Recurrent C.diff Infections

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Objectives

- To review latest guidelines for the testing and treatment of first episodes of c.diff as well as first and/or subsequent recurrences
- To discuss treatment strategies for the management of patients with recurrent clostridium difficile
- To review 3 novel adjunct therapies that have become available for the management of patients with recurrent clostridium difficile
- Take home points

Disclosures

- I have no disclosures and receive no compensation from any of the manufactures of products mentioned in this presentation.

Overview

- Clostridium difficile is an anaerobic spore forming bacteria which produces Toxin A and Toxin B
- Symptoms of disease/overgrowth include 3-15+ liquid stools in a 24 hour period, fevers, loss of appetite, fever, nausea, abdominal pain
- Fecal-oral transmission
- Increased risk with:
  - Age >65yo
  - Prior antibiotic use – especially fluoroquinolones, cephalosporins, penicillins, clindamycin in the last few months
  - Use of PPIs and H2 blockers
  - Use of NSAIDs
  - Healthcare exposure in the last 3 months

Most Recent Update?

- New Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults published in 2021
- Developed by the IDSA and SHEA and was an update on the 2017 guidelines

Practice Guideline › Clin Infect Dis. 2021 Sep 7;73(5):e1029-e1044. doi: 10.1093/cid/ciab549.

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

Stuart Johnson [1 2], Valéry Lavergne [3 4], Andrew M Skinner [1 2], Anne J Gonzales-Luna [5], Kevin W Garey [5], Ciaran P Kelly [6], Mark H Wilcox [7]

Affiliations + expand

PMID: 34164674 DOI: 10.1093/cid/ciab549

Abstract

This clinical practice guideline is a focused update on management of Clostridioides difficile infection (CDI) in adults specifically addressing the use of fidaxomicin and bezlotoxumab for the treatment of CDI. This guideline was developed by a multidisciplinary panel representing the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). This guideline is intended for use by healthcare professionals who care for adults with CDI, including specialists in infectious diseases, gastroenterologists, hospitalists, pharmacists, and any clinicians and healthcare providers caring for these patients. The panel's recommendations for the management CDI are based upon evidence derived from topic-specific systematic literature reviews. Summarized below

https://pubmed.ncbi.nlm.nih.gov/34164674/

Clostridium Difficile Testing

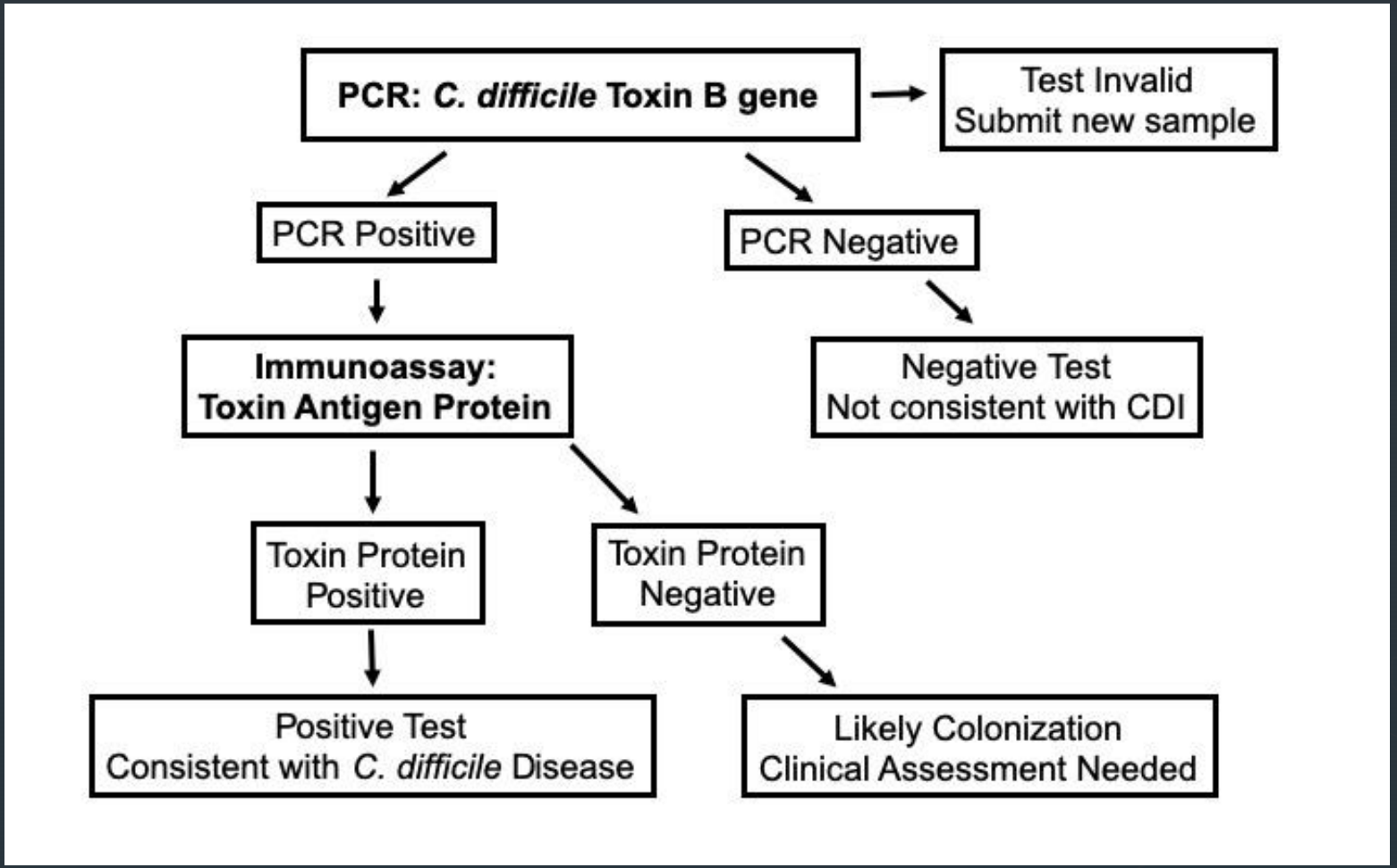
T1 Summary of various testing methodologies for *C. difficile*.

