

## Drug Class Update with New Drug Evaluation: *Clostridioides difficile* Drugs

**Date of Review:** June 2023

**Date of Last Review:** May 2018

**Generic Name:** fecal microbiota, live-jslm

**Dates of Literature Search:** 03/14/2018 – 02/07/2023

**Brand Name (Manufacturer):** Rebyota (Ferring Pharmaceuticals)

**Dossier Received:** yes

**Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

To review a new Food and Drug Administration (FDA)-approved biotherapeutic, fecal microbiota live-jslm (REBYOTA), indicated for the prevention of recurrent *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) in adults. In addition, any new comparative evidence for existing agents approved to treat CDI or prevent CDI recurrence will be reviewed and summarized.

### **Plain Language Summary:**

- This review looks at new evidence for medicines used to manage infections in the large intestine (colon) caused by a bacterium called *Clostridioides difficile* (also called *C. difficile*). Illness from *C. difficile* can occur after the use of antibiotic medicines to treat another infection elsewhere in the body. Many antibiotics destroy the healthy bacteria that normally live in the large intestine. This allows *C. difficile* to take over and release toxins that can damage the large intestine. Symptoms of this infection include frequent episodes of watery diarrhea, nausea, and stomach cramps. *C. difficile* can be difficult to treat because it may come back within 8 weeks after a finishing antibiotic therapy, also known as *C. difficile* recurrence.
- Currently, providers can prescribe 2 antibiotics to treat infections caused by *C. difficile*. These antibiotics are fidaxomicin and vancomycin. Studies show these antibiotics improve diarrhea caused by *C. difficile* and prevent recurrence of infection. These 2 medicines have similar side effects. Multiple organizations including the Infectious Diseases Society of America and American College of Gastroenterology recommend one of 2 these medicines to treat the first onset of a *C. difficile* infection and to prevent recurrent *C. difficile* infections.
- The Food and Drug Administration has also approved another medicine, called bezlotoxumab, to prevent *C. difficile* infections from coming back. This medicine is an infusion administered in the veins by a health care provider. It is not used to treat *C. difficile* infection, only to prevent recurrence of infection.
- Since 2013, the Food and Drug Administration has authorized use of stool transplants, or fecal microbiota transplantation, where providers administer donor stool to a person with *C. difficile* infection. This process replaces the good bacteria that help maintain healthy large intestine activity and helps prevent *C. difficile* infection from recurring.
- The Food and Drug Administration recently approved a commercial formulation of fecal microbiota suspension (REBYOTA) which is used to prevent recurrent infections caused by *C. difficile*. This medicine is administered as an enema and contains human stool microbiota from healthy donors.

- The British Society of Gastroenterology and Healthcare Infection Society suggest providers offer fecal microbiota transplantation to people who have experienced at least 2 recurrences of *C. difficile* infection. The American College of Gastroenterology and National Institute for Health and Care Excellence also support this recommendation to prevent additional recurrences.
- The Oregon Health plan covers vancomycin capsules. Providers must explain to the Oregon Health Authority why someone needs fidaxomicin, vancomycin suspension, or bezlotoxumab before Medicaid will pay for it. This process is called prior authorization.
- We recommend updates to policies for fidaxomicin and bezlotoxumab to align with current evidence. We recommend that the Oregon Health plan only pay for fecal transplant when other therapies have not cured *C. difficile* infection after 2 recurrences.

### Research Questions:

1. What is the comparative efficacy or effectiveness of metronidazole, vancomycin and fidaxomicin for treatment of an initial CDI or recurrent CDI?
2. What are the comparative harms of metronidazole, vancomycin and fidaxomicin when used for treatment of an initial CDI or recurrent CDI?
3. Is there new evidence or guidance for the use of bezlotoxumab for preventing recurrent CDI?
4. What is the evidence for the safety and efficacy of fecal microbiota live-*jslm* (REBYOTA) in preventing recurrent CDI?
5. Are there specific subpopulations of patients (specifically by race, age, socio-economic status, or comorbidities) for which one therapy is more effective or associated with more harm than other therapies when used to manage CDI or recurrence?

### Conclusions:

- Since the Drug Use Research Management (DURM) 2018 class update of CDI treatment, 2 systematic reviews<sup>1,2</sup> and 5 guidelines<sup>3-7</sup> have been published to evaluate the use of fidaxomicin, metronidazole, or vancomycin in treating initial and recurrent CDI and the use of bezlotoxumab or fecal microbiota transplant to prevent recurrent CDI.  
*Treatment of Initial or Recurrent CDI with Vancomycin or Fidaxomicin and Prevention of Recurrent CDI with Bezlotoxumab*
- A 2022 systematic review and meta-analysis evaluated the safety and efficacy of oral fidaxomicin versus oral vancomycin in a mixed population of patients with an initial CDI episode and patients with recurrent CDI.<sup>1</sup> The primary endpoint was global cure for efficacy, calculated as the ratio of the number of patients who did not experience CDI recurrence after achievement of clinical cure (resolution of diarrhea and no need for further CDI treatment) with the total number of patients enrolled in the studies.<sup>1</sup> Compared to vancomycin, moderate quality evidence showed fidaxomicin was associated with higher global cure rates (risk ratio [RR]=1.18, 95% confidence interval [CI]=1.09 to 1.26; p<0.00001).<sup>1</sup> Clinical cure rates were calculated as the ratio of the number of patients with resolution of diarrhea following the end of treatment to the total number of patients enrolled in the studies.<sup>1</sup> Clinical cure rates were similar between fidaxomicin and vancomycin (RR=1.02, 95% CI=0.98 to 1.06, p=0.31; moderate quality evidence).<sup>1</sup> Fidaxomicin was associated with lower CDI recurrence rates than vancomycin (RR=0.59, 95% CI=0.47 to 0.75, p<0.0001; moderate quality evidence).<sup>1</sup> Adverse event rates were not different between the 2 antibiotics (P=0.41).<sup>1</sup>
- For initial treatment of CDI, 2021 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) recommend oral fidaxomicin 200 mg given twice daily for 10 days as first line treatment (conditional recommendation, moderate certainty of evidence).<sup>4</sup> Oral vancomycin 125 mg taken 4 times daily for 10 days is a reasonable alternative.<sup>4</sup> If patients have non-severe CDI symptoms or if fidaxomicin or vancomycin are unavailable, oral metronidazole 500 mg taken 3 times a day for 10 to 14 days is a treatment of last resort.<sup>4</sup> Fidaxomicin and vancomycin are considered standard-of-care (SOC) antibiotics for initial management of CDI.<sup>4</sup> These recommendations are supported by 2021 American College of Gastroenterology guidance.<sup>5</sup>
- National Institute for Health and Care Excellence (NICE) guidance for initial CDI antibiotic treatment was published in 2021,<sup>6</sup> and differs slightly from IDSA/SHEA and ACG recommendations. For treatment of an initial episode of CDI, NICE recommends oral vancomycin as the first-line antibiotic of choice.<sup>6</sup>

Fidaxomicin is recommended as the second-line antibiotic for a first episode of *C. difficile* infection of any severity when vancomycin is ineffective (i.e., treatment failure).<sup>6</sup> Although fidaxomicin was more effective than vancomycin for sustained symptomatic cure in an indirect network meta-analysis, the cost of fidaxomicin is substantially higher than vancomycin in the United Kingdom.<sup>6</sup> Metronidazole is not recommended for treating an initial CDI episode per NICE guidance.<sup>6</sup>

- A 2020 systematic review assessed safety and efficacy of interventions to prevent recurrent CDI.<sup>2</sup> Recurrent CDI is defined by IDSA/SHEA as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.<sup>4</sup> For prevention of recurrent CDI, there is at least one study to support fidaxomicin (compared to a 10-day vancomycin course; low-quality evidence), fecal microbiota transplant (FMT) (compared to a 14 day vancomycin regimen; moderate quality evidence), and bezlotoxumab (compared to placebo; moderate-quality evidence).<sup>2</sup> While the results of 3 low-quality RCTs using probiotics or prebiotics found benefit in preventing recurrent CDI, the studies were underpowered and further research with larger samples sizes is needed to draw definitive conclusions regarding their efficacy in CDI.<sup>2</sup>
- The 2021 IDSA/SHEA updated guidance focused on recently published evidence for the use of fidaxomicin in treating recurrent CDI compared with vancomycin and the use of bezlotoxumab as monotherapy or in conjunction with standard-of-care antibiotics (SOC) in preventing recurrent CDI.<sup>4</sup> In patients with recurrent CDI episodes, IDSA/SHEA guidance suggests fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin (conditional recommendation, low certainty of evidence).<sup>4</sup> For patients with a recurrent CDI episode within the last 6 months, guidance suggests bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone (conditional recommendation, very low certainty of evidence).<sup>4</sup> The 2021 ACG guidelines for treating recurrent CDI are similar to IDSA/SHEA, including a statement that there is insufficient evidence to recommend any probiotic for the primary or secondary prevention of CDI.<sup>5</sup> For recurrent CDI which develops more than 12 weeks after symptom resolution, either vancomycin or fidaxomicin is recommended by 2021 NICE guidance.<sup>6</sup>

#### Fecal Microbiota Transplant for Prevention of Recurrent CDI

- A 2018 joint guideline developed by the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) provided recommendations for best practices for the provision of fecal microbiota transplant (FMT) in adults with CDI before commercial products were available.<sup>3</sup> Strength of recommendations and quality of evidence for which patients are the best candidates for FMT are as follows:
  - FMT should not be administered as initial treatment for CDI (strong recommendation, low-quality evidence).<sup>3</sup>
  - FMT should be offered to patients with recurrent CDI who have had at least 2 recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong recommendation, high-quality evidence).<sup>3</sup>
  - FMT should be considered in cases of severe CDI (strong recommendation, moderate-quality evidence).<sup>3</sup>
- The ACG 2021 guidance includes a recommendation that patients experiencing their second or more recurrence of CDI be treated with FMT to prevent additional recurrences (strong recommendation, moderate-quality evidence).<sup>5</sup> This recommendation is supported by 2022 NICE guidance.<sup>7</sup>

#### Safety and Efficacy of Fecal Microbiota Suspension (REBYOTA)

- Fecal microbiota (REBYOTA) is a live biotherapeutic suspension for rectal administration FDA-approved for prevention of recurrent CDI in adults aged 18 years and older following SOC antibiotic treatment for recurrent CDI.<sup>8</sup> Approval was based on findings from a placebo-controlled phase 3 RCT (PUNCH CD3) and a phase 2 RCT (PUNCH CD2).<sup>9</sup> In a pooled analysis of both trials, low-quality evidence shows the overall estimated rate of success in preventing recurrent CDI was higher in the fecal microbiota group (70.6%) than in the placebo group (57.5%) 8 weeks after transplantation.<sup>9</sup> The most commonly reported adverse events reported after a single dose of fecal microbiota suspension included abdominal pain (9%), diarrhea (7%), abdominal distention (4%), flatulence (3%) and nausea (3%).<sup>8</sup> Safety and efficacy of REBYOTA in people younger than 18 years of age have not been established.<sup>8</sup> There is insufficient evidence to assess comparative safety and efficacy of REBYOTA with compounded FMT products.

