Clostridioides difficile Infection Epidemiology and Treatment

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LEARNING OBJECTIVES

1. Assess the burden of *Clostridioides difficile* infection (CDI) on hospitalized and non-hospitalized patients.
2. Analyze the phenotypic and molecular epidemiology of *C. difficile* to gain insight into the prognosis of CDI and direct antimicrobial stewardship efforts.
3. Distinguish between the drug therapy recommendations in several of the leading CDI guidelines.
4. Evaluate FDA-approved therapies and agents currently used off-label to determine their place in therapy.

ABBREVIATIONS IN THIS CHAPTER

ACG	American College of Gastroenterology
CDI	*Clostridioides difficile* infection
CO-CDI	Community-onset *Clostridioides difficile* infection
CO-HCFA	Community-onset healthcare facility-associated *Clostridioides difficile* infection
HO-CDI	Healthcare facility-onset *Clostridioides difficile* infection
IDSA	Infectious Diseases Society of America
IVIG	Intravenous immune globulin
NAP1	North American pulsed-field type 1
PFGE	Pulsed-field gel electrophoresis
PK/PD	Pharmacokinetic/ pharmacodynamic
rCDI	Recurrent *Clostridioides difficile* infection
RCT	Randomized controlled trial
REA	Restriction endonuclease analysis
SHEA	Society for Healthcare Epidemiology of America

Table of other common abbreviations.

INTRODUCTION

Burden of Infection

Clostridioides difficile infection (CDI) is caused by a toxin-producing, spore-forming, gram-positive, anaerobic bacillus. This bacteria, originally termed *Bacillus difficilis*, was first isolated from the stool of four healthy neonates in 1935 (Hall 1935). Since then, *B. difficilis* was renamed *C. difficile*, which has become the most common cause of health care-associated infections and the leading cause of gastroenteritis-associated mortality in the United States (Magill 2018; Hall 2012). Although the annual incidence of CDI appears to be decreasing, *C. difficile* continues to cause an estimated 113 infections per 100,000 persons per year (Guh 2020). Despite an influx of resources dedicated to antimicrobial stewardship initiatives targeted at reducing CDI rates and development of new CDI treatments, *C. difficile* remains one of only five CDC-designated urgent threats (CDC 2019). Furthermore, only three drugs—vancomycin, fidaxomicin, and bezlotoxumab—have FDA approval to manage CDI, highlighting the need for continued focus in this area.

About one in four patients treated with metronidazole or vancomycin for CDI experience recurrent CDI (rCDI) (Wilcox 2017; Johnson 2014; Cornely 2012; Louie 2011; Zar 2007). Despite the development of agents such as fidaxomicin and bezlotoxumab that are proven to decrease CDI recurrence, the incidence of rCDI remains about 15% (Wilcox 2017; Cornely 2012; Louie 2011). The risk of continued rCDI episodes increases with each subsequent recurrence, with up to about 45%–65% of patients experiencing another episode after their first recurrence (Feuerstadt 2022; Sheitoyan-Pesant 2016; Kelly 2012). Notably, rCDI is such a concern that all contemporary clinical trials have incorporated it into their composite efficacy end point, termed *global cure*, *sustained response*, *sustained clinical response*, or *sustained clinical cure*, all of which are defined as *clinical cure without*

recurrence (Carlson 2019; Guery 2018; Mikamo 2018; Wilcox 2017; Cornely 2012; Louie 2011).

Infection with *C. difficile* causes significant morbidity and mortality. Although the mortality rates reported vary depending on circulating strains, about 5%–10% of patients with CDI die within 30 days of diagnosis in the endemic setting, and mortality rates are higher in patients with severe disease than in those with nonsevere disease (Carlson 2020d; Appaneal 2018; Kwon 2015). Progression to fulminant disease is rare; however, the mortality rate in this subset of patients is between 30% and 40% (Sailhamer 2009; Juo 2019). Unfortunately, no drug therapy has been proven to decrease mortality in randomized controlled trials (RCTs).

In addition, CDI has also been associated with higher rates of discharge to a non-home location, such as a skilled nursing facility; higher rates of hospital readmission; and poorer quality of life compared with patients without CDI (Reveles 2019; Heinrich 2018; Dubberke 2008). Notably, patients with rCDI have higher rates of rehospitalization and mortality and poorer quality of life relative to patients with primary CDI (Han 2021; Garey 2016; Olsen 2015a, 2015b; Zilberberg 2015). These data highlight the importance of using treatment agents that reduce the risk of rCDI.

Not surprisingly, the financial burden of CDI is significant, with estimations that CDI is responsible for billions of dollars in annual health care costs (CDC 2019; Rodrigues 2017; Kwon 2015). Hospital costs attributable to primary CDI are estimated to range from $3000 to $30,000 per episode, and costs increases in the case of rCDI (Rodrigues 2017; Shah 2016; Kwon 2015; Nanwa 2015; Dubberke 2014; Ghantoji 2010).

Clinical Presentation

Patients with CDI may present with abdominal pain, tenderness, cramping, and distension—and, of course, diarrhea (Bartlett 2008). The diarrhea is typically watery and profuse (10 or more stools per day) and is rarely bloody. Guidelines recommend only testing patients with new-onset diarrhea, defined as 3 or more unformed stools in a 24-hour period (Kelly 2021; McDonald 2018). However, patients with fulminant CDI may not have diarrhea because of the presence of a paralytic ileus (Sailhamer 2009). Signs of CDI may include fever, leukocytosis, hypoalbuminemia, hypotension, colonic wall thickening, pseudomembranous colitis, and toxic megacolon (Bartlett 2008). To classify CDI severity, guidelines advocate using laboratory values, including white blood cell count and serum creatinine, in addition to other clinical findings, including hypotension, shock, ileus, and megacolon (Kelly 2021; McDonald 2018). Table 1 lists the specific criteria for classification of CDI severity. As true for most infections, these signs and symptoms are nonspecific to CDI and may be caused by other enteric pathogens, ischemic colitis, idiopathic inflammatory bowel disease, tube feeding, and medications, such as antibiotics, chemotherapy, and laxatives. Guidelines specify that diagnostic testing should only be performed in patients with diarrhea unexplained by other

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- A basic understanding of the human gut microbiome and the concept of colonization resistance
- General knowledge of the risk factors and pathogenesis of CDI
- A basic understanding of statistics, including calculations for NNT

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- McDonald LC, 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;66:987-94.
- Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. Clin Infect Dis 2021;73:e1029-44.
- Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol 2021;116:1124-47.

Table 1. Criteria for Classification of CDI Severity

Severity	Clinical Criteria
Nonsevere	WBC < 15 x 10^3 cells/mm^3 and SCr < 1.5 mg/dL
Severe	WBC ≥ 15 x 10^3 cells/mm^3 or SCr ≥ 1.5 mg/dL
Fulminant	Hypotension, shock, ileus, or megacolon

Information from: McDonald LC, 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:e1-48; Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol 2021; 116:1124-47.

causes. Thus, it is important to rule out other causes for diarrhea before considering CDI.

Diagnosis

C. difficile is somewhat distinct among bacterial infections in that it is diagnosed almost exclusively with molecular tests, specifically because the toxins of *C. difficile* are key to its pathogenesis, which can be quickly identified using nucleic acid amplification tests and enzyme immunoassays. In addition, isolation of a single bacterial species from a stool sample is resource intensive, and it is difficult to grow a strict anaerobe, such as *C. difficile*, using traditional culture-based methods. Thus, only a small number of laboratories in the United States have the capabilities to grow, type, and perform antibiotic susceptibility testing on a large-scale basis. Because of this limitation, much less is known about between strain differences in virulence, antibiotic susceptibility, and clinical outcomes than for other bacteria.

Guidelines advocate using one of several multistep algorithms listed in Table 2 that balance clinical sensitivity and specificity to diagnose CDI (Kelly 2021; McDonald 2018). As noted in the Clinical Presentation section, only patients with new-onset diarrhea, defined as 3 or more unformed stools in a 24-hour period, that is unexplained by other causes should be tested for CDI.

Table 2. Multistep Algorithms Used to Diagnose *Clostridium difficile* Infection

Scenario	Diagnostic algorithms
Established institutional criteria[a] for stool submission	• NAAT alone • GDH EIA + toxin EIA • GDH EIA + toxin EIA, arbitrated by NAAT • NAAT + toxin EIA
No established institutional criteria for stool submission	• GDH EIA + toxin EIA • GDH EIA + toxin EIA, arbitrated by NAAT • NAAT + toxin EIA

[a]For example, clinicians agree to only test patients with new-onset ≥3 stools in a 24-hour period that are unexplained by other causes (e.g., other enteric pathogens, ischemic colitis, idiopathic inflammatory bowel disease, tube feeding, and/or medications (e.g., antibiotics, chemotherapy, laxatives)) and microbiology laboratory staff agree to reject specimens that are not liquid (i.e., type 6 or 7 stool on the Bristol Stool Chart).

EIA = enzyme immunoassay; GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test.

Information from: McDonald LC, 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:e1-48; Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol 2021;116:1124-47.

EPIDEMIOLOGY

Epidemiologic Classifications

Health Care Facility-Onset CDI

The CDC classifies CDI into three categories: *community-onset* (CO), *health care facility-onset* (HO), and *community-onset, health care facility-associated* (CO-HCFA) (CDC 2022). Specifically, *HO-CDI* is defined as CDI that is diagnosed in an inpatient location 3 or more days after admission to the facility, meaning on or after day 4, and *CO-HCFA-CDI* is defined as CDI that is diagnosed in an outpatient location or within 3 days of hospital admission in a patient with an overnight stay in a health care facility in the 28 days before stool specimen collection. In the literature, these categories are occasionally combined into a single category, such as *health care-associated CDI*. The aforementioned decline in CDI incidence was driven by changes in health care-associated CDI, which decreased by about 6% annually from 2011 to 2017 (Guh 2020). Because health care facility-level antibiotic use has been positively correlated with HO-CDI rates, antimicrobial stewardship programs will continue to be essential in the fight against CDI (Kazakova 2020, 2021).

Community-Onset CDI

Community-onset CDI (CO-CDI) is defined as CDI that is diagnosed in an outpatient location or within 3 days of hospital admission in a patient who was not discharged from a health care facility in the past 28 days (CDC 2022). Despite a lower incidence of CO-CDI (53 infections per 100,000 person-years) relative to health care-associated CDI (61 infections per 100,000 person-years), CO-CDI still accounts for an estimated 170,000 cases annually (Guh 2020). Furthermore, rates of CO-CDI remained stable between 2011–2017. Unlike HO-CDI, in which almost 100% of patients have had recent exposure to antibiotics, a significant proportion (35.9%) of patients with CO-CDI have no reported exposure to antibiotics (Chitnis 2013; Loo 2011). Although these data are subject to recall bias and may underestimate antibiotic exposure in patients with CO-CDI, they highlight the presence of other nonantibiotic risk factors that ultimately lead to CDI.

Typing and Antibiotic Susceptibility Testing

Contemporary *C. difficile* typing methods were not developed until the 1980s and did not become widely used until the 2000s, coinciding with the discovery of the hypervirulent BI/North American pulsed-field type 1 (NAP1)/027 strain (Killgore 2008). Common typing methods in the United States include restriction endonuclease analysis (REA), pulsed-field gel electrophoresis (PFGE), and PCR-ribotyping. As an example of how the results of these methods are reported, the

hypervirulent BI/NAP1/027 strain is type BI by REA, NAP1 by PFGE, and ribotype 027 by PCR-ribotyping. Although there is a large degree of overlap among the strain type assigned by each of these methods, the type assigned to a given *C. difficile* isolate may differ between methods (Tenover 2011).

Given the pathogenesis of CDI, it can be useful to use circulating strain types and their associated antibiotic susceptibility patterns to guide antimicrobial stewardship efforts. For example, ribotype 027 is notorious for expressing high-level resistance to fluoroquinolones (MIC_{90} 32 mcg/mL or greater) (Tickler 2019; McDonald 2005). One can imagine a hospital with a high prevalence of ribotype 027 and high fluoroquinolone use: fluoroquinolones given to patients will be able to kill commensal gut bacteria but will be unable to kill *C. difficile*, thereby leaving a niche for *C. difficile* to thrive. In this scenario, the knowledge that ribotype 027 is prevalent and that it is associated with high-level fluoroquinolone resistance may help antibiotic stewards to develop an intervention to decrease fluoroquinolone use. Characteristic phenotypic susceptibility patterns of certain *C. difficile* strains (the clindamycin-resistant "J" strain and the fluoroquinolone-resistant ribotype 027) have been used to direct antimicrobial stewardship efforts in outbreak settings (Dingle 2017; Aldeyab 2011; Pear 1994). Unfortunately, each ribotype has specific antibiotic susceptibility profiles, and ribotype 027 is becoming less prevalent, making prospective *C. difficile* surveillance, including typing and antibiotic susceptibility testing, more important than ever (Cheknis 2018; Thorpe 2019; Tickler 2019).