Test Methodology	Advantages	Disadvantages
Glutamate Dehydrogenase EIA	Relatively high sensitivity; rapid	Not for use as a standalone test since toxin must be confirmed
Toxin A/B EIA	Rapid; moderate specificity	Low sensitivity
Culture	High sensitivity; recovery of the organism aids in typing or antimicrobial susceptibility studies	Long turnaround time to results; not for use as a standalone test since toxin must be confirmed
Cell culture cytotoxicity assay	High sensitivity	Long turnaround time to results; highly complex for a laboratory to perform
NAAT	High sensitivity; rapid	Expensive; concern of detection of colonization state

EIA: enzyme immunoassay; NAAT: nucleic acid amplification test

https://www.aacc.org/cln/articles/2018/november/diagnosis-of-c-d-difficile

Interpretation of Clostridium Difficile Testing



https://www.testmenu.com/UCSFClinLab/Tests/811738

Initial CDI Episode Recommendations

- Preferred – Fidaxomicin 200mg p.o. BID x 10 days ($$$$)
- Alternative – Vancomycin 125mg p.o. QID x 10 days
- When other agents are not available – metronidazole 500mg p.o. TID x 10-14 days
  - Not to be used in cases of severe c.diff where WBCs >15K or crea >1.5mg/dL

https://pubmed.ncbi.nlm.nih.gov/34164674/

Recommendations for First CDI Recurrence

- Preferred - Fidaxomicin 200mg p.o. BID x 10 days OR BID x 5 days followed by QOD x 20 days
- Alternative – Vancomycin tapering regimen – 125mg p.o. QID x 10-14 days followed by a taper every 7 days
- If metronidazole was used first? – Use a standard course of vancomycin 125mg p.o. QID x 10 days
- Bezlotuxumab 10mg/kg*

