

# Evolution of clinical guidelines for antimicrobial management of *Clostridioides difficile* infection

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Ther Adv Gastroenterol

2021, Vol. 14: 1–16

DOI: 10.1177/  
17562848211011953

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**Abstract:** *Clostridioides difficile* infection (CDI) has been an epidemic for many years. Our biggest challenge in treating CDI is preventing recurrence, which is seen in approximately 25% of patients with initial infection and in 40–60% of those with subsequent episodes. Given the major disease burden of this infection, appropriate data-driven treatment remains essential. Clinical treatment guidelines provide an unbiased critical analysis of the literature, integrating the quality of the available data to make recommendations. As CDI has been evolving and more research has become available, the frequency of guideline issue from various global societies has increased, as has the detail of the recommendations to fit more relevant clinical scenarios. In this review, we will discuss clinical guideline recommendations over three time periods: The Initial Guidelines 1995–1997, The Second Wave 2009–2013, and The Modern Era 2014–present. We see the changing recommendations from metronidazole or vancomycin for initial infection during earlier times to preferential treatment with fidaxomicin within the Infectious Diseases Society of America (IDSA) and Society of Healthcare Epidemiology of America (SHEA) joint guidelines provisional update in late 2020. The recommended treatments for first recurrence were initially with the same antimicrobial as the first episode but have since changed to having multiple options for one or more recurrences. We have also seen the addition of immune boosting treatments, including fecal microbiota transplantation (FMT)/microbiota restoration therapy (MRT) and bezlotoxumab in the more modern recommendations. As the guidelines are evolving with the times, it remains important to understand the differences among them so we can apply this information clinically and optimize patient outcomes.

**Keywords:** antibiotics, antimicrobials, *Clostridioides difficile*, guidelines

Received: 10 January 2021; revised manuscript accepted: 31 March 2021.

## Introduction

Evolution of Guideline-Based Antimicrobial Recommendations to Treat *C. difficile* Infection. *Clostridioides difficile* infection (CDI) is the most common healthcare-associated infection in the United States (US),<sup>1</sup> imposing a major burden on our healthcare system and affecting approximately 365,000 people annually.<sup>2</sup> The financial burden of managing this infection is significant as well. It is estimated that all-cause direct medical costs for a population aged 18–64 were approximately US\$72,000 for those with no recurrence and approximately US\$200,000 for those with three or

more recurrences.<sup>3</sup> Given these considerations, optimizing therapies with data-driven recommendations by experts in the field can be most beneficial to minimize the burden of this disease on our patients, lessen the frequency of recurrence, and improve overall outcomes. Clinical guideline recommendations are an essential tool guiding treatment as they summarize data for a disease and provide algorithms to manage patients based on data that has been critically validated.

The CDI epidemic essentially began in the mid-1990s and continues to this day. As this epidemic has extended, there have been more reports and

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studies considering this infection. When searching “*C. difficile*” in PubMed, there were 68 references in 1995. In 2020, there were 726. With this influx of new studies, there have been surprisingly few well-performed prospective randomized controlled trials comparing treatments head-to-head. As a result, we rely on smaller studies or non-standard designs to guide our treatments for CDI and recurrent disease. This reliance on imperfect studies has led to certain foundational treatments becoming standard without the supporting data that we would typically expect from a clinical guideline that impacts care as significantly as guidelines for the management of CDI. Given these limitations, it is important to understand how the guidelines have changed over time, and, most importantly, what foundational studies have paved the way for the most recent recommendations in order for clinicians to make decisions that are most appropriate for their patients with the best insights to the data that support those decisions.

There are currently only two US Food and Drug Administration (FDA) approved treatments for CDI: vancomycin and fidaxomicin. Fidaxomicin was approved for use in adult patients with initial episode of CDI in 2011. Metronidazole has never received FDA approval and is used off label. With this basic understanding, this manuscript is designed to describe the evolution of the antimicrobial treatment guidelines in the US, including all global guidelines to compare and contrast the recommendations understanding the differences among these documents and how they have evolved over time. It is important to consider that, outside of the US, the impact of CDI and associated strains are seen differently and this will influence the recommendations made. The priority of this manuscript is to focus on the changes in these guideline documents over the prior decade.

### Pathophysiology of CDI and overview of treatments

In order to best understand the antimicrobial approach to treatment of CDI, it is important to review the basic pathophysiology of this infection. *C. difficile* is a Gram-positive, spore-forming anaerobic rod. As such, there are two main phases: the spore phase and the vegetative phase. The vegetative phase, which is susceptible to gastric acid and alcohol-based hand sanitizers, releases two main toxins that stimulate the diarrheal syndrome most commonly associated with CDI: toxin A and toxin B.<sup>4-6</sup> Since this bacterium

is anaerobic, its vegetative phase is unable to survive outside of the host. This is the phase of infection that antimicrobials target. The spore phase, alternatively, is much heartier in that it is resistant to gastric acid and alcohol-based hand sanitizers. It can remain viable for many months on dry surfaces.<sup>4-6</sup> The spore phase can germinate and in effect convert itself to the vegetative phase when in an optimal environment for this process. This restarts the active infection either in a new host as part of a *de novo* infection or in the same host in the form of a recurrence.

There are several treatment options for CDI. These include therapies that target the vegetative phase, including the antimicrobials metronidazole, vancomycin, and fidaxomicin. Other supplementary treatments boost the immune system. Bezlotoxumab is a fully humanized monoclonal antibody that is specific to toxin B. This treatment enhances the blood-borne immune system targeting and blocking toxin B, minimizing some of the inflammatory effects of this toxin.

Microbiota replacement therapy (MRT) enhances colonization resistance. MRT will be discussed in more detail in other sections of the special issue but will be alluded to within this manuscript simply to reference to how guidelines chose to include this treatment as part of their algorithm.