### Expanded Indications for Antibiotics in the *C. difficile* PDL Class

- A new oral suspension formulation of vancomycin (FIRVANQ) was approved in January 2018.<sup>10</sup> This product is indicated in adults and pediatric patients less than 18 years of age (no lower age limit is stated in the prescribing information) for treatment of *C. difficile*-associated diarrhea and enterocolitis caused by *Staphylococcus aureus*.<sup>10</sup>
- In January 2020, the FDA expanded the approved population eligible to receive fidaxomicin (DIFICID) to include pediatric patients aged 6 months and older.<sup>11</sup>

### Specific Populations at Higher Risk for Adverse Effects with FMT

- The 2018 BSG/HIS guidance identified several groups of patients who may experience more harm from non-commercial FMT products based on low to moderate quality evidence which includes: patients with significant/anaphylactic food allergy, other infectious cause of diarrhea, inflammatory bowel disease, immunodeficiency due to recent chemotherapy and/or neutropenia, human immunodeficiency virus, prolonged use of corticosteroids, and decompensated cirrhosis.<sup>3</sup> REBYOTA is manufactured from human fecal matter and may contain food allergens. However, the potential for REBYOTA to cause adverse effects due to food allergens is currently unknown.<sup>8</sup>

### **Recommendations:**

- Maintain fidaxomicin as a non-preferred drug on the Practitioner-Managed Prescription Drug Plan (PMPDP) with PA criteria to ensure appropriate use.
- Designate fecal microbiota (REBYOTA) as a non-preferred drug on the PMPDP subject to PA.
- Create a new set of PA criteria titled “Prevention of *C. difficile* Recurrence” and include bezlotoxumab infusion and fecal microbiota enema in the new document.
- Retire current bezlotoxumab PA criteria.
- After review of costs in executive session, metronidazole capsules were made non-preferred.

### **Summary of Prior Reviews and Current Policy**

- Medications FDA-approved to treat CDI were last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the May 2018 meeting. The evidence for the safety and efficacy for a new monoclonal antibody, bezlotoxumab (ZINPLAVA), was presented. Bezlotoxumab is indicated for reducing the incidence of recurrent CDI in combination with SOC antibiotic therapy in adults at high risk for CDI recurrence.<sup>12</sup> Guideline updates published by IDSA/SHEA in 2017 recommend using oral vancomycin or fidaxomicin for an initial CDI episode.<sup>13</sup> Metronidazole is no longer recommended as a first line agent, except in circumstances where access to vancomycin or fidaxomicin is limited or in initial cases of non-severe CDI.<sup>13</sup> The recommendations for treating recurrent CDI suggest trying an alternative antibiotic (vancomycin or fidaxomicin) than the medication that was used for the first episode of CDI.<sup>13</sup> Metronidazole is not recommended for treatment of recurrent CDI.<sup>13</sup> Although the comparative effectiveness of metronidazole and vancomycin in pediatric CDI is insufficient, either weight-based oral metronidazole or vancomycin are recommended for an initial episode or first recurrence of CDI in children.<sup>13</sup> At that time, fidaxomicin was not FDA-approved for use in children less than 18 years of age, so it was not included in the 2017 IDSA/SHEA pediatric recommendations.<sup>13</sup>
- After reviewing the evidence, the P & T committee accepted the recommendation to designate bezlotoxumab as non-preferred drug on the PMPDP subject to PA. Fidaxomicin PA criteria were modified to remove metronidazole as a prerequisite to fidaxomicin in patients with recurrent CDI.
- The preferred drug list status for medications used to treat CDI or prevent recurrent CDI is summarized in **Appendix 1**. Vancomycin capsules and metronidazole tablets are preferred agents on the preferred drug list (PDL). Fidaxomicin, vancomycin oral suspension, and bezlotoxumab are non-preferred agents and require PA. The PA criteria for bezlotoxumab and fidaxomicin are presented in **Appendix 6**.
- In the third quarter of 2022, all claims for agents in the *C. difficile* class were for metronidazole tablets and preferred formulations of vancomycin. In the first 3 quarters of 2022, there were no physician administered claims for bezlotoxumab in the Fee-for-Service population.

## Background:

The bacterial genus *Clostridium* was reclassified as *Clostridioides* in 2016.<sup>14</sup> *Clostridioides difficile*, a spore-forming, gram-positive, anaerobic bacillus, is the primary pathogen of infectious diarrhea in hospitalized patients.<sup>15</sup> The bacteria produces 2 exotoxins, toxin A and toxin B, which disrupt colonic epithelial integrity, stimulate release of inflammatory mediators, and result in pseudomembrane formation.<sup>16</sup> Any surface or device (such as commodes, bathtubs, and electronic rectal thermometers) that becomes contaminated with feces could serve as a reservoir for the *C. difficile* spores.<sup>15</sup> The spores can also be transferred to patients via the hands of healthcare personnel who have touched a contaminated item.<sup>15</sup> The Centers for Disease Control and Prevention (CDC) has identified CDI as an urgent global public health threat due to the emerging prevalence of more virulent *C. difficile* strains and increasing mortality rates due to resistant strains of the bacteria.<sup>17</sup> According to a 2019 CDC report, an estimated 223,900 cases in hospitalized patients and 12,800 deaths in the United States were associated with CDI.<sup>17</sup> High CDI recurrence rates after appropriate treatment (30 to 65%) is a public health challenge.<sup>18</sup> Community associated CDI is on the rise and is estimated to occur in one third of all CDI cases.<sup>19</sup> *C. difficile* infection can result in pseudomembranous colitis, toxic megacolon, colon perforations, sepsis, and mortality.<sup>15</sup>

Broad spectrum antibiotic exposure, in particular clindamycin, carbapenems, cephalosporins and fluoroquinolones, increases the risk of developing CDI.<sup>20</sup> These antibiotics disrupt normal gut flora which results in *C. difficile* overgrowth in the colon. Other risk factors for CDI include: age greater than 65 years; long length of stay in healthcare settings; gastrointestinal surgical procedures; immunocompromising conditions; inflammatory bowel disease; or a serious underlying illness.<sup>15</sup> To reduce the risk of CDI, the frequency, number of agents prescribed, and duration of high-risk antibiotic therapy should be minimized.<sup>21</sup> In addition to antibiotic stewardship, strategies to reduce CDI include policies focused on effective infection control (e.g., contact isolation procedures, hand hygiene practices before and after patient contact) and healthcare facility cleaning and disinfection.<sup>17</sup>

The diagnosis of CDI is based on clinical history and laboratory findings of *C. difficile* toxins in the stool. Symptoms include presence of diarrhea (defined as 3 or more unformed stools in 24 hours), cramps, fever, loss of appetite, nausea and lower abdominal pain.<sup>15</sup> Laboratory testing cannot distinguish between colonization and infection. The gold standard for CDI diagnosis is lab verification of toxigenic *C. difficile* in stool along with histopathology showing pseudomembranes in patients with clinical symptoms.<sup>16</sup> Treatment goals include resolution of diarrhea and reduction of CDI recurrence. Severe CDI may be accompanied by leukocytosis with a white blood cell count (WBC) greater than 15,000 cells/ $\mu$ L and elevated serum creatinine 1.5 times the patients' baseline value secondary to dehydration from extensive diarrhea. Some of the literature uses a Zar score to stratify patients with CDI into mild or severe groups. In the Zar severity scoring, one point each is assigned for age greater than 60 years, temperature greater than 38.3°C, albumin level less than 2.5 mg/dL, and WBC greater than 15,000 cells/ $\mu$ L.<sup>22</sup> Patients that score greater than or equal to 2 points are considered to have severe CDI.<sup>22</sup> Severe, complicated CDI can result in shock, hypotension, ileus, or megacolon.

Treatment of CDI is based on risk of recurrence and severity of symptoms. For an initial episode of CDI, IDSA/SHEA (2017) recommends either vancomycin 125 mg orally four times a day or fidaxomicin 200 mg twice daily for 10 days.<sup>21</sup> Metronidazole is no longer recommended as first-line therapy for CDI in adults and is only indicated if allergy or intolerance limit prescribing vancomycin or fidaxomicin. Recurrent CDI is defined by IDSA/SHEA as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.<sup>21</sup> For the first recurrence of CDI, a prolonged tapered and pulsed vancomycin regimen (standard vancomycin course for 10-14 days followed by decreasing the dose by 25%-50% every 1-2 weeks with no skipped days and then pulsed at a 125-mg dose, skipping 1 to 2 days, for 2-4 weeks) or a 10-day course of fidaxomicin is recommended if vancomycin was used for the initial episode.<sup>21</sup> For recurrent CDI, IDSA/SHEA (2017) recommends 10 days of vancomycin followed by 20 days of rifaximin or fidaxomicin.<sup>21</sup> For non-severe CDI in children, either weight-based metronidazole or vancomycin dosing is recommended for an initial episode or first CDI recurrence.<sup>21</sup> For severe CDI in children, oral vancomycin is recommended over metronidazole by IDA/SHEA (2017).<sup>21</sup>

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Bezlotoxumab, an anti-toxin B monoclonal antibody, was FDA approved in 2016 for prevention of CDI recurrence in combination with CDI SOC antibiotics. Bezlotoxumab is not indicated for the treatment of CDI and is only approved for use in combination with antibiotics in adults at high risk for CDI recurrence as a single 10 mg/kg intravenous (IV) infusion.<sup>12</sup> The evidence for the safety and efficacy of bezlotoxumab was reviewed by the P and T Committee at the May 2018 meeting.

Probiotics are live, generally nonpathogenic bacteria capable of colonizing the colonic mucosa, and have been studied in the prevention of recurrent CDI because of their potential to restore the intestinal microflora.<sup>2</sup> Prebiotics are dietary components that foster the growth of beneficial bacteria, and therefore may serve a similar function as probiotics on the prevention of recurrent CDI.<sup>2</sup> None of these therapies are currently recommended for prevention of CDI in the IDSA (2017) guidelines.<sup>21</sup>

If there are 2 or more CDI recurrences despite appropriate antibiotic treatments, FMT is recommended by IDSA/SHEA (2017).<sup>21</sup> Transplantation occurs by instillation of processed stool donated by a healthy volunteer via nasogastric/nasoduodenal tube, colonoscopy, enema, or capsule.<sup>23</sup> An important barrier to the integration of FMT into regular clinical practice is the heterogeneity of administration routes and lack of standardization of FMT guidance.<sup>23</sup> Standardization of the methodological components of FMT includes: donor screening, stool preparation, storage, and instillation route.<sup>23</sup> In 2017, a FMT national registry including 20 North American practice sites was established by the AGA.<sup>24</sup> The purpose of the registry is to collect data on the efficacy of FMT on the cure of CDI within 6 months after treatment, and to evaluate short-term and long-term safety of FMT. As of 2021, 259 participants were enrolled in the program.<sup>24</sup> At 1-month follow-up, 90% of participants (n=222) had experienced cure of CDI and only required one treatment with FMT to achieve cure.<sup>24</sup> Of the participants who had a 6-month follow-up (n=145), 88% reported a CDI cure.<sup>24</sup> Post-FMT adverse effects occurred in 45% of participants (n=106).<sup>24</sup> The most commonly reported adverse effects at 1 month included non-CDI diarrhea (30%), abdominal pain (17%), bloating (15%), and constipation (10%).<sup>24</sup> New infections possibly related to FMT occurred in 2 participants (1%) and hospitalizations possible related to FMT occurred in 3 participants (1%) up to 1 month after transplantation.<sup>24</sup> Serious adverse events reported to the registry between 1 and 6 months after FMT included infections (4%) and hospitalizations (19%).<sup>24</sup>

In June 2019, the FDA released a statement warning of the risks associated with FMT due to transmission of multi-drug resistant organisms.<sup>25</sup> Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. Coli*); of the 2 adults, one of the individuals died.<sup>25</sup> Another warning was issued March 2020, reporting 6 additional cases of transmission of antibiotic-resistant organisms (enteropathogenic *E. coli* in 2 cases and Shigatoxin-producing *E. coli* in 4 cases) via FMT.<sup>26</sup> In April 2020, the FDA issued a safety alert requiring testing of stool donors for SARS-CoV-2 virus due to possible risk of viral transmission from donor to recipient.<sup>27</sup> In August 2022, a similar safety alert regarding possible transmission of monkeypox virus via FMT was published to recommend additional donor screening parameters.<sup>28</sup>