Epidemic Strains

The most widely used typing method is PCR-ribotyping, which is based on the size variation of the 16S–23S intergenic spacer regions in DNA (Huber 2013). A *ribotype* is defined as a group of strains that produce an identical band pattern; therefore, a single band difference warrants a new ribotype. Surveillance data from 26 centers in the United States between 2011–2012 identified ribotype 027 (30.6%), 014/020 (13.5%), and 106 (6.6%) as the three most common types (Tickler 2019). Between 2015–2017, the three most common ribotypes were 106 (18.8%), 027 (13.5%), and 014/020 (12.5%). In another surveillance study including six centers in the United States, ribotype 027 (35.3%), 106 (16.5%), and 014/020 (10.8%) were the three most prevalent strains in 2011, whereas ribotypes 106 (15.0%), 027 (13.1%) and 014/020 (11.8%) were the most prevalent in 2016 (Thorpe 2019). In a study of 50 centers in Texas, the most prevalent strains in 2011 were ribotype 027 (21.5%), 014/020 (15.8%), and 106 (10.3%) whereas the most prevalent strains in 2018 were ribotype 014/020 (18.5%), 027 (13.5%), and 106 (12.9%) (Gonzales-Luna 2020).

As part of its Emerging Infections Program, the CDC has been conducting surveillance since 2012 in the following 10 states: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee (CDC 2021). The data are stratified by health care setting—health care-associated CDI or CO-CDI. The three most prevalent strains among health care-associated infections in 2012 were ribotype 027 (21.2%), 106 (8.6%), and 002 (5.6%) whereas the most prevalent strains among CO-CDI was ribotype 027 (17.1%), 106 (9.2%), and 002 (8.7%). In 2017, the three most prevalent health care-associated strains were ribotype 027 (14.6%), 106 (9.7%), and 002 (6.8%) whereas the most prevalent CO-CDI strains were ribotype 106 (12.1%), 002 (9.7%), and 020 (6.5%).

Total genomic DNA is used to perform REA, in which the DNA is digested by a restriction enzyme (HindIII), and the resulting fragments are resolved by classical agarose electrophoresis (Huber 2013). Although REA may provide greater discrimination between variants, it is labor-intensive and reproducibility between laboratories is difficult (Huber 2013; Killgore 2008). Currently, only the Hines Veterans Administration Hospital in Chicago, Illinois, performs REA (Cheknis 2018; Thorpe 2019; Snydman 2015). Surveillance data in the United States from 2011–2012 identified BI (ribotype 027) (25.5%), Y (ribotype 014/020) (15.8%), and DH (ribotype 106) (9.8%) as the three most common types (Snydman 2015). Between 2015–2016, the three most common types were Y (ribotype 014/020) (15.6%), DH (ribotype 106) (13.3%), and BI (ribotype 027) (12.8%), highlighting a drastic reduction in the proportion of CDI caused by the hypervirulent epidemic strain (Thorpe 2019).

Pulsed-field gel electrophoresis is performed using total genomic DNA, which is digested by a restriction enzyme (SmaI), and the resulting fragments are resolved by PFGE (Huber 2013). Like REA, PFGE is also highly discriminatory, but it carries the same limitations (Huber 2013; Killgore 2008). The CDC has historically used PFGE; however, there are no contemporary United States surveillance studies reporting PFGE types (See 2014). Notably, this method is still commonly used in Canada (Katz 2018). Taken together, these data demonstrate that the once dominant ribotype 027 strain is decreasing in the United States, whereas ribotype 106 has become the most common strain, particularly among CO-CDI cases.

Outcomes studies for CDI with between-strain comparisons are uncommon in the literature, and most have focused on ribotype 027 (Almutairi 2021; Reveles 2019; Aitken 2015; See 2014; Walker 2013; Walk 2012; Goorhuis 2008). In general, these studies have demonstrated that ribotype 027 is associated with higher mortality and other poor clinical outcomes, such as discharge to a nonhome location, compared with all non-027 ribotypes (Almutairi 2021; Reveles 2019; Aitken 2015; See 2014; Walker 2013). Recently, toxin A and B concentration has been proven to correlate with poor clinical outcomes (Alonso 2021). Ribotype 027 has demonstrated higher levels of toxin A and B production compared with non-027 ribotypes, which may explain the increased virulence of

this strain (Warny 2005). Ribotype 078 has also been associated with higher mortality whereas ribotype 014/020 has been associated with lower rates of poor clinical outcomes (Almutairi 2021; Aitken 2015; Walker 2013). Although not proven convincingly, the binary toxin, which is produced by ribotypes 027 and 078, may also contribute to the virulence of these strains (Carlson 2020a).

Lastly, ribotype 106 has been associated with higher rates of poor clinical outcomes compared with ribotype 014/020, but not ribotype 027 (Almutairi 2021). Although ribotype 106 produces less toxin than ribotype 027, it appears to maintain higher spore concentrations for longer periods than other ribotypes, including ribotype 027 (Vohra 2011; Baines 2009). Although not proven to correlate with poor clinical outcomes, increased spore concentrations could theoretically affect recurrence rates and transmission. To date, no treatment or adjunctive agent is proven to reduce the rate of mortality in patients with CDI. However, toxin and spore dynamics of common strains have the potential to guide future efforts for drug discovery.

CLINICAL GUIDELINE UPDATES FOR MANAGEMENT WITH DRUG THERAPY

IDSA and SHEA Guidelines

In 1995, Society for Healthcare Epidemiology of America (SHEA) first published a position paper on CDI management (Gerding 1995). Subsequently, SHEA collaborated with Infectious Diseases Society of America (IDSA) on CDI treatment guidelines in 2010, 2017, and 2021 (Johnson 2021; McDonald 2018; Cohen 2010). Recommendations from the 2017 guideline and the 2021 IDSA/SHEA focused update regarding pharmacologic management of CDI are detailed in the following.

Prevention

The 2017 IDSA/SHEA guideline briefly discusses the use of probiotics and antibiotics as methods to prevent CDI; however, they do not provide a recommendation and instead cite insufficient data (McDonald 2018). Nondrug therapy recommendations for the prevention of CDI include implementing an antibiotic stewardship program to minimize the frequency and duration of antibiotic therapy, accommodating patients with CDI in a private room, and handwashing with soap and water after contact with a patient with CDI.

Treatment

Adults

Recommendations regarding metronidazole reflect the biggest change in CDI therapy between 1995 and 2017. In 1995, metronidazole and vancomycin were considered equivalent (Gerding 1995). Subsequently, based on the results of a landmark trial by Zar et al., the 2010 guideline recommended against the use of metronidazole for patients with severe disease, given the lower rates of clinical cure compared with vancomycin (Cohen 2010; Zar 2007). In 2014, the results of two phase 3 clinical trials comparing tolevamer with metronidazole and vancomycin revealed similar findings: metronidazole demonstrated inferior clinical cure rates compared with vancomycin, regardless of disease severity (Johnson 2014). In addition, two large phase 3 clinical trials published since 2010 demonstrated fidaxomicin noninferiority to vancomycin (Cornely 2012; Louie 2011). Thus, the 2017 guideline recommended against metronidazole for all adult patients with CDI and instead recommends vancomycin or fidaxomicin (McDonald 2018). Since then, two additional RCTs have been published comparing fidaxomicin versus vancomycin, leading the 2021 focused update to recommend fidaxomicin over vancomycin for the treatment of CDI in adults (Johnson 2021; Guery 2018; Mikamo 2018).

The IDSA/SHEA recommendations for therapeutic management of CDI were based on adult data from RCTs of metronidazole, vancomycin, fidaxomicin, rifaximin, and bezlotoxumab, as follows: four RCTs of metronidazole (Johnson 2014; Zar 2007; Wenisch 1996; Teasley 1983); eight RCTs of vancomycin (Guery 2018; Mikamo 2018; Johnson 2014; Cornely 2012; Louie 2011; Zar 2007; Wenisch 1996; Teasley 1983); four RCTs of fidaxomicin (Guery 2018; Mikamo 2018; Cornely 2012; Louie 2011); one RCT of rifaximin (Garey 2011); and one RCT of bezlotoxumab (Wilcox 2017). In addition, they considered three retrospective cohort studies of metronidazole and vancomycin (Musher 2005; Pepin 2005; Wilcox 1995). Notably, the 2021 IDSA/SHEA guideline specifically excluded retrospective studies (Johnson 2021). These recommendations for various adult patient populations are outlined in Table 3.

Children

To create treatment recommendations for children, the 2017 IDSA/SHEA CDI guideline relied on data from adults and one small observational study in children because of a lack of high-quality evidence in children at the time of publication (Khanna 2013). These recommendations for various pediatric patient populations are outlined in Table 4. Notably, a phase 3 RCT named SUNSHINE has since been published that demonstrated the safety and efficacy of fidaxomicin in children and adolescents compared with vancomycin (Wolf 2020). Pediatric treatment recommendations were not addressed in the 2021 IDSA/SHEA focused update.

ACG Guidelines

The American College of Gastroenterology (ACG) first released their CDI guideline in 2013, followed by an update in 2021 (Kelly 2021; Surawicz 2013). The 2021 ACG guideline recommendations on pharmacologic management of CDI are detailed in the following text.

Table 3. Adult Treatment Recommendations from the 2017 and 2021 IDSA/SHEA and 2021 ACG CDI Guidelines

Clinical Scenario	IDSA/SHEA Recommendations	ACG Recommendations
Primary CDI[a, b]	Fidaxomicin 200 mg BID for 10 days (preferred) —OR— Vancomycin 125 mg QID for 10 days —OR— Metronidazole 500 mg TID for 10–14 days (for nonsevere CDI if fidaxomicin and vancomycin are unavailable)	Nonsevere: Vancomycin 125 mg QID for 10 days —OR— Fidaxomicin 200 mg BID for 10 days —OR— Metronidazole 500 mg TID for 10 days (for low-risk patients)[d] Severe: Vancomycin 125 mg QID for 10 days —OR— Fidaxomicin 200 mg BID for 10 days —OR— FMT[e]
First recurrence[b, c]	Fidaxomicin 200 mg BID for 10 days (preferred) —OR— Fidaxomicin 200 mg BID for 5 days, and then once daily every other day for 20 days (preferred) —OR— Vancomycin tapered and pulsed —OR— Vancomycin 125 mg QID for 10 days (if metronidazole was used for primary infection)	Vancomycin tapered and pulsed —OR— Fidaxomicin 200 mg BID for 10 days (unless fidaxomicin was used for primary infection)
Second or subsequent recurrence[b, c]	Fidaxomicin 200 mg BID for 10 days (preferred) —OR— Fidaxomicin 200 mg BID for 5 days, and then once daily every other day for 20 days (preferred) —OR— Vancomycin tapered and pulsed —OR— Vancomycin 125 mg QID for 10 days, and then rifaximin 400 mg TID for 20 days —OR— FMT	FMT
Fulminant CDI	Vancomycin 500 mg QID —PLUS— Metronidazole IV 500 mg TID —PLUS— Vancomycin rectal 500 mg in 100-mL saline QID (if ileus present)	Vancomycin 500 mg QID[f] —PLUS— Metronidazole IV 500 mg TID —PLUS— Vancomycin rectal 500 mg in 100-mL saline QID (if ileus present) —OR— FMT[e]

[a]IDSA/SHEA: Consider adding bezlotoxumab 10 mg/kg once in patients who are age ≥ 65 years, are immunocompromised, or have severe CDI (no recommendation).

[b]ACG: Add bezlotoxumab 10 mg/kg once in patients who are age ≥ 65 years and have one of the following: CDI episode within the past 6 months, immunocompromise, or severe CDI (conditional recommendation, moderate quality of evidence).

[c]IDSA/SHEA: Add bezlotoxumab 10 mg/kg once in patients with a CDI episode within the past 6 months (conditional recommendation, very low certainty of evidence).

[d]*Low-risk patients* are defined as "younger outpatients with minimal comorbidities."

[e]Consider FMT in patients with CDI refractory to antibiotic therapy, particularly for patients considered poor surgical candidates.

[f]A higher vancomycin dose (500 mg) should be given for the first 48–72 hours, followed by standard dosing (125 mg QID).

ACG = American College of Gastroenterology; BID = twice daily; CDI = *Clostridioides difficile* infection; FMT = fecal microbiota transplantation; IDSA = Infectious Diseases Society of America; IV = intravenous; QID = four times daily; SHEA = Society for Healthcare Epidemiology of America; TID = three times daily.

Information from: McDonald LC, 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:e1-48; Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. Clin Infect Dis 2021;73:e1029-44; Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol 2021;116:1124-47.