Treatment of CDI requires two things: eradication of the vegetative phase with antimicrobials and subsequent elimination of the spore phase *via* the patient’s microbiota. Therefore, if the microbiota is not able to eradicate the spore phase, it is likely to convert to the vegetative phase, resulting in a recurrence. Recurrence is a major challenge as it is estimated that approximately 25% of patients treated initially for this infection will recur and, of those, approximately 40% will go on to recur after that, with 50–60% thereafter.<sup>6-8</sup> Breaking this cycle of recurrence is of the utmost importance in effectively treating this infection. Given this, guidelines frequently focus on reduction of recurrence.

One final, but important, consideration with regards to treatments of CDI, is that a therapy must gain access to the lumen of the colon to be effective. If a treatment does not concentrate in the colon, then it will be unable to treat CDI.

Metronidazole (Table 1) is an antimicrobial belonging to the nitroimidazole class of antibiotics. It

**Table 1.** Antimicrobials to treat *C. difficile* infection.

Antimicrobial	Dose/duration	Mechanism of action
Metronidazole	500 mg TID orally for 10–14 days	Nitroimidazole class of antimicrobial that blocks the helical DNA structure, causing strand breakage, inhibition of protein synthesis and ultimately cell death in susceptible organisms <sup>9</sup>
Vancomycin	Vancomycin, 125 mg PO QID for 10–14 days Vancomycin 500 mg PO QID Vancomycin 500 mg PR QID	Glycopeptide antimicrobial that inhibits bacterial cell wall synthesis and at therapeutic concentrations this is believed to be bacteriostatic. <sup>11</sup> The oral formulation is minimally absorbed into systemic circulation.
Fidaxomicin	200 mg PO Bid for 10 days	Macrocyclic antibiotic that is bactericidal acting by inhibiting RNA synthesis. <sup>12</sup> This is minimally absorbed into systemic circulation.

PO, by mouth; QID, four times per day; TID, three times per day; Bid, two times per day.

blocks the helical DNA structure, causing strand breakage, inhibition of protein synthesis, and ultimately cell death in susceptible organisms.<sup>9</sup> Metronidazole is unique in that it is the only antimicrobial we use to treat CDI that can be used intravenously. The reason for this is that metronidazole is released from the biliary tree into the fecal stream in an active form. Therefore, the intravenous form is released into the fecal stream and accesses the colon, as does the oral form. The oral form is also absorbed into systemic circulation and thought to be released at sites of inflammation such as the colon in the setting of CDI infection. Once inflammation is brought under control, metronidazole is thought to have a lower concentration; that is one theory explaining why recurrence rates are higher with this treatment.<sup>10</sup> Side effects of metronidazole include a metallic taste in the mouth, nausea, headache, dizziness, and abdominal pains.<sup>6</sup>

Vancomycin (Table 1) is a glycopeptide antimicrobial with minimal systemic absorption when taken orally. This medication stays within the lumen of the bowel and has high concentrations in the colon.<sup>11</sup> Intravenous vancomycin is excreted renally and so plays no role in the treatment of CDI as this formulation never accesses the colon. Vancomycin inhibits bacterial cell wall synthesis and, at therapeutic concentrations, this is believed to be bacteriostatic.<sup>11</sup> It is this bacteriostatic effect that some believe results in the recurrences seen with this antimicrobial. Side effects of vancomycin include abdominal pain, flatulence, nausea, headache, and

peripheral edema. It is also important to remember that patients receiving vancomycin can, rarely, develop red-man syndrome from this therapy.<sup>9</sup>

Fidaxomicin (Table 1) is a bactericidal macrocyclic antibiotic acting by inhibiting RNA synthesis. Fidaxomicin is minimally absorbed into systemic circulation and is lumenally active throughout the digestive tract.<sup>12</sup> This antimicrobial, approved by the FDA for the treatment of initial episode of CDI in 2011, is the first to target *C. difficile* and have a minimal effect on surrounding colonization resistance. Metronidazole and vancomycin both have activity against CDI, but also impact the surrounding microbiota, whereas fidaxomicin has minimal effect on surrounding microbial species. Clinically, this translates to lower recurrence rates.<sup>12</sup> Side effects of fidaxomicin include nausea, vomiting, abdominal pains, gastrointestinal bleeding, anemia, and neutropenia.<sup>12</sup>

Bezlotoxumab is a fully humanized monoclonal antibody that is given as a one-time infusion, in addition to a standard of care antimicrobial. It is specific for toxin B, is associated with decreased rates of recurrence, and was approved by the FDA in 2017 for those patients at increased risk of recurrence.<sup>13</sup> Bezlotoxumab has a half-life of approximately 19 days and, therefore, will remain within patients systems in appreciable quantities for 3 months. Side effects of this therapy include nausea, pyrexia, and headache.<sup>13</sup> There is one group that requires specific attention when considering bezlotoxumab; those with congestive

heart failure (CHF). In the original randomized controlled trials comparing standard of care antimicrobial plus either bezlotoxumab or placebo, those who received bezlotoxumab with CHF went on to have an exacerbation of their CHF more frequently than those who received placebo.<sup>13</sup>

Microbiota replacement therapy or fecal microbiota transplantation has progressed over the prior decade, with very few providers performing this 10 years ago but more recently much greater access. Access was greatest prior to the onset of the COVID-19 pandemic; however, since that time many stool banks have been unable to distribute this therapy to providers due to concerns regarding transmission of COVID-19.<sup>14</sup> MRT is used following a standard of care antimicrobial treatment course. It is known that patients with CDI are deficient in two main phyla: Bacteroidetes and Firmicutes.<sup>15</sup> By replacing these phyla with MRT, this reinforces colonization resistance and helps eradicate the spore phase of CDI, thereby reducing rates of recurrence of the infection.<sup>16,17</sup> There have been some concerns regarding safety of MRT when performed using banked stool but these appear to be rare.<sup>18</sup> Side effects of MRT in general include abdominal cramps, bloating, constipation, transient loose stools, and flatulence.<sup>16</sup>

### Guideline overview

*C. difficile* is a unique disease in that both infectious disease providers and gastroenterologists see and manage these patients. As such, guidelines from both disciplines will be reviewed, compared and contrasted. The goal of this manuscript is to focus on the evolution of the guidelines and changes over the last few years, but it is important from a foundational standpoint to understand the recommendations prior to the modern era to contextualize how they have evolved into what is recommended today. It is best to break these publications into three time frames: 1995–1997, 2009–2013, and 2014 to the present.

