccine. All of these agents have shown promise in phase 1 and 2 trials. Additionally, several other antibiotic and microbiome candidates are currently in phase 1 or phase 2 trials.

A qualitative review and evaluation of the literature on the cost-effectiveness of treatments for CDI in the U.S. setting was conducted, and the summary provided herein. Due to the higher cost of newer agents, cost-effectiveness evaluations will continue to be critical in clinical decision making for CDI.

This paper reviews the updated CDI guidelines for prevention and treatment, the role of the microbiome in new and recurrent infections, pipeline medications, and comparative effectiveness research (CER) data on these treatments.

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Clostridioides difficile (*C. difficile*), formerly known as *Clostridium difficile*, is a spore-forming and toxin-producing gram-positive obligate anaerobic bacillus capable of causing severe infections, resulting in significant morbidity and mortality.[1,2] Symptoms of *C. difficile* infection (CDI) range from abdominal pain and watery diarrhea to pseudomembranous colitis, toxic megacolon, and death.

The Centers for Disease Control and Prevention (CDC) classifies different antibiotic-resistant organisms into the following 3 categories based on their level of concern to human health: urgent, serious, and concerning. CDI is classified as urgent, the highest level threat. It accounts for almost 40% of the 35,000 annual deaths attributed to antibiotic-resistant pathogens.[3]

The CDC Emerging Infections Program (EIP) conducts population-based surveillance in 10 counties across the United States and includes a CDI component.[4] For purposes of the EIP, a new CDI case is defined as "a positive *C. difficile* toxin assay or a positive *C. difficile* molecular assay of a stool specimen greater than 8 weeks after the last positive specimen."[4] Recurrent cases are those with a positive stool culture within 2-8 weeks of the previous positive specimen.

The true incidence of confirmed CDI is confounded by the type of laboratory test used and the variability in database structure for reporting.[5] Using EIP data estimates, CDI rose considerably during the first decade of the millennium and appeared to plateau at an estimated 476,000 cases in 2011 without adjustment for type of assay used

to confirm infection.[2,6] Nucleic acid amplification tests (NAATs) are more sensitive than traditional assays for CDI. The increased sensitivity has the potential to lead to overdiagnosis and falsely elevated incidence rates if detected in those who are asymptomatic carriers and not experiencing true infection.

Guh and Kutty (2018) estimated 462,100 cases of CDI in 2017 without adjustment for NAAT.[6] Estimated incidence varied widely depending on use of NAAT, with approximately 245,000 cases of CDI if no laboratories used NAAT versus 508,900 cases estimated if all laboratories used NAAT. Of the total estimated cases, approximately 50% were estimated to be health care acquired in 2017, a decrease of about 36% since 2011.[6] CDC reports CDI accounted for almost 13,000 deaths in 2017.[3]

Despite an overall decrease in incidence, there remain alarming trends in CDI along with a significant economic burden, estimated to be 1 billion dollars annually on the United States health care system.[3] Historically, this disease typically occurred in older patients with comorbid conditions who were hospitalized and receiving broad-spectrum antimicrobials. Since the mid-2000s, there has been an increase in CDI in the community setting in patients previously thought to be at low risk.[1]

Clostridioides difficile

Recognized as a leading cause of infectious diarrhea since the late 1970s, *C. difficile* is ubiquitous in nature and is prevalent in soil and the waste of most mammals. Its ability to persevere for long periods is due largely to the ability to form spores. These spores can tolerate wide ranges in temperature and pH changes that the bacteria alone are usually unable to survive. Additionally, *C. difficile* spores are resistant to heat, 70% ethanol, and quaternary ammonium detergents.[7]

C. difficile is not a significant component in the human gastrointestinal (GI) tract, although there is increasing evidence of asymptomatic carrier cases.[8-10] A study by Curry et al. (2010) reported 29% of hospitalized CDI cases were linked to asymptomatic carriers, compared with 30% being linked to symptomatic patients.[11] At this time, the Infectious Diseases Society of America (IDSA) does not recommend widespread screening to identify asymptomatic carriers or placing them on contact precautions.[1] As long as the GI microflora is still intact, colonization does not usually occur.

Often pathogenesis of *C. difficile* occurs through ingestion after contamination of food or hands. The vegetative bacteria are typically killed by stomach acid, whereas the spores are highly resistant and pass through the GI tract intact. In nonimmunocompromised hosts or those who have not been recently exposed to antibiotics, the spores will often pass through without establishing an infection. In an individual with an altered microbiome, spores can germinate once they reach the small intestine and become vegetative upon exposure to bile acids. Once an active vegetative bacterium reaches the colon, *C. difficile* adheres to the epithelium and produces toxins A (TcdA), toxin B (TcdB), and hydrolytic enzymes, leading to epithelial necrosis.[12] The cascade that follows necrosis involves loss of epithelial integrity and increased intestinal permeability, resulting in infection of deeper tissue layers. TcdA is an enterotoxin that activates inflammatory cells. This causes the release of cytokines, leading to increased mucosal permeability and loss of fluids which manifests, in part, as watery diarrhea. TcdB is a cytotoxin that causes additional damage to the GI mucosa after the initial damage from TcdA.

Watery diarrhea is the most prevalent symptom of infection, with the IDSA guidelines defining new onset CDI as at least 3 unformed stools in 24 hours.[1] This is generally associated with severe abdominal pain, cramps, nausea, and vomiting. If the patient is progressing to a more serious manifestation, such as pseudomembranous colitis or toxic megacolon, they may also experience fever, anorexia, and malaise.

Hypervirulent *C. difficile* strains emerged in the early 2000s, adding to the health care burden and resulting in epidemic pockets worldwide. In particular, the strain ribotype 027 (also known as 027BI/NAPI) is associated with more severe disease, outcomes, and death compared with other strains.[1] Outbreaks of this strain have occurred across North America, parts of Europe, and Asia. The increase in incidence of this strain may be due, in part, to the worldwide overuse of fluoroquinolones. Isolates of this strain documented during recent outbreaks manifest much higher resistance to the fluoroquinolones when compared with historic isolates of the same strain; thus, increased use of the fluoroquinolones may have promoted more widespread dissemination of this virulent strain.[13] The current incidence of this strain appears to be decreasing, likely due to better antimicrobial stewardship efforts to decrease fluoroquinolone prescribing.[14] Despite the decreasing incidence of ribotype 027, other hypervirulent strains, such as ribotype 078, continue to emerge.[15]

TESTING

Tests for CDI vary in sensitivity and specificity, and the IDSA Guidelines provide specific guidance on the use of these tests.[1] In an effort to ensure that CDI testing is focused on patients with active infection and not asymptomatic colonization, the guidelines recommend that testing only be performed on diarrheal or unformed stools. Similarly, a test of cure, which involves testing patients who have been

actively treated for CDI to determine if the bacterium is still present, is not recommended in clinical practice because patients may continue to test positive for several weeks after complete resolution of symptoms.[1] The gold standard for diagnosis is a stool culture. However, the slow turnaround time to obtain results is not well suited for clinical practice. Other available tests include NAAT, glutamate dehydrogenase (GDH) tests, and toxin tests. Toxigenic cultures and GDH tests are both highly sensitive but have low specificity. NAATs were first approved in 2009 and, as described previously, have a high sensitivity for *C. difficile* nucleic acid (toxin genes) but a low/moderate specificity. The 2 tests to detect free toxins, cell culture cytoxicity neutralization assay and the toxin A and B enzyme immunoassays, have varying levels of sensitivity and specificity, with the former assay having both high sensitivity and specificity. Due to the varying degrees of sensitivity and specificity with the different tests, a multistep algorithm is the best approach for diagnosis of CDI. This may include GDH plus toxin, GDH plus toxin and arbitrated by NAAT, or NAAT plus toxin.[1]

RISK FACTORS

Health care facility–onset *C. difficile* infection (HO-CDI) is defined as a laboratory-confirmed case from a specimen collected on or after day 4 of admission. Infection may also result from exposure to a health facility, but the onset of symptoms may occur after the patient has returned to the community setting. This is known as community-onset, health care–associated (CO-HCFA) CDI, which occurs within 28 days of discharge from the health care facility. The most common risk factors for HO-CDI and CO-HCFA CDI include the following[1,2,16]:

- Exposure to antibiotics
- Advanced age, most often described as ≥65 years
- Duration of hospitalization
  - Risk increases with each day of hospitalization
- Severity of underlying disease
- Chemotherapy, possibly due to the antibiotic activity of some agents and more likely due to the patient being immunocompromised
- Immune system compromise (i.e., patients receiving chemotherapy, HIV patients, prolonged steroid use)
- Proton pump inhibitor use
- Vitamin D deficiency
- Patients undergoing GI tract manipulation (i.e., GI tube insertion, GI surgery)

Community-acquired CDI, defined as onset of symptoms within 48 hours of admission to the hospital or more than 12 weeks after discharge, is increasing and may account for as many as 50% of CDI cases in the United States.[6,17] Community-acquired CDI risk factors vary slightly from hospital-acquired and were described by Khanna et al. (2012).[18] Of the 385 total cases included in the analysis, of definite CDI of any origin, the vast majority were female with a median age of 67.6 years; on average, these patients were younger than hospital-acquired cases. Moreover, community-acquired cases were less likely to have had antibiotic exposure in the previous 90-day period, to have comorbidities, and to be on acid suppression agents.[18] Recurrence rates were similar in both groups.