#### **Methods:**

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

### **Systematic Reviews:**

#### Oral Fidaxomicin Versus Oral Vancomycin for Treatment of *C. Difficile* Infection

A 2022 systematic review and meta-analysis evaluated the safety and efficacy of oral fidaxomicin versus oral vancomycin in patients with CDI.<sup>1</sup> Literature was searched through October 2021 and 6 RCTs (n=682) met inclusion criteria.<sup>1</sup> Five studies were conducted in Western countries (America, Canada, or Europe), and one study was conducted in Japan.<sup>1</sup> The studies included a mixed population of patients with an initial CDI episode and patients with recurrent CDI. Three RCTs provided CDI severity data and reported the percentage of patients with severe CDI ranged from 22.2% to 39.4%.<sup>1</sup> The primary endpoint was global cure for efficacy and secondary endpoints included clinical cure, recurrence, and adverse events.<sup>1</sup> Two of the RCTs were open-label clinical trials and had high risk of performance and detection bias.<sup>1</sup> The other 4 RCTs had low risk of bias and were conducted without industry support.<sup>1</sup>

The primary endpoint, global cure for efficacy, was calculated as the ratio of the number of patients who did not experience CDI recurrence after achievement of clinical cure (resolution of diarrhea and no need for further CDI treatment) with the total number of patients.<sup>1</sup> Compared to vancomycin, moderate quality evidence showed fidaxomicin was associated with higher global cure rates (RR=1.18, RD=0.11, 95% CI=1.09 to 1.26; p<0.00001).<sup>1</sup> Fidaxomicin was also associated with lower recurrence rates than vancomycin (RR=0.59, 95% CI=0.47 to 0.75, p<0.0001; moderate quality evidence).<sup>1</sup> Clinical cure rates were calculated as the ratio of the number of patients with resolution of diarrhea (during treatment and at the end of treatment) and no further need for treatment of CDI with the total number of patients.<sup>1</sup> Clinical cure rates were comparable between fidaxomicin and vancomycin (RR=1.02, 95% CI=0.98 to 1.06, p=0.31; moderate quality evidence).<sup>1</sup> Adverse event rates were not different between the 2 antibiotics (P=0.41).<sup>1</sup>

Most of the studies were conducted in the United States, Canada, and Europe. Regional resistance patterns may impact these results, and it is unclear if other clinical locations would have similar outcomes.<sup>1</sup> In addition, this systematic review was limited by heterogeneous trial populations and outcome measures, with different time points for efficacy evaluation and follow-up periods (38 to 60 days), and mixed populations of patients with CDI (initial episode versus recurrent episodes).<sup>1</sup>

#### Prevention of Recurrent *C. Difficile* Infection

A 2020 systematic review assessed safety and efficacy of interventions to prevent recurrent CDI.<sup>2</sup> The literature search for eligible RCTs was conducted through February 2018. Thirty-eight RCTs (n=8,102) met inclusion criteria.<sup>2</sup> Of the 38 studies, 19 assessed antibiotics (n=3,743); 8 assessed FMT (n=582); 3 assessed monoclonal antibodies (n=2,805); and 8 assessed prebiotics, probiotics, and non-antibiotic polymers (n=972).<sup>2</sup> Studies were included irrespective of patient demographics, disease severity, type of intervention, comparator used, or time-point of outcome evaluation.<sup>2</sup> Overall, the majority of studies included adult participants aged 55 years and older.<sup>2</sup> There were two exceptions: one FMT study included patients as young as 7 years of age, resulting in the enrollment of 3 children, and another FMT study excluded patients 75 years and older.<sup>2</sup> All studies required participants to have at least one episode of CDI at the time of enrollment. However, the number of prior CDI episodes accepted at inclusion was not uniform across the trials.<sup>2</sup> Five studies evaluating FMT and 6 trials assessing antibiotics were open-label trials with high risk of performance and detection bias.<sup>2</sup> Four studies had a high risk of attrition bias.<sup>2</sup> Six trials were pilot studies and were likely underpowered.<sup>2</sup> The study methodology was not clear in 4 trials.<sup>2</sup> There was low of risk of bias for 14 of the 38 included RCTs.<sup>2</sup> Four studies compared fidaxomicin to vancomycin in patients with recurrent CDI.<sup>2</sup> One study was a small pilot (n=12) and was underpowered to detect differences between therapies. Two trials were non-inferiority RCTs, and one trial was an open-label Phase 3b/4 trial. Low-quality evidence from these trials found a reduction in recurrent CDI in the fidaxomicin treatment group compared with vancomycin (RR 0.39, 95% CI 0.24 to 0.65; RR 0.10, 95% CI 0.03 to 0.33; RR

0.54, 95% CI 0.35 to 0.84).<sup>2</sup> The adverse effects associated with fidaxomicin included electrolyte imbalances, laboratory abnormalities, pruritus, bile stone formation, and drug hypersensitivity.<sup>2</sup> Adverse effects observed with vancomycin were not reported in the systematic review. Of the 8 FMT studies, 3 moderate-quality RCTs (n=110 participants) compared the efficacy of FMT to vancomycin therapy. The first study (n=39) found that FMT was more effective in preventing recurrent CDI compared to a ten-day course plus three-week taper of oral vancomycin (RR 0.47, 95% CI 0.25 to 0.91).<sup>2</sup> A second study (n=43) demonstrated FMT was more effective in preventing recurrent CDI than a 14-day vancomycin course (RR 0.27, 95% CI 0.09 to 0.80) and a 14-day vancomycin course plus bowel lavage (RR 0.24, 95% CI 0.08 to 0.71).<sup>2</sup> A third study (n=28) included a vancomycin taper regimen of 6 weeks, but was stopped for futility at the interim analysis (RR 1.35, 95% CI, 0.61 to 2.99).<sup>2</sup> In 2 of the 3 trials, moderate-quality evidence showed that FMT appeared to be superior to treatment with oral vancomycin in the prevention of recurrent CDI.<sup>2</sup> The other 5 studies (n=473) compared different preparations and routes of administration of FMT including: frozen FMT administered by colonoscopy compared with fresh FMT and lyophilized microbiota, frozen FMT compared to fresh FMT administered via enema, FMT capsules compared with colonoscopic infusion, and nasogastric tube versus colonoscopic administration of FMT.<sup>2</sup> Overall, there were no significant differences in outcomes for the different routes or preparations of FMT.<sup>2</sup> All of the studies evaluating FMT reported adverse events including bloating, abdominal cramping and distension, nausea, and vomiting.<sup>2</sup> No trials reported serious adverse events that were considered to be related to FMT.<sup>2</sup>

Two moderate-quality phase 3 trials (MODIFY I and MODIFY II) were conducted to evaluate the safety and efficacy of bezlotoxumab, a monoclonal antibody, in reducing the incidence of recurrent CDI.<sup>29</sup> In both MODIFY I and MODIFY II, the rate of CDI recurrence through week 12 was significantly lower in the bezlotoxumab arms compared to the placebo arms (MODIFY I: 17% vs. 28%; 95% CI, -15.9 to -4.3; p <0.001; MODIFY II: 16% vs 26%; 95% CI -15.5 to -4.3; p < 0.001).<sup>29</sup> Bezlotoxumab is not indicated for the treatment of CDI and is only approved for use in combination with SOC antibiotics in adults at high risk for CDI recurrence as a single 10 mg/kg infusion.<sup>30</sup> In these 2 RCTs, there were infusion-related adverse events and serious adverse events related to bezlotuoxumab.<sup>2</sup> Five patients who received bezlotoxumab alone experienced diarrhea, ventricular tachyarrhythmia, hematuria, cerebral hemorrhage, and sepsis.<sup>2</sup> The patient who had cerebral hemorrhage and sepsis died as a result of their complications.<sup>2</sup>

Compared to placebo, prebiotics or probiotics were more effective for prevention of recurrent CDI in 3 RCTs. These low-quality RCTs evaluated the prebiotic, oligofructose (RR 0.24, 95% CI, 0.11 to 0.56), the probiotic, *S. boulardii* (RR 0.59, 95% CI, 0.35 to 0.98), and 7-day course of nontoxigenic *C. difficile* strain M3 (RR 0.11, 95% CI, 0.02 to 0.54).<sup>2</sup> While the results of 3 RCTs using probiotics or prebiotics found benefit in preventing recurrent CDI, the studies were underpowered and further research with larger samples sizes is needed to draw definitive conclusions regarding their efficacy in CDI.<sup>2</sup> The other 5 probiotic studies did not demonstrate proven benefit in preventing recurrent CDI with these agents.<sup>2</sup> No RCTs evaluating probiotics, prebiotics, or non-antibiotic polymers reported serious adverse events related to the study intervention.<sup>2</sup>

In summary, for prevention of recurrent CDI, there is at least one study to support fidaxomicin (compared to a 10-day vancomycin course; low-quality evidence), fecal microbiota transplant (FMT) (compared to a 14 day vancomycin regimen; moderate quality evidence), and bezlotoxumab (compared to placebo; moderate-quality evidence).<sup>2</sup> While the results of 3 low-quality RCTs using probiotics or prebiotics found benefit in preventing recurrent CDI, the studies were underpowered and further research with larger samples sizes is needed to draw definitive conclusions regarding their efficacy in CDI.<sup>2</sup>

After review, 24 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses),<sup>31-39</sup> wrong study design of included trials (e.g., observational),<sup>40-53</sup> comparator (e.g., no control or placebo-controlled),<sup>54</sup> or outcome studied (e.g., non-clinical).<sup>55</sup>



## New Guidelines:

### High-Quality

#### Infectious Diseases Society of America/Society for Healthcare Epidemiology of America: Focused Update on *C. difficile* Infections

In 2021, the IDSA and SHEA revised guidance on management of CDI in adults.<sup>4</sup> Updates were focused on recently published evidence for the use of fidaxomicin in initial and recurrent CDI compared with vancomycin and the use of bezlotoxumab as monotherapy or in conjunction with SOC antibiotics in preventing recurrent CDI. The guideline committee concluded fidaxomicin and bezlotoxumab may have increased clinical efficacy over older agents, but implementation may be challenging because of initial monetary cost and administration logistics.<sup>4</sup> **Table 1** summarizes 2017 IDSA/SHEA recommendations combined with 2021 IDSA/SHEA focused guidance for the treatment of CDI in adults. No changes were made to the 2017 pediatric guidance.

Three new recommendations were published by the guideline development panel:

1. *For patients with an initial CDI episode, it is suggested to use fidaxomicin rather than a standard course of vancomycin (preferred treatment, conditional recommendation, moderate certainty of evidence).*<sup>4</sup>

Comment: This recommendation places a high value in the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources.<sup>4</sup> Additional, well-designed, independent, cost-effectiveness studies for patients with CDI are needed to improve the strength of this recommendation given that cost is a substantial barrier to fidaxomicin use.<sup>4</sup> Vancomycin remains an acceptable alternative.<sup>4</sup>

2. *In patients with recurrent CDI episodes, it is suggested to use fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin (preferred treatment, conditional recommendation, low certainty of evidence).*<sup>4</sup>

Comment: More well-designed RCTs for patients with recurrent CDI, particularly multiple recurrent CDIs, are needed to improve the strength of recommendations.<sup>4</sup> Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first CDI recurrence.<sup>4</sup> For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and FMT are options in addition to fidaxomicin.<sup>4</sup>

3. *For patients with a recurrent CDI episode within the last 6 months, it is suggested to use bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone (alternative treatment) (conditional recommendation, very low certainty of evidence).*<sup>4</sup>

Comment: This recommendation places a high value on potential clinical benefits, but implementation is often limited by feasibility considerations.<sup>4</sup> In settings where administration logistics are not an issue, patients with a primary CDI episode and other risk factors for CDI recurrence (such as age  $\geq 65$  years, immunocompromised host [per history or use of immunosuppressive therapy], and severe CDI on presentation) may particularly benefit from receiving bezlotoxumab.<sup>4</sup> Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited.<sup>4</sup>

**Table 1. IDSA/SHEA Recommendations for Treatment of *Clostridioides difficile* infections in adults<sup>4</sup>**

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin 200 mg given twice daily for 10 days	Implementation depends upon available resources
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Vancomycin remains an acceptable alternative to fidaxomicin
	Alternative for non-severe CDI, if above agents are unavailable: Metronidazole, 500 mg 3 times daily by mouth for 10–14 days	Definition of non-severe CDI is supported by the following laboratory parameters: White blood cell count of 15,000 cells/ $\mu$ L or lower and a serum creatinine level $<1.5$ mg/dL
	Preferred: Fidaxomicin 200 mg given twice daily for 10 days.	