Table 4. Pediatric CDI Treatment Recommendations from the 2017 IDSA/SHEA Guideline

Clinical Scenario	IDSA/SHEA Treatment Recommendations[a]
Primary CDI	Metronidazole 7.5 mg/kg/dose TID or QID for 10 days —OR— Vancomycin 10 mg/kg/dose QID for 10 days
First recurrence	Metronidazole 7.5 mg/kg/dose TID or QID for 10 days —OR— Vancomycin 10 mg/kg/dose QID for 10 days
Second or subsequent recurrence	Vancomycin 10 mg/kg/dose QID for 10 days[b] —OR— Vancomycin tapered and pulsed —OR— Vancomycin 10 mg/kg/dose QID for 10 days, and then rifaximin[c] 400 mg TID for 20 days —OR— FMT
Severe or fulminant CDI (primary CDI or recurrent CDI)	Vancomycin 10 mg/kg/dose QID for 10 days —PLUS— Metronidazole IV 10 mg/kg/dose TID for 10 days —PLUS— Vancomycin rectal 500 mg in 100-mL saline QID (if ileus present)

[a]Maximum doses: metronidazole 500 mg/dose; vancomycin 125 mg/dose (nonsevere) or 500 mg/dose (severe/fulminant); rifaximin 400 mg/dose.

[b]A standard course of vancomycin should only be used if all previous CDI episodes were treated with metronidazole.

[c]Rifaximin does not have FDA approval for use in children age < 12 years. Dosing listed is for children age ≥ 12 years and based on doses used in adults with CDI.

CDI = *Clostridioides difficile* infection; FMT = fecal microbiota transplantation; IV = intravenous; QID = four times daily; TID = three times daily.

Information from: McDonald LC, 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:e1-48.

Prevention

Unlike the IDSA/SHEA guidelines, the ACG guideline makes recommendations regarding the use of probiotics and antibiotics for the primary and secondary prevention of CDI (Kelly 2021). For both primary (strong recommendation) and secondary (conditional recommendation) prevention of CDI, the ACG Guideline Committee recommends against the use of probiotics. However, the guideline does state that secondary vancomycin prophylaxis can be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence (conditional recommendation).

Treatment

Adults

The 2013 ACG guideline did not advocate for fidaxomicin, citing limited data at the time of publication, and instead recommended metronidazole for nonsevere CDI and vancomycin for severe CDI based on the results of the landmark trial by Zar et al. (Surawicz 2013; Zar 2007). For the 2021 update, the ACG Guideline Committee considered the same 10 RCTs as the IDSA/SHEA Guideline Committee but concluded that metronidazole may still be considered as first-line for treatment of nonsevere, primary CDI in younger outpatients with minimal comorbidities, based on the results of an observational study (Appaneal 2018). In addition, either vancomycin or fidaxomicin are recommended interchangeably based in part on the results of another observational study not considered by IDSA/SHEA (Gentry 2019). Based on two RCTs, rifaximin follow-on therapy is not recommended (Major 2019; Garey 2011). Lastly, the use of fecal microbiota transplantation (FMT), especially in patients with multiply rCDI, is emphasized the ACG guideline. See Table 3 for recommendations for various adult patient populations.

Children

The 2021 ACG guideline does not make any recommendations specific to pediatric patients (Kelly 2021).

FIRST-LINE THERAPIES

Pharmacokinetics and Pharmacodynamics

Given the aforementioned challenges with isolating and culturing *C. difficile*, testing for antibiotic susceptibilities has not been prospectively performed to direct antibiotic treatment in individual patients and instead is conducted for pharmacokinetic/pharmacodynamic (PK/PD) analyses in drug development. With the exception of metronidazole, all antibiotics used to treat CDI have MIC_{90} values that are several orders of magnitude lower than the concentration of that antibiotic in feces (Table 5).

From a PK/PD perspective, vancomycin and fidaxomicin have the best chance at attaining adequate exposures throughout all 10 days of treatment. Epidemiologic findings from the United States between 2013–2016 suggest fidaxomicin is the most potent *C. difficile* active antibiotic with a MIC_{90} of 0.5 mcg/mL and MIC range of 0.004–1 mcg/mL (Thorpe 2019). In two recent studies, vancomycin has demonstrated MIC_{90} values of 2 mcg/mL (2013–2016) and 2 mcg/mL (2015–2017) with corresponding MIC ranges of 0.25–8 mcg/mL or less and 1–4 mcg/mL, respectively (Thorpe 2019; Tickler 2019). Lastly, metronidazole has MIC_{90} values of 1 mcg/mL (2013–2016) and 0.5 mcg/mL (2015–2017) and MIC ranges of 0.06–4 mcg/mL or less and 0.125–1 mcg/mL, respectively. Notably, metronidazole MICs may be underestimated using current methods without the addition of fresh heme with no exposure to light (Boekhoud 2021; Wu 2021). Thus, undetected metronidazole resistance may be contributing to the clinical failure rates of 16.5%–27.3% in contemporary clinical trials (Zar 2007; Johnson 2014). In fact, recent evidence suggests that *C. difficile* metronidazole MICs 1 mcg/mL or greater may predict clinical failure in patients treated with metronidazole (Gonzales-Luna 2021). The effects of reduced antibiotic susceptibility on clinical outcomes are just beginning to be explored, and the findings of such investigations may affect clinical practice moving forward.

Treatment

Currently two treatments for CDI have FDA approval, vancomycin and fidaxomicin, both of which are antibiotics and further disrupt the remaining gut microbiota, thus leading to CDI recurrence in a subset of patients (Louie 2012; Edlund

Table 5. Comparison of Antibiotic Fecal Concentrations in Patients with CDI, *C. difficile* MIC_{90} Values, and Resistance Breakpoints

Antibiotic	Mean fecal concentration (mcg/g) (SD)	*C. difficile* MIC_{90} (mcg/mL)	Mean fecal concentration to MIC_{90} ratio	Resistance Breakpoints and ECOFFs
Fidaxomicin	1433 (975); range 389–3975 1225 (759); range 32–4640 1985 (1368)	0.5	2866:1 2450:1 3970:1	NA
Metronidazole	Watery stool: 9.3 (7.5); range 0.8–24.2 Semi-formed stool: 3.3 (3.6); range 0.4–10.4 Formed stool: 1.2 (2.8); range 0.0–10.2 1.2 (0.4–4.6)[a]; minimum 0.0	1	9:1 3:1 1:1 1:1	Breakpoint: ≥ 32 mcg/mL ECOFF: > 2
Vancomycin	~1000; minimum 15 ~2000; range 17–5277	2	500:1 1000:1	ECOFF: > 2

[a]Median (interquartile range).

CDI = *Clostridioides difficile* infection; ECOFF = epidemiologic cutoff value; NA = not applicable.

Information from: Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. Gut 1986;27:1169-72; Louie T, Miller M, Donskey C, et al. Clinical outcomes, safety, and pharmacokinetics of OPT-80 in a phase 2 trial with patients with *Clostridium difficile* infection. Antimicrob Agents Chemother 2009;53:223-8; Gonzales M, Pepin J, Frost EH, et al. Faecal pharmacokinetics of orally administered vancomycin in patients with suspected *Clostridium difficile* infection. BMC Infect Dis 2010;10:363; Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422-31; Thabit AK, Nicolau DP. Impact of vancomycin faecal concentrations on clinical and microbiological outcomes in *Clostridium difficile* infection. Int J Antimicrob Agents 2015;46:205-8; Mikamo H, Tateda K, Yanagihara K, et al. Efficacy and safety of fidaxomicin for the treatment of *Clostridioides (Clostridium) difficile* infection in a randomized, double-blind, comparative phase III study in Japan. J Infect Chemother 2018;24:744-52; Thorpe CM, McDermott LA, Tran MK, et al. U.S.-based national surveillance for fidaxomicin susceptibility of *Clostridioides difficile*-associated diarrheal isolates from 2013 to 2016. Antimicrob Agents Chemother 2019;63:e00391-19; Saunders M, Jeffery J, Vincent Z, et al. Relationship between faecal metronidazole and lactoferrin concentrations to clinical response of patients with *Clostridioides difficile*. Eur J Clin Microbiol Infect Dis 2020;39:1781-4; Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing, 31st ed. Wayne, PA: CLSI, 2022; European Committee on Antimicrobial Susceptibility Testing (EUCAST). Clinical Breakpoints – Bacteria (v 12.0). Växjö, Sweden: EUCAST, 2022.

1997). A third agent, bezlotoxumab, is a nonantibiotic and has FDA approval to reduce the rate of rCDI. Although bezlotoxumab does not directly affect the gut microbiome, it must be paired with a standard-of-care antibiotic (Wilcox 2017). Thus, all management options for CDI further harm the gut microbiome instead of restoring it, a paradox that must change with the hope to prevent rCDI altogether.

Fidaxomicin

Fidaxomicin is an oral antibiotic available as a tablet, which in 2011 became only the second CDI treatment with FDA approval, according to the package insert. In 2020, the indication for fidaxomicin was expanded to include children aged 6 months and older. Coinciding with its approval in children was the introduction of an oral suspension formulation.

Mechanism of Action

Fidaxomicin is a macrocyclic antibiotic, which, like the rifamycins, blocks bacterial gene transcription by inhibiting RNA polymerase (Artsimovitch 2012). This mechanism of action prevents *C. difficile* from forming spores by inhibiting the transcription of sporulation genes (Babakhani 2012). Furthermore, fidaxomicin can prevent the outgrowth of vegetative *C. difficile* by attaching to the exosporium layer of the spore (Bassères 2021; Chilton 2016). These characteristics, together with its narrow spectrum of activity, makes fidaxomicin an ideal antibiotic for preventing recurrence.

Effect on the Gut Microbiome

Although fidaxomicin is considered a narrow-spectrum antibiotic, it still has activity against several bacteria that colonize the human gut, especially given the high concentrations achieved there (see Table 5). Specifically, fidaxomicin is potent against *Clostridium perfringens* (MIC_{90} 0.0625 mcg/mL), but less potent against other *Clostridium* spp., such as *C. innocuum* (MIC_{90} 256 mcg/mL) and *C. ramosum* (MIC_{90} greater than 512 mcg/mL) (Goldstein 2013). Fidaxomicin also has potent activity against *Bifidobacterium* spp. (MIC_{90} 0.125 mcg/mL). However, MIC_{90} values for other bacteria associated with a healthy gut microbiome, such as *Bacteroides* spp., *Lactobacillus* spp., and *Prevotella* spp. are greater than 512 mcg/mL. A microbiome analysis of patients enrolled in the phase 2 trial for fidaxomicin confirmed these in vitro findings: concentrations of *Bacteroides* spp., *Clostridium coccoides* group, *Clostridium leptum* group, *Lactobacillus* spp., and *Prevotella* spp. remained stable from days 0–10 of treatment with fidaxomicin (Louie 2012). Of interest, *Bifidobacterium* spp. levels appeared to remain stable as well, despite the potent activity of fidaxomicin against these bacteria. The fact that fidaxomicin does not further disrupt the gut microbiome is appealing and likely contributes to the lower rates of CDI recurrence observed in patients treated with fidaxomicin versus vancomycin.

Efficacy

To date, four phase 3 RCTs have been conducted comparing fidaxomicin to vancomycin for the treatment of CDI (Guery 2018; Mikamo 2018; Cornely 2012; Louie 2011). In two of these clinical trials, the primary efficacy end point was clinical cure, defined as the resolution of symptoms without the need for additional CDI therapy (Cornely 2012; Louie 2011). In the other two trials, the primary efficacy end point was sustained clinical response, defined as clinical cure without recurrence in the month after treatment (Guery 2018; Mikamo 2018). Three of the four studies were designed as double-blinded noninferiority trials with a 10% noninferiority margin (Cornely 2012; Louie 2011; Mikamo 2018), and the other was an open-label superiority trial (Guery 2018). The latter study, named the EXTEND trial, also used an extended-pulsed fidaxomicin dosing regimen (Guery 2018). While the same total dose (4000 mg) is administered over the course of therapy, the extended-pulsed regimen includes fidaxomicin 200 mg twice daily on days 1–5, followed by 200 mg every other day on days 7–25. Notable secondary outcomes consistent across studies were time to resolution of diarrhea and CDI recurrence. Rates of clinical cure, CDI recurrence, and sustained clinical response observed in the modified intention-to-treat populations of clinical trials for fidaxomicin and vancomycin are shown in Figure 1.

Patients treated with fidaxomicin experience clinical cure rates of 80.2%–88.2%, which are similar to those seen in patients treated with vancomycin. However, of the proportion of patients who experience sustained clinical response ranges from 67.3% to 76.6% and was significantly higher than those seen in patients treated with vancomycin in three of the four clinical trials (Guery 2018; Cornely 2012; Louie 2011). In the trial by Mikamo et al., the rCDI rate in the fidaxomicin group was numerically higher (19.5%) than observed in the other three clinical trials, which affected the rate of sustained clinical response and lack of difference between fidaxomicin and vancomycin (Mikamo 2018). When considering only the rCDI rate, the absolute difference between patients treated with fidaxomicin and vancomycin ranged from 5.8% to 14.2%, which correlates to an NNT of 8–18 patients treated with fidaxomicin to prevent one recurrence (see Figure 1).