Aside from reducing *C. difficile* exposure from all sources, exposure to antibiotics is the most impactful and modifiable risk factor where pharmacists and other health care providers can have a significant effect. Antibiotic use results in the disruption of normal GI flora. This reduces colonization resistance and increases the risk of infection from virulent organisms, such as *C. difficile*.[12] Almost every antibiotic agent has the potential to cause CDI; however, the agents most commonly implicated include fluoroquinolones, clindamycin, third- and fourth-generation cephalosporins, and carbapenems.[1] Some agents, such as vancomycin, the aminoglycosides, and metronidazole, are not usually implicated as causative agents.

The prevalence of CDI has been affected by a variety of factors over the past several decades. Increased use of broad-spectrum antibiotics is the most common risk factor linked to the dramatic rise in cases in the early 2000s.[1,2] Similarly, hypervirulent strains of CDI began to increase during this time period. The number of patients aged older than 65 years has also increased as the baby boomer generation continues to age, possibly contributing to the increased incidence. Fortunately, antimicrobial stewardship, better understanding of hypervirulent strains, strict hand hygiene and personnel protective equipment (PPE) policies, and increased isolation of positive patients has contributed to the gradual decline occurring today.

CDI CLASSIFICATION

The 2017 IDSA clinical practice guidelines stratify the classification of severity of CDI into 3 categories: nonsevere, severe, and fulminant.[1] Clinical presentation and laboratory values dictate the severity category as summarized in Table 1. White blood cell count is a surrogate marker of systemic spread beyond localized inflammation and infection. Similarly, increased serum creatinine values are considered a marker for secondary organ damage. This version of the guidelines changed the serum creatinine values to an absolute number versus a change in serum creatinine values. Baseline serum creatinine levels are not always available lending to the need for a concrete metric versus a trend.

TABLE 1 CDI Severity Classification[1]

Severity Classification	Criteria
Nonsevere	WBC count ≤15,000 cells/μL PLUS SCr <1.5 mg/dL
Severe	WBC count ≥15,000 cells/μL OR SCr ≥1.5 mg/dL
Fulminant	Hypotension or shock, ileus, megacolon

CDI = C. difficile infection; SCr = serum creatinine; WBC = white blood cell count.

Human Gut Microbiome

The use of antimicrobial agents is always associated with killing both the intended pathogens as well as components of the normal microbiome of the human body. When individuals who have been exposed to *C. difficile* or are asymptomatic carriers are also exposed to antibiotics, the spores are able to proliferate in the GI tract due to decreased suppression from more dominant organisms in the host's microbiome. Serving as 1 of the most effective lines of defense against infections, the human microbiome consists of all the microorganisms, not just bacteria, found on or within the body. The GI portion of the human microbiome contains the largest variety of microbiota, but it is not the sole body system to harbor beneficial microbes to protect the host. As mentioned previously, the ability of the GI microbiome to assist with prevention of infection by opportunistic pathogens is called colonization resistance. Factors such as diet, gastric acid levels, genetics, and host age play a role in the flora composing each host's GI microbiome. When the microbiome is damaged or disrupted, there is a reduction in colonization resistance capacity. When this capacity is decreased, *C. difficile* is better able to thrive and replicate.

Prevention of CDI

Antimicrobial stewardship and infection control measures are the 2 most effective prevention strategies for CDI. Sodium hypochlorite, or household bleach, is effective in killing the bacteria and various dilutions have been studied and used with success. IDSA guidelines provide detailed options for cleaning agents and incorporate the use of Environmental Protection Agency registered sporicidal agents when cleaning rooms and equipment. Automated terminal disinfection, such as ultraviolet radiation or hydrogen peroxide vapor, have been found to be effective in reducing *C. difficile* spores, but the IDSA makes no recommendation for their use.[1,19,20] PPE, particularly gowns and gloves, must be worn when caring for CDI patients, and these patients should be isolated in private rooms whenever possible.[1] Hand washing with soap and water is recommended over alcohol-based hand sanitizers in outbreak or hyperendemic situations, as evidence supports increased efficacy of spore removal with soap and water.[1]

Antimicrobial stewardship, which often involves restricting the use of antimicrobials, continues to be recommended as an element of CDI prevention.[1] Many health systems have used robust antimicrobial stewardship programs aimed at decreasing both antimicrobial resistance as well as associated costs. A hallmark of effective antimicrobial stewardship programs is to switch from broad-spectrum empiric therapy to narrow-spectrum agents when culture and sensitivity results are available. A positive effect of this practice over the past 2 decades is decreased use of broad-spectrum antibiotics, such as fluoroquinolones.

The IDSA does not recommend the use of probiotics as prevention or treatment of *C. difficile* outside of clinical trials.[1] The reasoning for this hinges on the limitations to existing clinical trials outlined in several meta-analyses. Smaller trials have shown promise in this area, but it remains unclear the place in therapy for these agents. Although rare, probiotics can cause infections in some patients. Because of the lack of beneficial evidence and the possible risks, probiotics are not recommended at this time.

Treatment of Initial (New Onset) CDI

The first step in treating new onset CDI is immediate discontinuation of any contributing antimicrobial agent.[1] For patients without expected laboratory delays or fulminant CDI, antibiotics for the treatment of CDI should not be initiated until infection is confirmed. In those patients where there is an expected delay, antibiotics directed at CDI should be initiated empirically. In situations where discontinuation of the offending antibiotic is not feasible, such as severe or life-threatening infections, empiric CDI antibiotics may be added to the current regimen until the offending antibiotic can safely be stopped.

Use of antiperistaltic agents, such as loperamide, have not been historically recommended, but studies are lacking. Theoretically, these agents may be harmful in CDI as they may not allow the bacteria to be excreted from the body. As such, they are not currently recommended.[1] Due to the rapid loss of electrolytes when patients are having multiple diarrhea episodes daily, it is recommended to carefully monitor fluid and electrolytes and replenish as needed.

TABLE 2 IDSA Treatment Recommendations[1]

Classification	Treatment
Initial, nonsevere	• Vancomycin 125 mg orally 4 times daily for 10 days OR • Fidaxomicin 200 mg orally 2 times daily for 10 days Can use metronidazole 500 mg orally 3 times daily for 10 days only if above agents are unavailable. Extending regimen to 14 days in nonresponders can be considered in the event of resistance.
Initial, severe	• Vancomycin 125 mg orally 4 times daily for 10 days OR • Fidaxomicin 200 mg orally 2 times daily for 10 days
Initial, fulminant	• Vancomycin 500 mg orally 4 times daily + metronidazole 500 mg IV every 8 hours • Add rectal vancomycin if ileus is present: 500 mg in 100 mL normal saline every 6 hours as retention enema

IDSA = Infectious Diseases Society of America; IV = intravenous.

The current guidelines made a significant change in treatment recommendations for first-time CDI episodes by removing metronidazole as a first-line treatment and instead recommending the use of oral vancomycin or fidaxomicin (Table 2).[1] Metronidazole and oral vancomycin have historically been the 2 mainstays of CDI treatment. This was derived primarily from 2 clinical trials that demonstrated no difference between vancomycin and metronidazole for the treatment of CDI. However, these trials were small and included fewer than 50 patients in each study group.[21,22] Since 2000, larger clinical trials have demonstrated that vancomycin is superior to metronidazole for both CDI resolution and decreasing recurrence.[23-25] These trials led to the current recommendation that vancomycin should be used preferentially to metronidazole.[1] The exception to this new recommendation is when vancomycin or fidaxomicin is contraindicated or are not available. In these cases, metronidazole can be considered only in initial, nonsevere CDI episodes.[1] It is important to note that if metronidazole is used, length of treatment should be ideally limited to 10 days, with a maximum of 14 days in those patients without full response. Similarly, metronidazole should not be used for treatment of recurrence if it was used for the initial episode due to increased risk of irreversible neurotoxicity with prolonged use.

For patients who are experiencing an initial CDI episode categorized as severe, metronidazole should not be used, and every effort should be made to allow the patient to use oral vancomycin or fidaxomicin. Fulminant CDI episodes should be treated with high dose, usually 500 mg 4 times daily, oral vancomycin in combination with intravenous metronidazole. Rectal vancomycin can be used in patients with ileus.

