Practical Updates in Primary Care

Combating Recurrent *C. Difficile* Infection: From Diagnosis to Cure

Jessica R. Allegretti, MD, MPH, FACG

Medical Director, Crohn's and Colitis Center
Director, Fecal Microbiota Transplant Program
Director, Clinical Research
Division of Gastroenterology, Brigham and Women's Hospital
Associate Professor of Medicine, Harvard Medical School

Joel J. Heidelbaugh, MD, FAAFP, FACG

Clinical Professor, Department of Family Medicine
University of Michigan Medical School
Co-Chair, ROME V Primary Care Committee

Supported by an educational grant from Nestlé Health Science.

Disclosures

- **Jessica R. Allegretti, MD, MPH, FACG:** Consultant – AbbVie, Bristol Myers Squibb, Celltrion, Ferring, Genentech, GSK, Janssen, Merck, Pfizer, Roivant, Seres Therapeutics, Shattuck Labs, TRXBio, Vedanta; Speaker – AbbVie, Janssen

- **Joel J. Heidelbaugh, MD, FAAFP, FACG** has nothing to disclose in relation to this activity

Learning Objectives

- Apply evidence-based strategies for the timely and accurate identification of rCDI
- Evaluate the safety/efficacy data and routes of administration of newer therapeutic strategies for rCDI, with a focus on live biotherapeutic products
- Implement comprehensive strategies to enhance follow-up care and optimize patient-centered treatment for rCDI

rCDI = recurrent *Clostridioides difficile* infection.

Practical Updates in Primary Care

Introduction to *Clostridioides Difficile*

Joel J. Heidelbaugh, MD, FAAFP, FACG

Clinical Professor, Department of Family Medicine

University of Michigan Medical School

Co-Chair, ROME V Primary Care Committee

What Is *Clostridioides Difficile*?

- A NORMAL bacteria in the gut of healthy people!
- Gram-positive, spore-forming bacteria
- Anaerobic, motile, lives everywhere (eg, soil, fomites)
- Ingested, destroyed in stomach when pH ~1
  - Can survive with acid suppression (eg, PPIs → pH >4)
- Once colonized, people can carry for years and be asymptomatic
- Problem – overgrowth, toxin production (A and B)
- Hypervirulent, antibiotic-resistant strain NAP1/B1/027
- Can lead to infectious diarrhea, toxic megacolon, sepsis + septic shock, prolonged length of hospital stay, increased mortality

PPIs = proton pump inhibitors.

Guh AY, et al. *N Engl J Med*. 2020;382(14):1320-1330. Mada PK, et al. StatPearls. Updated April 10, 2024. Accessed July 28, 2025. https://www.ncbi.nlm.nih.gov/books/NBK431054/.

Why Does *Clostridioides Difficile* Cause Disease?

- Transmitted fecal-oral route (eg, food poisoning, limited hand-washing and hygiene, inadequate cleaning of rooms and equipment)
- Antibiotic use
  - Cephalosporins
  - Clindamycin
  - Fluoroquinolones
  - Penicillins
  - Vancomycin
- Chronic medical illnesses and conditions (eg, cancer, IBD, renal failure)
- Disruption of microbiome
- Hospital or extended-care environment
- Immunosuppression

Carling PC, et al. *Antimicrob Resist Infect Control*. 2023;12(1):94.

Epidemiology

- Traditionally considered a healthcare-associated infection, incidence increasing in community over recent years
- Colonizes
  - Healthy intestines in 4-15% of healthy adults
  - Up to 21% of hospitalized adults
  - Up to 15-30% of residents in long-term care facilities
- Contaminated surfaces pose significant risk
- (PROPER) HAND-WASHING!!!
- Hospital policies and precautions
- Caution in families

Mada PK, et al. StatPearls. Updated April 10, 2024. Accessed July 28, 2025. https://www.ncbi.nlm.nih.gov/books/NBK431054/. Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Epidemiology

- By 2007, *C. diff* colitis leading cause of gastroenteritis, with 5-fold increase in mortality
- In 2022, incidence rates increased with age
- Higher in women and White persons
- 116.1 cases per 100,000 persons
- 56% of cases used antibiotics in prior 12 weeks
- ANTIBIOTIC STEWARDSHIP!!!