https://pubmed.ncbi.nlm.nih.gov/34164674/

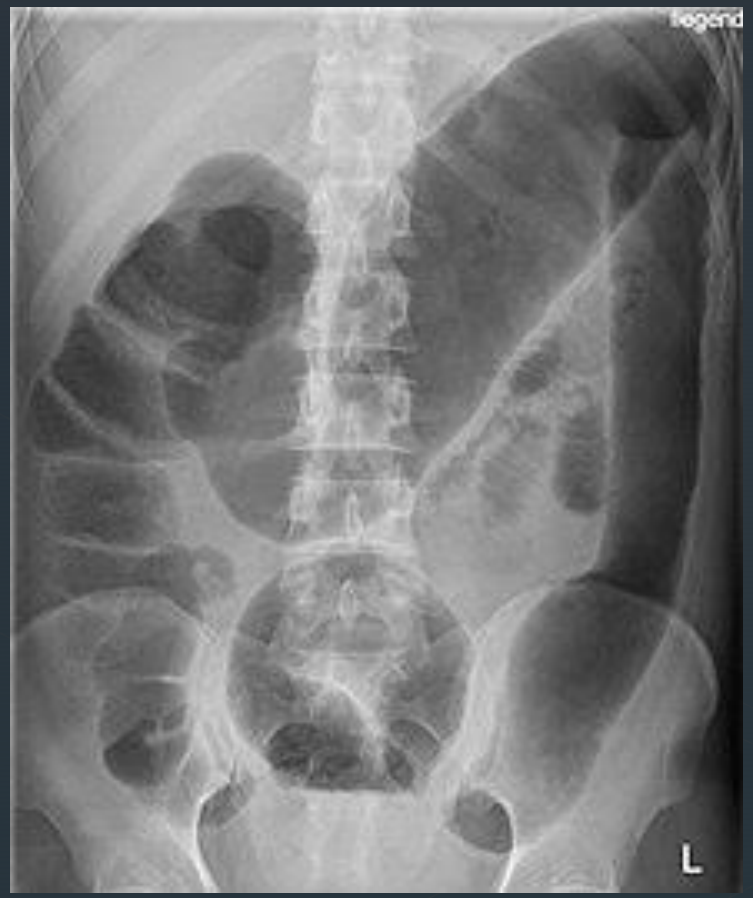
Recommendations for Second or Subsequent CDI Recurrence

- Fidaxomicin 200mg p.o. BID x 10 days or BID x 5 days followed by QOD x 20 days
- Vancomycin tapering strategy
- Vancomycin 125mg p.o. QID x 10 days followed by rifaximin 400mg p.o. TID x 20 days
- Bezlotoxumab 10mg/kg*
- FMT after 2 recurrences (3 total CDI episodes)*

https://pubmed.ncbi.nlm.nih.gov/34164674/

Management of Fulminant CDI

- Vancomycin 500mg p.o. QID or via NGT, if ileus present will consider adding rectal instillation of vancomycin
- Add metronidazole 500mg IV q8h if hypotension, shock, ileus, megacolon