### The initial guidelines: 1995–1997

#### *Society of Healthcare Epidemiology of America*

The first major position paper outlining diagnosis and treatment of CDI came from the Society for Healthcare Epidemiology of America (SHEA) in 1995 from Gerding *et al.*<sup>19</sup> There were limited data and mostly expert recommendations. Within

this manuscript, it was recommended that patients receive either metronidazole orally at a dose of 250 mg four times a day (QID) or 500 mg three times a day (TID) or vancomycin 125 mg QID orally for 10 days, though metronidazole was preferred given its lower cost and decreased risk of developing vancomycin-resistant infections. They recommended that those who had a recurrence be treated in the same manner as the initial infection. The simplistic nature of this position paper mimicked the less frequent occurrence of the disease at the time and the lack of challenge around recurrence that would be seen in the future.

#### *American College of Gastroenterology guidelines*

American College of Gastroenterology wrote their initial guidelines in 1997.<sup>20</sup> Within these, they advised that oral metronidazole be used as a first line in confirmed and ‘highly suspicious’ cases. They recommended oral vancomycin for those with metronidazole-resistant organisms, who are critically ill, pregnant, or under the age of 10 years. For those with a recurrence, the same treatment was recommended again following the criteria listed for usage of metronidazole or vancomycin for an initial infection.<sup>20</sup> Within this guideline, multiple recurrences were addressed, albeit with the notation that ‘No treatment in the United States has been proven to prevent recurrences.’ For those patients with multiply recurrent CDI, it was recommended that they receive either a standard course of oral metronidazole or vancomycin, vancomycin, or metronidazole for 1–2 months, given either intermittently or with gradual tapering, with or without adjunctive therapy including an oral anion-binding regimen such as cholestyramine or colestipol to be started at the end of antimicrobial course and gradually tapered or oral vancomycin plus rifampin.<sup>20</sup> Although the data were limited, consideration was recommended for oral yogurt, *Lactobacillus* preparations or *Lactobacillus* GG, *Saccharomyces boulardii* (500 mg orally twice daily) for immunocompetent patients for 1 month, starting day 6 of a 10-day antimicrobial course, or human immunoglobulin for those with immune deficiencies.<sup>20</sup> This guideline introduced some more variation in options to treat recurrences and also provided specific indications for specialized patient populations, but was again limited by a lack of data to support the various treatments.

### The second wave: 2009–2013

This group of guidelines was built largely upon many small trials comparing vancomycin with mostly metronidazole but also placebo, bacitracin, rifaximin, teicoplanin, and nitazoxanide.<sup>21</sup> One trial that pre-dated this guideline era was perceived to be foundational, changing the way we thought about antimicrobial indications in those with CDI and creating a structure for the guidelines published between 2009 and 2013. Zar *et al.* conducted a study comparing metronidazole 250 mg PO QID head-to-head with vancomycin 125 mg PO QID for 10 days. Within this trial, patients were triaged into those with mild or severe disease based on non-standard criteria. Patients with at least two of the following criteria were deemed to have severe disease: age >60 years, temperature >38.3°C, albumin ≤2.5 mg/dl, or white blood cell count (WBC) >15,000 cells/mm<sup>3</sup>.<sup>22</sup> For those with mild disease, the initial response (98% versus 90%) and recurrence rates (5% versus 8%) were similar for those receiving metronidazole and vancomycin; however, those with severe disease had statistically significantly better initial response rates (97% versus 76%) and lower recurrence rates (10% versus 21%) when receiving vancomycin.<sup>22</sup> This trial was, at that time, the best prospective randomized controlled trial comparing metronidazole and vancomycin and was widely referenced as evidence for making guideline recommendations. Of note, this study had limitations. It included a total of 150 patients who were enrolled between 1994 and 2002. Thus, a small number of patients were enrolled over a long time while the epidemic was evolving. In addition, this study used non-standard criteria to separate those with mild versus severe disease. Regardless, this was the best performed study to date and, as a result, this next generation of guidelines and recommendations for treatment of initial infection were based largely upon this trial.

### European Society of Clinical Microbiology and Infectious Diseases

In 2009, Bauer *et al.* organized the first true European treatment guideline (Table 2)<sup>21</sup>. Within these guidelines, we saw the evolution of recommendations now acknowledging the importance of triaging the patient's severity of disease. The authors were less definitive with regards to which factors were most important, instead choosing to list a group of considerations for disease severity including laboratory investigations (e.g., WBC > 15 × 10<sup>9</sup>/L,

band neutrophils >20% of leukocytes, rise in serum creatinine (Cr) >50% above baseline, elevated serum lactate), endoscopic findings (e.g., pseudomembranous colitis), and imaging (e.g., distension of the large bowel).<sup>21</sup> The authors felt that there was insufficient evidence to set more definitive criteria for severity, but remarked that severity of disease should play a role in antimicrobial treatment choice. This relates back to the Zar *et al.* study that supported vancomycin use ahead of metronidazole in those with more severe forms of CDI.<sup>22</sup>

These guidelines were also the first to acknowledge that some patients are unable to take oral intake either due to an ileus or other medical comorbidities. Given this, they recommended instilling vancomycin directly *via* enema. This was a foundational addition that was clinically relevant and remains in the current guidelines as well.