Mada PK, et al. StatPearls. Updated April 10, 2024. Accessed July 28, 2025. https://www.ncbi.nlm.nih.gov/books/NBK431054/. CDC. Accessed July 29, 2025. https://www.cdc.gov/healthcare-associated-infections/media/pdfs/2022-CDI-Report-508.pdf.

Epidemiology

- Causes ~ half million illnesses in US each year
- Estimated 29,300 deaths
- 1 in 6 who get *C. diff* will get it again in 2-8 weeks
- 1 in 11 over 65 years diagnosed with healthcare-associated *C. diff* infection die within a month
- People are 7-10X more likely to get *C. diff* infection while taking an antibiotic and during month after
- More than 80% of deaths occur in people over 65 years

Mada PK, et al. StatPearls. Updated April 10, 2024. Accessed July 28, 2025. https://www.ncbi.nlm.nih.gov/books/NBK431054/. CDC. Accessed July 29, 2025. https://www.cdc.gov/c-diff/media/pdfs/Cdiff-Factsheet-P.pdf.

Primary Care Perspective

- Most PCPs practice outpatient medicine
  - How much do we see? (How much do we miss…?)
  - How often do we even consider *C. diff*?
  - Workup of infectious diarrheas
- Hospitalists, ER, urgent care
- Who is most likely to get *C. diff*?
- Who is most likely to get recurrent *C. diff*?
- What advice do you give to family members and friends?
  - Can easily spread within 48 hours, even after symptoms disappear!

C. Diff Risks

- Abdominal pain and diarrhea
- Bowel perforation
- Chronic anemia
- Pseudomembranous colitis
- Reactive arthritis
- Toxic megacolon
- Weight loss
- Chronic sequela – pain, recurrence, surgery

Clinical Presentation – Who Should Be Tested?

- Traditionally considered a healthcare-associated infection, incidence increasing in community
- "Diarrhea" – *be sure to appropriately define*
- New-onset watery diarrhea, with risk factors
  - 2-4 (ACG = 3) loose, watery stools per day, +/- odor
  - Abdominal pain and cramping (do an exam!)
  - Should not be febrile
- Anytime you are suspicious (risk of over-testing…)

ACG = American College of Gastroenterology.
McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48. Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Testing for *Clostridioides Difficile*

- Stool tests
  - PCR tests
    - Highly sensitive and specific for toxin-producing *C. diff*
    - Can be positive in asymptomatic people and those without infection
    - Other causes of diarrhea may be positive, leading to over-diagnosis and over-treatment (may artificially increase incidence)
  - Antigen tests
    - Rapid test, detects glutamate dehydrogenase
  - Toxin tests (A, B)
    - Toxin is unstable, requires testing within 2 hours of collection
- Imaging
  - Signs of colitis may be detected on abdominal imaging (CT) in patients with symptoms
- Colonoscopy
  - Not recommended for diagnosis, may be required if diagnosis not established

PCR = polymerase chain reaction; CT = computed tomography.
Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Testing for *Clostridioides Difficile*