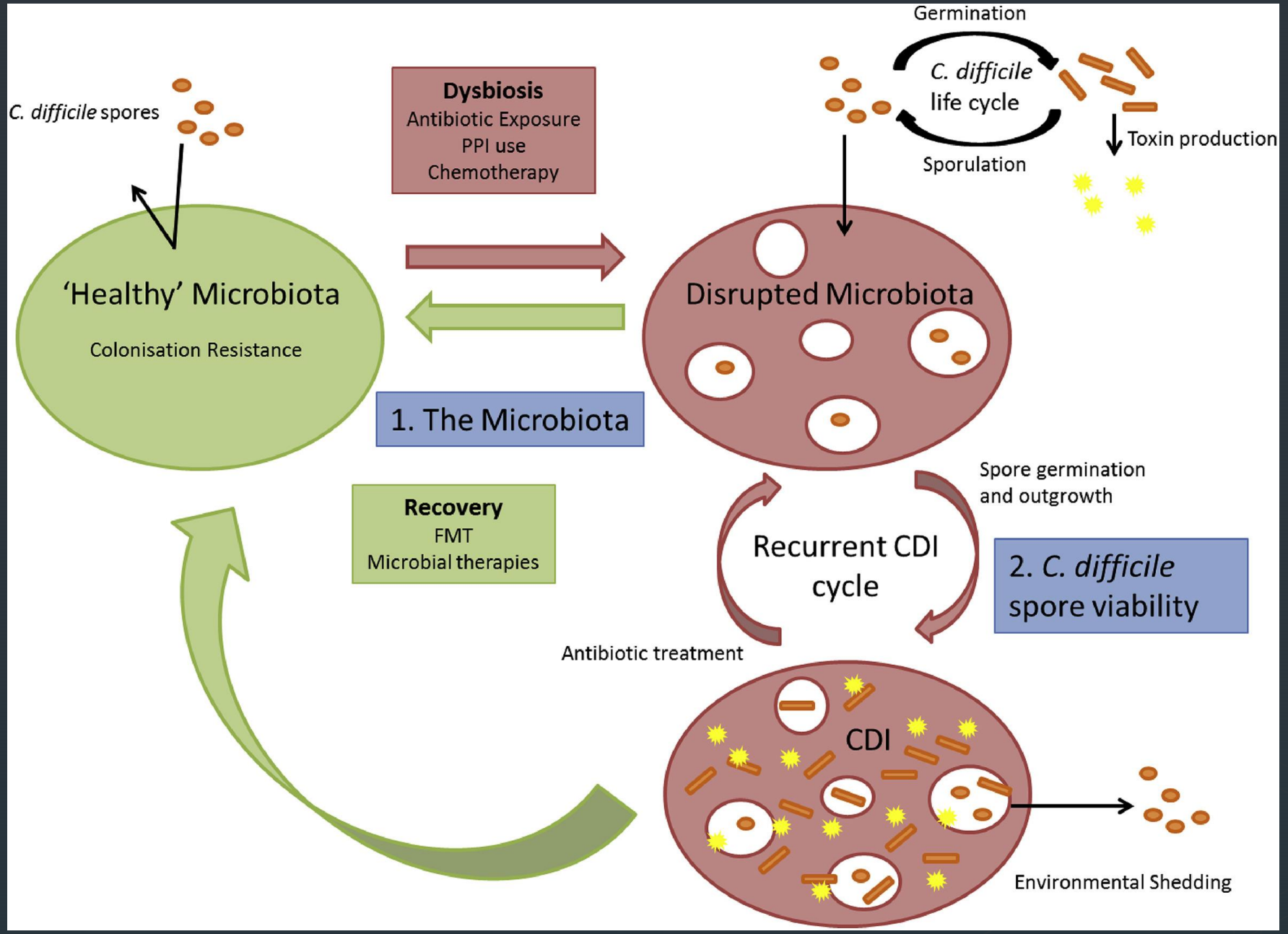
Recurrent CDI

- Recurrent CDI occurs in 20-30% of all patients who experience a primary episode of c.diff infection
- A first recurrence will double the chances of having 2 or more recurrent episodes of c.diff
- One study suggested that the median cost associated with length of stay increased from $20,693 to $45,148 for primary CDI vs. rCDI

J Hosp Infect, 93 (2016), pp. 286-289

The Cycle of Recurrence - Dysbiosis

- A healthy gut microbiome is generally refractory to c.diff spores and colonization
- Once the gut microbiome is disrupted (antibiotics, PPIs, healthcare exposure), c.diff infection can occur and treatment is initiated
- The INFECTION can resolve, but the disrupted microbiome is left vulnerable to residual spores present in the gut
- If these spores germinate and proliferate, the can release toxin and cause symptomatic, recurrent c.diff disease



Clinical Microbiology and Infection. Volume 24, Issue 5, May 2018, Pages 476-482.

Three New(ish) Treatment Modalities for rCDI

- Zinplava (bezlotoxumab)
- Rebyota (fecal microbiota, live-jslm)
- VOWST (fecal microbiota, live-brpk)

Zinplava (bezlotoxumab)

- First selective human IgG1 monoclonal antibody approved to reduce the recurrence of a bacterial infection
- Binds to clostridium difficile toxin B and neutralizes its effects
- FDA approved in 2016 to reduce the incidence of rCDI in adult patients receiving antibiotic treatment for CDI who are at high risk for recurrent CDI infection
- NOT indicated for treatment of CDI

PT 2017 Dec; 42(12): 735-738

Zinplava Clinical Trials

Phase 3 Trial	Treatment Arms	Stratification
MODIFY I	ACTO BEZLO ACTO+BEZLO Placebo	Oral SoC Metronidazole Vancomycin Fidaxomicin
MODIFY II	BEZLO ACTO+BEZLO Placebo	Hospitalization status Inpatient Outpatient

ACTO – actoxumab, BEZLO - bezlotoxumab
SoC – standard of care

- C.diff recurrence in highest risk groups (>65yo, immunocompromised, etc) ranged from 10.7% to 15.4% at 12 wees in bezlotoxumab arm vs. 22.4% to 31.4% in placebo arm over the same interval
- Side effects (mild) headache, fever, nausea