Given the concern about differential clinical cure rates in those with severe disease treated with metronidazole versus vancomycin, three of the trials stratified their clinical cure analysis by severity, although different definitions of "severe" were used (Guery 2018; Cornely 2012; Louie 2011). Although the rates of clinical cure were generally lower in patients with severe CDI regardless of treatment, this difference was not significant between patients treated with fidaxomicin versus vancomycin. Not surprisingly, patients with fulminant CDI, defined by hypotension, shock, ileus, or megacolon, were excluded from all four clinical trials (Guery 2018; Mikamo 2018; Cornely 2012; Louie 2011).

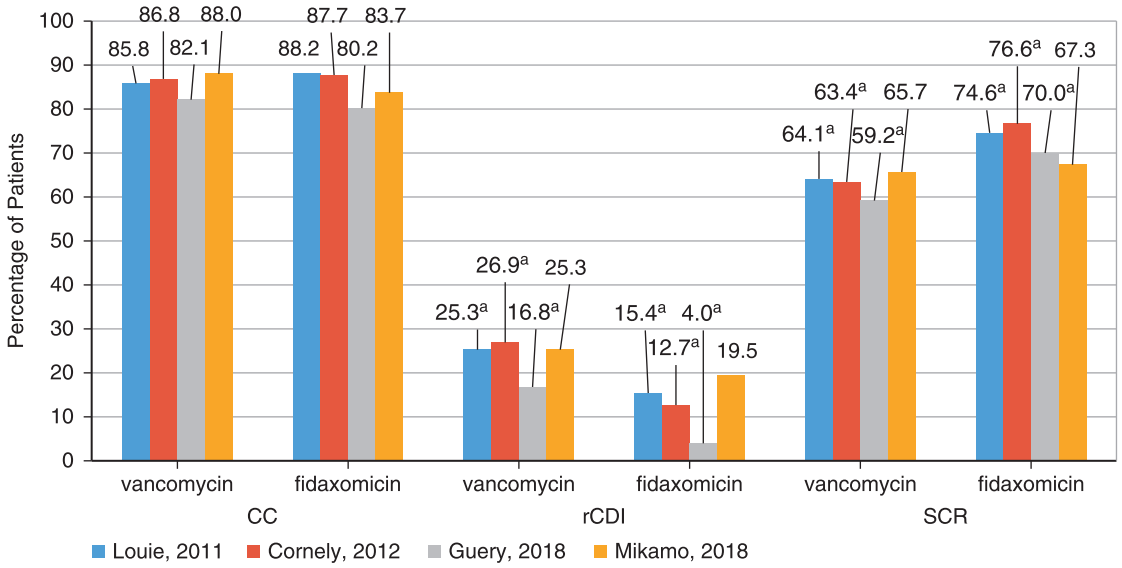

Figure 1. Rates of clinical cure, rCDI, and sustained clinical response among patients who received fidaxomicin or vancomycin in four clinical trials.

[a]Statistically significant finding ($p<0.05$).

CC = clinical cure; rCDI = recurrent *Clostridioides difficile* infection; SCR = sustained clinical response.

Information from: Louie TJ, Miller MA, Mullane KM, et al., Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422-31; Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012;12:281-9; Guery B, Menichetti F, Anttila VJ, et al. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. Lancet Infect Dis 2018;18:296-307; Mikamo H, Tateda K, Yanagihara K, et al. Efficacy and safety of fidaxomicin for the treatment of *Clostridioides (Clostridium) difficile* infection in a randomized, double-blind, comparative phase III study in Japan. J Infect Chemother 2018;24:744-52.

In a single-center case series, 20 patients were treated with fidaxomicin while in the ICU (Penziner 2015). Only 8 patients (40%) had fulminant CDI, and all 20 patients received vancomycin plus metronidazole initially before transitioning to a fidaxomicin-based salvage therapy. Of the 8 patients fulminant CDI, 3 (38%) responded to fidaxomicin therapy. These data support the use of fidaxomicin for the treatment of severe CDI; however, more data are needed before fidaxomicin can be recommended for the treatment of fulminant CDI.

Two fidaxomicin clinical trials also stratified their analyses by the number of CDI episodes in the past 3 months (Cornely 2012; Louie 2011). Both trials included patients with either no or 1 episode of CDI in the past 3 months; however, more patients were enrolled with primary CDI (82.9%–85.1%) than with rCDI (14.9%–17.1%). Comparison of the rates of rCDI between fidaxomicin and vancomycin in these subgroups show the rate of rCDI was only significantly different in those with primary CDI (Figure 2). However, both studies were underpowered to detect a difference in the small subgroup of patients with rCDI, and the magnitude of reduction in rCDI rates was actually higher in patients being treated for rCDI (Cornely 2012; Louie 2011). Patients with up to 2 CDI episodes in the 3 months before randomization were included in the study by Guery et al; however, only 5.6% of such patients were enrolled (Guery 2018). These results demonstrate the effectiveness of fidaxomicin in patients with primary CDI or one recurrence in the past 3 months. Unfortunately, in clinical practice, fidaxomicin is often reserved for patient populations with several episodes of rCDI for whom the data demonstrating benefit are limited.

In the only RCT conducted in children with CDI, the SUNSHINE trial, clinical cure rates were compared in neonates and children up to age 18 who received fidaxomicin (98 patients) or vancomycin (44 patients) (Wolf 2020). The rates of clinical cure were 77.6% with fidaxomicin and 70.5% with vancomycin (adjusted treatment difference, 7.5%; 95% CI, –7.4% to 23.9%). Furthermore, the rate of sustained clinical response was 68.4% with fidaxomicin and 50.0% with vancomycin (adjusted treatment difference, 18.8%; 95% CI, 1.5%–35.3%). This trial led to the FDA approval of fidaxomicin for the treatment of CDI in children aged 6 months and older in January 2020. Although these data have not been incorporated into the IDSA/SHEA or ACG guidelines, they are likely to affect clinical practice and future guideline recommendations.

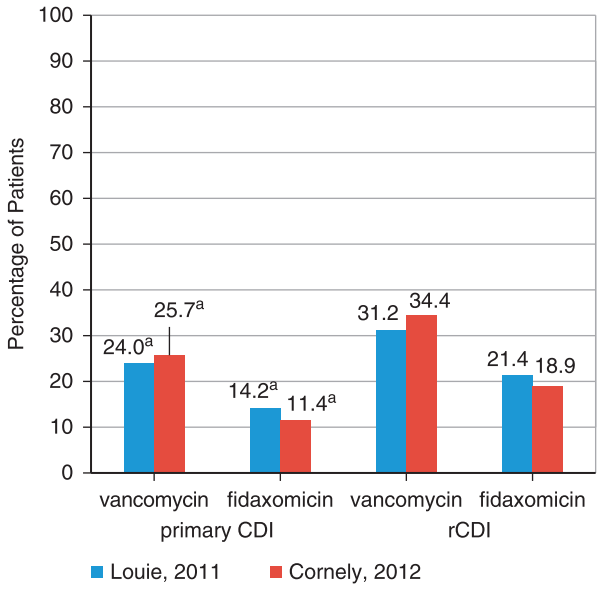

Figure 2. Rate of rCDI among patients who received fidaxomicin or vancomycin stratified by number of CDI episodes in the past 3 months.

[a]Satistically significant finding (i.e., p<0.05).

CDI = *Clostridium difficile* infection; rCDI = recurrent *C. difficile* infection.

Information from: Louie TJ, Miller MA, Mullane KM, et al., Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422-31; Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012;12:281-9.

Safety

Because fidaxomicin is minimally absorbed, systemic adverse effects are uncommon (Guery 2018; Louie 2011). Adverse events reported in clinical trials that were considered possibly or probably related to fidaxomicin were mild, including nausea, vomiting, diarrhea, and abdominal pain; occurred in 7.7%–11.7% of patients, and occurred at similar rates to those observed in patients treated with vancomycin (Guery 2018; Mikamo 2018; Cornely 2012; Louie 2011). Of the 836 patients randomized to receive fidaxomicin across four clinical trials, only 36 (4.3%) of patients discontinued the study drug because of adverse events.

Similar rates were observed in children. Adverse events that were considered possibly or probably related to fidaxomicin occurred in 7.1% of patients compared with 11.4% of patients treated with vancomycin (Wolf 2020). Only one adverse event (i.e., moderate colitis) led to fidaxomicin discontinuation. Considered together, these data demonstrate the safety of fidaxomicin in adults and children with CDI.

Vancomycin

Vancomycin was first drug to receive FDA approval for the treatment of staphylococcal enterocolitis as an oral solution in 1972 (FDA 2018). In 1978, the first case series describing the use of vancomycin for CDI in 9 patients was published in *The Lancet* (Tedesco 1978). Notably, the vancomycin regimen used in that study was 500 mg four times daily for 7 days. Later that year, the first randomized placebo-controlled trial for the treatment of CDI was published (Keighley 1978). The investigators of this RCT (16 patients) performed a preliminary dose-finding PK/PD investigation in and determined that a vancomycin dose of 125 mg four times daily was adequate from a PD standpoint. Of the 9 patients treated with vancomycin, 7 (77.8%) experienced clinical cure, defined as normal stool frequency and consistency, compared with 1 (14.3%) of the 7 patients in the placebo group. In an RCT 5 years later, vancomycin 500 mg four times daily for 10 days was compared with metronidazole (Teasley 1983). In this trial, the primary outcome was clinical cure, defined as improvement of diarrhea by day 6 of treatment without relapse of symptoms in the 21 days after the end of therapy. Notably, this definition is similar to the definition of sustained clinical response in contemporary clinical trials. This outcome occurred in 86.5% and 88.1% of patients treated with vancomycin and metronidazole, respectively. Based on these studies, the FDA approved a capsule formulation in 1986 (FDA 2018). The oral solution was eventually withdrawn from the market but again received FDA approval in 2018, according to the package insert.

Mechanism of Action

Vancomycin is a glycopeptide antibiotic that inhibits bacterial cell wall synthesis by irreversibly binding to the D-alanyl-D-alanine residues of a peptidoglycan precursor (Sinha 1968). Based on this mechanism, activity against *C. difficile* spores would not be expected; this assumption has since been confirmed (Babakhani 2012). Whereas vancomycin can be administered intravenously to treat other infections, intravenous vancomycin cannot be used to treat CDI because it does not adequately concentrate in the colon (Tedesco 1978).

Effect on the Gut Microbiome

Given the high concentrations attained in the gut (see Table 5), vancomycin is potent against many bacteria found in a healthy human gut, including gram-negative bacteria (Goldstein 2013). For relevant gram-positive bacteria, MIC_{90} values for *Clostridium* spp. range from 1 to 16 mcg/mL whereas the MIC_{90} for *Bifidobacterium* spp. is 1 mcg/mL. Vancomycin is relatively less potent against gram-negative bacteria, but MIC_{90} values are lower than those for fidaxomicin. Fecal concentrations of vancomycin increase in a dose-dependent manner; thus one may hypothesize that higher doses have a greater effect on the gut microbiome (Gonzales 2010). However, this hypothesis has never been tested.

Detrimental microbiome effects caused by vancomycin have been documented in healthy volunteers as well as in those with established dysbiosis caused by CDI and/or antibiotic use (Garey 2020; Thorpe 2018; Louie 2012; Edlund 1997). In general, treatment with vancomycin 125 mg four times daily for 10 days leads to significant decreases in *Bacteroides* spp., nonpathogenic *Clostridium* spp. (*C. leptum* and *C. coccoides*), and *Prevotella* spp. and increases in *Enterobacteriaceae*. These microbiome changes may help explain the higher rate of CDI recurrence in patients treated with vancomycin compared with more narrow-spectrum agents.

Efficacy

As the long-standing standard of care, vancomycin has been compared with either metronidazole or fidaxomicin in eight RCTs (Guery 2018; Mikamo 2018; Johnson 2014; Cornely 2012; Louie 2011; Zar 2007; Wenisch 1996; Teasley 1983). Vancomycin and fidaxomicin were discussed previously; this section focuses on the comparison of vancomycin and metronidazole.

Early studies comparing vancomycin and metronidazole revealed similar rates of clinical cure (Figure 3) (Wenisch 1996; Teasley 1983). However, contemporary clinical trials documented significantly lower rates of clinical cure among patients treated with metronidazole, especially in those with severe CDI (Johnson 2014; Zar 2007). A recent retrospective study revealed lower rates of clinical cure among patients who were infected with a *C. difficile* strain with a metronidazole MIC of 1 mcg/mL or greater (Gonzales-Luna 2021). Because metronidazole already has disadvantageous PK/PD (see Table 5), it is plausible that a changing epidemiology may have contributed to this observation.

In contrast, rCDI rates after vancomycin and metronidazole treatment have been consistently similar over the years (see Figure 3) (Johnson 2014; Zar 2007; Wenisch 1996; Teasley 1983). It is worth noting that although none of the between-group differences were statistically significant, these studies were not powered to detect differences in the rate of rCDI.