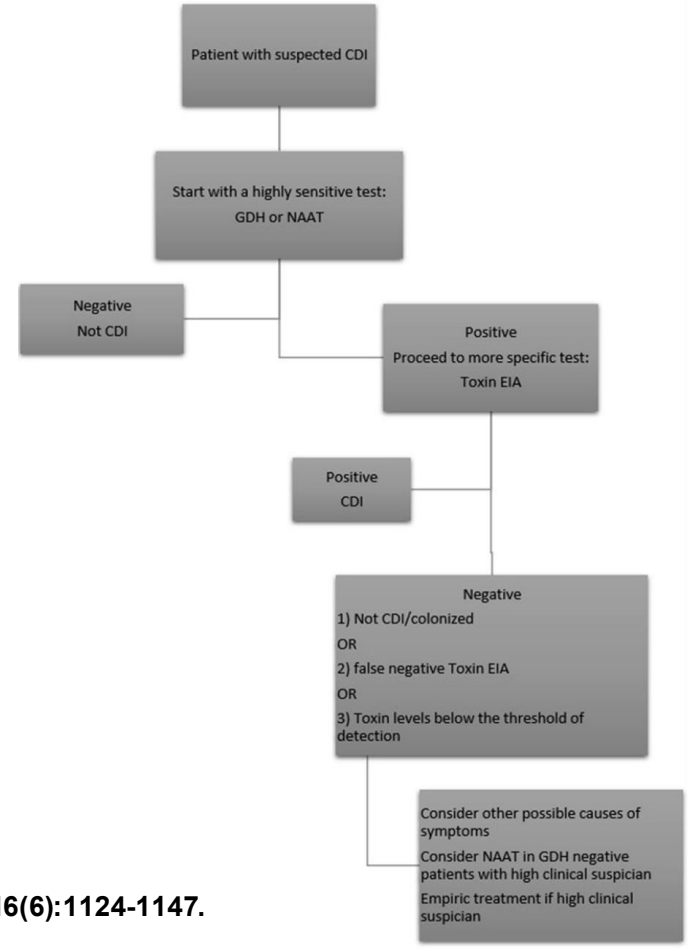
Test	Sensitivity (%)	Specificity (%)	Positive predictive value (%)[a]	Negative predictive value (%)[a]	Distinguishes colonization from active infection	Other considerations
Toxigenic culture (47)	94	99	—	—	No	Detects toxin producing *C. difficile* strains in culture. Not used clinically.
CCNA (12,47)	93	98	—	—	Yes	Demonstrates presence of free toxin B. Not used clinically.
GDH (4,45)	94–96	90–96	34–38	100	No	Does not distinguish nontoxigenic from toxigenic strains.
NAAT (PCR or LAMP) (4,44)	95–96	94–98	46	100	No	Detects gene for toxin B
EIA for toxins A and B (4)	57–83	99	69–81	99	Yes	Detects presence of free toxin

CCNA, cell cytotoxicity neutralization assay; CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; LAMP, loop-mediated isothermal amplification assay; NAAT, nucleic acid amplification testing; PCR, polymerase chain reaction.
[a]Assuming *C. difficile* infection prevalence of 5%.

Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Practical Updates in Primary Care

Testing for *Clostridioides Difficile*



Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Practical Updates in Primary Care

Prevention of *Clostridioides Difficile*

- ACG Guidelines (2021)
  - Recommend against probiotic use in patients treated with antibiotics
  - Recommend against probiotic use
  - Primary prevention (*Lactobacillus*)
    - Probiotics helpful in hospitalized patients if given at start of antibiotic therapy, 70% lower risk if started within 2 days of antibiotics, but 30% if started after 2 days
  - Secondary prevention (*Saccharomyces boulardii*)
    - Small trials, no proven benefit

Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

When to Refer to Gastroenterology

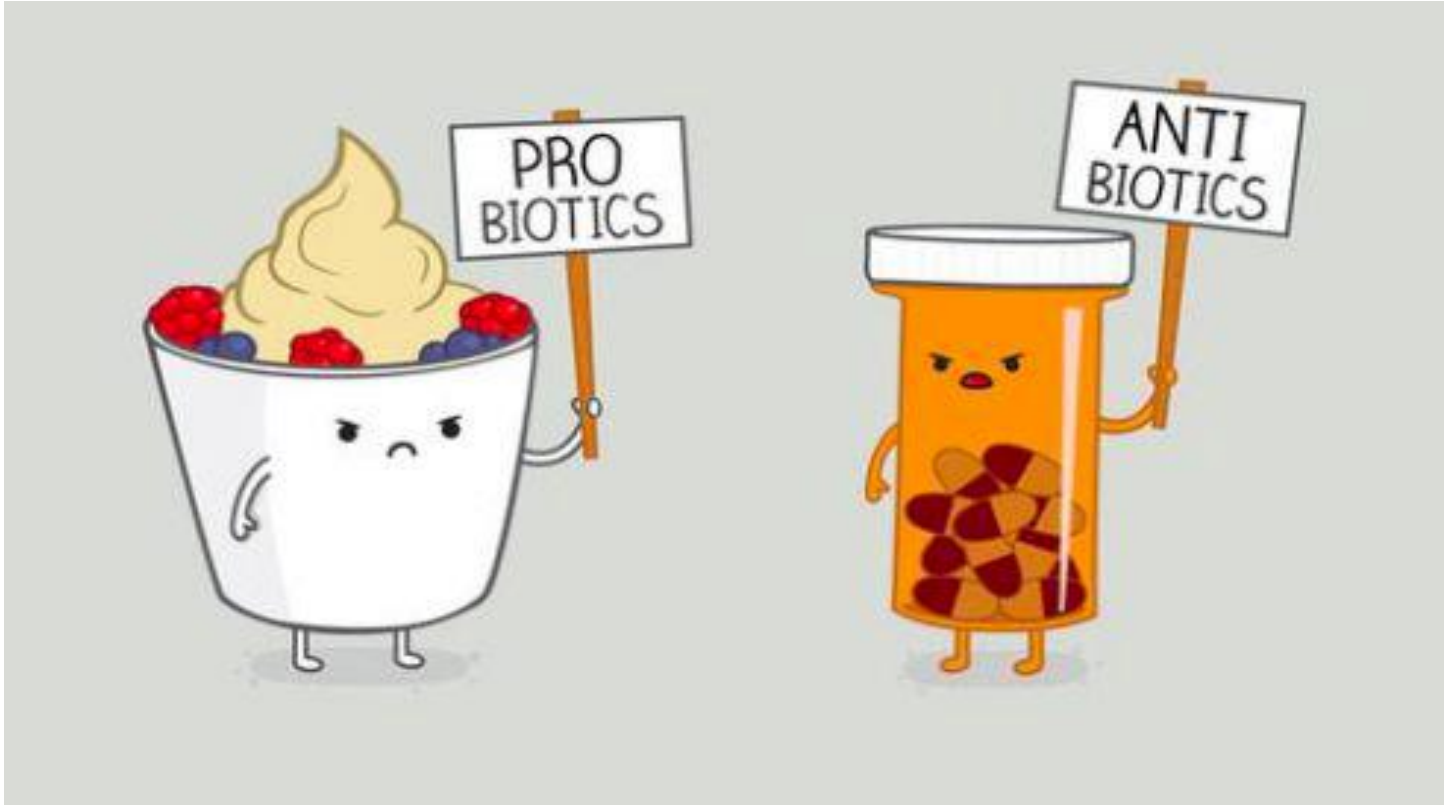
- After a thorough consideration of differential diagnosis and workup
- Colonoscopy may not be indicated…
- Colonoscopy may be indicated for surveillance
- For guidance on treatment, especially with refractory/resistant cases
- In patients with prior history of surgery/colectomy

Practical Updates in Primary Care

Clostridioides Difficile Infection Diagnosis and Management: Latest Concepts

Jessica R. Allegretti, MD, MPH, FACG
Medical Director, Crohn's and Colitis Center
Director, Fecal Microbiota Transplant Program
Director, Clinical Research
Division of Gastroenterology, Brigham and Women's Hospital
Associate Professor of Medicine, Harvard Medical School

Treatment



Metronidazole vs Vancomycin

- These two were previously the treatments of choice for initial CDI
- Prior to the year 2000, failure rates were identical (2.5% vs 3.5%)
- After the year 2000, failure rates of metronidazole were as high as 18.2%

Mezoff E, et al. *J Pediatr Gastroenterol Nutr*. 2011;52(4):437-441. Kelly CP, LaMont JT. *N Engl J Med*. 2008;359(18):1932-1940.

IDSA Guidelines 2018/2021

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR • FDX 200 mg given twice daily for 10 days • Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	
Initial episode, severe	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR • FDX 200 mg given twice daily for 10 days	
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	
		10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

IDSA = Infectious Diseases Society of America; VAN = vancomycin; FDX = fidaxomicin.
McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Practical Updates in Primary Care

ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections

Colleen R. Kelly, MD, AGAF, FACG[1], Monika Fischer, MD, MSc, AGAF, FACG[2], Jessica R. Allegretti, MD, MPH, FACG[3], Kerry LaPlante, PharmD, FCCP, FIDSA[4], David B. Stewart, MD, FACS, FASCRS[5], Berkeley N. Limketkai, MD, PhD[6], Millie D. Long, MD, MPH, FACG (GRADE Methodologist)[7], and Neil H. Stollman, MD, FACG[8]

Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Practical Updates in Primary Care