VANCOMYCIN (VANCOCIN)

Studies have shown vancomycin to be effective for the treatment of *C. difficile* because it achieves high concentrations in the stool.[26] Vancomycin was the predominant agent used until the mid-1990s. At that time, vancomycin-resistant Enterococcus was beginning to emerge as a significant pathogen, and efforts were implemented to reduce the use of vancomycin. At the same time, studies demonstrated metronidazole to be equally effective to vancomycin. Because metronidazole was cheaper and more widely available, it became the first-line recommended therapy. As previously stated, more recent data support the use of vancomycin over metronidazole because vancomycin has consistently been shown to be superior to metronidazole for both treatment and risk of CDI recurrence.[1] Although recurrence rates vary between studies, vancomycin recurrence rates can be approximately 25% after first treatment, compared with approximately 40% with metronidazole.[1] Oral or rectal vancomycin is dosed 4 times a day and is associated with few adverse effects, with GI disturbances, such as nausea and abdominal pain, being the most common.

METRONIDAZOLE (FLAGYL)

Metronidazole is significantly less expensive than oral vancomycin, but when risk of recurrence is considered, the cost-benefit deteriorates. Metronidazole has lower fecal concentrations than oral vancomycin, which may play a role in the higher incidence of recurrence found in patients treated with metronidazole. For these reasons, the current guidelines have relegated the use of metronidazole to a second-line therapy only in initial CDI cases.[21,22]

FIDAXOMICIN (DIFICID)

Fidaxomicin, a macrolide antibiotic, was approved by U.S. Food and Drug Administration (FDA) in 2011 for treatment of *C. difficile*–associated diarrhea.[27] It has a lower minimum inhibitory concentration in vitro compared with metronidazole or vancomycin and a prolonged postantibiotic effect, which allows for twice-daily dosing. Fidaxomicin is poorly absorbed from the GI tract, resulting in high fecal concentrations and low systemic absorption, translating into better efficacy and fewer systemic adverse effects. There are

TABLE 3 Treatment of Recurrent Episodes of CDI[1]

First Recurrence	Second or Subsequent Recurrence

• Vancomycin 125 mg orally 4 times daily × 10 days
  • If metronidazole was used for initial episode
• Prolonged or pulsed vancomycin if standard dose was used for initial episode
  • Vancomycin 125 mg orally 4 times daily × 10-14 days, then 125 mg 2 times daily × 7 days, then daily × 7 days, then once every 2-3 days × 2-8 weeks
• Fidaxomicin 200 mg orally 2 times daily × 10 days
  • If vancomycin was used initially
	• Pulsed or tapered vancomycin
	• Vancomycin 125 mg orally 4 times daily for 10 days, followed by rifaximin 400 mg orally 3 times daily for 20 days
	• Fidaxomicin 200 mg orally 2 times daily for 10 days
	• Fecal microbiota transplantation
	  • Antimicrobial treatment should be attempted for at least 2 recurrences (3 total episodes) before fecal microbiota transplantation

CDI = C. difficile infection.

minimal effects on the GI microbiome compared with vancomycin or metronidazole, and fidaxomicin has the added benefit of blocking the production of *C. difficile*–associated toxins.[26] There is also some evidence that fidaxomicin might better inhibit spore formation when compared with vancomycin. Clinical trials found equal efficacy in CDI cure rate episodes; however, it was shown to be superior to vancomycin in preventing any CDI recurrences ($P < 0.001$).[1,28,29]

BEZLOTOXUMAB (ZINPLAYVA)

Bezlotoxumab is a monoclonal antibody that binds TcdB to neutralize this toxin and ultimately prevent damage to the colon. It is approved for adjunct therapy in patients aged 18 years and older who have active CDI with a high risk of recurrence and are currently receiving appropriate antimicrobial treatment for CDI.[1] Bezlotoxumab is administered as a 1-time intravenous infusion. A post hoc analysis of the MODIFY I and II trials did not find a difference in efficacy compared with whether the infusion was given early, middle, or late in the antibiotic course.[30] This gives providers the flexibility to administer as an outpatient infusion. Bezlotoxumab is generally well tolerated, but caution must be used in patients with congestive heart failure (CHF), as some trials suggest it may worsen CHF symptoms. Bezlotuxumab was approved in late 2016, after the completion of the most recent IDSA guideline and could not be evaluated for inclusion.

FECAL MICROBIOTA TRANSPLANTATION

FMT has been shown to be effective for the treatment of *C. difficile* with a >90% success rate reported in some trials.[1] The goal of FMT is to restore GI microflora, which is achieved by transplanting microflora from a healthy individual to a patient experiencing a CDI episode. This can occur through an enema, colonoscopy, gastric tube, or oral capsule. Although highly efficacious, it remains reserved for patients with repeated infection or those with antimicrobial resistance or contraindications.[1] FMT is considered a medical procedure and has associated risks and costs. Although risks appear to be minimal, there have been reports of multidrug resistance transmission, and long-term risks are not well defined.[31] IDSA guidelines currently consider this option for patients who have at least 3 total episodes of *C. difficile*.[1]

CDI Recurrence

Risk factors for CDI recurrence are similar to the risk factors for first incidents, with the most common risk factors being concomitant antibiotic treatment during previous CDI treatment or antibiotic treatment initiated after conclusion of previous CDI therapy.[1] Advanced age, worsening underlying conditions, and decreased or inadequate humoral response to *C. difficile* toxins are also risk factors for recurrence.

Options for first recurrence are based on what the patient received for the first occurrence. It is critical to know the patient's treatment history to determine therapy for subsequent episodes. Table 3 summarizes the treatment options for recurrence. It should be noted that, if vancomycin was used for the initial episode, it can be used for recurrence, but a prolonged pulse dosing schedule is required.

Second or subsequent recurrences should be treated with several different options, including vancomycin plus rifaximin, vancomycin using pulse dosing, or fidaxomicin.[1] For patients who have failed approved standard antibiotic CDI treatments or those who have had at least 3 total CDI cases, FMT should be considered.[1]

Emerging Therapies

A number of novel therapies for the treatment of CDI are in various stages of development. Treatments currently in phase 3 trials include the antibiotic ridinilazole, the microbiome products SER-109 and RBX2660, and a vaccine. All of these agents have shown promise in phase 1 and 2 trials. Additionally, several other antibiotic and microbiome candidates are currently in phase 1 or phase 2 trials.

TABLE 4 Emerging CDI Therapies in Phase 3 Clinical Trials[36-39,41-43]

Therapeutic Agent	Therapy Type	Route of Administration	Current Status	Potential Place in Therapy
Ridinilazole	Antibiotic	Oral	Phase 3 trials underway	First-line agent similar to vancomycin and fidaxomicin
SER-109	Microbiome	Oral	Phase 3 trial underway	Only for recurrent infections, similar to FMT
RBX2660	Microbiome	Enema	Phase 3 trial underway	Only for recurrent infections, similar to FMT
PF-06425090	Vaccine	Injectable	Phase 3 trial underway	Prophylaxis
Ribaxamase	Beta-lactamase	Oral	Phase 2 completed	Given with beta-lactam antibiotics to prevent infection

CDI=C. difficile infection; FMT=fecal microbiota transplantation.

RIDINILAZOLE

Ridinilazole, formerly known as SMT19969, is a novel antimicrobial agent that interferes with cell division, resulting in rapid bactericidal activity.[32] This agent is specific for *C. difficile* and showed little effect on gut microflora while exhibiting activity against both TcdA and TcdB, properties comparable to fidaxomicin.[33]

Primarily excreted as unchanged drug in the feces, this results in a high fecal drug concentration with minimal systemic exposure. Ridinilazole is designated as a Qualified Infectious Disease Product (QIDP), with phase 3 trials currently ongoing. In a phase 2, double-blind, active-controlled trial in the United States and Canada, ridinilazole 200 mg orally twice daily was compared with oral vancomycin 125 mg 4 times daily.[34] Primary endpoints were sustained clinical response (clinical cure at test of cure) and absence of CDI recurrence 30 days after end of treatment. Secondary endpoints were time to hospital discharge, time to diarrhea resolution, and tolerability of ridinilazole compared with vancomycin. In the modified intention-to-treat population of 69 patients, ridinilazole was shown to be noninferior to vancomycin for clinical response at test of cure, with a statistically significant sustained clinical response ($P=0.0004$).[34] Reported adverse effects have been minimal and similar to vancomycin, with the most frequently reported being GI-related reactions, including nausea and abdominal pain. The phase 3 Ri-CoDIFy 1 and Ri-CoDIFy 2 trials are currently underway, which compare ridinilazole with vancomycin. Approximately 680 patients aged 18 years or older were enrolled to receive 10 days of either ridinilazole 250 mg orally twice daily or vancomycin 125 mg orally 4 times daily treatment, with the estimated completion of the trial being September 2021. Ridinilazole's place in therapy is currently unknown, but it appears to be most similar to fidaxomicin and is likely to be used in patients for initial or recurrent infections. There are currently no trials enrolling patients to compare fidaxomicin with ridinilazole.

SER-109

SER-109 is an orally administered microbiome indicated for the prevention of recurrent *C. difficile* infections in patients who have experienced multiple recurrent infections.[35] It is composed of a biologically sourced group of spore-based bacteria designed to create a new, healthy microbiome in patients whose natural microbiome has been damaged or is imbalanced. It has been granted orphan drug and breakthrough therapy designations by the FDA.