<b>First CDI recurrence</b>	Off-label recommendation: Fidaxomicin 200 mg twice daily for 5 days followed by once every other day for 20 days.	
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Tapered/pulsed vancomycin regimen example: 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics <sup>a</sup>	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure. <sup>b</sup>
<b>Second or subsequent CDI recurrence</b>	Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	
	Vancomycin by mouth in a tapered and pulsed regimen	
	Vancomycin 125 mg 4 times daily by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days	
	Fecal microbiota transplantation	The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics <sup>a</sup>	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure. <sup>a</sup>
<b>Fulminant CDI</b>	Vancomycin 500 mg 4 times daily by mouth or nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present.	Definition of fulminant CDI is supported by: Hypotension or shock, ileus, megacolon

<sup>a</sup> *Bezlotoxumab may also be considered for patients with other risks for CDI recurrence but implementation depends upon available resources and logistics for intravenous administration, particularly for those with an initial CDI episode. Additional risk factors for CDI recurrence include age >65 years, immunocompromised host (per history or use of immunosuppressive therapy), and severe CDI on presentation.*

<sup>b</sup> *The Food and Drug Administration warns that “in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk.”*

Abbreviations: CDI = *Clostridioides difficile* infection; IDSA/SHEA = Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; SOC = standard of care

The guideline panel identified areas where additional research is needed. These areas included:

- Evaluation of total costs with fidaxomicin (e.g., with reduced CDI recurrences and greater initial acquisition cost);
- Comparison of standard and extended-dosing fidaxomicin versus extended-dosing of vancomycin;

- Evaluation of fidaxomicin for treatment of fulminant CDI;
- Direct comparisons of narrow-spectrum antibiotics for prevention of recurrence;
- Evaluation of biotherapeutics or FMT to restore the microbiome; and
- Evaluation of bezlotoxumab (or similar agents) alone or in combination with other antibiotics (e.g., in combination with fidaxomicin) to augment the host immune response.<sup>4</sup>

#### American College of Gastroenterology: Treatment of *C. difficile* Infection

In 2021, the ACG updated 2013 recommendations on the prevention, diagnosis, and treatment of CDI.<sup>5</sup> This publication was intended to complement the IDSA/SHEA 2021 updates.<sup>5</sup> THE ACG panel chose to expand on areas of particular interest to gastroenterologists, including diagnostic issues around diarrhea and distinguishing *C. difficile* colonization from active infection, the evaluation and management of CDI in the setting of inflammatory bowel disease, and the current evidence and best practices around FMT.<sup>5</sup> This class update focuses on recommendations for medical treatment of CDI.

#### *Antibiotics For Treatment of Initial CDI Episode*

The previous ACG Practice Guideline (2013) recommended oral metronidazole for mild-to-moderate CDI and vancomycin for severe CDI.<sup>56</sup> Fidaxomicin was mentioned, but not yet recommended because of increased cost and evolving data. Recent data supports the efficacy of vancomycin and fidaxomicin as primary treatment in nonsevere CDI.<sup>5</sup> Fidaxomicin has been demonstrated to be generally equivalent to vancomycin in this population for cure, with data demonstrating decreased CDI recurrence rates.<sup>5</sup> For lower-risk patients (i.e., younger outpatients with minimal comorbidities), particularly in cost-sensitive environments, metronidazole is an appropriate alternative.<sup>5</sup>

In patients with severe disease, fidaxomicin was noninferior to vancomycin in achieving clinical cure at the end of therapy and associated with decreased risk of recurrence in one phase 3 clinical trial.<sup>5</sup> This and other clinical trials of fidaxomicin have excluded patients with fulminant CDI and life-threatening illness, therefore limited evidence supports fidaxomicin use in these populations.<sup>5</sup> Metronidazole should not be used for the treatment of severe CDI because it was shown to be inferior to vancomycin in multiple RCTs and cohort studies.<sup>5</sup>

In cases of fulminant CDI, a higher dose of oral vancomycin at 500 mg every 6 hours is recommended by IDSA/SHEA (2017)<sup>21</sup> and ACG (2013).<sup>56</sup> Given lack of clinical trial data, this recommendation is based on expert opinion.<sup>5</sup> Direct comparison of low-dose (less than 500 mg/day) and high-dose (greater than 500 mg per day) vancomycin therapies failed to demonstrate significant differences in rates of cure, time to cure, mortality, or complication rates in severe infection.<sup>5</sup> In patients with ileus, the addition of vancomycin enemas (500 mg in 100 mL saline) is also recommended by 2 guidelines<sup>21,56</sup> based on assumptive improvement in colonic drug delivery.<sup>5</sup> Although vancomycin monotherapy is superior to metronidazole in severe CDI, previously published guidelines<sup>21,56</sup> recommend addition of intravenous metronidazole to oral vancomycin in patients with fulminant disease.<sup>5</sup> This recommendation is based on a single-center, retrospective study, where patients with fulminant CDI in the intensive care unit who received vancomycin plus metronidazole had lower rates of mortality compared with vancomycin monotherapy (15.9% vs 36.4%, P=0.03).<sup>5</sup> Although fidaxomicin was shown to be noninferior to vancomycin in the treatment of severe CDI, there are no data supporting its use in fulminant CDI.<sup>5</sup> Strength of recommendations and quality of evidence for initial antibiotic treatment of nonsevere, severe, and fulminant disease are as follows:

- Initial episode of nonsevere disease:
  - Fidaxomicin 200 mg orally twice daily for 10 days (strong recommendation, moderate-quality evidence) or vancomycin 125 mg orally 4 times daily for 10 days (strong recommendation, low-quality evidence).<sup>5</sup>

- Metronidazole 500 mg orally 3 times daily for 10 days may be considered in patients with low risks (strong recommendation, moderate-quality evidence).<sup>5</sup>
- Severe disease:
  - Vancomycin 125 mg orally 4 times daily for 10 days (strong recommendation, low-quality evidence) or fidaxomicin 200 mg orally twice daily for 10 days (conditional recommendation, very low-quality evidence).<sup>5</sup>
- Fulminant disease:
  - Vancomycin 500 mg orally 4 times daily for the first 48 to 72 hours; if clinical improvement observed, decrease to 125 mg orally 4 times daily for 10 days (strong recommendation, very low-quality evidence).<sup>5</sup>
  - Parenteral metronidazole 500 mg every 8 hours can be considered as an addition to oral vancomycin therapy (conditional recommendation, very low-quality evidence).<sup>5</sup>
  - For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hours) may be beneficial (conditional recommendation, very low-quality evidence).<sup>5</sup>

#### *Treatment of Recurrent CDI*

Recurrent CDI is generally defined as the recurrence of diarrhea within 8 weeks after treatment of an initial episode of CDI.<sup>5</sup> Approximately 20% of patients will experience an initial recurrence, and rates of further recurrences continue to increase significantly after each one.<sup>5</sup> Another course of antibiotics is generally required for the treatment of a first recurrence of CDI, and the choice of treatment is dependent on what was used to treat the initial episode.<sup>5</sup> For sustained clinical cure with no recurrence in patients with recurrent CDI, existing data slightly favor fidaxomicin over vancomycin.<sup>5</sup> There are limited data on extended or pulsed vancomycin tapers, and no randomized trials specifically assessing this therapy.<sup>5</sup>

Fecal microbiota transplantation has emerged as a safe and effective therapy for recurrent CDI, which most studies have defined as 3 or more confirmed episodes, although some trials have performed FMT after a second episode.<sup>5</sup> The efficacy of FMT after SOC antibiotics for preventing recurrent CDI has been described in numerous case series and RCTs.<sup>5</sup> There have been a few trials comparing the effectiveness of different FMT delivery modalities.<sup>5</sup> The choice of the most appropriate route of instillation should be driven partly by the options available to the provider, the preferences of the patient, and the clinical circumstances.<sup>5</sup> Minor transient adverse effects associated with FMT have been reported in case series and include bloating, cramps, abdominal pain, nausea, gas, diarrhea, irregular bowel movements, constipation, and low-grade fevers.<sup>5</sup> Serious adverse events have rarely been reported, even among immunocompromised patients, although risk of infection is an important consideration.<sup>5</sup>

Considering the high cost of bezlotoxumab and the minimal benefits over placebo in patients at low risk of recurrent CDI, the ACG panel recommends bezlotoxumab be considered for patients in whom the observed benefits in clinical trials were greatest including those aged 65 years or older with at least one of the following additional risk factors: experiencing a second episode of CDI within the past 6 months, immunocompromised, or severe CDI.<sup>5</sup> Strength of recommendations and quality of evidence for treatment of recurrent CDI are as follows:

- ACG suggests tapering/pulsed-dose vancomycin for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole (strong recommendation, very low-quality evidence).<sup>5</sup>
- ACG recommends fidaxomicin for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole (strong recommendation, moderate-quality evidence).<sup>5</sup>
- ACG recommends patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences (strong recommendation, moderate-quality evidence).<sup>5</sup>

- ACGs recommend FMT be delivered through colonoscopy (strong recommendation, moderate-quality evidence) or capsules (strong recommendation, moderate-quality evidence) for treatment of recurrent CDI; delivery by enema is suggested if other methods are unavailable (conditional recommendation, low-quality evidence).<sup>5</sup>
- ACG suggests repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT (conditional recommendation, very low-quality evidence).<sup>5</sup>
- ACG suggests bezlotoxumab be considered for prevention of CDI recurrence in patients who are at high risk of recurrence (conditional recommendation, moderate-quality evidence).<sup>5</sup>

### *Probiotics*

Evidence to evaluate probiotics for preventing CDI is primarily derived from meta-analyses which pooled data from small trials of different probiotic formulations and methodologies.<sup>5</sup> There is a paucity of high-quality clinical trial data of probiotics in CDI, and most studies are underpowered, with CDI as a secondary outcome in studies performed to assess prevention of antibiotic-associated diarrhea.<sup>5</sup> The ACG guideline panel determined that there is insufficient evidence to recommend any probiotic for the primary or secondary prevention of CDI.<sup>5</sup> Strength of recommendations and quality of evidence for the use of probiotics are as follows:

- ACG recommends against probiotics for the primary prevention of CDI in patients being treated with antibiotics (conditional recommendation, moderate-quality evidence).<sup>5</sup>
- ACG recommends against probiotics for the secondary prevention of CDI recurrence (strong recommendation, very low-quality evidence).<sup>5</sup>

### National Institute for Health and Care Excellence: Antibiotics for *C. difficile* Infection

NICE guidance for CDI antibiotic treatment was published in July 2021.<sup>6</sup> For treatment of an initial episode of CDI, NICE recommends oral vancomycin as the first-line antibiotic for CDI of any severity.<sup>6</sup> Fidaxomicin is recommended as the second-line antibiotic for a first episode of *C. difficile* infection of any severity when vancomycin is ineffective (treatment failure).<sup>6</sup> Although fidaxomicin was more effective than vancomycin for sustained symptomatic cure in a network meta-analysis, the cost of fidaxomicin is substantially higher in the United Kingdom.<sup>6</sup> Metronidazole is not recommended for treating an initial CDI episode or recurrence of CDI.<sup>6</sup>

For another CDI within 12 weeks of symptom resolution from the first episode (relapse), the NICE committee recommends fidaxomicin.<sup>6</sup> However, if the recurrence develops more than 12 weeks after symptom resolution, either vancomycin or fidaxomicin are recommended.<sup>6</sup> A tapered or pulsed regimen of vancomycin is not recommended because, in the evidence review, its use was limited to studies in which there was co-administration of FMT.<sup>6</sup> The committee agreed that there was insufficient evidence of benefits from a fidaxomicin extended-pulsed regimen to justify recommending an unlicensed treatment regimen over a licensed one in the United Kingdom.<sup>6</sup> If a patient is experiencing a life-threatening CDI, the recommendation is seek specialist advice, with high dose vancomycin (500 mg orally four times a day x 10 days) accompanied by metronidazole 500 mg IV three times a day for 10 days as the suggested antibiotic regimen.<sup>6</sup>

### British Society of Gastroenterology and Healthcare Infection Society: Use of Fecal Microbiota Transplant for *C. Difficile* Infection

A joint guideline published by the BSG and HIS in August 2018 provided best practice recommendations for the provision of FMT in adults with CDI based upon the available evidence at that time.<sup>3</sup> If published evidence was insufficient, consensus multidisciplinary expert opinion contributed to recommendation development.<sup>3</sup> The BSG/HIS working group only considered studies that used the administration of manipulated whole stool (including encapsulated feces).<sup>3</sup> Studies using cultured microorganisms (or their proteins, metabolites or other components), or microbiota suspensions, were considered to be in the preclinical

research stage, without firm evidence, and excluded from the evidence analysis.<sup>3</sup> Fifty-eight studies were included as the basis of evidence for writing this guideline.<sup>3</sup> Thirty-nine reports were case studies in CDI including at least 10 patients and 10 were randomized studies in CDI.<sup>3</sup> Nine studies examined FMT efficacy for non-CDI indications (i.e., inflammatory bowel disease, hepatic encephalopathy, metabolic syndrome).<sup>3</sup> For the purposes of this review, the focus will be on guidance for FMT to prevent recurrent CDI.