ACG CDI Guidelines 2021: Graded Statements – Treatment

	Treatment
Primary CDI: Non-Severe	4. We recommend that oral vancomycin 125 mg 4 times daily for 10 days be used to treat an initial episode of non-severe CDI (strong recommendation, low quality of evidence).
	5. We recommend that oral fidaxomicin 200 mg twice daily for 10 days be used for an initial episode of non-severe CDI (strong recommendation, moderate quality of evidence).
	6. Oral metronidazole 500 mg 3 times daily for 10 days may be considered for treatment of an initial non-severe CDI in low-risk patients (strong recommendation/moderate quality of evidence).
Primary CDI: Severe	7. As initial therapy for severe CDI, we recommend vancomycin 125 mg 4 times a day for 10 days (strong recommendation, low quality of evidence)
	8. As initial therapy for severe CDI, we recommend fidaxomicin 200 mg twice daily for 10 days (conditional recommendation, very low quality of evidence)
Fulminant	9. Patients with fulminant CDI should receive medical therapy that includes adequate volume resuscitation and treatment with 500 mg of oral vancomycin every 6 hours daily (strong recommendation, very low quality of evidence) for the first 48-72 hours. Combination therapy with parenteral metronidazole 500 mg every 8 hours can be considered (conditional recommendation, very low quality of evidence).
	10. For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hours) may be beneficial (conditional recommendation, very low quality of evidence).
	11. We suggest fecal microbiota transplantation (FMT) be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly when patients are deemed poor surgical candidates (strong recommendation, low quality of evidence).
First Recurrence	12. We suggest tapering/pulsed-dose vancomycin for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole (strong recommendation, very low quality of evidence).
	13. We recommend fidaxomicin for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole (conditional recommendation, moderate quality of evidence).

ACG = American College of Gastroenterology.

Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

- The MIC_{90} of vancomycin against *C. difficile* is 1.0-2.0 mcg/mL
  - The 125 mg oral dose of vancomycin achieves fecal concentrations of 350-400 mcg/mL
  - Doses >125 mg PO Q6hr are not likely to improve the antimicrobial efficacy of vancomycin
  - Exception: In cases of severe *C. difficile*
    - Recommend 250 mg PO Q6hr given some evidence of higher fecal concentrations in the first 48 hrs of treatment.
    - There is no evidence to support doses >250 mg

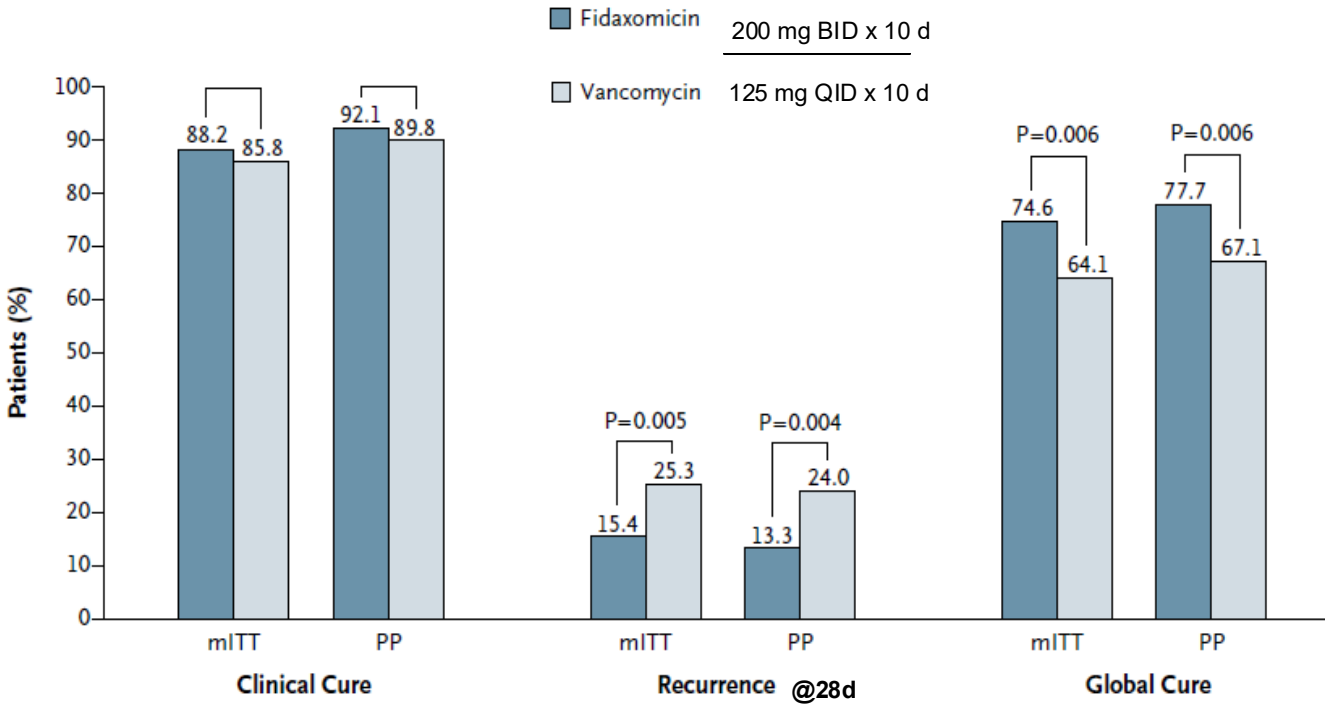
Odenholt I, et al. *Chemotherapy*. 2007;53(4):267-274.