Phase 1 and phase 2 studies have been completed, and the phase 3 ECOSPOR III and IV are currently underway. ECOSPOR III is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study examining the safety, tolerability, and efficacy of SER-109 versus placebo.[36] Eligible patients are at least aged 18 years with a history of at least 3 or more CDI episodes within 9 months, including the enrolling episode. Patients must be receiving either vancomycin 125 mg orally 4 times daily or fidaxomicin 200 mg orally twice daily for 10-21 days for the enrolling episode of CDI. SER-109 is delivered as 4 capsules once daily for 3 days. The enrollment goal was 188 patients, but enrollment was stopped at 181 patients due to the COVID-19 pandemic. The primary endpoint is the reduction of *C. difficile* infection recurrence at up to 8 weeks. Secondary endpoints will evaluate recurrence at 4, 12, and 24 weeks posttreatment, time to recurrence of CDI, and safety and tolerability of SER-109. Place in therapy is yet to be determined, but it is projected to be indicated for patients with recurrent CDI infections as outlined by phase 3 trial inclusion criteria.

RBX2660

RBX 2660, a standardized microbiota suspension of intestinal microbes, is administered as a single 1-time enema that has been granted fast-tracked, orphan drug, and breakthrough drug status by FDA.[37] Phase 1 and multiple phase 2 clinical trials have been

conducted, and a phase 3 clinical trial (PUNCHCD3) finalized enrollment in 2020.[38,39] PUNCHCD3 is a multicenter, randomized, double-blind, placebo-controlled trial with the primary outcome being recurrence of infection at 8 weeks. Patients were aged at least 18 years and had at least 2 episodes (1 initial and at least 1 recurrence) of CDI with at least 1 course of standard of care antibiotic therapy or have 2 severe CDI episodes that resulted in hospitalization in the previous year. Two hundred sixty-seven patients were enrolled to evaluate the primary endpoints of efficacy compared to placebo at 1, 4, and 8 weeks after treatment. Secondary endpoints included the number of subjects with adverse events at 6 months and health-related quality of life assessments conducted at various intervals over the 6-month trial period.[39] The place in therapy is likely to be in those patients with recurrent infections.

PF-06425090

PF-06425090 is a toxoid-based *C. difficile* vaccine that neutralizes TcdA and TcdB by inducing a functional antibody response in the host patient.[40] A phase 2 randomized, placebo-controlled, observer-blinded study evaluating the safety, tolerability, and immunogenicity of 2 dose levels (100 µg and 200 µg) of two 3-dose vaccination schedules (days 1/8/30 and months 0/1/6) was conducted, with the primary endpoint of the percentage of participants achieving a prespecified antibody titer level for toxin A at month 7. Interim analysis demonstrated positive results, and paved the way for the currently ongoing phase 3 trial.[41] The phase 2 study included more than 850 healthy volunteers aged 65-85 years, whereas the phase 3 trial has enrolled almost 2,000 healthy volunteers aged at least 50 years evaluating a 2-dose versus a 3-dose regimen.[42]

RIBAXAMASE (SYN-004)

Ribaxamase is an orally administered beta-lactamase given in conjunction with intravenous beta-lactam antibiotics for the protection of GI microflora by preventing antibiotic mediated gut microbiota dysbiosis.[43] This is achieved by degrading excess antibiotic in the upper GI tract. In a phase 2b parallel-group, double-blind, randomized placebo-controlled trial, 413 patients with pneumonia were randomized to receive ceftriaxone plus ribaxamase 150 mg 4 times daily or ceftriaxone plus placebo. Two patients in the ribaxamase group and 7 patients in the placebo group ultimately developed CDI ($P=0.045$).[43] The results of this trial resulted in progression to phase 3 trials, which have not started enrolling patients.

Summary of Cost-Effectiveness Research for CDI in the United States

A qualitative review and evaluation of the literature on the cost-effectiveness of treatments for CDI in adults in the U.S. setting was conducted, and the summary provided herein. We searched PubMed from inception through June 2020 for full cost-effectiveness, cost-utility, or cost-benefit analyses published. Conference abstracts, commentaries, editorials, reviews, or letters to the editor were excluded. Additionally, studies that did not report cost per unit of health outcomes and those that included hypothetical or under-investigation treatments were not included.

Eleven papers that were ultimately selected for this review are summarized in Table 5.[44-54] Four studies evaluated treatments for the initial episode of CDI with no specific disease severity, 1 evaluated mild to moderate initial CDI, 4 evaluated recurrent CDI, and 2 included both initial and recurrent CDI. Five studies were funded publicly or through nongovernment organizations (NGOs), 2 had industry support ,and the remainder had no financial support. One third of the investigated patients were aged at least 60 years, and only 1 study evaluated patients with high risk of CDI recurrence.

STUDY DESIGNS

In cost-effectiveness analysis using decision models, decision tree is the simplest model type and includes distinct branches and a series of decision nodes to represent different sets of outcomes for patients depending on which option they choose.[55] A Markov model is a more complex type and includes mutually exclusive disease states. Patients move between states over a number of discrete time periods called cycles, and cost and effects are accrued along the way.[56] Microsimulation is the most complex type among the 3. It considers individual patients separately and allows for variability between patients.[57] In our review, the most common model design was decision-tree analysis, and 1 study used microsimulation (Table 5).[44,54] Two thirds of the studies allowed for follow-up of at least 2 recurrences following the index episode. Two thirds also used a short-term time horizon of less than 1 year. Most studies reported health outcomes as quality-adjusted life-years (QALYs), and more than half used $100,000/QALY as the decision threshold, whereas the rest used $50,000/QALY. All but 1 used a health-system or third-party payer perspective.

TABLE 5 Summary of CDI Cost-Effectiveness Research by CDI Stage

Author (Year)	Model	Funding	Population	Recurrences, n	Time Horizon	Health Outcomes	Decision Threshold, USD
Initial CDI: no specific disease severity							
Gidengil[44] (2014)	Markov (NR)	Industry	Adult inpatients	≥2	1 year	Recurrences, persistent cases, readmissions, deaths, VRE colonization, infections	NR
Stranges[45] (2013)	Decision tree	None	Patients aged 59.9 years	2	23 years (3%)	QALYs	100,000
Varier[46] (2014)	Decision tree	NGO	Adult outpatients	1	90 days	QALYs	100,000
Rajasingham[47] (2020)	Markov (2 months)	Public	Patients aged 67 years	≥2	1 year	QALYs	100,000
Initial CDI: mild to moderate							
Ford[48] (2018)	Decision tree	None	Adult inpatients	1 or 3	NR	Clinical cure, %	NR
Recurrent CDI							
Konijeti[49] (2014)	Decision tree	Public	Patients aged 65 years	2	1 year	QALYs	50,000
Varier[50] (2015)	Decision tree	Public	Adult outpatients	1	90 days	QALYs	NR
Lam[51] (2018)	Decision tree	None	Adult outpatients	2	1 year	QALYs	100,000
Luo[52] (2020)	Decision tree	None	Patients aged 65 years	2	6 months	QALYs	100,000
Initial and recurrent CDI							
Bartsch[53] (2013)	Microsimulation	Public	Patients aged ≥18 years	1	NR	QALYs	50,000
Prabhu[54] (2018)	Markov (15 days, then annual)	Industry	Adult patients with high-risk of CDI recurrence	3	Lifetime (3%)	QALYs	50,000

CDI = C. difficile infection; NR = not reported; QALY = quality-adjusted life-year; USD = U.S. dollars; VRE = vancomycin-resistant enterococcus.

MODEL INPUTS

Previous systematic reviews have found that cure rate, recurrence rate, and cost of therapy are among the most influential parameters on cost-effectiveness findings.[58,59] Indeed, the U.S.-based studies included in this qualitative summary varied substantially regarding these parameters.

Different cure rates were used for the 5 studies focused on treatment of initial episodes (Table 6). Studies conducted by Gidengil et al. (2014), Varier et al. (2014), and Ford et al. (2018) used a single cure rate for vancomycin, whereas Stranges et al. (2013) and Rajasingham et al. (2020) used varying cure rates based on factors such as severity of disease, patient location, concomitant antimicrobials, presence of hypervirulent strains, and recurrence.[44-48] Even among the 3 studies that only assigned 1 value, the cure rate of vancomycin ranged from 0.817 to 0.9. It is critical to consider this to understand the difference in findings. Given everything else being equal, studies using a higher cure rate would have a higher estimate of effectiveness, hence a lower incremental cost-effectiveness ratio, resulting in a favorable cost-effectiveness result toward the treatment compared with ones using a lower cure rate. Similarly, the variability among recurrence rates was also significant. For example, Ford et al. used a recurrence rate for vancomycin that was double that of Varier et al.[46,48] Everything else being equal, a higher recurrence rate would mean the treatment is less effective and less cost-effective than a lower recurrence rate.