#### *Candidates for FMT*

Evidence for the use of FMT as initial therapy for CDI is very limited, however, there is widespread consensus that FMT is an efficacious treatment for recurrent CDI.<sup>3</sup> In defining recurrent CDI, some studies have relied on a minimum threshold of return of clinical symptoms (e.g., at least 3 unformed bowel movements within 24 hours, for at least 2 consecutive days) following previous successful CDI treatment; most studies have also included a requirement for a positive microbiological test.<sup>3</sup> All of the reviewed studies for this guideline included patients with recurrent CDI, but some studies offered FMT to patients at the first recurrence (second episode), whereas others offered FMT after the second recurrence (third episode).<sup>3</sup> Some protocols offered FMT after 3 or more recurrences, while others did not define the point at which FMT was administered.<sup>3</sup> As FMT was an unlicensed medicine in 2018 with poorly-studied long-term sequelae, the working group recommended that it should generally be reserved for patients who have had 3 or more episodes of infection.<sup>3</sup> There were no studies directly comparing its effectiveness with some of the newer agents, such as fidaxomicin or bezlotoxumab, so this recommendation was made on the basis of safety.<sup>3</sup> However, the working group agreed that it may be reasonable in certain patient groups with ongoing risk factors for further CDI recurrence to offer FMT after the second episode.<sup>3</sup>

Two randomized trials assessing FMT efficacy permitted the recruitment of patients with refractory CDI.<sup>3</sup> The first study defined refractory CDI as at least 3 weeks of ongoing severe symptoms despite standard antimicrobial therapy for CDI.<sup>3</sup> The second study required persistent or worsening diarrhea and one of the following: ongoing abdominal pain, fever greater than 38°C, or white blood cell count greater than  $15 \times 10^9/L$  despite oral vancomycin at a dose of 500 mg four times daily for at least 5 days.<sup>3</sup> Both studies included very small numbers of patients with refractory CDI ( $n=4/20$  [20%] and  $n=15/219$  [6.8%], respectively).<sup>3</sup> There did not appear to be any significant difference in primary outcome measure (clinical cure) in patients who received FMT with recurrent or refractory CDI, although neither study was designed to assess this difference.<sup>3</sup> Overall, the working group concluded that there is little consensus on the definition of refractory CDI, with some studies using the terms refractory and recurrent interchangeably.<sup>3</sup> For these reasons, the quality of evidence for the use of FMT in refractory cases of CDI is lower than for recurrent CDI.<sup>3</sup> Strength of recommendations and quality of evidence for which patients are the best candidates for FMT are as follows:

- FMT should not be administered as initial treatment for CDI (strong recommendation, low-quality evidence).<sup>3</sup>
- FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe complicated CDI (strong recommendation, high-quality evidence).<sup>3</sup>
- FMT should be considered in cases of severe, refractory CDI (strong recommendation, moderate-quality evidence).<sup>3</sup>

#### *Comorbidity Exclusions for FMT*

Most published studies had a core set of general recipient exclusions which included: significant/anaphylactic food allergy, pregnancy, breastfeeding, admission to intensive care or requirement for vasopressors, chronic diarrhea or other infectious cause of diarrhea, inflammatory bowel disease, immunodeficiency due to recent chemotherapy and/or neutropenia, human immunodeficiency virus, prolonged use of corticosteroids, graft versus host disease and decompensated cirrhosis.<sup>3</sup> In addition, only a limited number of studies included specific detail about the presence of comorbidities in patients receiving FMT.<sup>3</sup> Strength of recommendations and quality of evidence for patients with comorbidities and at higher risk for FMT adverse effects are as follows:

- FMT should be avoided in those with anaphylactic food allergy (strong recommendation, low-quality evidence).<sup>3</sup>

- FMT should be offered with caution to patients with CDI and decompensated chronic liver disease (weak recommendation, very low-quality evidence).<sup>3</sup>
- FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong recommendation, moderate-quality evidence).<sup>3</sup> Immunosuppressed patients should only receive FMT from donors negative for Epstein–Barr virus (EBV) and cytomegalovirus (CMV) due to risk of severe infection if exposed to EBV or CMV (strong recommendation, very low-quality evidence).<sup>3</sup>
- FMT should be offered to those with recurrent CDI and inflammatory bowel disease (IBD), but patients should be counselled about a small but recognized risk of exacerbation of IBD (strong recommendation, moderate-quality evidence).<sup>3</sup>

This guideline also provides best practice recommendations for FMT donor selection and screening, FMT preparation and administration, and route of FMT administration (upper versus lower gastrointestinal tract).<sup>3</sup> For more information, please refer to the publication.

#### National Institute for Health and Care Excellence: Fecal Microbiota Transplant for Recurrent CDI

In August 2022, NICE issued guidance for the use of FMT in recurrent CDI.<sup>7</sup> The guideline committee identified and assessed 5 eligible RCTs (n=274) which compared FMT, given via different routes of administration and with a preceding course of antibiotics, with antibiotic treatment.<sup>7</sup> Four RCTs compared FMT and vancomycin and 1 RCT compared FMT with fidaxomicin.<sup>7</sup> Three trials found lower CDI recurrence in the FMT group (range 6% to 10%) compared with the antibiotic group (vancomycin range 62% to 69%, fidaxomicin 46%).<sup>7</sup> However, none of the trials reported statistical significance.<sup>7</sup> Clinical trial evidence shows that FMT treatment is better than antibiotics alone at resolving a CDI in people who have had 2 or more previous infections.<sup>7</sup>

- Recommendation: FMT is recommended as an option to treat recurrent CDI in adults who have had 2 or more previous confirmed episodes.<sup>7</sup>

#### **New Formulations or Indications:**

1. A new oral suspension formulation of vancomycin (FIRVANQ) was approved in January 2018.<sup>10</sup> This product is indicated in adults and pediatric patients less than 18 years of age (no clarity regarding lower limit for age provided in prescribing information) for treatment of *C. difficile*-associated diarrhea and enterocolitis caused by *Staphylococcus aureus*.<sup>10</sup> Orally administered vancomycin is not effective for treatment of other types of infections.<sup>10</sup>
2. In January 2020, the FDA expanded the approved population eligible to receive fidaxomicin (DIFICID) to include pediatric patients.<sup>11</sup> Fidaxomicin is now indicated in adult and pediatric patients aged 6 months and older for the treatment of *C. difficile*-associated diarrhea.<sup>11</sup> Pediatric patients must weigh at least 4 kg for the fidaxomicin suspension FDA-approved weight-based dosing parameters.<sup>11</sup> The safety of fidaxomicin in pediatric patients aged 6 months and older was evaluated in a phase 2 single arm trial (n=38).<sup>11</sup> An additional phase 3 RCT (n=142) in which fidaxomicin was compared to vancomycin was also submitted to the FDA for expanded approval in pediatric patients.<sup>11</sup> The details of this RCT are summarized in **Table 3**.

#### **Randomized Controlled Trials:**

A total of 225 citations were manually reviewed from the initial literature search. After further review, 221 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in **Table 3** below. Full abstracts are included in **Appendix 2**.

**Table 3. Description of Randomized Comparative Clinical Trials.**

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Guery B., et al <sup>57</sup>  Phase 3b/4 RCT  MC, OL, PG	1. Fidaxomicin 200 mg orally two times a day x 5 days, followed by 200 mg every other day x 20 days (n=181)  2. Vancomycin 125 mg orally four times a day x 10 days (n=181)	Hospitalized patients with CDI aged 60 yo and older with less than 2 CDI episodes in the previous 3 mos  Sites: 86 hospitals in 21 European countries	Sustained clinical cure: resolution of diarrhea at end of therapy and no recurrent CDI 30 days after end of treatment (day 40 for vancomycin and day 55 for fidaxomicin)	Percent of patients with sustained clinical cure 30 days after end of treatment 1. 70% (n=124/177) 2. 59% (n=106/179)  Difference: 11% (95% CI 1.0% to 20.7%)  OR: 1.62 (95% CI 1.04 to 2.54) P=0.03	-Open label study design -Recurrence was calculated using the entire study population as a denominator; however, earlier trials excluded clinical failures from the denominator -All study sites were located in Europe -Pulsed fidaxomicin dose is not FDA-approved -Patient population excluded people under 60 yo -64% of patients had non-severe CDI -80% of patients were enrolled at diagnosis of first CDI episode
Wolf J., et al <sup>58</sup>  Phase 3 RCT  MC, PG, investigator-blinded	1. Fidaxomicin 16 mg/kg oral suspension twice daily (ages 0 to 5 yo) or 200 mg twice daily (ages 6 to 18 yo) x 10 days (n=100)  2. Vancomycin 10 mg/kg oral liquid four times a day (ages 0 to 5 yo) or 125 mg four times a day (ages 6 to 17 yo) 10 days (n=48)	Patients less than 18 yo with CDI  Sites: 39 sites across the United States, Canada, and Europe  Randomized 2:1  Total enrollment = 142 (30 patients < 2 yo)	Confirmed clinical response (resolution of diarrhea) rate 2 days after the end of treatment  Secondary endpoint: global cure rate (clinical cure without CDI recurrence) 30 days after end of treatment	Rate of confirmed clinical response 2 days after the end of treatment 1. 77.6% (n=76/98) 2. 70.5% (n=31/44) Adjusted treatment difference: 7.5% (95% CI -7.4% to 23.9%) NS  Rate of global cure 30 days after end of treatment 1. 68.4% (n=67/98) 2. 50.0% (n=22/44) Adjusted treatment difference: 18.8% (95% CI 1.5% to 35.3%)	-The study was not designed as a superiority trial and was not powered for this purpose - Single blinded study design (due to different formulations and dosing regimens) -Proportions of treatment-emergent adverse effects were similar for fidaxomicin and vancomycin (74% vs. 75%)
Hvas CL, et al <sup>59</sup>  OL, RCT	1. FMT administered via colonoscopy or nasojejunal tube after 4 to 10 days of vancomycin orally 125 mg four times day (n=24)	Adults aged 18 yo and older with recurrent CDI and documented recurrence within 8 weeks after finishing antibiotic (vancomycin or	Combined clinical resolution and a negative PCR test for CD toxin 8 weeks after treatment	Combined clinical resolution and a negative PCR test for CD toxin 8 weeks after treatment 1. 17/24 (71%) 2. 8/24 (33%) 3. 3/16 (19%)  1 vs. 2: p=0.009	-Open label study design -Randomization strategy not described -Small sample size -Study was not powered to detect differences between the 2 antibiotics