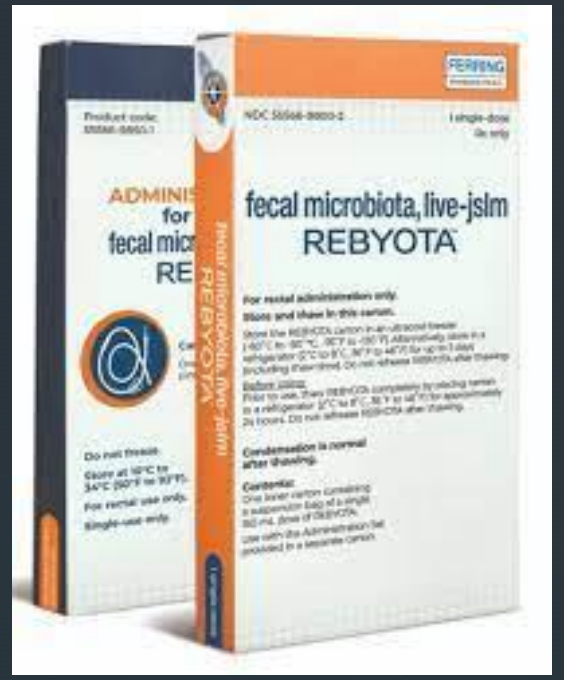
Merck and Co AC Briefing Document 2016

Zinplava (bezlotoxumab) cont'd.

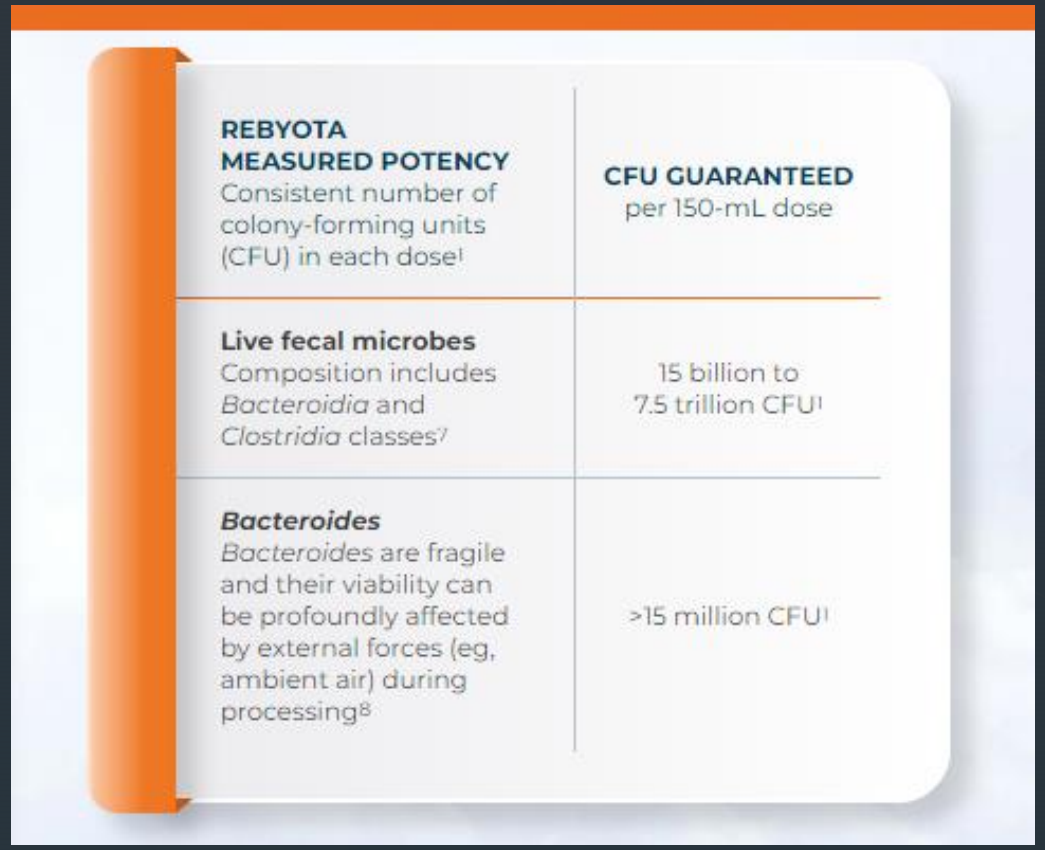
- Administered as a single 10mg/kg IV infusion over 60min DURING treatment for clostridium difficile infection
  - Cost ~$4,000/infusion, with Co-Pay assistance, patients pay $100/dose
- Caution in patients with a history of heart failure
- Category C in pregnancy
- Half life T1/2 19 days
- Does NOT repair disruption in gut microbiome

Rebyota (fecal microbiota, live-jslm)

- Fecal microbiota treatment indicated for prevention of rCDI in adults following antibiotic treatment for as early as their first rCDI
- Restores gut microbiome with donor stool
- FDA approved in November 2022
- NOT indicated for treatment of CDI



Rebyota cont’d.