TABLE 6 Cost-Effectiveness in *C. difficile* by Disease Stage

Author	Comparators	Results	Cure Rate	Recurrence Rate	Treatment Cost[a]
Initial CDI: no specific disease severity					
Gidengil[44]	MET, MET for 1st, VAN taper for ≥2 MET, VAN for 1st, VAN taper for ≥2 VAN, VAN for 1st, VAN taper for ≥2 FID, FID for 1st, VAN taper for ≥2	FID: more effective and more costly	MET: 0.735 VAN: 0.817 FID: 0.841	MET: Initial: 0.267 1st recurrence: 0.330 ≥2 recurrence: 0.308 VAN: Initial episode: 0.253 1st recurrence: 0.355 ≥2 recurrences: 0.308 FID: Initial episode: 0.154 1st recurrence: 0.197 ≥2 recurrences: 0.308	MET: $2/day VAN: $136/day FID: $359/day
Stranges[45]	VAN, VAN 1st, VAN taper 2nd FID, FID 1st, VAN taper 2nd	FID vs. VAN: $67,576/QALY	VAN: Inpatient: 0.781 Outpatient: 0.975 Mild-to-moderate CDI: 0.839 Severe CDI: 0.886 Concomitant antimicrobials: 0.794 NAP1/BI/027: 0.807 FID: Inpatient: 0.814 Outpatient: 0.975 Mild-to-moderate CDI: 0.920 Severe CDI: 0.821 Concomitant antimicrobials: 0.900 NAP1/BI/027: 0.787	VAN: Inpatient: 0.274 Outpatient: 0.227 Previous CDI: 0.312 Mild-to-moderate CDI: 0.244 Severe CDI: 0.266 Concomitant antimicrobials: 0.292 NAP1/BI/027: 0.209 FID: Inpatient: 0.179 Outpatient: 0.128 Previous CDI: 0.214 Mild-to-moderate CDI: 0.168 Severe CDI: 0.130 Concomitant antimicrobials: 0.169 NAP1/BI/027: 0.271	VAN: Outpatient: $1,445 Inpatient: $25 FID: $3,487
Varier[46]	MET (not clear what was used for recurrence) VAN FMT colonoscopy	VAN dominated by FMT FMT: colonoscopy vs. MET: $143,614/QALY	MET: 0.800 VAN: 0.900 FMT colonoscopy: 0.910	MET: 0.168 VAN: 0.084 FMT colonoscopy: 0.076	MET: $71 VAN: $1,677 FMT: $1,352

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TABLE 6 Cost-Effectiveness in *C. difficile* by Disease Stage *(continued)*

Author	Comparators	Results	Cure Rate	Recurrence Rate	Treatment Cost[a]
Initial CDI: no specific disease severity					
Rajasingham[47]	48 treatment strategies	Strategy 44: $31,751/QALY	MET: Initial nonsevere: 0.783 VAN: Initial nonsevere: 0.898 Initial severe: 0.846 Fulminant (+MET IV): 0.515 ≥2 recurrence (+RIF): 0.848 FID: Initial nonsevere: 0.917 Initial severe: 0.8 1st recurrence: 0.937 2nd recurrence: 0.816 FMT: colonoscopy: 0.896 capsule: 0.913	MET: Initial nonsevere: 0.208 VAN: Initial nonsevere: 0.215 Initial severe: 0.253 Fulminant (+MET IV): 0.253 ≥2 recurrence (+RIF): 0.151 FID: Initial nonsevere: 0.134 Initial severe: 0.114 1st recurrence: 0.197 2nd recurrence: 0.290 FMT: colonoscopy: 0.113 capsule: 0.087	MET: $9 (IV $40) VAN: $14 FID: $1,817 FMT: $1,546
Initial CDI: mild to moderate					
Ford[48]	MET VAN FID Primary analysis: FMT for recurrence Secondary analysis: 15 strategies	MET dominated by VAN FID vs. VAN: $2,829/1% gain in cure (primary model) and $6,000/1% gain in cure (secondary model)	MET: 0.784 VAN: 0.845 FID: 0.920	MET: 0.195 VAN: 0.188 FID: 0.168	MET: $24 VAN: $38 FID: $4,502 FMT: $1,297
Recurrent CDI					
Konijeti[49]	MET, VAN 2nd, VAN taper 3rd VAN, VAN taper 2nd, FMT (or FID) 3rd FID, VAN taper 2nd, FMT (or FID) 3rd FMT colonoscopy/ duodenal infusion/ enema, FMT 2nd, VAN taper 3rd	Base case MET, FID dominated by FMT: colonoscopy FMT: colonoscopy vs. VAN: $17,016/QALY	MET: 0.710 VAN: 0.916 FID: 0.937 FMT: colonoscopy: 0.945 duodenal infusion: 0.813 enema: 0.815	MET: 0.421 VAN: 0.355 FID: 0.197 FMT: colonoscopy: 0.091 duodenal infusion: 0.063 enema: 0.091	MET: $26 VAN: Outpatient: $817 Inpatient: $300 FID: $3,363 FMT colonoscopy: $2,691 FMT duodenal infusion: $2,585 FMT enema: $2,345
Varier[50]	VAN taper FMT Colonoscopy	FMT colonoscopy dominant (higher QALYs and lower costs)	VAN taper: 0.690 FMT colonoscopy: 0.910	VAN taper: 0.260 FMT colonoscopy: 0.076	VAN: Taper $2,576 FMT: $1,352

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TABLE 6 Cost-Effectiveness in *C. difficile* by Disease Stage *(continued)*

Author	Comparators	Results	Cure Rate	Recurrence Rate	Treatment Cost[a]
Recurrent CDI					
Lam[51]	VAN, VAN taper 1st, FMT 2nd FID, VAN taper 1st, FMT 2nd BEZ + VAN, VAN taper 1st, FMT 2nd	BEZ + VAN dominated by FID FID vs. VAN: $500,975/QALY	VAN: 0.844 FID: 0.841 BEZ: 0.8	VAN: 0.325 FID: 0.203 BEZ: 0.165	VAN: Inpatient: $2/dose Outpatient $45/dose FID: $232/dose FMT: $1,320 BEZ: $4,782/dose
Luo[52]	VAN taper, not clear 1st, FMT 2nd FID, not clear 1st, FMT 2nd VAN + FMT via colonoscopy, FMT for all recurrences VAN + FMT via oral capsules, FMT for all recurrence BEZ + VAN, not clear 1st, FMT 2nd	VAN taper, FID, BEZ + VAN: dominated FMT colonoscopy: least cost and highest QALYs	VAN taper: 0.776 FID: 0.885 FMT colonoscopy: 0.914 FMT capsules: 0.83 BEZ: 0.8	VAN taper: 0.363 FID: 0.179 FMT colonoscopy: 0.084 FMT capsules: 0.084 BEZ: 0.165	VAN: Taper $2,542 FID: $4,639 FMT colonoscopy: $2,671 FMT capsules: $1,950 BEZ: $4,560/dose
Initial and Recurrent CDI					
Bartsch[53]	MET (nonsevere) and VAN (severe) FID FID with strain typing (not clear what was used for recurrence)	FID dominated FID with strain typing vs. "no FID" > $43.7mil	MET: 0.710 VAN: NAP1/BI/027: 0.820 Non-NAPI/BI/027: 0.897 FID: NAP1/BI/027: 0.859 Non-NAP1/BI/027: 0.926	MET: 0.136 VAN: NAP1/BI/027: 0.295 Non-NAP1/BI/027: 0.278 FID: NAP1/BI/027: 0.247 Non-NAP1/BI/027: 0.098	MET: $7/day VAN: $124/day FID: $404/day
Prabhu[54]	• Bezlotoxumab + Standard of Care • Placebo + Standard of Care	BEZ + SOC vs Placebo + SOC (2015 USD) All patients: $19,824/QALY ≥ 65 years: $15,298/QALY Immunocompromised: $12,597/QALY Severe CDI: $21,430/QALY	SOC: Initial: 0.809 1st recurrence: 0.787 ≥ 2 recurrence: 0.814 BEZ: Same as SOC	SOC: 1st recurrence: 0.266 ≥ 2 recurrence: 0.45 BEZ: 1st recurrence: 0.165 ≥ 2 recurrence: 0.45	6-month CDI-attributable cost of a recurrence $14,934

[a]*Treatment cost is either the cost of the drug or FMT only and does not include hospitalization cost. All costs adjusted to 2019 dollars based on the Consumer Price Index in medical care.*

BEZ = bezlotoxumab; CDI = C. difficile infection; FID = fidaxomicin; FMT = fecal microbiota transplant; MET = metronidazole; QALY = quality-adjusted life-year; SOC = standard of care; USD = U.S. dollars; VAN = vancomycin.

Same as for initial CDI, there is a huge variation in cure rate and recurrence rate among studies on recurrent CDI. Both cure rate and recurrence rate of fidaxomicin and FMT colonoscopy were different among the studies evaluating them. Specifically, Lam et al. (2018) used the lowest cure rate and highest recurrence rate of fidaxomicin, while Varier et al. assigned the lowest value for both cure rate and recurrence rate of FMT colonoscopy.[46,51] Of all treatments being evaluated, only the values for bezlotoxumab has been consistent among studies (Table 6).