Although guidelines recommend a tapered and pulsed vancomycin regimen for patients with multiply rCDI, there are few

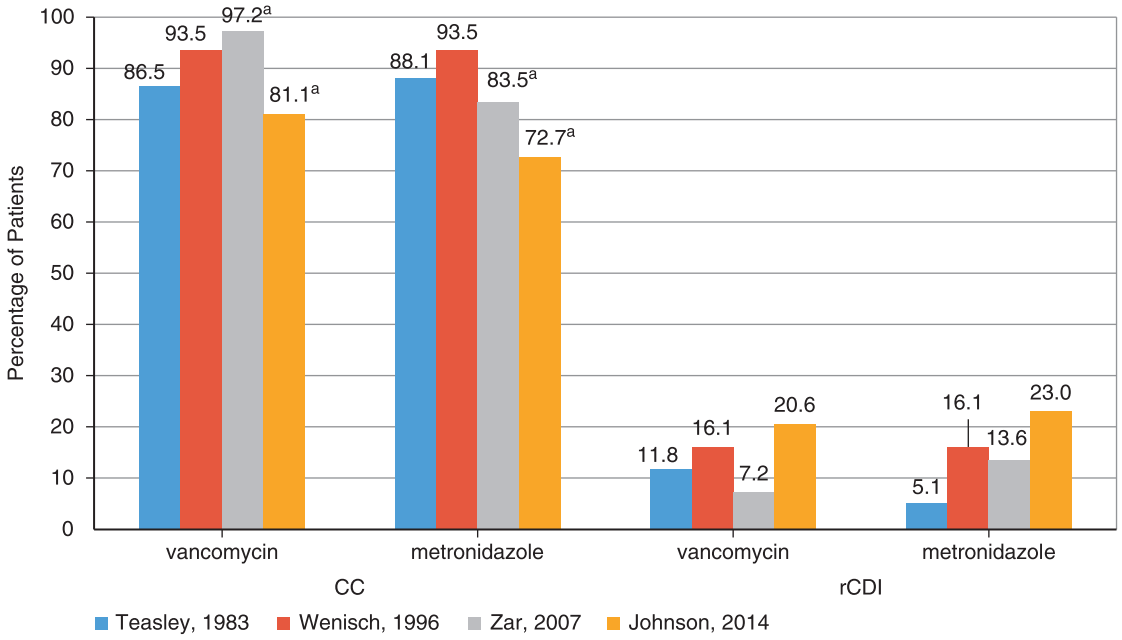

Figure 3. Rates of clinical cure and rCDI among patients who received vancomycin or metronidazole in four clinical trials.

[a]Satistically significant finding ($p<0.05$).

CC = clinical cure; rCDI = recurrent *C. difficile* infection.

Information from: Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium difficile*-associated diarrhoea and colitis. Lancet 1983;2:1043-6; Wenisch C, Parschalk B, Hasenhündl M, et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. Clin Infect Dis 1996;22:813-8; Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis 2007;45:302-7; Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. Clin Infect Dis 2014;59:345-54.

published data describing the efficacy of this strategy (Kelly 2021; McDonald 2018). The data supporting this practice are limited to one open-label RCT, two case series, and a post hoc analysis of a RCT (McFarland 2002; Hota 2017; Sirbu 2017; Tedesco 1985). The dosing regimens used in these studies were heterogenous, and there was no comparison between tapered and pulsed vancomycin versus the standard of care, which was vancomycin 125 mg four times daily or fidaxomicin 200 mg twice daily. The IDSA/SHEA guideline provides some direction regarding a tapered and pulsed vancomycin regimen: 125 mg four times daily for 10–14 days, followed by 125 mg twice daily for 7 days, followed by 125 mg once daily for 7 days, followed by 125 mg every 2–3 days for 2–8 weeks (McDonald 2018). Clearly, there is a need for additional studies comparing a tapered and pulsed vancomycin regimen to the present-day standard of care.

Despite evidence from 1978 that low-dose vancomycin (125 mg/dose) was adequate from a PK/PD perspective, early clinical trials studied high-dose vancomycin (500 mg/dose) (Wenisch 1996; Teasley 1983; Keighley 1978). One RCT compared vancomycin 125 mg four times daily (24 patients) to vancomycin 500 mg four times daily (22 patients), which found similar between-group rates of clinical cure (87.5% vs. 95.4%) and CDI recurrence (20.8% vs. 18.9%) for the low- and high-dose groups, respectively (Fekety 1989). An observational study compared outcomes in patients with severe CDI who received vancomycin 125 mg four times daily (25 patients) versus vancomycin doses 500 mg/day or more (53 patients) (Lam 2013). The investigators concluded that the rates of clinical cure (64.0% vs. 60.4%) and CDI recurrence (12.0% vs. 1.9%) were similar between the low- and high-dose groups, respectively. Lastly, a prospective trial of 15 patients investigated the effect of vancomycin fecal concentration on clinical cure and did not find any association (Thabit 2015). Taken together, these studies did not demonstrate a need for high-dose vancomycin in a general CDI population. Ileus may prevent or slow the transit of oral medications within the gut, whereas a higher stool frequency may reduce the contact time of vancomycin in the colon (Gonzales 2010). Therefore, critically ill patients, particularly those with ileus or profuse diarrhea, may benefit from a higher dose of vancomycin. Unfortunately, all three studies excluded patients with fulminant CDI, so future studies are needed to determine the role of high-dose vancomycin in these patients.

Local administration of vancomycin by a retention enema is recommended in patients with ileus (Kelly 2021; McDonald 2017). Literature describing the dosing and administration of rectal vancomycin is heterogenous, but the most commonly reported dose is 1000 mg vancomycin in 500-mL saline given every 6 hours (Akamine 2016; Malamood 2015; Saffouri 2014; Kim 2013; Apisarnthanarak 2002; Olson 1994). Current guidelines recommend 500 mg vancomycin in 100 mL saline given every 6 hours (Kelly 2021; McDonald 2017). In the only matched cohort study (72 patients) investigating the effectiveness of rectal vancomycin, rates of mortality (16.7% vs. 16.7%) and colectomy (45.5% vs. 41.7%) did not differ between patients were treated with rectal vancomycin versus those who were not treated with rectal vancomycin, respectively (Malamood 2015). Notably, only 55.6% of the sample had fulminant CDI, and the proportion of patients with ileus was not mentioned. Furthermore, only 65.2% of patients received concomitant intravenous metronidazole, no patients received high-dose vancomycin, and the doses of rectal vancomycin used ranged from 125 to 250 mg in 100 mL of tap water given every 6 hours. Because CDI can affect any part of the colon, it is important for rectally administered vancomycin to reach all parts of the organ. Unfortunately, medication instilled by enema tends to be contained to the descending (left) colon and may not reach the transverse or ascending (right) colon (van Bodegraven 1996). It is possible to perform colonoscopy and place a colonic catheter or fenestrated tube for intracolonic vancomycin administration, but this procedure requires sedation and carries a risk for colon perforation (Shetler 2001; Pasic 1993). Similar to the support for vancomycin dosing in fulminant CDI, the data are lacking to support rectal vancomycin for use in patients with ileus; however, given the urgency of fulminant CDI it is reasonable to continue these practices to ensure adequate vancomycin concentrations at the site of infection.

All clinical trials to date comparing vancomycin and metronidazole have only included adults (Johnson 2014; Zar 2007; Wenisch 1996; Teasley 1983). However, several observational studies have reported clinical outcomes in children who received either vancomycin or metronidazole (Yin 2019; Khanna 2013). The first observational study, which included children with nonsevere (80 patients) or severe (12 patients) CDI, reported clinical cure and rCDI rates of 100% and 82.4% and 0.0% and 21.3% in those who received vancomycin and metronidazole, respectively (Khanna 2013). Although outcomes appeared to numerically favor vancomycin, neither difference was deemed statistically significant. In a more recent study published since the release of the 2017 IDSA/SHEA CDI guideline (192 patients), outcomes were compared in patients aged 2–18 years with nonsevere CDI who received either vancomycin or metronidazole (Yin 2019). The investigators used an inverse probability of treatment-weighted propensity-score analysis. Children who received metronidazole were significantly less likely to experience clinical cure compared with those who received vancomycin (OR 0.40; 95% CI, 0.17–0.97). These results suggest that children, including those with nonsevere CDI, should be treated with vancomycin over metronidazole.

Safety

Similar to fidaxomicin, vancomycin is minimally absorbed after oral administration (Pettit 2015). However, certain patient and treatment characteristics, such as higher vancomycin doses (greater than 500 mg/day), concomitant rectal

vancomycin, kidney dysfunction (creatinine clearance 50 mL/minute or less), and underlying GI comorbidities, including inflammatory bowel disease or graft versus host disease, are associated with vancomycin accumulation. In clinical trials, adverse events in patients treated with vancomycin were uncommon, and when they did occur were typically mild, including nausea, vomiting, and diarrhea (Johnson 2014; Louie 2011; Zar 2007; Wenisch 1996; Teasley 1983). Adverse events possibly or probably related to vancomycin occurred in 4.9% to 31.2% of patients. Furthermore, adverse events that led to discontinuation occurred in 0.9% to 6.2% of patients.

Similar rates were observed in children. Adverse events that were considered possibly or probably related to vancomycin occurred in 11.4% of patients (Wolf 2020). Only one adverse event led to vancomycin discontinuation, which was severe vomiting. Considered together, these data highlight the excellent safety profile of oral vancomycin in adults and children with CDI.

Metronidazole

Metronidazole has long been used as a cheaper alternative to vancomycin to treat CDI; however, it has never received FDA approval for this indication (Matuchansky 1978). Metronidazole has been compared with vancomycin in four clinical trials (Johnson 2014; Zar 2007; Wenisch 1996; Teasley 1983).

Mechanism of Action

Metronidazole is a nitroimidazole antibiotic prodrug that is directly toxic to anaerobic bacterial DNA by three steps: 1) passive diffusion into the cell, 2) reductive activation by intracellular pyruvate/ferredoxin oxidoreductases, leading to the formation of cytotoxic free radicals, and 3) free radical interaction with host cell DNA and subsequent DNA strand breakage and cell death (Edwards 1993).

Effect on the Gut Microbiome

Metronidazole is selectively active against anaerobic bacteria because aerobic bacteria lack the intracellular proteins needed to activate the drug. This characteristic makes metronidazole far more broad-spectrum than fidaxomicin and vancomycin. Except for *Lactobacillus* spp. (MIC_{90} greater than 512 mcg/mL) and *Bifidobacterium* spp. (MIC_{90} 128 mcg/mL), metronidazole is potent against almost all gram-positive and gram-negative anaerobic species (MIC_{90} 4 mcg/mL or less) found in a healthy human gut (Goldstein 2013). The ability of metronidazole to kill commensal gut bacteria likely contributes to its relatively high rates of CDI recurrence (13.6%–23.0%) in contemporary clinical trials (see Figure 3).

Efficacy

Metronidazole monotherapy has demonstrated inferior rates of clinical cure compared with vancomycin in RCTs (Johnson 2014; Zar 2007) (see Figure 3). The difference in the rate of clinical cure was statistically significant in the subgroup of patients with severe CDI but not for those with nonsevere CDI. However, neither study was powered to detect a difference in clinical cure rate based on severity. Two recent observational studies performed in military veteran populations have suggested continued use of metronidazole for nonsevere CDI may be justified given similar rates of 30-day all-cause mortality and CDI recurrence in patients who received metronidazole or vancomycin (Appaneal 2018; Stevens 2017). However, rates of rCDI have been consistently similar between metronidazole and vancomycin (see Figure 3), and neither study was powered to detect small absolute differences in mortality. Furthermore, differential rates in clinical cure (see Figure 4) were used to inform recent guideline recommendations to avoid metronidazole (McDonald 2018), which were not assessed in either observational study. Another recent observational study demonstrated an association between a metronidazole MIC 1 mcg/mL or greater and lower rates of clinical cure, indicating a potential role for susceptibility testing in selecting patients who may benefit from metronidazole (Gonzales-Luna 2021).