Fidaxomicin

- Non-systemic (minimally absorbed)
- Bactericidal
- Dose 200 mg BID x 10 days

FDA. Accessed July 11, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213138lbl.pdf.

Fidoxamicin vs Vancomycin: Phase III



Louie TJ, et al. *N Engl J Med*. 2011;364(5):422-431.

Practical Updates in Primary Care

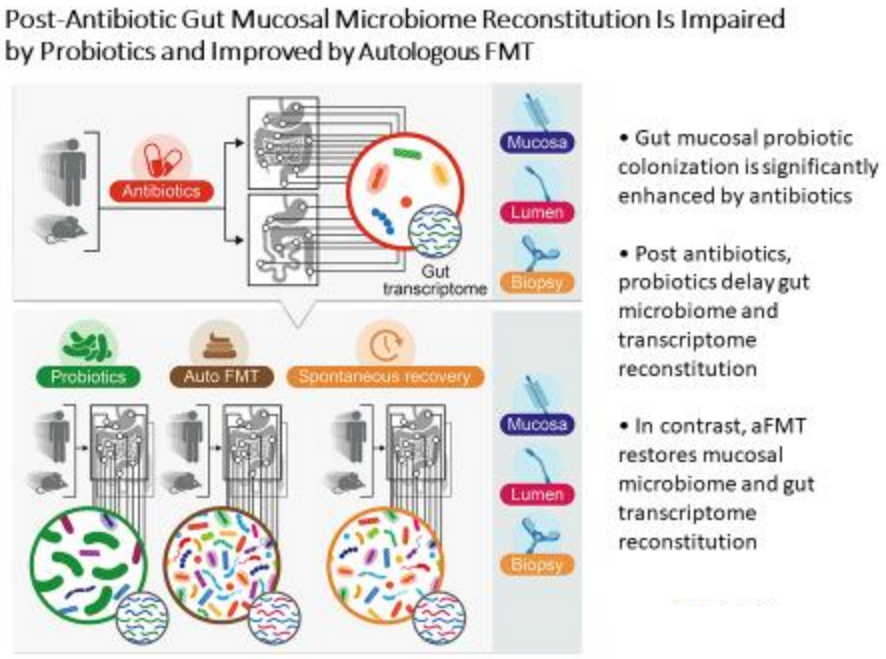
Non-Antibiotic Therapies: Probiotics ACG 2021

Prevention
1. We recommend against probiotics for the prevention of CDI in patients being treated with antibiotics (primary prevention) (conditional recommendation, moderate quality of evidence).
2. We recommend against probiotics for the prevention of CDI recurrence (secondary prevention) (strong recommendation, very low quality of evidence).

Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Probiotics

- This trial examined the effects of multi-strain probiotics or autologous fecal microbiome transplantation (aFMT) on post-antibiotic reconstitution of the microbiome
- Compared to spontaneous post-antibiotic recovery, probiotics induced a markedly delayed and persistently incomplete indigenous stool/mucosal microbiome reconstitution
- aFMT induced a rapid and near-complete recovery within days of administration



Suez J, et al. *Cell*. 2018;174(6):1406-1423.e16.