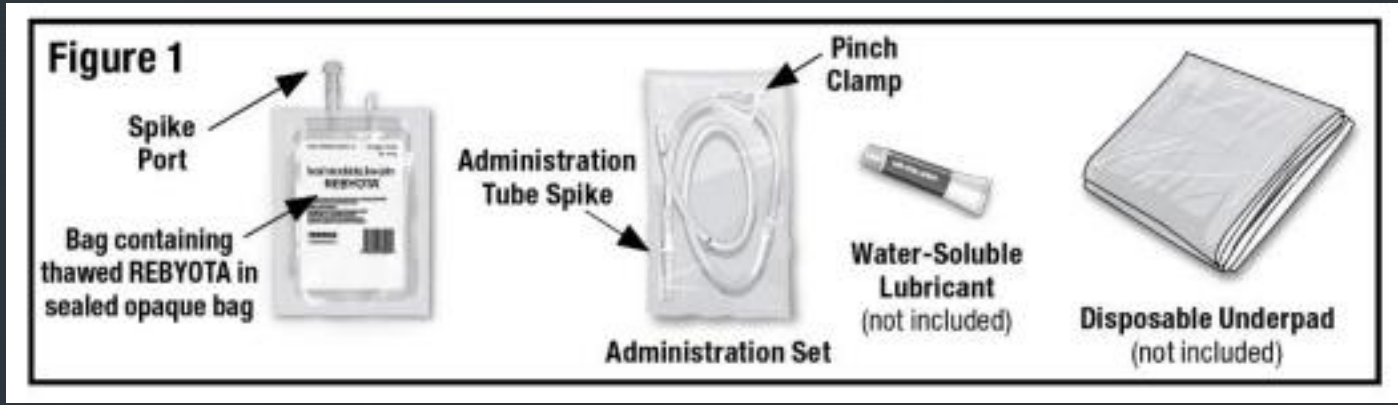


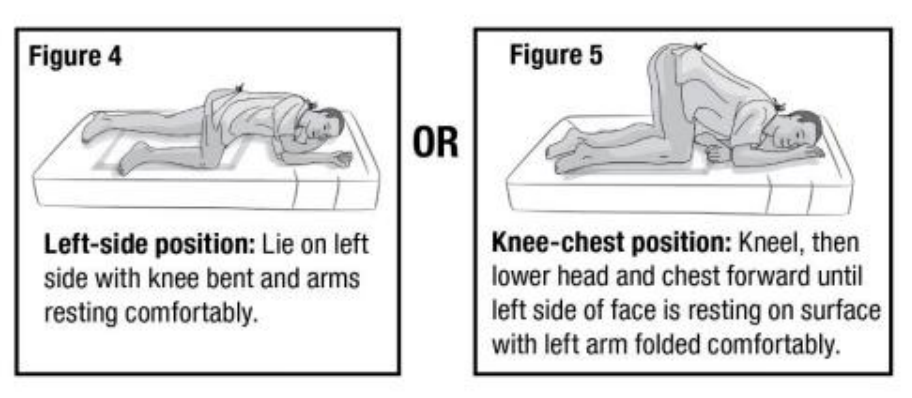
REBYOTA MEASURED POTENCY Consistent number of colony-forming units (CFU) in each dose[1]	CFU GUARANTEED per 150-mL dose
Live fecal microbes Composition includes *Bacteroidia* and *Clostridia* classes[7]	15 billion to 7.5 trillion CFU[1]
Bacteroides *Bacteroides* are fragile and their viability can be profoundly affected by external forces (eg, ambient air) during processing[8]	>15 million CFU[1]