The novelty of this guideline continued by recommending a vancomycin taper or pulse as treatment of recurrent CDI. A 'taper' is defined as slowly decreasing the dose of the medication over an extended period of time and a 'pulse' involves giving a fixed dose on a schedule that skips days between medication administration. Theoretically, a taper will continue to suppress *C. difficile* from proliferating while the lower dose will minimize 'collateral' damage to the microbiota, allowing the microbiota to rejuvenate and minimizing the risk of recurrence. A pulse is believed to work by mimicking the life cycle of CDI and therefore minimizing the ability of the bacterium to proliferate. The most quoted study to validate a taper/pulse method was that by McFarland and colleagues, who took a cohort from another trial considering *Saccharomyces boulardii* to prevent recurrent CDI and assessed those patients who recurred who did not receive the *S. boulardii* and randomized them to receive either vancomycin 1 g per day for 7–14 days, vancomycin 2 g per day for 7–14 days, a taper of vancomycin, or a pulse of vancomycin. It turned out that those who received the high dose vancomycin recurred frequently, those who received the tapered dose recurred 31.0%, while those that received a pulse recurred 14.3%.<sup>8</sup> Studies such as this supported adding these alternative treatment regimens to the guidelines. Within the 2009 European guideline, a vancomycin taper or pulse was reserved for those patients with two or more recurrences given a shortage of well-controlled trials to assess this regimen's efficacy.

**Table 2.** European society of clinical microbiology and infectious diseases.<sup>21</sup>

Clinical definition	Recommended treatment in adults
Initial, mild clearly induced by the use of antibiotics	Stop the inducing antibiotic. Observe patients closely for any signs of clinical deterioration and place on therapy immediately if this occurs.
Initial and first recurrence, non-severe	If oral therapy possible: Metronidazole, 500 mg TID orally for 10 days
	If oral therapy not possible: Metronidazole 500 mg TID intravenously for 10 days
Initial and first recurrence, severe	If oral therapy possible: Vancomycin, 125 mg QID orally for 10 days
	If oral therapy not possible: Metronidazole 500 mg TID intravenously for 10 days plus intracolonic vancomycin 500 mg in 100 ml of normal saline every 4–12 h and/or vancomycin 500 mg QID by nasogastric tube
	Second and later recurrences
Second and later recurrences	If oral therapy is possible:
	<ul style="list-style-type: none"> <li>• Vancomycin 125 mg QID orally for at least 10 days</li> <li>• Consider a taper (for example, decreasing daily dose with 125 mg every 3 days)/pulse (e.g. a dose of 125 mg every 3 days for 3 weeks) strategy</li> </ul>
	If oral therapy is impossible: <ul style="list-style-type: none"> <li>• Metronidazole 500 mg TID intravenously for 10–14 days plus retention enema of vancomycin 500 mg in 100 ml of normal saline every 4–12 h and/or vancomycin 500 mg QID by nasogastric tube</li> </ul>
QID, four times per day; TID, three times per day.	

*Infectious Diseases Society of America and Society of Healthcare Epidemiology of America joint guidelines*

In 2010, the Infectious Diseases Society of America (IDSA) and Society of Healthcare Epidemiology of America (SHEA) put forward joint guidelines for the diagnosis and management of CDI in the US (Table 3).<sup>4</sup> These guidelines focused their recommendations on triaging disease severity, choosing WBC > 15,000 × 10<sup>9</sup>/l and a creatinine > 1.5 times baseline value as two thresholds to define severe disease.<sup>4</sup> This was different from the European guidelines as this allowed for more definitive simplistic criteria to triage severity.

The IDSA/SHEA followed the findings of Zar *et al.* for treatment of initial infection, recommending

oral metronidazole for “mild or moderate” CDI and vancomycin for severe disease.<sup>4</sup> They chose to define ‘severe, complicated’ as those who have hypotension, shock, ileus, or megacolon, and that cohort would receive the higher dose vancomycin 500 mg by mouth (PO) QID with intravenous metronidazole 500 mg TID. For those with an ileus or unable to take oral intake, rectal instillation of vancomycin was recommended. Their recommendations for the first recurrence, and two or more recurrences, were similar to the European guidelines from 2009 as well.

*Australasian society for infectious disease*

As the third contribution from this grouping, the Australasian guidelines mostly followed suit with

**Table 3.** IDSA and SHEA joint guidelines.<sup>4</sup>

Clinical definition	Recommended treatment
Initial episode	Metronidazole, 500 mg TID orally for 10–14 days
Mild or moderate	
Initial episode	Vancomycin, 125 mg QID orally for 10–14 days
Severe	
Initial episode	Vancomycin, 500 mg, QID orally or nasogastric tube, plus metronidazole, 500 mg Q8H intravenously. If complete ileus, consider adding rectal instillation of vancomycin
Severe, complicated	
First recurrence	Same as for initial episode
Second recurrence	Vancomycin in a tapered and/or pulsed regimen

IDSA, Infectious Diseases Society of America; QID, four times per day; SHEA, Society of Healthcare Epidemiology of America; TID, three times per day.

the previously published recommendations (Tables 4 and 5).<sup>23</sup> They were similar to the European and IDSA/SHEA guidelines with regards to treatment of initial, first, and two or more recurrences, with the caveat that they recommended metronidazole 400 mg orally three times daily instead of the 500 mg dose recommended by the other societies. Also, the Australasian guidelines recommended triaging severity using a long list of potential factors, similar to the European guidance from 2009, instead of the two factors recommended by the IDSA/SHEA in 2010.

What we can see from the Australasian contribution is the great interest in CDI and the many different treatment approaches being considered as the incidence of disease was increasing and the epidemic worsening (Table 5). From this extensive list of ‘potential’ regimens, this guideline was the first to mention fecal enema, rifaximin, and antibodies to toxin A or B as having some evidence but an unclear role.<sup>23</sup> This was in fact a vision of the future among many other therapies that did not ultimately gain the evidence needed to be formally placed within subsequent guideline recommendations.