Treatment costs used by all studies, converted to 2019 dollars, are summarized in Table 6 for ease of comparison. Similar to cure and recurrence rates, studies differed substantially in how much they assigned treatment costs. For example, some studies applied a cost of FMT that was twice the value of other studies. There was also a huge variation in cost of fidaxomicin or vancomycin. Source of drug costs might partly explain these differences. Only 2 studies specified that drug costs were average wholesale price (AWP).[45,47] Three studies based the price on Red Book published prices[51-53]; the study by Gidengil et al. used manufacturer supplied cost[44] whereas Ford et al. used price from McKessonConnect,[48] but none of these studies explicitly report if it was AWP or wholesale acquisition cost price. The remaining studies used prices from other published papers. Of note, Prabhu et al. (2018) used a different costing model than any of the other studies.[54] The authors assigned a 6-month CDI-attributable cost of a recurrence, instead of separate costs for bezlotoxumab and hospitalization. This makes comparing their conclusion on the cost-effectiveness of bezlotoxumab versus those made by Lam et al. and Luo et al. (2020) difficult.[51,52,54]

COST-EFFECTIVENESS OF CDI TREATMENTS

Results for the cost-effectiveness of CDI treatments are summarized in Table 6. For initial CDI, Gidengil et al. concluded that fidaxomicin was more effective and more costly but could not comment about its cost-effectiveness because the evaluation did not estimate QALYs.[44] Stranges et al. compared fidaxomicin with vancomycin and estimated an incremental cost-effectiveness ratio (ICER) of $67,576/QALY.[45] Based on a decision threshold of $100,000/QALY, they concluded that fidaxomicin was cost-effective compared with vancomycin. In contrast, Varier et al. found that vancomycin was dominated by FMT, that is, vancomycin had a higher cost and lower effectiveness than FMT.[46] Because the ICER of FMT colonoscopy compared with metronidazole was higher than their selected $100,000/QALY decision threshold, the authors concluded that FMT colonoscopy was not cost-effective, meaning metronidazole would be the treatment of choice.

Rajasingham et al. performed the most comprehensive analysis, evaluating 48 treatment strategies for treatment of CDI based on the 2017 IDSA guidelines.[47] Of the 48 strategies, the most cost-effective was using fidaxomicin for nonsevere initial CDI, vancomycin for severe initial CDI, fidaxomicin for first recurrence, and FMT for second or later recurrences. Ford et al. focused only on mild-to-moderate initial CDI and compared metronidazole, vancomycin, and fidaxomicin in 2 analyses.[48] The primary analysis considered FMT for any recurrence whereas the secondary analysis included a variety of combinations for recurrence, which resulted in 15 different strategies. The authors found that metronidazole was dominated by vancomycin, and compared with vancomycin, fidaxomicin had an ICER of almost $3,000/1% gain in cure in the primary analysis and $6,000/1% gain in cure in the secondary analysis. The study did not estimate QALYs; hence, no conclusion about the cost-effectiveness was made.[48]

For recurrent CDI, studies were more consistent in their cost-effectiveness conclusion. Three of 4 studies found FMT colonoscopy was the most cost-effective option. Specifically, Konijeti et al. (2014) found that metronidazole and fidaxomicin were dominated, whereas FMT colonoscopy has an ICER of $17,016/QALY compared with vancomycin.[49] In sensitivity analysis, FMT colonoscopy was still the most cost-effective strategy when other delivery modes were included, and when FMT colonoscopy was not available, vancomycin should be selected. Studies by Varier et al. and Lou et al. were also in agreement with the Konijeti et al. study, finding FMT colonoscopy to be the cost-effective treatment for recurrent CDI.[46,49,52] In contrast, Lam et al. concluded that vancomycin should be used instead.[51] Bezlotoxumab had lower QALYs and higher cost than fidaxomicin, which in turn had an ICER of more than $500,000/QALY compared to vancomycin. The Lam et al. study did not examine FMT as a treatment option.[51]

For initial and recurrent CDI, Bartsch et al. (2013) compared 3 options: (1) no fidaxomicin, that is, metronidazole for nonsevere and vancomycin for severe CDI, (2) fidaxomicin for all patients regardless of disease severity and *C. difficile* strain, and (3) fidaxomicin based on strain typing (Table 6).[53] This is the only study accounting for *C. difficile* strain typing, and the authors concluded that the no fidaxomicin option was the best. Prabhu et al. compared bezlotoxumab versus standard of care for initial therapy in patients at high-risk of recurrence.[54] In contrast to Lam's and Luo's studies, the authors found bezlotoxumab to be highly cost-effective despite its high cost.

Discussion

CDI is a significant burden to the health care system and is associated with patient morbidity and mortality, and the incidence of infection has risen dramatically in recent years. Additionally, the treatment of CDI continues to evolve. Historically, oral metronidazole and oral vancomycin were considered first-line therapies. Over the years, clinical trials have consistently shown oral vancomycin to be superior to metronidazole for the treatment of CDI, and vancomycin is associated with a lower risk of recurrent infections. Therefore, metronidazole is no longer considered a first-line therapy and should only be used when other first-line treatments are contraindicated or not available.[1] Fidaxomicin, a more recently approved agent, has comparable efficacy to vancomycin and is also active against the toxins produced by C. *difficile*.[27] Therefore, it is also considered a first-line therapy.[1] A variety of treatments exist for recurrent infections, and the selection depends on the initial treatment used. In patients who have had at least 3 episodes of CDI, FMT is a highly efficacious therapy.[1]

A number of investigational therapies are currently in various stages of clinical trials. Ridinilazole is a novel antibiotic with strong activity against C. *difficile* and minimal effects on other gastrointestinal microorganisms, as well as low potential for adverse effects. Its role in therapy will likely be as an alternative therapy to vancomycin or fidaxomicin.[32] Two microbiome products are under investigation, SER-109 (an orally administered agent) and RBX2660 (administered as a single enema), which will likely be similar to FMT.[35,37] Several vaccines are currently under investigation, although PF-06425090 has currently progressed to a phase 3 trial.[40] Finally, ribaxamase is an oral beta-lactamase inhibitor administered in conjunction with IV beta-lactams.[43] Unlike the other investigational products, it works to prevent CDI by preventing antibiotic-related gut microbiota dysbiosis.

It is not uncommon for more effective medications to come with a higher price, making cost-effectiveness and clinical decision making more interdependent than ever. Clinicians and payers must understand the pharmacoeconomics of therapies and make educated decisions about whether increased costs are tied to increased benefit. Our qualitative review found that fidaxomicin tended to be cost-effective for initial infection and FMT colonoscopy may be the best option for recurrent infection in the U.S. setting.[44-54] The value of bezlotoxumab is not conclusive, as 2 of 3 studies found it not cost-effective.[51,52,54] Studies differed in choosing values for cure rate, recurrence rate, and cost of therapy, which were influential to the results.

Besides the 3 model inputs reviewed in more detail in this summary, there are other important factors that need attention when evaluating cost-effectiveness studies of CDI treatments. For instance, therapies for initial treatment should be evaluated together, and those for first recurrence may need to be evaluated separately from those therapies for multiple recurrences. Therapies should be clearly delineated as to which doses or routes of administration are being compared because these elements affect cost of therapy. Treatments assessed for the general population may have a different ICER value and conclusion than an evaluation of some specific subgroups, such as older patients, those with high risk of recurrence, or inpatient populations. Similarly, studies that excluded fulminant disease should not generally be compared with those where the focus of the study was patients with fulminant disease because cost-effectiveness will likely be skewed. For example, an expensive yet effective drug for fulminant disease might be cost-effective in studies focusing on fulminant disease but dominated in those excluding fulminant disease.

The analytical perspective of the study will determine which costs should be included in further analysis. In studies with a third-party payer or health-system perspective, direct medical costs are typically the cost focus whereas in those studies with a societal perspective, all costs that are relevant to society including direct medical and nonmedical costs and indirect costs, such as productivity lost, will be included. It is necessary to understand the perspective taken for the evaluation. Time horizon also affects outcomes because a short-term (i.e., less than 1 year) model generally ignores long-term or lifelong benefits. In addition, because the United States does not have a standard cost-effectiveness threshold like some European countries, the cost-effectiveness conclusion might be different when different thresholds are used. Most studies in the past have used $50,000, but more recent studies used $100,000. Finally, sensitivity analysis, including 1-way, threshold, and probabilistic sensitivity analyses, test if the conclusion changes when model inputs are modified. It allows interpretation of which parameters are influential in the findings.

Among the studies summarized, there are potential confounding variables that were not specifically addressed but may need to be considered when evaluating CER. Location of service (e.g., inpatient versus outpatient) was provided for some of the studies, but for 3 studies, Rasajasingham et al., Bartsch et al., and Prabu et al., no specific setting or location details are mentioned.[47,53,54] Place of contamination and environmental spore burden were not described in any of the studies.

In conclusion, a thorough understanding of the underlying parameters that come into play in the cost-effectiveness calculation will help policy makers, payers, physicians, pharmacists, and patients make an informed decision about which treatments would be of value in their situation.