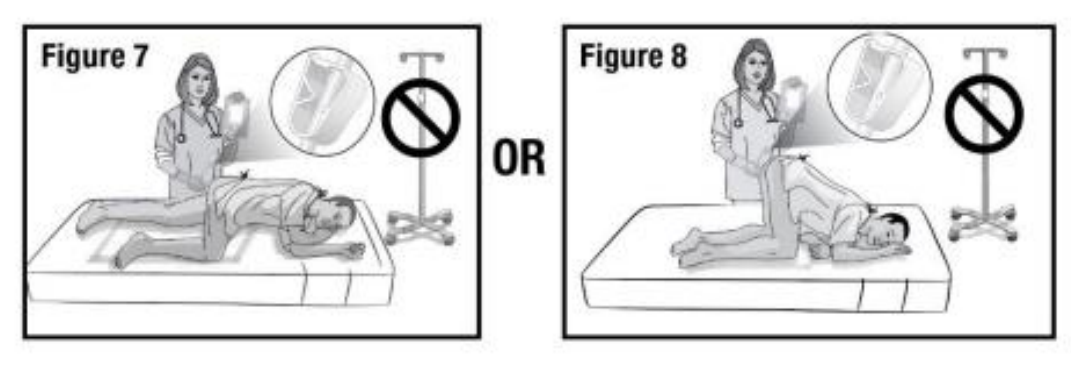
- Pre-packaged 150mL non-pooled single donor stool suspension administered as a 1x enema by a healthcare professional
- To be given 24-72 hours after last dose of CDI treatment
- No bowel prep, laxatives, or colonoscopy required
- PUNCH trial with 70.6% success at 8 weeks, 92% of whom sustained for >6mo
- Side effects – abdominal pain, bloating, diarrhea, gas nausea

https://www.rebyotahcp.com/

Rebyota Administration







https://www.fda.gov/media/163587/download

Rebyota cont’d.

- Priced at $9,000/treatment
- 96% of all commercial and government insurances will cover
- Dedicated J code – J1440
- Pharmaceutical assistance covers up to $10,000 per calendar year
- Caution in patients with food allergies

VOWST (live-brpk)

- First orally administered fecal microbiota treatment indicated for prevention of rCDI in adults following antibiotic treatment for as early as their first rCDI
- Consists of firmicutes bacterial spores from qualified human donors, formulated in 88-96% w/w glycerol in saline and encapsulated
- Restores gut microbiome with donor stool
- FDA approved in April 2023
- NOT indicated for treatment of CDI

VOWST Trial Data

- ECOSPOR III Trial
  - Primary endpoint – 88% of recipients were relapse free at 8 weeks
  - Secondary endopoint – 79% were relapse free at 24 weeks
- ECOSPOR IV Trial
  - 94% recurrence free if Vowst given after first recurrence
  - 90% recurrence free if Vowst given after 2 or more recurrences
- Side effects – abdominal distention, fatigue, constipation, chills, diarrhea

Feuerstadt P, Louie TJ, Lashner B, et al. N Engl J Med. 2022;236:220-229. doi:10.1056/NEJMoa2106516.

VOWST Administration

- Start with a traditional 10-14 day c.diff treatment course
- 2-4 days after completion of treatment, a single 10oz bottle of magnesium citrate is consumed to cleanse the colon of residual antibiotics
- Vowst is administered as 4 capsules taken each day for 3 consecutive days (first dose at least 8 hours after magnesium citrate administration)
  - No eating or drinking at all for at least 8 hours after magnesium citrate administration
  - Each dose is taken on an empty stomach in the morning, prior to first meal of the day

VOWST cont’d.

- Priced at $17,500/treatment
- Pharmaceutical company committed to broad access for patients and most will pay $0 if not covered by insurance
- Capsules must be kept refrigerated
- Caution in patients with food allergies

Future Vaccine?

- Studies ongoing since 2014 with potential vaccine candidates for prevention of CDI
- Most recently the CLOVER trial failed to meet phase III endpoints in March 2022
  - Did demonstrate 31% efficacy after 3 doses and 28.6% after 2 doses
  - Shorter duration and severity of illness in breakthrough cases
  - Favorable side effect profile

Take Home Points

- When covered, fidaxomicin is now the preferred first line treatment modality for the treatment of a first episode of CDI
- 20-30% of patients with a first episode of CDI will experience a relapse of infection
- For those at high risk for relapse, a single infusion of Zinplava (belotuxumab) can be given during an episode of CDI to help prevent recurrence
- For those who have had a first recurrence – consideration for FMT using either novel agent Rebyota (enema) or VOWST (oral) are a consideration post-treatment to help prevent future recurrences