#### *American College of Gastroenterology*

In 2013, the American College of Gastroenterology (ACG) published their guidelines (Table 6).<sup>5</sup>

They recommended triaging severity based upon patients having an albumin <3 mg/dl plus either WBC  $\geq 15,000$  cells/mm<sup>3</sup> or abdominal tenderness.<sup>5</sup> This was in contrast to the IDSA/SHEA 2010 guideline recommending a focus on WBC and creatinine. The justification for using albumin and WBC was that these were direct indicators of toxin activity (e.g., protein losing colopathy and leukemoid reaction) *versus* the creatinine being an indicator of volume shifts secondary to the diarrheal syndrome. One could argue that albumin is an acute-phase reactant and that those patients who are nutritionally depleted, and therefore have a low albumin, are at risk for CDI as well, making this a less accurate measurement. Various studies support all three (e.g., WBC, Cr, and albumin) being predictors of 30-day colectomy, mortality, or both.<sup>4,5</sup>

It is important to note that there was a major development in the treatment of CDI that occurred between the Australasian Guideline publication and the ACG manuscript: fidaxomicin was approved by the FDA and became available. The foundational studies that validated fidaxomicin usage were two parallel phase III, randomized controlled trials including over 1000 patients in total. These studies were the first well-structured, large-scale trials considering any treatment of CDI and comparing it with a standard of care therapy. One trial was a North American analysis and the other included a global population. These studies showed

**Table 4.** Australasian Society for Infectious Disease guidelines.<sup>23</sup>

Clinical definition	Recommended treatment in adults
Initial episode, non-severe	If oral therapy possible: Metronidazole 400 mg PO TID for 10 days
	If oral therapy not possible: Metronidazole 500 mg IV every 8 h for 10 days
Initial episode, severe	If oral therapy possible: Vancomycin 125 mg PO QID for 10 days
	If oral therapy not possible: Metronidazole 500 mg IV every 8 h for 10 days plus a retention enema of vancomycin, 500 mg in 100 ml of normal saline every 4–12 h and/or vancomycin 500 mg four times daily by nasogastric tube
First recurrence	Same as initial episode
Second recurrence	Vancomycin in a pulsed and/or tapering course (e.g., 125 mg orally, four times daily for 14 days, then 125 mg twice daily for 7 days, then 125 mg every second day for 2–8 weeks)

PO, by mouth; QID, four times per day; TID, three times per day.

**Table 5.** Australasian Society for Infectious Disease.<sup>23</sup>

Alternative Potential Regimens with 'some evidence of efficacy but unclear role'
Bacitracin, 20 000 units orally, four times daily for 7 days
Fusidic acid, 500 mg orally, three times daily for 10 days
Teicoplanin, 100–400 mg orally, twice daily for 10 days
Tigecycline, 100 mg intravenous loading dose, then 50 mg twice daily for 14–21 days
Rifampicin, 300–600 mg orally, twice daily (in combination with vancomycin for relapse) for 7–10 days
Rifaximin, 200 mg orally, three times daily for 10 days
Nitazoxanide, 500 mg orally, twice daily for 7–10 days
Tolevamer, 6 g orally, daily for 14 days
Antibodies to <i>C. difficile</i> toxins A and B (anti-TcdA and anti-TcdB, 10 mg/kg, single dose in combination with metronidazole or vancomycin)
Fecal enema — consider logistical issues; donor screening required
Intravenous gammaglobulin

that fidaxomicin at a dose of 200 mg orally twice daily for 10 days was similar to vancomycin when considering initial treatment response following completion of the antimicrobial, but that, when

comparing rates of recurrence, fidaxomicin had statistically significantly lower rates of recurrence compared with vancomycin.<sup>12,24</sup> The authors of the ACG guideline chose not to recommend use of



**Table 6.** American College of Gastroenterology guidelines.<sup>5</sup>

Clinical definition	Recommended treatment in adults
Initial episode, mild-moderate	Metronidazole 500 mg orally TID for 10 days
Initial episode, severe	Vancomycin 125 mg orally QID for 10 days  Vancomycin should be given in patients who are pregnant, breast feeding, intolerant/allergic to metronidazole or those who have not responded within 5–7 days of metronidazole therapy
	In those unable to take oral antimicrobials: Vancomycin delivered <i>via</i> enema should be added to treatments above until the patient improves
Initial episode, severe-complicated	Those without ileus: Metronidazole 500 mg IV TID in addition to vancomycin 500 mg PO QID.  Those with ileus or toxic megacolon and/or significant abdominal distention: Give both oral and rectal vancomycin along with intravenous metronidazole.
First recurrence	Utilize the same regimen used in the initial episode (if severe then vancomycin should be given)
Second recurrence	Repeat metronidazole or vancomycin pulse regimen
Third recurrence and beyond	Consider fecal microbiota transplantation

ACG, American College of Gastroenterology; IV, intravenous; PO, by mouth; QID, once per day; TID, three times per day.

fidaxomicin for several reasons. They felt that the follow up in the trials for fidaxomicin (25 days) was insufficient to truly compare rates of recurrence. They thought that fidaxomicin's non-inferiority to vancomycin with regards to the NAP1/BI/027 strain was unclear. Finally, they were concerned that potential resistance of CDI to fidaxomicin and the associated costs of this therapy were all potential hindrances. These thoughts were very surprising at the time since the alternative treatments, including metronidazole, had undergone much less rigorous trials, but were mainstays in the recommended algorithm. Over time and with more data, the efficacy of fidaxomicin was reinforced and this became a fixture within subsequent guidelines.

The ACG guidelines did provide several new elements, including being the first to formally recommend consideration for MRT/FMT for those patients with three or more recurrences. They also provided guidance on management of CDI in special populations such as those with inflammatory bowel disease. Although controversial, with their handling of factors to consider with regards to severity and leaving fidaxomicin out of their treatment algorithm, these guidelines

pushed the meter forward with regards to structuring a guideline, addressing specific populations, and including MRT/FMT as a consideration for those with multiply recurrent disease.

### The modern era, 2014–present

The modern era of therapeutics to treat CDI includes further consideration of next-generation therapies including fidaxomicin, MRT/FMT, and bezlotoxumab.