Summary

CDI continues to be a significant burden to the U.S. health care system and patients. Updated guidelines aim to improve outcomes and prevent further episodes. Additional efforts may be needed to effectively curb the rise in community-based CDI being seen in certain subsets of patients in the United States. Fortunately, several pipeline agents are showing promise for treatment. Due to the higher cost of newer agents, cost-effectiveness evaluations will continue to be critical in clinical decision making for CDI.

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REFERENCES

1. McDonald CL, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):e1-48. doi:10.1093/cid/cix1085

2. Centers for Disease Control and Prevention. FAQs for clinicians about *C. diff.* March 27, 2020. Accessed October 31, 2020. https://www.cdc.gov/cdiff/clinicians/faq.html

3. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States 2019. December 2019. Accessed October 31, 2020. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

4. Centers for Disease Control and Prevention. Healthcare-associated infections—community interface (HAIC): *Clostridioides difficile* infection (CDI) tracking. July 30, 2019. Accessed October 31, 2020. https://www.cdc.gov/hai/eip/cdiff-tracking.html

5. Marra AR, Perencevich EN, Nelson RE, et al. Incidence and outcomes associated with *Clostridium difficile* infections: a systematic review and meta-analysis. *JAMA Netw Open.* 2020;3(1):e1917597. doi:10.1001/jamanetworkopen.2019.17597

6. Guh AY, Kutty PK. *Clostridioides difficile* Infection. *Ann Intern Med.* 2018;169(7):ITC49-64. doi:10.7326/AITC201810020

7. Fawley WN, Underwood S, Freeman J, et al. Efficacy of hospital cleaning agents and germicides against epidemic *Clostridium difficile* strains. *Infect Control Hosp Epidemiol.* 2007;28(8):920-25. doi:10.1086/519201

8. Bien J, Palagani V, Bozko P. The intestinal microbiota dysbiosis and *Clostridium difficile* infection: is there a relationship with inflammatory bowel disease? *Therap Adv Gastroenterol.* 2013;6(1):53-68. doi:10.1177/1756283X12454590

9. Viscidi R, Willey S, Bartlett JG. Isolation rates and toxigenic potential of *Clostridium difficile* isolates from various patient populations. *Gastroenterology.* 1981;81(1):5-9.

10. Zacharioudakis IM, Zervou FN, Pliakos EE, Ziakas PD, Mylonakis E. Colonization with toxinogenic *C. difficile* upon hospital admission, and risk of infection: a systematic review and meta-analysis. *Am J Gastroenterol.* 2015;110(3):381-90.

11. Curry S. *Clostridium difficile*. *Clin Lab Med.* 2010;30(1):329-42. doi:10.1016/j.cll.2010.04.001

12. Abt MC, McKenney PT, Pamer EG. *Clostridium difficile* colitis: pathogenesis and host defence. *Nat Rev Microbiol.* 2016;14(10):609-20. doi:10.1038/nrmicro.2016.108

13. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med.* 2005;353:2433-41.

14. Wilcox MH, Shetty N, Fawley WN, et al. Changing epidemiology of *Clostridium difficile* infection following the introduction of a national ribotyping-based surveillance scheme in England. *Clin Infect Dis.* 2012;55(8):1056-63.

15. Goorhuis A, Bakker D, Corver J, et al. Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. *Clin Infect Dis.* 2008;47(9):1162-70.

16. Deshpande A, Pasupuleti V, Thota P, et al. Risk factors for recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol.* 2015;36(4):452-60. doi:10.1017/ice.2014.88

17. Kim G, Zhu NA. Community-acquired *Clostridium difficile* infection. *Can Fam Physician.* 2017;63(2):131-32.

18. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *Am J Gastroenterol.* 2012;107(1):89-95. doi:10.1038/ajg.2011.398

19. Sitzlar B, Deshpande A, Fertelli D, Kundrapu S, Sethi AK, Donskey CJ. An environmental disinfection odyssey: evaluation of sequential interventions to improve disinfection of *Clostridium difficile* isolation rooms. *Infect Control Hosp Epidemiol.* 2013;34:459-65.

20. Boyce JM, Havill NL, Otter JA, et al. Impact of hydrogen peroxide vapor room decontamination on *Clostridium difficile* environmental contamination and transmission in a healthcare setting. *Infect Control Hosp Epidemiol.* 2008;29(8):723-29.

21. Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium-difficile*-associated diarrhoea and colitis. *Lancet*. 1983;2(8358):1043-46.

22. Wenisch C, Parschalk B, Hasenhündl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis*. 1996;22(5):813-38.

23. Johnson S, Louie TJ, Gerding DN, et al; Polymer Alternative for CDI Treatment (PACT) Investigators. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59(3):345-54.

24. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302-07.

25. Siegfried J, Dubrovskaya Y, Flagiello T, et al. Initial therapy for mild to moderate *Clostridium difficile* infection. *Infect Dis Clin Pract*. 2016;24(4):210-16.

26. Fekety R, Silva J, Kauffman C, Buggy B, Deery HG. Treatment of antibiotic-associated *Clostridium difficile* colitis with oral vancomycin: comparison of two dosage regimens. *Am J Med*. 1989;86(1):15-19.

27. Sullivan KM, Spooner LM. Fidaxomicin: a macrocyclic antibiotic for the management of *Clostridium difficile* infection. *Ann Pharmacother*. 2010;44(2):352-59.

28. Louie TJ, Miller MA, Mullane KM, et al.; OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364(5):422-31.

29. Cornely OA, Crook DW, Esposito R, et al.; OPT-80-004 Clinical Study Group. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomized controlled trial. *Lancet Infect Dis*. 2012;12(4):281-89.

30. Birch T, Golan Y, Rizzardini G, et al. Efficacy of bezlotoxumab based on timing of administration relative to start of antibacterial therapy for *Clostridium difficile* infection. *J Antimicrob Chemother*. 2018;73(9):2524-28.

31. U.S. Food and Drug Administration. Important safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse reactions due to transmission of multi-drug resistant organisms. June 13, 2019. Accessed October 31, 2020. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse

32. Cho JC, Crotty MP, Pardo J. Ridinilazole: a novel antimicrobial for *Clostridium difficile* infection. *Ann Gastroenterol*. 2019;32(2):134-40. doi:10.20524/aog.2018.0336

33. Baines SD, Crowther GS, Freeman J, Todhunter S, Vickers R, Wilcox MH. SMT19969 as a treatment for *Clostridium difficile* infection: an assessment of antimicrobial activity using conventional susceptibility testing and an in vitro gut model. *J Antimicrob Chemother*. 2015;70(1):182-89.

34. Vickers RJ, Tillotson GS, Nathan R, et al.; CoDIFy study group. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of *Clostridium difficile* infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study. *Lancet Infect Dis*. 2017;17(7):735-44.

35. Seres Therapeutics. Our programs. 2020. Accessed October 31, 2020. https://www.serestherapeutics.com/our-programs/

36. U.S. National Library of Medicine ClinicalTrials.gov. ECOSPOR III - SER-109 versus placebo in the treatment of adults with recurrent *Clostridium difficile* infection (ECOSPORIII). April 2020. Accessed October 31, 2020. https://clinicaltrials.gov/ct2/show/NCT03183128

37. Biospace. Rebiotix and Ferring's microbiome-based C. *diff* treatment shows early positive data. May 6, 2020. Accessed October 31, 2020. https://www.biospace.com/article/rebiotix-and-ferring-s-microbiome-based-therapy-positive-for-c-diff-treatment/

38. Rebiotix. RBX2660 clinical trials. 2020. Accessed October 31, 2020. https://www.rebiotix.com/clinical-trials/rbx2660-clinical-trials/

39. U.S. National Library of Medicine ClinicalTrials.gov. Microbiota restoration therapy for recurrent *Clostridium difficile* infection (PUNCHCD3). February 18, 2020. Accessed October 31, 2020. https://clinicaltrials.gov/ct2/show/record/NCT03244644?term=Rebiotix

40. Businesswire. Pfizer announces positive top-line results from phase 2 study of investigational *Clostridium difficile* vaccine for the prevention of *C. difficile* infection. January 26, 2017. Accessed October 31, 2020. https://www.businesswire.com/news/home/20170126005338/en/Pfizer-Announces-Positive-Top-Line-Results-Phase-2

41. U.S. National Library of Medicine ClinicalTrials.gov. A study to investigate two 3-dose schedules of a *Clostridium difficile* vaccine in health adults aged 65 to 85 years. June 11, 2020. Accessed October 31, 2020. https://clinicaltrials.gov/ct2/show/NCT02561195?term=02561195&rank=1

42. U.S. National Library of Medicine ClinicalTrials.gov. *Clostridium difficile* vaccine 2-dose versus 3-dose study. October 20, 2020. Accessed October 31, 2020. https://clinicaltrials.gov/ct2/show/NCT03918629

43. Kokai-Kun JF, Roberts T, Coughlin O, et al. Use of ribaxamase (SYN-004), a β-lactamase, to prevent *Clostridium difficile* infection in β-lactam-treated patients: a double-blind, phase 2b, randomised placebo-controlled trial. *Lancet Infect Dis*. 2019;19(5):487-96. doi:10.1016/S1473-3099(18)30731-X

44. Gidengil CA, Caloyeras JP, Hanson M, Hillestad R, Mattke S. Comparative effectiveness of fidaxomicin for treatment of *Clostridium difficile* infection. *Am J Pharm Benefits*. 2014;6(4):161-70.