Although the recommendations surrounding metronidazole monotherapy differ between guidelines, the use of intravenous metronidazole in combination with vancomycin for fulminant CDI is still recommended by both the IDSA/SHEA and the ACG (see Table 3) (Kelly 2021; McDonald 2018). The benefit of this combination has been investigated in three retrospective cohort studies, and results are mixed (Vega 2020; Wang 2020; Rokas 2015). The first was a single-center study of 88 patients who received a diagnosis of CDI in the ICU, for whom the investigators observed a lower rate of all-cause inpatient mortality in those who received combination therapy with intravenous metronidazole plus vancomycin versus those who received vancomycin monotherapy (15.9% vs. 36.4%; p=0.03) (Rokas 2015). Notably, patients were matched 1:1 according to their Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Since then, two additional studies with contrasting results have been published. One was a single center study of 138 patients who received a diagnosis of CDI in the ICU that included a subgroup analysis of patients matched by APACHE II score (Vega 2020). Investigators did not observe a difference in all-cause 30-day mortality (18.3% intravenous metronidazole plus vancomycin vs. 12.8% vancomycin monotherapy; p=0.37). The results of the matched subgroup analysis were consistent with those of the primary analysis. In a two-center study of 2114 patients, including 905 (43%) patients who received a diagnosis of CDI in the ICU, a significantly higher rate of mortality or colectomy within 90 days of CDI diagnosis was found in patients who received combination therapy with intravenous metronidazole plus vancomycin (27.6%) versus those who received vancomycin monotherapy (18.0%) (p<0.01) (Wang 2020). However, after adjusting for confounders, no association was observed between combination therapy and mortality or

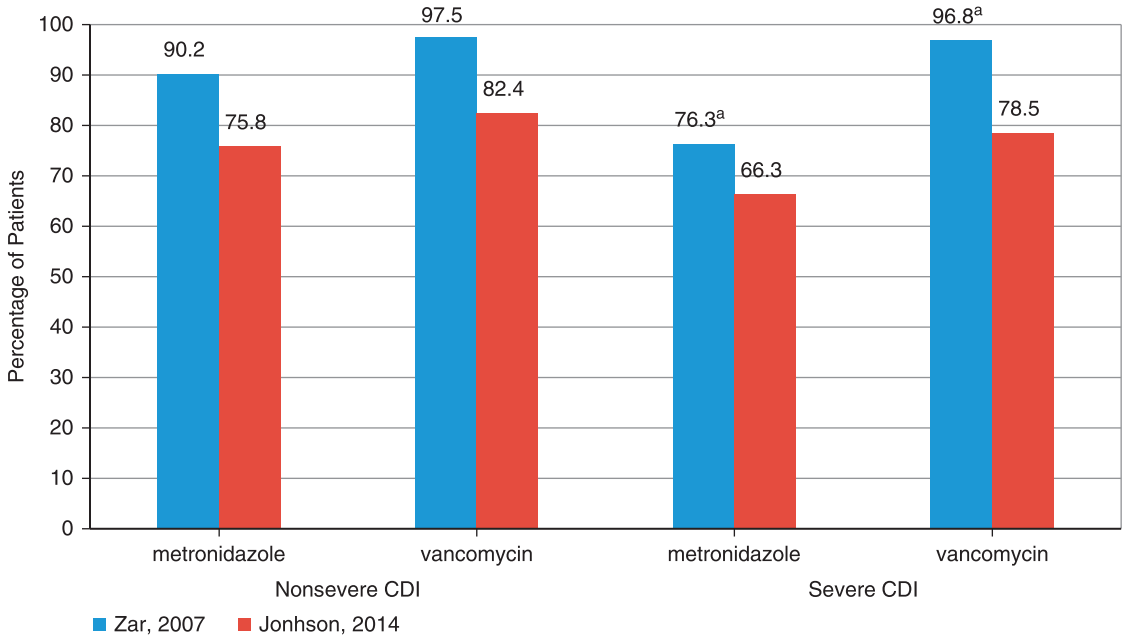

Figure 4. Rate of clinical cure among patients who received metronidazole or vancomycin stratified by CDI severity.

[a]Statistically significant finding ($p<0.05$).

CDI = *Clostridioides difficile* infection.

Information from: Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis 2007;45:302-7; Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. Clin Infect Dis 2014;59:345-54.

colectomy (OR 1.07; 95% CI, 0.79–1.45). A subgroup analysis of patients with fulminant CDI (n=526) demonstrated results consistent with the primary analysis. Notably, only between 2%–6% of patients in these studies had a documented ileus, which is the patient population most likely to benefit from the addition of intravenous metronidazole (Vega 2020; Wang 2020; Rokas 2015). Considered together, these results suggest that intravenous metronidazole should continue to be added in patients with confirmed or suspected ileus, but high-quality data are lacking supporting its benefit in all critically ill patients with fulminant CDI.

Safety

Unlike fidaxomicin and vancomycin, metronidazole is readily absorbed and thus has a higher likelihood of causing systemic adverse events. In one clinical trial for CDI, adverse events that were considered possibly or probably related to metronidazole occurred in 35.3% of patients (Johnson 2014). In addition, significantly more patients receiving metronidazole than vancomycin (6.3% vs. 2.7%; p=0.04) discontinued metronidazole therapy because of an adverse event. In another clinical trial, only one patient discontinued metronidazole because of vomiting (Zar 2007). Other notable adverse events associated with metronidazole, although not observed in clinical trials for CDI, include a disulfiram-like reaction when administered with alcohol and peripheral neuropathy after high cumulative doses and/or longer durations (Mergenhagen 2020; Goolsby 2018).

Adjunctive Management: Bezlotoxumab

Bezlotoxumab received FDA approval in 2016 and is the most recently approved medication used in the management of CDI, according to the package insert. It is administered as a single dose of 10 mg/kg (actual body weight) over 1 hour in conjunction with fidaxomicin or vancomycin as the standard-of-care antibiotics.

Mechanism of Action

Bezlotoxumab is a fully human monoclonal antibody that neutralizes *C. difficile* toxin B by binding to it and preventing it from binding to target host cells (Orth 2014; Babcock 2006).

Effect on the Gut Microbiome

Because bezlotoxumab is not an antibiotic, it has no direct effect on the gut microbiome. However, because bezlotoxumab only has FDA approval to reduce the rate of rCDI in conjunction with standard-of-care antibiotics, the gut microbiome will be affected by those antibiotics.

Efficacy

Bezlotoxumab was studied as an adjunct to standard-of-care antibiotics (metronidazole, vancomycin, or fidaxomicin) versus standard-of-care antibiotics plus placebo in adults with CDI (Wilcox 2017). Of the 2559 patients in two phase 3 clinical trials, MODIFY I/II, 46.7%, 47.7%, and 3.6% were treated with metronidazole, vancomycin, and fidaxomicin, respectively. Because randomization was stratified by treatment antibiotic, the use of metronidazole, vancomycin, and fidaxomicin was balanced between groups. The primary outcome for these trials was CDI recurrence during 12 weeks of follow-up, which was 16.5% and 26.6% in the bezlotoxumab and placebo groups, respectively ($p<0.0001$) corresponding to a NNT of 10 to prevent one recurrence. Differences in the absolute rate of recurrence between bezlotoxumab and placebo were similar in those who received metronidazole, vancomycin, or fidaxomicin (–8.0%, –12.6%, and –6.9%, respectively), although the reduction was not significant in the small patient subgroup who received fidaxomicin. Clinical cure was chosen as an exploratory end point, and rates did not differ between groups (80.0% with bezlotoxumab vs. 80.3% with placebo).

Several post hoc analyses of the bezlotoxumab MODIFY I/II trials have been published. Because toxins are required for the pathogenesis of CDI, neutralization of toxin B by bezlotoxumab has been hypothesized to hasten diarrheal resolution and improve rates of clinical cure. However, clinical cure rates did not differ between patients who received bezlotoxumab and placebo in the phase 3 clinical trials (Wilcox 2017).

A second post hoc analysis sought to assess the impact of bezlotoxumab administration timing relative to the initiation of antibiotic therapy (Birch 2018). In phase 3 clinical trials, bezlotoxumab was administered between 1 day before the start of antibiotic therapy and day 14 of antibiotic therapy, with a median of day 3 of antibiotic therapy (Wilcox 2017). Specifically, 41.8%, 30.1%, and 28.1% of patients received bezlotoxumab 0–2, 3–4, and 5 or more days after the onset of antibiotic therapy. The post hoc analysis concluded that rates of clinical cure and the time to resolution of diarrhea did not differ between groups in any patient subgroups. In addition, patients who received bezlotoxumab experienced lower rates of recurrence regardless of bezlotoxumab timing (Birch 2018). These data suggest that bezlotoxumab can be administered at any point during antibiotic therapy for CDI.

Another post hoc analysis investigated the rates of CDI recurrence in subgroups of patients with prespecified risk factors for recurrence: age 65 years or older, history of CDI in the previous 6 months, immunocompromise, severe CDI according to the Zar score, and infection with ribotype 027, 078, or 244 (Gerding 2018; Zar 2007). Only 27.5% of patients enrolled in the phase 3 clinical trials had a history of at least one CDI episode in the previous 6 months (Wilcox 2017). Of 1554 patients, 379 (24.4%) randomized to either bezlotoxumab or placebo had no risk factors for recurrence, whereas the remaining 1175 (75.6%) had at least one risk factor for recurrence (Gerding 2018). Of those with no risk factors, the rates of recurrence in the bezlotoxumab versus placebo group did not differ (18.8% vs. 20.9%, respectively). However, the recurrence rates were significantly lower in the subset of patients with at least one risk factor (21.2% vs. 37.2% in the bezlotoxumab vs. placebo group, respectively). The absolute reduction in CDI recurrence rate because of bezlotoxumab increased with the number of risk factors, as follows –14.2%, –14.2%, –24.8% in patients with one, two, and three or more risk factors. These data suggest that bezlotoxumab should be reserved for those patients who are 65 years or older, have a history of CDI in the previous 6 months, are immunocompromised, have severe CDI, or are infected with ribotype 027, 078, or 244 (see Table 3).

Safety

Adverse events reported in clinical trials that were considered possibly or probably related to bezlotoxumab were mild (e.g., nausea, headache, dizziness, pyrexia), occurred in 7.5% of patients randomized to bezlotoxumab, and occurred at rates similar to those observed in the placebo group (5.9%) (Wilcox 2017). Of the 781 patients randomized to receive bezlotoxumab, only 1 patient discontinued the study drug because of an infusion-related reaction.

Although these data have not been published, the package insert for bezlotoxumab provides adverse events and mortality rates for patients with underlying congestive heart failure who received bezlotoxumab (118 patients) versus placebo (104 patients). A serious adverse event categorized as heart failure occurred in 15 patients (12.7%) receiving bezlotoxumab versus 5 patients (4.8%) receiving placebo, and the mortality rate was 19.5% (23 patients) with bezlotoxumab versus 12.5% (13 patients) with placebo, according to the package insert. Although there is no mechanistic explanation for this observation, the risks of bezlotoxumab should be considered before prescribing it to patients with underlying congestive heart failure.

SECOND-LINE THERAPIES

Treatment

Rifaximin

Rifaximin is a synthetic derivative of rifamycin that first received FDA approval in 2004 and is currently indicated for the treatment of traveler's diarrhea, the treatment of irritable bowel syndrome with diarrhea, and the prevention of hepatic encephalopathy recurrence, according to the package insert. Although rifaximin has never been approved for the treatment of CDI, it has been included in CDI treatment guidelines since 2010 (Cohen 2010).

Mechanism of Action

Like its parent compound, rifamycin, and similar to fidaxomicin, rifaximin blocks bacterial gene transcription by inhibiting

Patient Care Scenario

A 67-year-old man presents to the hospital with acute kidney injury and profuse watery diarrhea. He reports having about 15 bowel movements in the past 24 hours. He also says that he has never had CDI before. A basic metabolic panel and CBC were obtained and revealed a SCr of 2.2 mg/dL and a WBC of 12.5 × 10^3 cells/mm^3. In addition, a *C. difficile* enzyme immunoassay is ordered, which returns positive. Which antibiotic and nonantibiotic therapies should be considered for this patient?

ANSWER

This patient seems to be experiencing pre-renal acute kidney injury cause by dehydration secondary to his profuse diarrhea. Although antibiotic therapy is important, this patient will also benefit from fluid resuscitation. Because this presentation is his first episode of CDI and his SCr is 1.5 mg/dL or greater, this infection would be classified as primary and severe CDI. Per the IDSA/SHEA and ACG guidelines, this patient would qualify for either vancomycin 125 mg four times per day or fidaxomicin 200 mg twice daily for 10 days. The benefit of fidaxomicin is a reduced risk of CDI recurrence. This patient may also benefit from the monoclonal antibody, bezlotoxumab, administered as a one-time dose of 10 mg/kg because he has two risk factors for CDI recurrence—age 65 years or older and severe CDI. It is worth noting that only 3.6% of patients enrolled in the phase 3 clinical trials for bezlotoxumab received fidaxomicin, so the added benefit of bezlotoxumab in patients treated with fidaxomicin is unknown. The two best options are either fidaxomicin 200 mg twice daily for 10 days or vancomycin 125 mg four times per day for 10 days plus bezlotoxumab 10 mg/kg administered intravenously once at some point between now and day 10 of vancomycin therapy.

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RNA polymerase (Scarpignato 2005). Unlike fidaxomicin, however, rifaximin does not inhibit *C. difficile* spore formation (Babakhani 2012).