	<p>2. Fidaxomicin 200 mg orally twice daily x 10 days (n=24)</p> <p>3. Vancomycin 125 mg orally four times a day x 10 days (n=16)</p>	<p>fidaxomicin) therapy</p> <p>1 site in Denmark</p> <p>Total enrollment = 64</p>		<p>1 vs. 3: p=0.001</p> <p>95% CI not reported</p>	<p>-Not clear why investigators chose vancomycin to precede FMT therapy, but did not compare fidaxomicin + FMT with the combination treatment of vancomycin + FMT</p>
<p>Mikamo H, et al<sup>60</sup></p> <p>Phase 3 RCT MC, NI, DB, PG</p>	<p>1. Fidaxomicin 200 mg orally twice daily x 10 days (n=106)</p> <p>2. Vancomycin 125 mg orally four times a day x 10 days (n=109)</p>	<p>Hospitalized patients with CDI aged ≥20 years who had not received antibiotic treatment for CDI, or had treatment failure after ≥3 days of metronidazole therapy</p> <p>Total enrollment = 212</p> <p>Sites: 82 hospitals in Japan</p>	<p>Global CDI cure rate (proportion of patients cured at end of treatment with no recurrence during 28-day follow-up)</p> <p>Lower limit of NI margin = -10%</p>	<p>Global CDI cure rate</p> <p>1. n=70/104 (67.3%)</p> <p>2. n=71/108 (65.7%)</p> <p>Difference: 1.2%</p> <p>95% CI -11.3 to -13.7</p> <p>Non-inferiority was not demonstrated</p>	<p>-Non-inferiority trial</p> <p>-Limited to sites in Japan</p> <p>-77% of patients had mild to moderate CDI</p> <p>-85% of patients were enrolled at diagnosis of first CDI episode and were inpatients, cannot extrapolate results to outpatient population</p>
<p>Abbreviations: CD = <i>Clostridioides difficile</i>; CDI = <i>Clostridioides difficile</i> infection; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; FMT = fecal microbiota transplantation; mos = months; MC = multi-center; NI = non-inferiority; NS = non-significant; OL = open label; OR = odds ratio; PCR = polymerase chain reaction; PG = parallel group; RCT = randomized controlled trial; yo = years old</p>					

### **NEW DRUG EVALUATION: Fecal Microbiota, live-jslm (REBYOTA)**

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

#### **Clinical Efficacy:**

Fecal microbiota, live-jslm (REBYOTA), a live biotherapeutic suspension for rectal administration, is indicated for the prevention of recurrent CDI in adults aged 18 years and older following antibiotic treatment for recurrent CDI.<sup>8</sup> The FDA granted Breakthrough Therapy status, Fast Track, and Orphan Drug designations for this new biotherapeutic in November 2022.<sup>61</sup> The commercial formulation of fecal microbiota suspension is FDA-regulated as a biologic drug.<sup>9</sup> It is not indicated for treatment of CDI.<sup>8</sup> Safety and efficacy in pediatric patients have not been established.<sup>8</sup> The recommended dose is 150 mL administered rectally 24 to 72 hours after the last dose of antibiotics for CDI treatment.<sup>8</sup> The product is manufactured from human fecal matter sourced from qualified donors and tested for transmissible pathogens.<sup>8</sup>

The FDA granted approval of fecal microbiota based on findings from the PUNCH CD3 trial, a phase 3, multicenter, double-blinded, placebo-controlled RCT.<sup>9</sup> Forty-one study sites in the United States and Canada participated in this RCT.<sup>9</sup> Patients (n=267) were enrolled and randomized 2:1 to receive a single-dose of fecal microbiota enema (n=180) or a single-dose of placebo (n=87) 24 to 72 hours after the last dose of the CDI antibiotic regimen.<sup>61</sup> Eligible patients met one of the following parameters: 1) had one or more recurrent CDI episodes with completion of a recent SOC 10-day antibiotic regimen or 2) had experienced 2 or more severe CDI episodes resulting in hospitalization within the previous year.<sup>61</sup> In addition, within 30 days before enrollment, patients were required to have a positive stool test for the presence of *C. difficile* with the capability to produce toxins.<sup>61</sup> Patients were excluded if they had a known history of severe CDI, inflammatory bowel disease, irritable bowel syndrome, celiac disease, colostomy, active colitis, continued diarrhea despite antibiotic therapy, required antibiotic therapy for another condition, or had received a previous FMT.<sup>61</sup>

Patients were stratified by antibiotic use at enrollment (vancomycin monotherapy, vancomycin in combination with either metronidazole and/or fidaxomicin, fidaxomicin monotherapy, or other antibiotic).<sup>61</sup> The primary endpoint was treatment success, defined as absence of recurrent CDI diarrhea (passage of 3 or more unformed stools in 24 hours for at least 2 days) 8 weeks after treatment.<sup>61</sup> Secondary endpoints included sustained clinical response rate (recurrent CDI successfully treated and no new CDI episodes 6 months after completed treatment) and the incidence of adverse effects.<sup>61</sup> Treatment with open-label fecal microbiota enema was an option for patients who experienced treatment failure within 8 weeks. A total of 65 (25%) patients including 23% in the fecal microbiota arm and 28% in the placebo arm were designated as treatment failures and received one dose of open-label fecal microbiota enema.<sup>9</sup>

For PUNCH CD3, a total of 320 study participants were screened for study inclusion.<sup>61</sup> Thirty-one participants did not meet inclusion criteria or withdrew consent prior to receiving treatment.<sup>61</sup> The intention-to-treat (ITT) population (n=289) was defined as all randomized patients allocated to the 2 treatment groups; if participants withdrew prior to receiving blinded treatment they were not included in the ITT analysis.<sup>61</sup> The modified intention-to-treat (mITT) population (n=262) was defined as all participants who successfully completed treatment and were evaluated for the primary endpoint at 8 weeks.<sup>61</sup> The mITT population was pre-specified as the primary analysis population.<sup>9</sup> The per protocol (PP) population (n=245) was defined as all participants who successfully completed treatment and did not discontinue the trial for reasons not related to CDI or protocol violations.<sup>61</sup> Baseline characteristics were comparable between the 2 treatment arms, however, the placebo arm had a higher proportion of participants younger than 65 years of age than the fecal microbiota arm (62% vs. 51%, respectively).<sup>61</sup> The median age of study participants was 63 years, most participants were White (92.1%), and female (68.5%).<sup>61</sup> Most participants received vancomycin (88%) prior to treatment with fecal microbiota as that was the SOC antibiotic during the time period of the study (conducted July 2017 to April 2020).<sup>6</sup>

In the PUNCH CD3 trial, mITT population results for the primary outcome were not significant, as 71.2% treated with fecal microbiota enema and 62.4% treated with placebo had treatment success (treatment difference: 8.8%; 95% CI -3.4 to 21.1; p=0.15).<sup>61</sup> The investigators found it was challenging to recruit enough study participants (due to the widespread availability of compounded FMT products) so in an interim assessment, an agreement was reached with FDA personnel to permit data from one previous phase 2 trial (PUNCH CD2) to be used in the statistical analysis of PUNCH CD3 results.<sup>9</sup> The PUNCH CD2 trial (n=133) was similar to PUNCH CD3 in study design, product formulation, and treatment success definitions.<sup>9</sup> However, in PUNCH CD2, 1 and 2 doses of fecal microbiota enema administered 1 week apart were compared to placebo. Also, the PUNCH CD2 trial enrolled participants who had 2 or more CDI recurrences compared with PUNCH CD3, which enrolled participants with at least one or more CDI recurrences.<sup>9,61</sup> The primary efficacy analysis in PUNCH CD2 was the treatment success rate after 2 doses of fecal microbiota versus 2 doses of placebo in the ITT population, which was not significant (55.6% vs. 43.2%, respectively, treatment difference = 12.4%; 95% CI -8.2 to 33; P=0.243).<sup>9</sup> A secondary outcome analysis, showed a superior response to one dose fecal microbiota vs. placebo (p=0.047); therefore, a single dose of fecal microbiota was selected for subsequent studies.<sup>9</sup>

Data from the 1-dose fecal microbiota arm compared with placebo (n=82) in PUNCH CD2 was used in Bayesian statistical analysis of the PUNCH CD3 results.<sup>61</sup> The investigators prespecified two superiority thresholds: (1) posterior probability of superiority > 0.999 was selected to control the nominal type I error rate without borrowing at one-sided 0.00125; and (2) posterior probability of superiority > 0.975 was selected to control the nominal type I error rate without borrowing at one-sided 0.025.<sup>61</sup> In the statistical analysis that took into account both studies, the overall estimated rate of success in preventing recurrent CDI through 8 weeks was higher in the mITT fecal microbiota group that received 1 dose (70.6%) than in the 1-dose placebo group (57.5%) with an estimated treatment effect of 13.1% (95% CI 2.3 to 24%) and a posterior probability of superiority of 0.991.<sup>9</sup> The details of PUNCH CD3 and PUNCH CD2 RCTs are described and evaluated below on **Table 5**.

The small number of non-White patients and lack of participants with irritable bowel syndrome, inflammatory bowel disease, and immunocompromising conditions limits the ability to generalize the data from PUNCH CD3.<sup>61</sup> An open-label study (PUNCH CD3-OLS) is ongoing, which includes a more diverse recurrent CDI population compared with prior fecal microbiota studies and allows enrollment of patients with immunocompromised conditions and chronic conditions such as irritable bowel syndrome or inflammatory bowel disease.<sup>61</sup> In PUNCH CD3, most of the patients received vancomycin (88%) and only 6% of patients received fidaxomicin before administration of fecal microbiota. More data is needed to assess the efficacy of fecal microbiota administration after completion of a fidaxomicin regimen for recurrent CDI. Of note, the placebo response in PUNCH CD3 was higher than expected. The investigators postulated that treatment success rates can be influenced by the diagnostic modality for confirming CDI.<sup>61</sup> Although the polymerase chain reaction (PCR) assay is the most commonly used diagnostic tool in clinical practice in the U.S., and was used in over 70% of PUNCH CD3 participants, it can result in a false positive result.<sup>61</sup> This may lead to the inclusion of patients who do not actually have CDI and therefore also impact treatment response rates.<sup>61</sup> Another possible explanation for the higher placebo effect is that approximately one-third of PUNCH CD3 participants were enrolled after only one CDI recurrence.<sup>61</sup> As the risk of recurrence increases with each subsequent infection, some PUNCH CD3 placebo participants may have had a lower risk of recurrence because of less severe dysbiosis.<sup>61</sup> There is insufficient data comparing the REBYOTA enema with unlicensed, compounded, forms of FMT (i.e. manipulated whole stool in capsule form). Additional data is also needed to assess long term safety and use in patients with severe CDI.