#### *European Society of Clinical Microbiology and Infectious Diseases*

Severity in the European Society of Clinical Microbiology and Infectious Diseases guidelines was again subtly different from prior recommendations (Table 7).<sup>25</sup> If patients had any one of the following, they were considered severe: WBC > 15 × 10<sup>9</sup>/l, decreased albumin < 3 mg/dl, or rise in serum creatinine to > 1.5 times pre-morbid level.<sup>25</sup> This combines the IDSA/SHEA 2010 and ACG 2013 guidance, including WBC, Cr, and albumin. In practice, this is probably the most relevant approach as the practicing clinician should know to consider

**Table 7.** European Society of Clinical Microbiology and Infectious Diseases guidelines.<sup>25</sup>

Clinical definition	Recommended treatment in adults
Initial episode, non-severe	Any of the following:
	Metronidazole orally 500 mg TID for 10 days (preferred)
	Vancomycin orally 125 mg QID for 10 days
	Fidaxomicin orally 200 mg BID for 10 days
	When oral treatment is not possible: IV metronidazole 500 mg TID for 10 days
Initial episode, severe	If oral therapy possible:
	Either: Vancomycin orally 125 mg QID for 10 days (may consider 500 mg QID if needed) or fidaxomicin orally 200 mg bid (only in non-life-threatening cases)
	If oral therapy not possible:
	IV metronidazole combined with rectal (or oral using nasogastric tube) vancomycin. Tigecycline is another option that can be used as a salvage therapy but with limited evidence
First recurrence	Any of the following:
	Fidaxomicin 200 mg orally BID for 10 days
	Vancomycin 125 mg orally QID for 10 days
	Metronidazole 500 mg orally TID for 10 days
Second recurrence	Any of the following:
	Fidaxomicin 200 mg orally BID for 10 days
	Vancomycin 125 mg orally QID for 10 days followed by either a pulse or a taper
Third recurrence and beyond	Patients with multiple recurrent cases non-responsive to oral antibiotics, FMT should be strongly considered

BID, two times per day; FMT, fecal microbiota transplantation; IV, intravenous; PO, by mouth; QID, four times per day; TID, three times per day.

each of these factors when trying to best understand the risks when a patient presents with CDI.

The addition of fidaxomicin within these guidelines was a major step forward in the treatment of CDI as this offered a new option for providers that had strong data supporting it. Debast *et al.* did note that for initial non-severe infection, patients should preferentially use metronidazole over vancomycin and fidaxomicin but, for severe disease, either vancomycin or fidaxomicin would be appropriate.<sup>25</sup> Within this manuscript, there is a comprehensive discussion considering whether metronidazole, vancomycin, or fidaxomicin would be superior, but

the authors felt that there was insufficient evidence to support one therapy over another so it was recommended to consider all three. This was the last guideline to consider metronidazole in the treatment of recurrent CDI as more data became available showing decreasing efficacy for this therapy.

#### *Australasian Society for Infectious Disease*

Triaging severity in the Australasian Society for Infectious Disease guidelines from 2016 was broader than some of the other recent guidelines (Table 8).<sup>26</sup> They once again provided an extensive list of important factors, including clinical (e.g.,

**Table 8.** Australasian society for infectious Disease.<sup>26</sup>

Clinical definition	Recommended treatment in adults
Initial episode, non-severe	Metronidazole 400 mg orally TID for 10 days
Initial episode, severe	If oral therapy possible: Oral vancomycin 125 mg QID for 10 days  If oral therapy not possible: IV metronidazole 400 mg TID with vancomycin 125 mg QID via nasogastric tube with consideration for rectal vancomycin 500 mg in 100 cc normal saline TID or QID
First recurrence	Vancomycin 125 mg orally QID for 10 days
Second or subsequent recurrence	Any of the following:  Vancomycin 125 mg orally QID for 14 days with or without a taper  Fidaxomicin 200 mg orally BID for 10 days  FMT  Rifaximin chaser 400 mg TID for 7–10 days or 400 mg TID 14–20 days post initial therapy

FMT, fecal microbiota transplantation; IV, intravenous; QID, four times per day; TID, three times per day.

fever >38.5°C, hemodynamic instability, peritonitis, ileus, or megacolon), laboratory (e.g., WBC >15 × 10<sup>9</sup>/l and >20% neutrophils, elevated lactate level, rise in creatinine >50% above baseline, albumin <25 mg/dl), and others (e.g., large intestine distension, colonic wall thickening, fat stranding, unexplained ascites, and pseudomembranes seen on colonoscopy).<sup>26</sup> If a patient had one or more of these factors, these guidelines classified them as having severe disease. While this is an inclusive approach, many clinicians might not be able to remember this extensive list of factors, so this approach might be more challenging to apply clinically when compared with the IDSA usage of WBC and Cr from 2010, the ACG's usage of decreased albumin with either abdominal tenderness or elevated WBC in 2013, or the European 2014 recommendations to use all three.<sup>4,5,25</sup>

When considering antimicrobial treatments, these guidelines were a lateral step from the 2014 recommendations from the European society. For the initial episode, despite the knowledge that fidaxomicin was efficacious and showed lower rates of recurrence in those with initial episodes and first recurrence,<sup>27</sup> these guidelines held back from recommending fidaxomicin for initial therapy, instead stating that this would be a treatment alternative in recurrent CDI, especially in those with a high risk of relapse. What was interesting about this recommendation was the mechanism by which

fidaxomicin is believed to lower recurrence rates. Essentially it does this by having a minimal effect on the surrounding microbiota, targeting *C. difficile* specifically. Therefore, using this earlier in the treatment algorithm, the way it was studied in the two pivotal phase III clinical trials, would be theoretically most effective since, once a patient recurs, there is known to be significantly decreased microbial diversity that is much more challenging to recover without MRT.<sup>15</sup> With this in mind, these guidelines were similar to the recommendations from the IDSA/SHEA in 2010 and ACG from 2013 when considering treatment of the initial episode and, for first recurrence, use of vancomycin 125 mg orally QID for 10 days was recommended, eliminating the possibility of a second course of metronidazole in those that recurred.<sup>4,5</sup> With this in mind, the epidemiology of CDI was different in Australia and Asia at the time, and these recommendations were most appropriate for that clinical milieu.