45. Stranges PM, Hutton DW, Collins CD. Cost-effectiveness analysis evaluating fidaxomicin versus oral vancomycin for the treatment of *Clostridium difficile* infection in the United States. *Value Health*. 2013;16(2):297-304. doi:10.1016/j.jval.2012.11.004

46. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of treatment strategies for initial *Clostridium difficile* infection. *Clin Microbiol Infect*. 2014;20(12):1343-51. doi:10.1111/1469-0691.12805.

47. Rajasingham R, Enns EA, Khoruts A, Vaughn BP. Cost-effectiveness of treatment regimens for *Clostridioides difficile* infection: an evaluation of the 2018 Infectious Diseases Society of America Guidelines. *Clin Infect Dis*. 2020;70(5):754-62. doi:10.1093/cid/ciz318

48. Ford DC, Schroeder MC, Ince D, Ernst EJ. Cost-effectiveness analysis of initial treatment strategies for mild-to-moderate *Clostridium difficile* infection in hospitalized patients. *Am J Health Syst Pharm*. 2018;75(15):1110-21.

49. Konijeti GG, Sauk J, Shrime MG, Gupta M, Ananthakrishnan AN. Cost-effectiveness of competing strategies for management of recurrent *Clostridium difficile* infection: a decision analysis. *Clin Infect Dis*. 2014;58(11):1507-14.

50. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Infect Control Hosp Epidemiol*. 2015;36(4):438-44. doi:10.1017/ice.2014.80

51. Lam SW, Neuner EA, Fraser TG, Delgado D, Chalfin DB. Cost-effectiveness of three different strategies for the treatment of first recurrent *Clostridium difficile* infection diagnosed in a community setting. *Infect Control Hosp Epidemiol*. 2018;39(8):924-30.

52. Luo Y, Lucas AL, Grinspan AM. Fecal transplants by colonoscopy and capsules are cost-effective strategies for treating recurrent *Clostridioides difficile* Infection. *Dig Dis Sci*. 2020;65(4):1125-33.

53. Bartsch SM, Umscheid CA, Fishman N, Lee BY. Is fidaxomicin worth the cost? An economic analysis. *Clin Infect Dis*. 2013;57(4):555-61.

54. Prabhu VS, Dubberke ER, Dorr MB, et al. Cost-effectiveness of bezlotoxumab compared with placebo for the prevention of recurrent *Clostridium difficile* infection. *Clin Infect Dis*. 2018;66(3):355-62.

55. York Health Economics Consortium. Decision tree. 2016. Accessed October 31, 2020. https://yhec.co.uk/glossary/decision-tree/

56. York Health Economics Consortium. Markov model. 2016. Accessed October 31, 2020. https://yhec.co.uk/glossary/markov-model/

57. Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal Hawre J, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: a tutorial. *Med Decis Making*. 2018;38(3):400-22.

58. Burton HE, Mitchell SA, Watt M. A systematic literature review of economic evaluations of antibiotic treatments for *Clostridium difficile* infection. *Pharmacoeconomics*. 2017;35(11):1123-40. doi:10.1007/s40273-017-0540-2

59. Le P, Nghiem VT, Mullen PD, Deshpande A. Cost-effectiveness of competing treatment strategies for *Clostridium difficile* infection: a systematic review. *Infect Control Hosp Epidemiol*. 2018;39(4):412-24. doi:10.1017/ice.2017.303

POSTTEST QUESTIONS

1. Which of the following antimicrobials is reported to be 1 of the highest risk antimicrobials for developing *Clostridioides difficile* (*C. difficile*) infection?
   A. Fluoroquinolones
   B. Macrolides
   C. Aminoglycosides
   D. Vancomycin

2. Which of the following is accurate about the human microbiome?
   A. The microbiome only contains bacteria.
   B. The microbiome only contains yeasts.
   C. The microbiome only contains virus particles.
   D. The microbiome is a compilation of bacteria, yeasts, and other microbes.

3. Which of the following is a true statement about the human microbiome?
   A. The whole of the human microbiome is found in the gastrointestinal tract.
   B. The gastrointestinal microbiome is not affected by age.
   C. Gastric acid levels affect the flora of the human microbiome.
   D. The use of antimicrobial agents strengthens the host's microbiome.

4. Which of the following terms is defined as the ability of the gastrointestinal microbiome to assist with prevention of infection by opportunistic pathogens?
   A. Inherent resistance
   B. Opportunistic resistance
   C. Colonization resistance
   D. Microbial resistance

5. Which of the following agents was approved by U.S. Food and Drug Administration after the update for the 2017 Infectious Diseases Society of America (IDSA) *C. difficile* Guidelines were completed and thus was not evaluated for incorporation into the current recommendations?
   A. Fidaxomicin
   B. Vancomycin
   C. Fecal microbiota transplantation
   D. Bezlotoxumab

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POSTTEST QUESTIONS *(continued)*

6. Which of the following antimicrobial agents are considered first-line treatment for new onset nonsevere *C. difficile* infection?
   A. Oral vancomycin or oral metronidazole
   B. Oral vancomycin or oral fidaxomicin
   C. Oral vancomycin or bezlotoxumab
   D. Oral vancomycin or ribaxamase

7. Which of the following is recommended as treatment for the first recurrence of *C. difficile* infection if oral vancomycin was used for the initial episode?
   A. Fecal microbiota transplantation
   B. Vancomycin at the same dose as the initial treatment dosing schedule
   C. Vancomycin using pulse dosing
   D. Rifaximin alone

8. Which of the following emerging *C. difficile* infection treatments is a standardized microbiota suspension of intestinal microbes to be administered as an enema?
   A. RBX2660
   B. SER-109
   C. Ridinilazole
   D. PF-06425090

9. Which of the following emerging therapies is an antimicrobial agent that is proposed to interfere with cell division and exhibits activity against both TcdA and TcdB?
   A. RBX2660
   B. SER-109
   C. Ridinilazole
   D. PF-06425090

10. A 65-year-old male is currently hospitalized for treatment of community-acquired pneumonia and is receiving broad-spectrum antibiotics. On day 7 of hospitalization, he is diagnosed with *C. difficile* infection, which he has never experienced before. Which of the following emerging treatments would be most appropriate for his *C. difficile* infection?
    A. SER-109
    B. Ridinilazole
    C. RBX2660
    D. *C. difficile* vaccine

continued on next page

POSTTEST QUESTIONS *(continued)*

11. Which of the following emerging therapies works to establish a new, healthy microbiome in the gut in patients who have experienced multiple occurrences of C. *difficile* infection?
    A. Ridinilazole
    B. Fidaxomicin
    C. SER-109
    D. C. *difficile* vaccine

12. H.J. is a 53-year-old female who is admitted to the hospital for treatment of her fifth episode of C. *difficile*. She is malnourished and not able to eat nor take medications by mouth and is receiving total parenteral nutrition. Because other therapies have been exhausted, her medical team would like to use an emerging therapy for treatment. Which of the following would be the best recommendation for the patient at this time?
    A. C. *difficile* vaccine
    B. Ridinilazole
    C. RBX2660
    D. SER-109

13. Which 1 of the following emerging therapies is a toxoid-based C. *difficile* vaccine that neutralizes TcdA and TcdB by inducing a functional antibody response in the host patient?
    A. RBX2660
    B. Ridinilazole
    C. Ribaxamase
    D. PF-06425090

14. Which of the following was the most frequently evaluated health outcome metric reported in the 11 studies included in the cost-effectiveness studies included?
    A. Readmissions
    B. Quality-adjusted life-years
    C. Percentage of clinical cure
    D. Recurrences

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POSTTEST QUESTIONS *(continued)*

15. Rajasingham et al (2020) evaluated 48 strategies based on C. *difficile* infection (CDI) treatment outlined by the 2017 IDSA guidelines. Which of the following outlines correctly the most cost-effective strategies from that study?
    A. Metronidazole for nonsevere initial CDI, vancomycin for severe initial CDI, fidaxomicin for first recurrence, and FMT for second or later recurrences.
    B. Vancomycin for nonsevere initial CDI, fidaxomicin for severe initial CDI, fidaxomicin for first recurrence, and FMT for second or later recurrences.
    C. Fidaxomicin for nonsevere initial CDI, vancomycin for severe initial CDI, fidaxomicin for first recurrence, and FMT for second or later recurrences.
    D. Fidaxomicin for nonsevere initial CDI, fidaxomicin for severe initial CDI, vancomycin for first recurrence, and FMT for second or later recurrences.

SUPPLEMENT

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