#### **Clinical Safety:**

Because rectal fecal microbiota is manufactured from human fecal matter is carries the risk of transmitting infectious agents and may contain food allergens.<sup>8</sup> The potential for fecal microbiota to cause adverse effects due to food allergens is unknown.<sup>8</sup> The most commonly reported adverse events reported after a single fecal microbiota dose compared with placebo in the phase 3 PUNCH CD3 trial were abdominal pain (8.9% vs. 6.9%), diarrhea (7% vs. 3.4%), abdominal distention (3.9% vs. 2.3%), flatulence (3.3% vs. 0) and nausea (3.3% vs. 1%).<sup>9</sup> Most adverse events occurred during the first 2 weeks of treatment.<sup>9</sup>

Look-alike / Sound-alike Error Risk Potential: None identified

#### **Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Resolution of CDI-associated diarrhea without CDI recurrence within 8 weeks
- 2) Sustained treatment response (no CDI 6 months after last dose)
- 3) Serious adverse events
- 4) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Treatment success (absence of CDI diarrhea within 8 weeks of treatment)



		<ul style="list-style-type: none"> <li>-Chronic diarrhea</li> <li>-Celiac disease</li> <li>-Short gut syndrome</li> <li>-Continued CDI diarrhea despite antibiotic treatment</li> <li>-Previous fecal transplant</li> <li>-Colitis</li> <li>-Irritable bowel syndrome</li> <li>-Inflammatory bowel disease</li> <li>-Compromised immune system</li> <li>-Taking &gt; 20 mg of prednisone</li> </ul>	<p>1. 39 2. 43</p> <p>Total from both trials (mITT): 1. 216 2. 128</p>	<p><b>Secondary Endpoint:</b> Percent of ITT PUNCH CD3 patients without rCDI at 6 mos (sustained clinical response) 1. 116 (64.4%) 2. 48 (55.2%) Difference: 9.3% 95% CI -3.3 to 21.9 P=0.145</p> <p>Percent of mITT PUNCH CD3 patients without rCDI at 6 mos (sustained clinical response) 1. 116 (65.5%) 2. 48 (56.5%) Difference: 9.1 95% CI -3.5 to 21.7 P=0.156</p>				<p><b>Applicability:</b> <u>Patient:</u> Enrolled patients were primarily White. Excluded patients with severe CDI, irritable bowel syndrome, and those who were immunocompromised. Cannot apply this data to those populations. This data is most applicable to the 88% of patients who received vancomycin. Only 6% of enrolled patients received fidaxomicin, and more data is needed to assess applicability of these results to these patients. Fidaxomicin appears to be more effective than vancomycin in preventing CDI recurrence. <u>Intervention:</u> Administration of 1 dose of fecal microbiota was shown to be effective in preventing rCDI in phase 2 clinical trials. FDA approved dose is 1 dose based on combined results from Phase 2 and Phase 3 RCTs. <u>Comparator:</u> Placebo was an effective comparator for a novel agent. Comparison to current standard of care including fidaxomicin or compounded FMT for rCDI is unknown. Guideline recommendations were updated in 2021, after completion of this study in 2020. <u>Outcomes:</u> Treatment success (defined as symptom resolution) at 8 weeks is a clinically relevant endpoint as defined in guidelines. <u>Setting:</u> 36 sites in the US and 5 sites in Canada. Conducted from 7/2017 to 4/2020.</p>
<p>2. Dubberke ER, et al.<sup>9,62</sup></p> <p>PUNCH CD2 Phase 2, MC, DB, PC, RCT</p>	<p>1. Fecal microbiota 150 ml enema x 2 doses 7 days apart, 24 to 48 hrs after antibiotic washout</p> <p>2. Placebo (saline) enema x 2 doses 7 days apart, 24 to 48 hrs after antibiotic washout</p> <p>3. Fecal microbiota 150 ml enema x 1</p>	<p><b>Demographics:</b> 1. Mean age: 64 yo 2. Female: 62% 3. White: 98 % 4. Antibiotic use -Vancomycin 90% -Fidaxomicin 4% -Metronidazole 5% 5. Median number of CDI episodes: 4</p> <p><b>Key Inclusion Criteria:</b> -Adults ≥ 18 yo with ≥ 2 episodes of rCDI and completion of 2 rounds of SOC antibiotics OR ≥ 2 episodes of severe CDI resulting in hospitalization</p>	<p><b>ITT:</b> 1. 45 2. 44 3. 44</p> <p><b>mITT:</b> 1. 40 2. 43 3. 38</p> <p><b>Attrition:</b> 1. 5 (11%) 2. 1 (2.3%) 3. 6 (13.6%)</p>	<p><b>Primary Endpoint:</b> Percent of ITT patients with treatment success (no rCDI diarrhea) at 8 weeks in Group 1 (fecal microbiota x 2 doses) versus Group 2 (placebo x 2 doses) 1. 25 (55.6%) 2. 19 (43.2%) Difference: 12.4% 95% CI -8.2 to 33 P=0.243</p> <p>Percent of mITT patients with treatment success at 8 weeks in Group 1 versus Group 2</p>	N/A	<p><b>All AEs 7 days post-treatment</b> 1. 34 (81%) 2. 35 (79.5%) 3. 29 (69%)</p> <p><b>TEAEs through 24 mos post-treatment</b> 1. 34 (81%) 2. 38 (86.4%) 3. 33 (78.6%)</p> <p><b>Severe TEAEs through 24 mos post-treatment</b> 1. 7 (16.7%)</p>	N/A	<p><b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Randomized 1:1:1 using permuted blocks stratified by antibiotic regimen. Baseline characteristics balanced between treatment groups. <u>Performance Bias:</u> Low. Study participants, investigators, and site personnel were blinded to treatment assignment. <u>Detection Bias:</u> Unclear. Fecal microbiota and placebo were both supplied in a brown enema bag with an opaque sleeve to cover bag and tubing to preserve blinding. Participants recorded daily symptoms in a diary up to 7 days after treatment, which may have been subject to recall bias. Treatment success determined by an independent blinded adjudication committee. <u>Attrition Bias:</u> High. Attrition was higher in active comparator arms versus placebo. Death was the reason most patients (n=6) withdrew from the study in both fecal microbiota arms (2 doses: 7%; 1 dose: 7%). Death was related to pre-existing condition, not treatment</p>

<p>dose plus 1 dose of placebo 7 days apart, 24 to 48 hrs after antibiotic washout</p>	<p>-Currently taking antibiotics to control rCDI symptoms (&lt; 3 stools per day) -Positive stool test for the presence of toxigenic <i>C. difficile</i> within 60 days of study enrollment</p> <p><u>Key Exclusion Criteria:</u> -Chronic diarrhea -Celiac disease -Short gut syndrome -Continued CDI diarrhea despite antibiotic treatment -Previous fecal transplant -Irritable bowel syndrome -Colitis -Inflammatory bowel disease -Compromised immune system -Taking ≥ 20 mg or equivalent of prednisone</p>			<p>1. 25 (62.5%) 2. 19 (44.2%) Difference: 18.3% 95% CI -2.8 to 39.4 P=0.095</p> <p><u>Secondary Endpoint:</u> Percent of ITT patients with treatment success (no rCDI) at 8 weeks in Group 2 (placebo x 2 doses) versus Group 3 (fecal microbiota x 1 dose plus 1 dose of placebo) 2. 19 (43.2%) 3. 25 (56.8%) Difference: 13.6% 95% CI -7.1 to 34.3 P=0.201</p> <p>Percent of mITT patients with treatment success at 8 weeks in Group 2 versus Group 3 2. 19 (44.2%) 3. 25 (65.8%) Difference: 21.6% 95% CI 0.4 to 42.8 P = 0.051</p>	<p>N/A</p> <p>N/A</p>	<p>2. 4 (9.1%) 3. 5 (11.9%)</p> <p><u>TEAEs leading to withdrawal</u> 1. 14 (31.1%) 2. 9 (20.5%) 3. 19 (43.2%)</p> <p><u>Death</u></p>	<p>N/A</p>	<p>(health decline, renal failure, respiratory failure, resistant bacteremia). Other reasons for study withdrawal included investigator withdrawal, loss to follow-up, and withdrawal by patient. <u>Reporting Bias:</u> Low. Clinical protocol available online. Outcomes reported as planned. <u>Other Bias:</u> High. Study was financially supported by the manufacturer. Six authors serve on the advisory board of the manufacturer.</p> <p><u>Applicability:</u> <u>Patient:</u> Enrolled patients were primarily White. Excluded patients with irritable bowel syndrome, inflammatory bowel disease, and those who were immunocompromised. Much higher proportion of patients received vancomycin compared with fidaxomicin (90% vs. 4%). Need for data to assess efficacy of fecal microbiota after rCDI treatment with fidaxomicin. <u>Intervention:</u> Dose finding Phase 2 trial: 1 vs. 2 doses of fecal microbiota enema were compared to placebo. Primary outcome was 2 dose regimen vs. placebo, which was not significant. <u>Comparator:</u> Placebo was a useful comparator for a novel therapy in a Phase 2 RCT. <u>Outcomes:</u> Treatment success at 8 weeks, as defined by guidelines. <u>Setting:</u> 19 sites in the US and 2 sites in Canada</p>
<p><u>Abbreviations:</u> AEs = adverse effects; ARR = absolute risk reduction; CD = <i>Clostridioides difficile</i>; CDI = <i>Clostridioides difficile</i> infection; CI = confidence interval; DB = double blind; FMT = fecal microbiota transplantation; hrs = hours; ITT = intention to treat; mos = months; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PP = per protocol; PC = placebo controlled; RCT = randomized controlled trial; rCDI = recurrent <i>Clostridioides difficile</i> infection; SEAs = serious adverse effects; SOC = standard of care; TEAEs = treatment emergent adverse effects; US = United States; yo = years old</p>								

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**Appendix 1: Current Preferred Drug List**

<b>Generic</b>	<b>Brand</b>	<b>Route</b>	<b>Form</b>	<b>PDL</b>
metronidazole	FLAGYL	ORAL	CAPSULE	Y
metronidazole	METRONIDAZOLE	ORAL	CAPSULE	Y
metronidazole	FLAGYL	ORAL	TABLET	Y
metronidazole	METRONIDAZOLE	ORAL	TABLET	Y
vancomycin HCl	VANCOMYCIN HCL	INTRAVEN	VIAL	Y
vancomycin HCl	VANCOCIN HCL	ORAL	CAPSULE	Y
vancomycin HCl	VANCOMYCIN HCL	ORAL	CAPSULE	Y
bezlotoxumab	ZINPLAVA	INTRAVEN	VIAL	N
fidaxomicin	DIFICID	ORAL	SUSP RECON	N
fidaxomicin	DIFICID	ORAL	TABLET	N
vancomycin HCl	FIRVANQ	ORAL	SOLN RECON	N
vancomycin HCl	VANCOMYCIN HCL	ORAL	SOLN RECON	N
vancomycin HCl	VANCOMYCIN HCL	INTRAVEN	VIAL	

## Appendix 2: Abstracts of Comparative Clinical Trials

### ***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.***<sup>57</sup>

**Background:** Clostridium difficile infection causes severe complications and frequently recurs. An extended-pulsed fidaxomicin regimen might facilitate sustained clinical cure by prolonging C difficile suppression and supporting gut microbiota recovery. We aimed to compare clinical outcomes of extended-pulsed fidaxomicin with standard vancomycin.

**Methods:** In this randomised, controlled, open-label, superiority study, we recruited hospitalized adults aged 60 years and older with confirmed *C. difficile* infection at 86 European hospitals. Patients were randomly assigned (1:1) using an interactive web response system to receive extended-pulsed fidaxomicin (200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25) or vancomycin (125 mg oral capsules, four times daily on days 1–10), stratified by baseline C difficile infection severity, cancer presence, age ( $\geq 75$  years vs  $< 75$  years), and number of previous C difficile infection occurrences. The primary endpoint was sustained clinical cure 30 days after end of treatment (day 55 for extended-pulsed fidaxomicin and day 40 for vancomycin), assessed in all randomised patients who met the inclusion criteria and received at least one dose of study medication (modified full analysis set). Adverse events were assessed in all patients who received at least one dose of study drug. The study is registered with ClinicalTrials.gov, number NCT02254967.

**Findings:** Between Nov 6, 2014, and May 5, 2016, 364 patients were enrolled and randomly assigned to receive extended-pulsed fidaxomicin or vancomycin. 362 patients received at least one dose of study medication (181 in each group). 124 (70%) of 177 patients in the modified full analysis set receiving extended-pulsed fidaxomicin achieved sustained clinical cure 30 days after end of treatment, compared with 106 (59%) of 179 patients receiving vancomycin (difference 11% [95% CI 1.0–20.7],  $p=0.030$ ; odds ratio 1.62 [95% CI 1.04–2.54]). Incidence of treatment-emergent adverse events did not differ between extended-pulsed fidaxomicin (121 [67%] of 181) and vancomycin (128 [71%] of 181) treatment arms. One death in the vancomycin arm was considered by the investigator to be related to study drug.

**Interpretation:** Extended-pulsed fidaxomicin was superior to standard-dose vancomycin for sustained cure of C difficile infection, and, to our knowledge, extended-pulsed fidaxomicin recurrence rates in this study are the lowest observed in a randomised clinical trial of antibiotic treatment for C difficile infection.