This guideline was the first to start to diversify options in the treatment of those with two or more recurrences. This reflects the trends being observed clinically. A study by Ma *et al.* considering a US cohort of patients who had commercial insurance from 2001 to 2012, found that the annual incidence of CDI increased 42.7%, but the annual incidence of those with multiple recurrences of CDI increased 188.8%.<sup>28</sup> The Australasian Guidelines from 2016 started to formally recommend alternative treatment

**Table 9.** IDSA and SHEA joint guidelines.<sup>6</sup>

Clinical definition	Recommended treatment of initial infection
Initial episode non-severe	Vancomycin 125 mg orally QID for 10 days, OR
	Fidaxomicin 200 mg orally BID for 10 days
	Alternate if above agents are unavailable: metronidazole, 500 mg TID by mouth for 10 days
Initial episode severe	Vancomycin 125 mg orally QID by mouth for 10 days, OR
	Fidaxomicin 200 mg orally BID for 10 days
Initial episode, fulminant	Vancomycin 500 mg QID by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole 500 mg every 8 h should be administered together with oral or rectal vancomycin, particularly if ileus is present.

BID, twice per day; IDSA, Infectious Diseases Society of America; FMT, fecal microbiota transplantation; IV, intravenous; QID, four times per day; SHEA, Society of Healthcare Epidemiology of America; TID, three times per day.

**Table 10.** Infectious Diseases Society of America (IDSA) and Society of Healthcare Epidemiology of America (SHEA) joint guidelines.<sup>6</sup>

Treatment of first recurrence
Vancomycin 125 mg orally given 4 times daily for 10 days if metronidazole was used for the initial episode, OR
Use a prolonged tapered and pulsed vancomycin oral regimen if a standard regimen was used for the initial episode (e.g., 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR
Fidaxomicin 200 mg orally given twice daily for 10 days if vancomycin was used for the initial episode

IDSA, Infectious Diseases Society of America; SHEA, Society of Healthcare Epidemiology of America.

options for these challenging patients. Within the management of second or subsequent recurrence, the authors again reinforced MRT as a viable option for those most appropriate to receive this treatment.

In addition, a novel usage of rifaximin, a rifamycin derivative that is poorly absorbed, was added to potential therapies for those patients with two or more recurrences. There were some precursor studies providing support for use of rifaximin in those with CDI, but probably the most quoted study was that by Garey *et al.*, including 68 patients with CDI who each received vancomycin 125 mg PO QID for 10 days and were then randomized to either receive placebo or rifaximin 400 mg PO TID for 20 days. Those who received the rifaximin showed a trend for decreased rates of recurrence of

CDI (31% *versus* 15%,  $p=0.11$ ).<sup>29</sup> Adding the option of a rifaximin chaser provided the practicing clinician with another choice for those with multiply recurrent CDI. By diversifying some of the options to treat these challenging patients with two or more recurrences, the Australasian guidelines from 2016 pushed the limits and moved CDI treatment options forward.

#### *DSA and SHEA joint guidelines*

The IDSA/SHEA 2017 guideline chose to subtly change their recommendations when triaging disease severity (Tables 9–11).<sup>6</sup> They followed suit with the 2010 recommendations, using both creatinine and WBC as the important factors; however, they realized that their recommendation of having a

**Table 11.** IDSA and SHEA joint guidelines.<sup>6</sup>

Treatment of second recurrence and beyond
Vancomycin orally administered in a tapered and pulsed regimen, OR
Vancomycin 125 mg orally given QID by mouth for 10 days followed by rifaximin 400 mg orally TID for 20 days OR
Fidaxomicin 200 mg orally given BID for 10 days, OR
FMT
BID, twice per day; FMT, fecal microbiota transplantation; IDSA, Infectious Diseases Society of America; QID, four times per day; SHEA, Society of Healthcare Epidemiology of America; TID, three times per day.

creatinine 1.5 times the baseline level was challenging to apply in clinical practice since patient baseline blood work is often not available. Given this, they updated their criteria to include either a WBC  $>15,000/\text{mm}^3$  or a creatinine  $>1.5\text{ mg/dl}$ . This also differs from the 2014 European guideline, eliminating the need for a baseline creatinine level and also not including albumin. The IDSA/SHEA 2017 recommendations also seemed more clinically applicable than the comprehensive list of criteria from the 2016 Australasian guideline.<sup>25,26</sup>

The 2017 IDSA/SHEA guidelines were a significant advancement forward for a number of reasons. This guidance included a significant shift away from metronidazole as a primary treatment of CDI. This shift away from metronidazole was fortified by a pivotal trial by Johnson *et al.* designed initially to consider an ion binder called Tolevamer that was thought of as a potential solitary therapy to treat CDI.<sup>30</sup> Within two parallel studies conducted between 2005 and 2007, Tolevamer was compared with two control groups: metronidazole and vancomycin. Tolevamer did not perform well and was inferior to both metronidazole and vancomycin<sup>30</sup>; however, using vancomycin ( $n=266$ ) and metronidazole ( $n=289$ ) as control groups provided prospective data comparing these treatments head-to-head. In the overall analysis, vancomycin was superior to metronidazole with regards to clinical success (81.1% versus 72.7%,  $p=0.02$ ). Therefore, as far back as 2005–2007, when the study was conducted, metronidazole was inferior to vancomycin and it was believed this gap in efficacy only widened with time. Therefore, within the 2017 IDSA/SHEA guidelines, metronidazole was largely removed from being a recommended treatment of an initial episode of CDI; essentially stating that it should be given only when either vancomycin or fidaxomicin are not available.<sup>6</sup>

Within the 2017 updated IDSA/SHEA guidelines, fidaxomicin was inserted as a main option to treat initial non-severe and severe CDI. This is very different from the other two guidelines from the modern era. The 2014 European guidelines mention fidaxomicin as a treatment option for initial non-severe CDI, but metronidazole remained the preferred therapy. The European guidelines recommended either vancomycin or fidaxomicin for those with an initial severe episode.<sup>25</sup> The Australasian guidelines from 2016 held back on fidaxomicin for initial non-severe or severe infection, opting to advise metronidazole for initial non-severe and vancomycin for initial severe episodes.<sup>26</sup>

When considering management of first recurrence, the IDSA/SHEA 2017 guideline also changed treatment recommendations. The 2014 European guideline recommended using any of metronidazole, vancomycin, or fidaxomicin.<sup>25</sup> The Australasian 2016 guideline chose to focus solely on vancomycin for those that have an initial recurrence.<sup>26</sup> The shift away from usage of metronidazole in the 2016 recommendations was a significant one. The IDSA/SHEA guideline essentially recommended either a vancomycin 10-day treatment course for those who received metronidazole initially or consideration for a prolonged vancomycin taper and pulse or fidaxomicin for 10-days for those who received vancomycin initially.<sup>6</sup> This again fits with the changing paradigm focusing on more aggressive treatments for patients earlier in the infection.