Effect on the Gut Microbiome

Because rifaximin is not absorbed in the gut, it maintains extremely high concentrations in feces (7961 mcg/g), which allows it to kill many anaerobic bacteria present in the human gut microbiome. For example, rifaximin is potent against certain *Clostridium* spp., such as *C. difficile* (MIC_{90} 0.25 mcg/mL), whereas it is much less potent against others such as *C. innocuum* and *C. orbiscindens* (MIC_{90} values greater than 1024 mcg/mL) (Finegold 2009). It is also potent against gram-negative anaerobes such as *Bacteroides* spp. (MIC_{90} 1 mcg/mL) and *Prevotella* spp. (MIC_{90} 0.5 mcg/mL). These data reveal that rifaximin attains much higher fecal concentrations than those obtained with fidaxomicin or vancomycin (see Table 1) and is more potent against gram-negative anaerobic bacteria—two characteristics with potential to cause further gut dysbiosis and rCDI.

Efficacy

Treatment with rifaximin for CDI was first mentioned in the 2010 IDSA/SHEA CDI guideline after a small case series was published (Johnson 2007). However, a formal recommendation was not made until the 2017 IDSA/SHEA CDI guideline after new evidence from a RCT (McDonald 2018; Garey 2011). In this RCT, 68 patients were randomized to receive rifaximin 400 mg or placebo three times daily for 20 days after standard treatment courses of either metronidazole or vancomycin for 10–14 days (Garey 2011). During 90-day follow-up, rCDI occurred in 15.2% and 31.4% of patients in the rifaximin and placebo groups, respectively (p=0.11). A second RCT was recently performed in which 151 patients received rifaximin 400 mg or placebo three times a day for 14 days, then 200 mg three times a day for 14 days after standard treatment courses of either metronidazole or vancomycin (Major 2019). The primary outcome of rCDI during 84-day follow-up occurred in 15.9% and 29.5% of the patients in the rifaximin and placebo groups, respectively (p=0.06). Because both trials were underpowered, their 95% CIs for absolute risk reduction included no effect from rifaximin. Therefore, although rifaximin "follow-on" or "chaser" therapy appears promising, it has not yet been definitively proved effective. Furthermore, these results cannot be extrapolated to patients treated with fidaxomicin, and, as the standard of care changes from metronidazole and vancomycin to agents with lower rates of CDI recurrence, the benefit of rifaximin may be nullified.

Safety

Rifaximin is distinct among the rifamycins in that it is ionized at all pH levels found in the gut, which prevents it from being absorbed and minimizes systemic adverse events (Scarpignato 2005). Treatment-related adverse events caused by rifaximin were uncommon in the two clinical trials described previously in this section and included nausea and pruritus (Major 2019; Garey 2011). A major limitation to rifaximin is the presence of resistance among *C. difficile* isolates, which may be present de novo or arise after rifamycin exposure (Huang 2013; Curry 2009).

Tigecycline

Tigecycline first received FDA approval in 2005 and is currently indicated for skin and skin structure infections, intra-abdominal infections, and community-acquired pneumonia, according to the package insert. For all indications, a loading dose of 100 mg is given, followed by a maintenance dose of 50 mg twice daily. Of note, tigecycline and metronidazole are the only two antibiotics used to treat CDI that have intravenous formulations.

Mechanism of Action

Tigecycline is a semisynthetic derivative of tetracycline, known as a *glycylcycline* (Projan 2000). Like other tetracyclines, it acts by binding to the 30S ribosomal subunit of bacteria and inhibiting protein translation.

Effect on the Gut Microbiome

Tigecycline is a broad-spectrum antibiotic and can inhibit the growth of gram-positive and gram-negative aerobic and anaerobic bacteria (Petersen 1999). Specifically, tigecycline has potent activity against many anaerobes found in the healthy human gut including *Bacteroides* spp. (MIC_{90} 2 mcg/mL or less) and *Prevotella* spp. (MIC_{90} 1 mcg/mL or less) (Edlund 2000; Petersen 1999). In addition, MIC_{90} values for *C. perfringens* and *C. difficile* are 1 mcg/mL or less and 0.125 mcg/mL or less, respectively. Microbiome studies in humans have not been performed, but an in vitro gut model interestingly demonstrated inhibition of spore germination and subsequent toxin production after tigecycline installation (Baines 2006). Although the results of the gut model are intriguing, the effect of tigecycline on the remaining gut microbiota should not be ignored because it can lead to a delay in the recovery of the microbiome and may increase the rate of rCDI.

Efficacy

Evidence for use of tigecycline in CDI is limited to observational studies for severe or fulminant CDI (Gergely Szabo 2021, 2016; Bishop 2018; Manea 2018; Brinda 2017; Dumitru 2017; LaSalvia 2017; Britt 2014; Thomas 2014; Herpers 2009). The dose of tigecycline used in these studies was universally 100 mg once, followed by 50 mg twice daily. Although many of these studies describe patients treated with combination therapy (e.g., vancomycin plus metronidazole plus tigecycline), several studies describe success with tigecycline monotherapy (Gergely Szabo 2021, 2016; Herpers 2009). In perhaps the two most robust comparative studies, the odds of all-cause inpatient mortality or a composite outcome including clinical cure, discharge from the hospital, and no requirement for surgery/transfer to the ICU for CDI were similar in patients receiving metronidazole and/or vancomycin, regardless of tigecycline receipt after propensity-score matching or adjustment (Manea 2018; LaSalvia 2017). In the only cohort study investigating tigecycline monotherapy for the treatment of severe or fulminant CDI, the rate of clinical cure among 90 patients was significantly higher in patients receiving tigecycline monotherapy (75.6%) versus vancomycin plus metronidazole (53.3%; p=0.02) (Gergely Szabo 2016). However, there was no attempt to control for confounding variables, despite several notable differences between groups, including fewer patients with fulminant CDI in the tigecycline monotherapy group (29% vs. 53%). Furthermore, only 15.6% of patients received tigecycline as first-line therapy, whereas the remainder were switched to tigecycline after experiencing failure to improve on vancomycin plus metronidazole. These data demonstrate the efficacy of tigecycline as part of a combination regimen for salvage therapy in patients with severe or fulminant CDI requiring intravenous therapy. However, data are insufficient to support tigecycline monotherapy or use in the nonsalvage setting.

Safety

Because no RCTs to date have investigated the safety and efficacy of tigecycline for CDI, these safety data have been extrapolated from non-CDI RCTs. Using data from 11 clinical trials, treatment-related adverse events occurred more often in patients receiving tigecycline versus comparator groups, and these adverse events led to more discontinuations in the tigecycline groups (Tasina 2011). Specifically, nausea (OR, 3.06; 95% CI, 2.02–4.63) and vomiting (OR, 3.35; 95% CI, 2.12–5.30) occurred significantly more often in patients treated with tigecycline versus comparator antibiotics. Because the antibiotics used to treat CDI are generally well tolerated compared with systemic antibiotics, this difference in adverse events may be more pronounced for comparison of tigecycline to fidaxomicin, oral vancomycin, or other CDI therapies.

Adjunctive Management

Intravenous Immune Globulin

A poor immune response was first associated with more severe CDI and CDI recurrence in the early 1980s (Aronsson 1985, 1983). Furthermore, passive immunization using intravenous immune globulin (IVIG) has shown a mortality benefit for other infections caused by toxin-producing bacteria when given in combination with antibiotic therapy (Parks 2018).

These findings have formed the theoretical basis for using IVIG in CDI. Of interest, data from the bezlotoxumab clinical trials have suggested that neutralizing antibodies do not improve rates of clinical cure or mortality, although these trials were not powered to detect a difference in the latter (Wilcox 2017). However, these trials did not enroll patients with fulminant CDI, and few patients had severe CDI (16.4%), which may be the patients who would benefit from such an intervention.

To prepare IVIG, the serum—and thus antibodies—of thousands of donors are pooled. If present, circulating antibodies could theoretically neutralize *C. difficile* toxins similarly to bezlotoxumab. Indeed, several commercially available IVIG products have demonstrated neutralizing antibodies against *C. difficile* toxin A, toxin B, and the binary toxin (Negm 2017; Salcedo 1997). However, because titers for anti-*C. difficile* toxin antibodies are not measured during preparation, it is unknown if every product or batch contains these antibodies.

Although IVIG has no direct effect on the gut microbiome, it is given in conjunction with standard-of-care antibiotics, which will affect the gut microbiome. In addition, although IVIG does not have FDA approval for CDI, it has been used as adjunctive therapy to treat refractory, recurrent, and severe/fulminant CDI for decades (Negm 2017; Juang 2007; Abougergi 2010; McPherson 2006; Wilcox 2004; Salcedo 1997). The dose of IVIG administered varied significantly across studies but was most commonly given as a one-time dose of 400 mg/kg. In the only comparative study to date, patients with severe CDI who received IVIG in addition to metronidazole and/or vancomycin had similar rates of mortality or colectomy versus those who received only metronidazole and/or vancomycin (Juang 2007). The limitations to this study were its size (36 patients) and the omission of CDI recurrence as an outcome, whereas its strength included the use of propensity score-matching. Several case series have shown a similar lack of benefit; however, most patients were either critically ill, had several CDI recurrences, or received IVIG late in the disease process (Negm 2017; Abougergi 2010; McPherson 2006; Wilcox 2004; Salcedo 1997). In addition, the FDA approval of bezlotoxumab has provided clinicians with a more specific IVIG alternative, largely making IVIG use for CDI irrelevant.

The observational studies previously described did not reliably document adverse events. However, common adverse events associated with IVIG include infusion-related reactions (e.g., headache, nausea, chills), whereas rare but possible adverse events include acute kidney injury, hypertension, thrombosis, and transfusion-related acute lung injury, according to the package insert.

Antibiotic Prophylaxis

Exposing patients to antibiotics—the largest risk factor for development of CDI—to decrease the risk of a disease seems counterintuitive, but interest in antibiotic prophylaxis to prevent CDI is quickly growing (Carlson 2020c). Although germination of *C. difficile* spores to vegetative cells is the first step in developing CDI, no known antibiotic can kill *C. difficile* spores. Therefore, the theory underlying antibiotic prophylaxis in CDI is to prevent disease by killing vegetative *C. difficile* if and when any spores germinate. Unfortunately, it is unknown which at-risk patients will become colonized with spores and which colonized patients will experience CDI. Because metronidazole, vancomycin, and fidaxomicin all disrupt the microbiome, albeit to differing degrees, universal prophylaxis in at-risk groups is likely more harmful than beneficial but may decrease CDI rates in select patient populations. Furthermore, fidaxomicin should theoretically provide the most protection given its anti-spore effects, but no trials to date have compared fidaxomicin to metronidazole or vancomycin for prophylaxis.

Unfortunately, the available data on this topic carry a high risk of bias. Observational studies of antibiotic prophylaxis vary widely in terms of their study populations; definitions of primary versus secondary prophylaxis; regimens, including antibiotic, dose, and duration; and follow-up periods. Furthermore, retrospective observational studies with shorter follow-up periods may underestimate the rate of CDI in the prophylaxis groups, given the prolonged timeframe in which patients are at risk of recurrence following antibiotic exposure and likelihood of attrition bias inherent in retrospective studies (Carlson 2020c). Only three RCTs have been published to date, and all studied primary prophylaxis: one studied metronidazole or vancomycin, one studied vancomycin, and one studied fidaxomicin (Johnson 2020, 1992; Mullane 2019). The first of these studies randomized patients colonized with *C. difficile* detected by rectal swab testing to receive a 10-day course of metronidazole 500 mg twice daily, vancomycin 125 mg four times daily, or placebo three times daily (Johnson 1992). During 60-day follow-up, only one patient in the vancomycin arm received a diagnosis of CDI. A more recent RCT randomized hospitalized patients older than 60 years with antibiotic receipt in the past 30 days to receive vancomycin 125 mg/day or no prophylaxis (Johnson 2020). Six (12.0%) patients in the no prophylaxis group subsequently received a diagnosis of CDI versus no patients in the vancomycin group (p=0.03). Lastly, in the only double-blind RCT, patients receiving fluoroquinolone prophylaxis after hematopoietic stem cell transplantation were randomized to receive fidaxomicin 200 mg or placebo once daily (Mullane 2019). Subsequently, CDI was diagnosed in 10.7% of patients randomized to placebo versus 5.6% of patients randomized to fidaxomicin (p=0.01). The latter two studies concluded that antibiotic prophylaxis can be considered in certain high-risk patient populations. However, because prophylaxis-associated microbiome dysbiosis may persist for 3 months or longer after discontinuation, appropriate follow-up rates and time frames are critical in determining the true effects of prophylaxis (Hensgens 2012; Rashid 2015).