**Funding:** Astellas Pharma, Inc.

### ***Safety and Efficacy of Fidaxomicin and Vancomycin in Children and Adolescents with Clostridioides (Clostridium) difficile Infection: A Phase 3, Multicenter, Randomized, Single-blind Clinical Trial (SUNSHINE)***<sup>58</sup>

**Background:** Fidaxomicin, a narrow-spectrum antibiotic approved for Clostridioides (Clostridium) difficile infection (CDI) in adults, is associated with lower rates of recurrence than vancomycin; however, pediatric data are limited. This multicenter, investigator-blind, phase 3, parallel-group trial assessed the safety and efficacy of fidaxomicin in children.

**Methods:** Patients aged  $< 18$  years with confirmed CDI were randomized 2:1 to 10 days of treatment with fidaxomicin (suspension or tablets, twice daily) or vancomycin (suspension or tablets, 4 times daily). Safety assessments included treatment-emergent adverse events. The primary efficacy end point was confirmed clinical response (CCR), 2 days after the end of treatment (EOT). Secondary end points included global cure (GC; CCR without CDI recurrence) 30 days after EOT (end of study; EOS). Plasma and stool concentrations of fidaxomicin and its active metabolite OP-1118 were measured.

**Results:** Of 148 patients randomized, 142 were treated (30  $< 2$  years old). The proportion of participants with treatment-emergent adverse events was similar with fidaxomicin (73.5%) and vancomycin (75.0%). Of 3 deaths in the fidaxomicin arm during the study, none were CDI or treatment related. The rate of CCR at 2 days after EOT was 77.6% (76 of 98 patients) with fidaxomicin and 70.5% (31 of 44) with vancomycin, whereas the rate of GC at EOS was significantly higher in participants receiving fidaxomicin (68.4% vs 50.0%; adjusted treatment difference, 18.8%; 95% confidence interval, 1.5%–35.3%). Systemic absorption of fidaxomicin and OP-1118 was minimal, and stool concentrations were high.

**Conclusions:** Compared with vancomycin, fidaxomicin was well tolerated and demonstrated significantly higher rates of GC in children and adolescents with CDI.

### ***Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent Clostridium difficile Infection***<sup>59</sup>

**Background:** Fecal microbiota transplantation (FMT) is recommended for treatment of recurrent Clostridium difficile infection (rCDI). We performed a single-center randomized trial to compare the effects of FMT with those of fidaxomicin and vancomycin.

**Methods:** We studied consecutive adults with rCDI seen at a gastroenterology clinic in Denmark from April 5, 2016 through June 10, 2018. Patients were randomly assigned to a group that received FMT, applied by colonoscopy or nasojejunal tube, after 4-10 days of vancomycin (125 mg 4 times daily; FMTv; n = 24), 10 days of fidaxomicin (200 mg twice daily; n = 24), or 10 days of vancomycin (125 mg 4 times daily; n = 16). Patients who had rCDI after this course of treatment and patients who could not be randomly assigned to groups were offered rescue FMTv. The primary outcome was combined clinical resolution and a negative result from a polymerase chain reaction test for Clostridium difficile (CD) toxin 8 weeks after the allocated treatment. Secondary end points included clinical resolution at week 8.

**Results:** All 64 patients received their assigned treatment. The combination of clinical resolution and negative results from the test for CD were observed in 17 patients given FMTv (71%), 8 patients given fidaxomicin (33%), and 3 patients given vancomycin (19%; P = .009 for FMTv vs fidaxomicin; P = .001 for FMTv vs vancomycin; P = .31 for fidaxomicin vs vancomycin). Clinical resolution was observed in 22 patients given FMTv (92%), 10 patients given fidaxomicin (42%), and 3 patients given vancomycin (19%; P = .0002; P < .0001; P = .13). Results did not differ significantly between patients who received FMTv as their initial therapy and patients who received rescue FMTv. There was 1 serious adverse event that might have been related to FMTv.

**Conclusions:** In a randomized trial of patients with rCDI, we found the FMTv combination superior to fidaxomicin or vancomycin based on end points of clinical and microbiological resolution or clinical resolution alone. ClinicalTrials.gov, number NCT02743234.

### ***Efficacy And Safety of Fidaxomicin For The Treatment Of Clostridioides (Clostridium) Difficile Infection In A Randomized, Double-Blind, Comparative Phase III Study In Japan***<sup>60</sup>

We assessed the efficacy and safety of fidaxomicin, a narrow-spectrum macrocyclic antibiotic, for treating inpatients with Clostridioides (Clostridium) difficile infection (CDI) in Japan. The objective was to demonstrate the non-inferior efficacy of fidaxomicin versus vancomycin.

This Phase III, vancomycin-controlled, double-blind, parallel-group study enrolled adults with CDI. Patients were randomly assigned to receive fidaxomicin (200 mg twice daily, orally) or vancomycin (125 mg four-times daily, orally) for 10 days. The primary endpoint was global cure rate of CDI (proportion of patients cured at end of treatment with no recurrence during 28-day follow-up). Non-inferiority margin of 10% was pre-specified.

Two-hundred and twelve patients were randomized and received treatment at 82 hospitals. Global cure rate was 67.3% (70/104) with fidaxomicin and 65.7% (71/108) with vancomycin: difference 1.2% [95% confidence interval (CI) -11.3-13.7]. Non-inferiority was not demonstrated. Post-hoc analysis in full analysis set patients who received at least 3 days' treatment revealed a higher global cure rate for fidaxomicin [70/97 (72.2%)] than vancomycin [71/106 (67.0%)]: difference 4.6% (95% CI -7.9-17.1). Recurrence rate in the full analysis set for recurrence was lower in fidaxomicin- [17/87 (19.5%)] than vancomycin-treated [24/95 (25.3%)] patients. Adverse event incidences and profiles were similar for both treatments.

Though non-inferiority was not demonstrated for fidaxomicin versus vancomycin, global cure rate was numerically higher and recurrence rate lower for fidaxomicin than vancomycin. Fidaxomicin could be an option for the treatment of CDI in an era of reduced antibiotic susceptibility, and to reduce the incidence of recurrence in Japanese patients.

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### Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1996 to January Week 4 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to February 07, 2023

1	clostridium difficile.mp. or exp Clostridium difficile/ or Clostridioides difficile.mp.	14511
2	vancomycin.mp. or Vancomycin/	26824
3	metronidazole.mp. or Metronidazole/	12917
4	fidaxomicin.mp.	538
5	bezlotoxumab.mp.	116
6	Fecal Microbiota Transplantation/ or fecal microbiota.mp.	5688
7	2 or 3 or 4 or 5 or 6	43959
8	1 and 7	3500
9	limit 8 to (english language and humans and yr="2018 -Current")	1160
10	limit 9 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	225

## Appendix 4: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REBYOTA safely and effectively. See [full prescribing information for REBYOTA](#).

**REBYOTA™ (fecal microbiota, live - jslm) suspension, for rectal use**  
**Initial U.S. Approval: 2022**

### INDICATIONS AND USAGE

REBYOTA is indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI. (1)

#### Limitation of Use:

REBYOTA is not indicated for treatment of CDI.

### DOSAGE AND ADMINISTRATION

**For rectal administration only.**

Administer REBYOTA 24 to 72 hours after the last dose of antibiotics for CDI. (2)

Administer a single dose of 150 mL rectally of REBYOTA. (2)

### DOSAGE FORMS AND STRENGTHS

Suspension. A single dose is 150 mL. (3)

### CONTRAINDICATIONS

Severe allergic reactions (e.g. anaphylaxis) to any component of REBYOTA. (4)

### ADVERSE REACTIONS

The most commonly reported ( $\geq 3\%$ ) adverse reactions occurring in adults following a single dose of REBYOTA were abdominal pain, (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%) (Table 1).

**To report SUSPECTED ADVERSE REACTIONS, contact Ferring Pharmaceuticals Inc. at 1-888-FERRING (1-888-337-7464) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). (6)**

**See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.**

**Revised: 11/2022**

**Prevention of Recurrent *Clostridioides difficile*-Associated Infection**

**Goal(s):**

- To optimize appropriate prevention of recurrent *Clostridioides difficile*-associated infection (CDI). Recurrent CDI is defined by Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.

**Length of Authorization:**

- Bezlotoxumab (ZINPLAVA): One time infusion
- Fecal microbiota, live-jslm (REBYOTA): One-time rectal administration

**Requires PA:**

- Drugs for prevention of *Clostridioides difficile* recurrence such as:
  - Bezlotoxumab for intravenous infusion (physician administered and pharmacy claims)
  - Fecal microbiota, live-jslm suspension for rectal administration (physician administered and pharmacy claims)
  - Non-preferred drugs

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the indication match the FDA-approved indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the request for an FDA approved age (e.g., 18 years or older)?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness



Approval Criteria		
4. Is the request for bezlotoxumab?	<b>Yes:</b> Go to #5	<b>No:</b> Go to #7
5. Is this recurrent of <i>Clostridioides difficile</i> -associated infection (CDI) within 6 months of CDI <b>OR</b> Is the patients presenting with a primary CDI episode and has other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host, or severe CDI on presentation)?*  *Per 2021 IDSA/SHEA guidance <sup>1</sup>	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness
6. Is the patient currently receiving vancomycin or fidaxomicin?	<b>Yes:</b> Approve for one dose	<b>No:</b> Pass to RPh. Deny; medical appropriateness
7. Is this the second or more recurrence of a <i>Clostridioides difficile</i> -associated infection?*	<b>Yes:</b> Go to #8	<b>No:</b> Pass to RPh. Deny; medical appropriateness
*Per 2021 ACG and 2022 NICE guidance <sup>2,3</sup>		
8. Will the patient have recently completed a 10-day course of vancomycin or fidaxomicin prior to starting therapy?	<b>Yes:</b> Approve for one course of therapy.  (For the fecal microbiota enema, 1 dose is the FDA-approved course of therapy).	<b>No:</b> Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: 6/23 (DM)  
Implementation: 7/1/23

1. 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(5):e1029-e1044.

2. Kelly CR, Fischer M, Allegretti JR, et al. American College of Gastroenterology Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. The American Journal of Gastroenterology. 2021; 116(6):1124-1147.

3. National Institute for Health and Care Excellence (NICE): Fecal microbiota transplant for recurrent Clostridioides difficile infection. August 31, 2022.

<https://www.nice.org.uk/guidance/mtg71> Accessed February 27, 2023.

## Fidaxomicin (Dificid®)

### Goal(s):

- To optimize appropriate treatment of *Clostridioides difficile*-associated infection.

### Length of Authorization:

- 10 days

### Requires PA:

- Fidaxomicin from pharmacy claims

### Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

### Approval Criteria

1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of <i>Clostridioides difficile</i> -associated infection (CDI)?	<b>Yes:</b> Go to #3.	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Does the patient have at least one documented trial of or contraindication to appropriate therapy with vancomycin?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness

## Approval Criteria

4. Does the patient have severe, complicated CDI (life-threatening or fulminant infection or toxic megacolon)?

**Yes:** Pass to RPh. Deny; medical appropriateness

**No:** Approve for up to 10 days

P&T / DUR Review: 6/23 (DM); 5/18 (DM); 5/15 (AG); 4/12  
Implementation: 7/1/23; 7/1/18; 10/15; 7/12

## Bezlotoxumab (Zinplava™)- RETIRE

### Goal(s):

- To optimize appropriate prevention of recurrent *Clostridium difficile*-associated infection.

### Length of Authorization:

- One time infusion

### Requires PA:

- Bezlotoxumab (physician administered and pharmacy claims)

### Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

## Approval Criteria

1.What diagnosis is being treated?	Record ICD10 code	
2.Does the patient have a diagnosis of recurrent <i>Clostridium difficile</i> -associated infection (CDI)?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3.Is the patient currently receiving vancomycin or fidaxomicin?	<b>Yes:</b> Approve for one dose	<b>No:</b> Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: 5/18(DM)  
Implementation: 7/1/18