For treatment of second recurrence and beyond, the modern guidelines have evolved. The 2014 European guidelines recommended using either a standard 10-day treatment course of fidaxomicin or a vancomycin taper or pulse.<sup>25</sup> Fitting with the

epidemiologic changes with more frequent episodes of multiply recurrent CDI, the guidelines evolved to include multiple options for these scenarios. The 2017 IDSA/SHEA guidelines are similar to the 2016 Australasian guidelines, including a vancomycin taper and/or pulse, a standard course of vancomycin followed by a rifaximin chaser or a standard 10-day fidaxomicin course.<sup>6,26</sup> MRT/FMT was recommended for those patients who were not responding to at least three antimicrobial courses.

Part of the IDSA/SHEA 2017 guideline stated that there was a lot of new information and data becoming available so it would be important to provide clinically relevant periodic updates. At IDWeek 2020, presented virtually, Dr. Stuart Johnson verbally presented a provisional update to the 2017 guideline. The following was specifically advised:

Treatment of primary *C. difficile* infection: for a patient with an initial episode of CDI, we recommend fidaxomicin instead of a standard course of vancomycin.

Treatment of recurrent *C. difficile* infection: in patients with recurrent *C. difficile* infection, we recommend fidaxomicin (either standard or extended pulse) rather than a standard course of vancomycin.

Prevention of recurrence of *C. difficile* infection: for patients with CDI and at least 1 risk factor for recurrence (e.g., age > 65, immunocompromise, severe CDI and history of CDI), we suggest using bezlotoxumab in addition to standard of care antimicrobial.

These updates to the IDSA/SHEA 2017 guideline further acknowledge the issue that was highlighted in the study by Ma *et al.* showing a significant increase in multiply recurrent CDI.<sup>28</sup> By treating more aggressively earlier in the disease with fidaxomicin preferentially, there should be less recurrence and better outcomes. This is a remarkable advancement with regards to the recommendations, since fidaxomicin was recommended provisionally in front of vancomycin for both initial and recurrent disease. There have been a number of studies that support this, but the two primary studies are referenced here. The first is a multi-center European study of inpatients with CDI who were randomized to receive either vancomycin 125 mg PO QID for 10 days or fidaxomicin 200 mg twice per day (BID) for

5 days and then one tablet every other day for days 7–25. The study showed that vancomycin and fidaxomicin are similar in terms of initial treatment response, but follow up at 90 days showed a significantly lower rate of recurrence in those who received fidaxomicin compared with vancomycin (6.2% versus 19.0%,  $p < 0.001$ ).<sup>31</sup> This study shows that, with an alternative usage of fidaxomicin, very low rates of recurrence can be achieved. The other study used to support fidaxomicin being used preferentially ahead of vancomycin was a meta-analysis by Okumura *et al.* including seven publications. This found that fidaxomicin and vancomycin were more effective treatments for those within initial CDI compared with metronidazole, and that fidaxomicin may be more effective at preventing recurrence than vancomycin.<sup>32</sup> It is important to consider the cost of fidaxomicin as this has been a recurring theme raised by the clinical guidelines and might be something that will limit access to this treatment, even if the finalized IDSA/SHEA update continues to favor fidaxomicin first line in those with initial episode and those with recurrence. Therefore, as with any treatment, accessibility of the treatment must be considered by the practitioner since the best treatment is one that a patient can both acquire and follow through with.

The other major development with this update was the addition of bezlotoxumab as a newly recommended therapy. This was not included in the 2017 version of the guideline since the cutoff for data review for that guideline was prior to FDA approval of this treatment. In two placebo-controlled randomized controlled trials considering patients receiving a standard of care anti-microbial followed by either bezlotoxumab or placebo, bezlotoxumab was associated with significantly lower rates of recurrence (28% versus 17%,  $p < 0.001$  and 26% versus 16%,  $p < 0.001$ ). This therapy will be covered in detail in a different section of this journal, but adding bezlotoxumab to the recommended treatment algorithm once again reflects the current need for more aggressive therapies that minimize recurrence.

## Conclusion

Over the years, the guidelines have reflected the changing epidemiology and outcomes seen with CDI. In the first wave of guidelines from 1995 through 1997, when the epidemic was in its infancy and there were limited therapies,

treatment recommendations were basic and focused on vancomycin and metronidazole. As the epidemic blossomed in early 2000s and 2010s, the second wave of guidelines from 2009 through 2013 were more extensive, but, due to a lack of data, still reflected the limited treatment options available, adding considerations for severity and a vancomycin taper. The modern era from 2014 through the present includes the addition of fidaxomicin as an initial treatment option and for recurrence, but the most recent 2020 provisional update added fidaxomicin ahead of vancomycin in both initial and recurrent disease. As we are seeing a leveling of the epidemic but still a remarkable number of recurrent episodes, the focus on minimizing recurrence through additional immune boosting therapies such as bezlotoxumab and MRT will take on added importance. It is likely that future guidelines will push MRT earlier in the treatment algorithm following a standard of care antimicrobial for first recurrence in those at greatest risk and eventually possibly for initial episode in those at high risk when more data and an FDA-approved product are available. It is such an exciting time in the world of therapeutics for CDI and the guidelines will hopefully continue to update based upon newer therapies thereby improving patient outcomes.

### Conflict of interest statement

Paul Feuerstadt: Consultant and advisory board for Ferring/Rebiotix, Speakers Bureau of Merck and Co., and Advisory Boards of SERES Therapeutics and Takeda Pharmaceuticals.  
Abdelkader Chaar: None.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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