Pipeline

An ideal antibiotic for the treatment of CDI should have potent and selective activity against *C. difficile* while sparing the remaining gut microbiota, have minimal systemic absorption to avoid systemic adverse effects, and demonstrate efficacy, including short-term measures (e.g., resolution of diarrhea) and long-term measures (e.g., prevent recurrence) of success. An agent that can neutralize *C. difficile* toxin(s) and/or prevent the formation of spores is not necessary, but such an agent would likely have an advantage in terms of resolving an acute infection and preventing recurrence. Current standard-of-care antibiotics (i.e., fidaxomicin and vancomycin) provide rates of clinical cure between 80.2% and 88.2% and rates of CDI recurrence between 4.0% and 26.9% (see Figure 1, see Figure 3), leaving plenty of room for improvement.

Fortunately, the antibiotic treatment pipeline for CDI contains several narrow-spectrum antibiotics with potent activity against *C. difficile* (Carlson 2020b). Agents currently in later stages of development, as well as some that have recently failed to demonstrate efficacy, are described in the following text.

Notable Failures of Drug Development for CDI

The increasing incidence of CDI that occurred in the 2000s, partly because of the ribotype 027 strain, sparked drug development efforts. The results of these efforts led to the FDA approval of fidaxomicin in 2011; however, two antibiotics and two nonantibiotics developed for the treatment or adjunctive management of CDI failed to demonstrate efficacy in their phase 3 clinical trials (Gerding 2019; Boix 2017; Daley 2017; Wilcox 2017; Johnson 2014). Tolevamer, a nonantibiotic polymer that binds *C. difficile* toxins, showed promise in its phase 2 trial, but was inferior to both metronidazole and vancomycin in its phase 3 clinical trials (Johnson 2014; Louie 2006). Surotomycin, a cyclic lipopeptide antibiotic, also had positive phase 2 results, but failed to demonstrate noninferiority to vancomycin in one of its two phase 3 clinical trials (Boix 2017; Daley 2017; Lee 2016). Actoxumab, a monoclonal antibody against *C. difficile* toxin A, was tested in combination with bezlotoxumab in a phase 2 clinical trial (Lowy 2010). However, when actoxumab was investigated as monotherapy in its phase 3 clinical trials, enrollment was halted after an interim analysis found higher rates of rCDI in the actoxumab group compared with the combination group and higher rates of mortality and serious adverse events compared with the placebo group (Wilcox 2017). Lastly, cadazolid, an oxazolidinone/quinolone hybrid antibiotic, after promising phase 2 results subsequently failed to demonstrate noninferiority to vancomycin in one of its two phase 3 clinical trials (Gerding 2019; Louie 2015).

Phase 3

One oral antibiotic, ridinilazole, has reached phase 3 clinical trials. Ridinilazole has a novel mechanism of action which is not yet fully understood (Bassères 2016). In a phase 2 trial, sustained clinical response rates were compared between ridinilazole 200 mg twice daily and vancomycin 125 mg four times daily for 10 days (Vickers 2017). Ridinilazole demonstrated a higher rate of sustained clinical response than vancomycin (66.7% vs. 42.4%, p=0.0004), and no adverse events led to the discontinuation of ridinilazole. Notably, the rate of sustained clinical response in patients treated with vancomycin (42%) was lower than rates previously observed in clinical trials (59.2%–65.7%) (see Figure 1). However, unpublished results from two of its three phase 3 clinical trials (Ri-CoDIFy 1 [ClinicalTrials.gov identifier: NCT03595553] and Ri-CoDIFy 2 [ClinicalTrials.gov identifier: NCT03595566]) indicate that ridinilazole resulted in a higher sustained clinical response rate than vancomycin but did not meet the study primary end point for superiority (Summit 2021). The Ri-CoDIFy 3 (ClinicalTrials.gov identifier: NCT04802837) trial is currently recruiting patients aged 12–18 years.

CONCLUSION

Over time, the best available CDI management has shifted from two relatively broad-spectrum antibiotics (metronidazole and vancomycin) to one narrow-spectrum antibiotic (fidaxomicin) and one nonantibiotic (bezlotoxumab) with significantly lower rCDI rates. The future of CDI therapy may further shift from antibiotic therapies to ultra-narrow-spectrum and *C. difficile*-selective antibiotics paired with microbiome-based therapies to prevent antibiotic-associated dysbiosis and quickly restore the microbiome if disruptions do occur.

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Practice Points

The treatment options available for CDI have largely remained unchanged since the 1980s. However, since the FDA approvals of fidaxomicin in 2011 and bezlotoxumab in 2016, updated guideline recommendations have changed drastically. Nevertheless, inconsistencies are evident between how these newer agents were studied and how clinicians are using them.

- **The IDSA/SHEA and ACG guidelines differ in their recommendations for CDI treatment, especially regarding the role of metronidazole and fidaxomicin.**
- **Vancomycin has long been the standard of care for CDI treatment; however, its negative effects on the gut microbiome and higher rates of CDI recurrence are of concern given the availability of fidaxomicin.**
- **Fidaxomicin clinical trials included mainly patients with primary, nonsevere CDI. Of the patients randomized to fidaxomicin in the four phase 3 clinical trials, between 11.5% and 20.3% had a previous episode of CDI in the 3 months before randomization and 24.0%–39.0% had severe CDI.**
- **Fidaxomicin is noninferior to vancomycin in terms of clinical cure; however, it is associated with lower rates of CDI recurrence. About 10 patients would need to be treated with fidaxomicin instead of vancomycin to prevent one episode of CDI recurrence in the 30 days after antibiotic therapy.**
- **Bezlotoxumab was studied mainly in patients with primary, nonsevere CDI. Of the patients randomized to bezlotoxumab in the two phase 3 clinical trials, 27.7% had at least one previous episode of CDI in the 6 months before randomization and 15.6% had severe CDI.**
- **Bezlotoxumab given concurrently with standard-of-care antibiotic therapy (i.e., metronidazole, vancomycin, or fidaxomicin) is superior to standard-of-care antibiotic therapy alone in preventing CDI recurrence. About 10 patients would need to be treated with bezlotoxumab with standard-of-care antibiotic therapy instead of standard-of-care antibiotic therapy alone to prevent one episode of CDI recurrence in the 84 days after bezlotoxumab infusion.**

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Self-Assessment Questions

1. Which of the following patients with *Clostridioides difficile* infection (CDI) would be most appropriately classified as having health care facility-onset (HO) CDI?

   A. Diagnosed with CDI at an urgent care clinic with no recent health care exposure
   B. Diagnosed with CDI on day 1 of hospitalization with an overnight stay in the hospital 2 weeks ago
   C. Diagnosed with CDI on day 3 of hospitalization with an overnight stay in the hospital 8 weeks ago
   D. Diagnosed with CDI on day 4 of hospitalization with no recent health care exposure

2. A 67-year-old man was recently diagnosed with prostatitis and was treated with levofloxacin for 4 weeks. He presents today because of 5 watery bowel movements in the past 24 hours. He was tested for CDI using a nucleic acid amplification test that can also detect *C. difficile* ribotype 027. Unfortunately, the patient's stool tested positive for ribotype 027, which has been associated with higher rates of mortality. The medical resident you are rounding with asks you if the patient's CDI treatment should be altered based on these results. Which one of the following actions is best to recommend to reduce this patient's risk of mortality?

   A. Add intravenous metronidazole to oral vancomycin.
   B. Administer bezlotoxumab on day 5 of oral vancomycin therapy.
   C. Treat with fidaxomicin monotherapy.
   D. No treatments have evidence demonstrating a lower mortality risk.

3. A 72-year-old woman was admitted 6 days ago for suspected pneumonia. In the past 24 hours she experienced 5 watery bowel movements and is complaining of severe abdominal pain. In addition, her white blood cell count is 16.0×10^3 cells/mm^3 and her SCr is 1.1 mg/dL. A *C. difficile* test is performed and returns positive. Of note, the patient has never been diagnosed with CDI. According to the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA), which one of the following is best to recommend for treatment of this patient's CDI?

   A. Bezlotoxumab
   B. Fidaxomicin
   C. Metronidazole
   D. Vancomycin

Questions 4–6 pertain to the following case.

M.V., a 47-year-old woman with type 2 diabetes mellitus, presents to the ED because of profuse watery diarrhea. A basic metabolic panel and CBC are performed and reveal a WBC of 8.2×10^3 cells/mm^3 and an SCr of 1.2 mg/dL. M.V. states she was recently treated for CDI with vancomycin, which she finished 3 weeks ago.

4. Which one of the following best evaluates M.V.'s CDI?

   A. Primary nonsevere CDI
   B. First CDI recurrence, nonsevere
   C. First CDI recurrence, severe
   D. Fulminant CDI

5. Which one of the following is best to recommend to reduce M.V.'s risk of a future CDI recurrence?

   A. Bezlotoxumab 10 mg/kg once
   B. Fidaxomicin 200 mg twice daily for 10 days
   C. Metronidazole 500 mg three times per day for 14 days
   D. Vancomycin 125 mg four times per day for 10 days

6. Which one of the following risk factors for CDI recurrence best justifies the use of bezlotoxumab for M.V.?

   A. Age
   B. Severity of CDI
   C. Immunocompromise
   D. Prior CDI in the previous 6 months

7. A 61-year-old man presents to the ED with profuse diarrhea. He states that he has had at least 12 unformed stools in the past 24 hours. You find out that he has had 2 previous episodes of CDI in the past 3 months. Which one of the following is best to recommend as "follow-on" or "chaser" therapy following 10 days of vancomycin in this patient?

   A. Bezlotoxumab 10 mg/kg once
   B. Fidaxomicin 200 mg twice daily for 10 days
   C. Rifaximin 400 mg three times daily for 20 days
   D. Tigecycline 100 mg once, followed by 50 mg twice daily for 10 days

8. A 67-year-old man is diagnosed with primary CDI and is prescribed vancomycin. You would like to educate the patient on the treatment and prognosis of his infection. Which one of the following is best to share with this patient regarding the recurrence rate after treatment?

   A. 5%
   B. 15%
   C. 25%
   D. 50%

9. Which one of the following patients with CDI is most likely to benefit from a high-dose vancomycin regimen (i.e., 500 mg four times daily)?

    A. 64-year-old woman admitted to the medicine ward with 3 stools in the past 24 hours
    B. 70-year-old man admitted to the ICU with 3 stools in the past 24 hours
    C. 71-year-old woman admitted to the ICU with decreased bowel sounds and intermittent diarrhea
    D. 56-year-old man admitted to the medicine ward with 6 stools in the past 24 hours

10. The sustained clinical response rates observed in the 2011 randomized controlled trial (RCT) by Louie et al. were 74.6% and 64.1% for those randomized to fidaxomicin and vancomycin, respectively (p=0.006). Which one of the following is the NNT with fidaxomicin instead of vancomycin to see one additional sustained clinical response?

    A. 6 patients
    B. 7 patients
    C. 9 patients
    D. 10 patients

11. The infectious diseases fellow you are rounding with asks you, "What is it about fidaxomicin that makes it less likely to cause CDI recurrence than vancomycin?" Which one of the following is the best educational point about fidaxomicin to share with this colleague?

    A. It is given twice daily whereas vancomycin is given four times daily.
    B. It achieves higher concentrations in the gut than vancomycin.
    C. It is more potent against *C. difficile* than vancomycin.
    D. It prevents sporulation and adheres to *C. difficile* spores while vancomycin does not.

12. You arrive Monday morning and see four new patients with CDI on your list. Based on the post hoc analysis of the MODIFY I/II trials by Gerding et al., which one of the following patients would be most likely to benefit from bezlotoxumab?

    A. 64-year-old woman with primary nonsevere CDI
    B. 70-year-old man with a history of congestive heart failure
    C. 71-year-old woman status post hematopoietic stem cell transplantation
    D. 56-year-old man with a history of CDI 3 years ago

13. A student proposes switching a patient with CDI from metronidazole to vancomycin. Which of the following is the best education point about the limitations of metronidazole for the treatment of CDI to share with this student?

    A. It is associated with higher rates of CDI recurrence compared with vancomycin.
    B. It is more expensive compared with vancomycin.
    C. It is associated with higher rates of mortality compared with vancomycin.
    D. It is associated with lower rates of clinical cure compared with vancomycin.

14. A 79-year-old man is diagnosed with CDI on admission. Shortly after admission he decompensated and is now requiring norepinephrine to maintain his blood pressure. Abdominal radiography does not reveal ileus or megacolon. He has been on oral vancomycin 500 mg four times daily for the past 3 days without any improvement in diarrhea or abdominal pain. Which one of the following intravenous antibiotics is best to recommend adding to oral vancomycin in this patient?

    A. Fidaxomicin
    B. Vancomycin
    C. Rifampin
    D. Tigecycline

15. A 55-year-old man with acute myeloid leukemia recently underwent an allogeneic hematopoietic stem cell transplantation. The patient is receiving levofloxacin 500 mg once daily for prophylaxis. The attending physician calls and asks you for a recommendation regarding antibiotic prophylaxis for CDI. Which one of the following is best to recommend for this patient?

    A. Fidaxomicin 200 mg once daily
    B. Metronidazole 500 mg twice daily
    C. Vancomycin 125 mg once daily
    D. Vancomycin 125 mg twice daily