Treatment Response

- Either stool frequency decreases or stool consistency improves
- Treatment response should be observed after at least 3 days
- After clinical response, it may take weeks for stool consistency and frequency to become entirely normal

Recurrent CDI

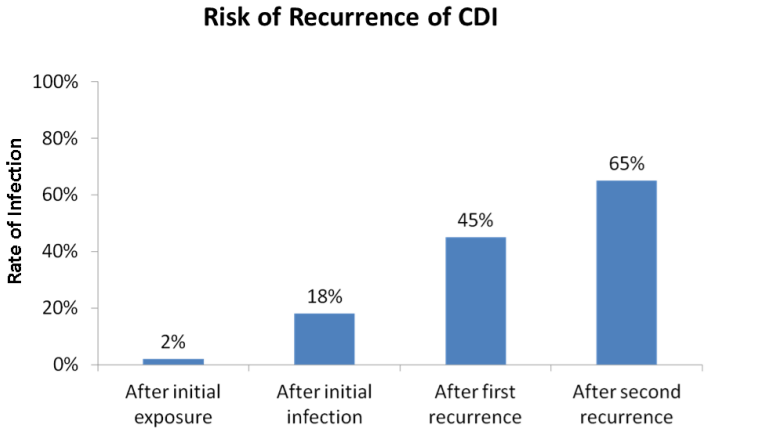
- Recurrence of symptoms after successful initial therapy for *C. difficile*
  - Endogenous persistence of *C. difficile* spores
  - Acquisition of a new strain from an exogenous source

- Strains analysis
  - 2 different serogroups in 21.5%
  - Same serogroup in 78.5%

Barbut F, et al. *J Clin Microbiol*. 2000;38(6):2386-2388.

Recurrent CDI

- Recurrence is present when CDI re-occurs within 8 weeks
  - Provided the symptoms from the previous episode resolved
  - May occur within days



Risk of recurrent infection increases with each treatment failure

Jiang ZD, et al. *Am J Gastroenterol*. 2006;101(5):1112-1116.

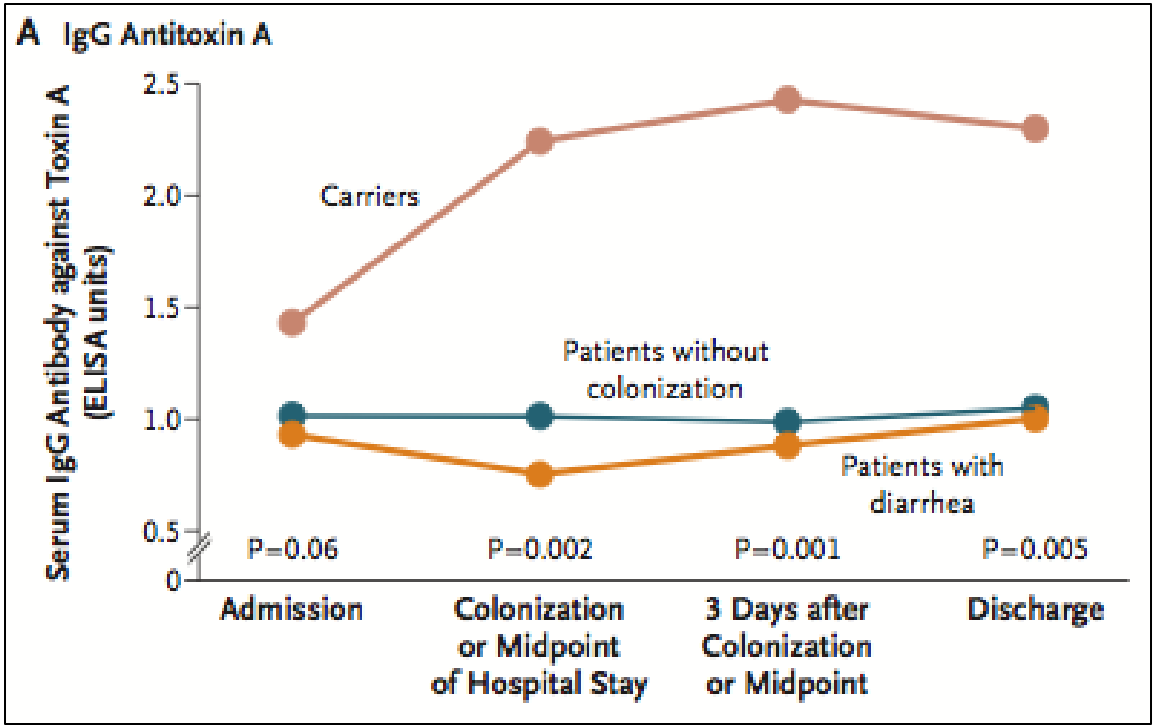
Practical Updates in Primary Care

Recurrent CDI: Why Does it Occur?

- Impaired host response

- Altered intestinal microbiome

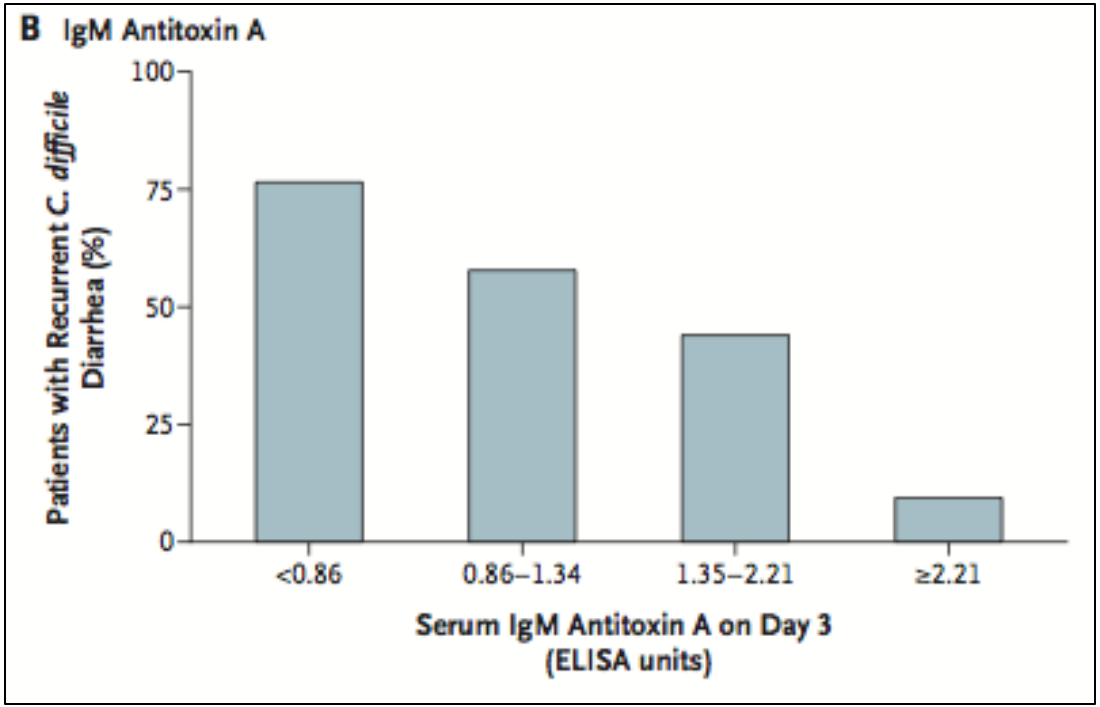
Impaired Host Response



Ig = immunoglobulin; ELISA = enzyme-linked immunosorbent assay.

Kyne L, et al. *N Engl J Med*. 2000;342(6):390-397.

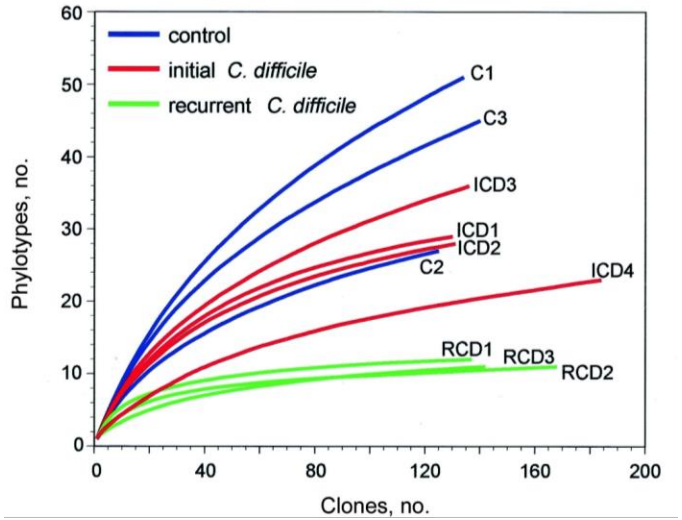
Impaired Host Response

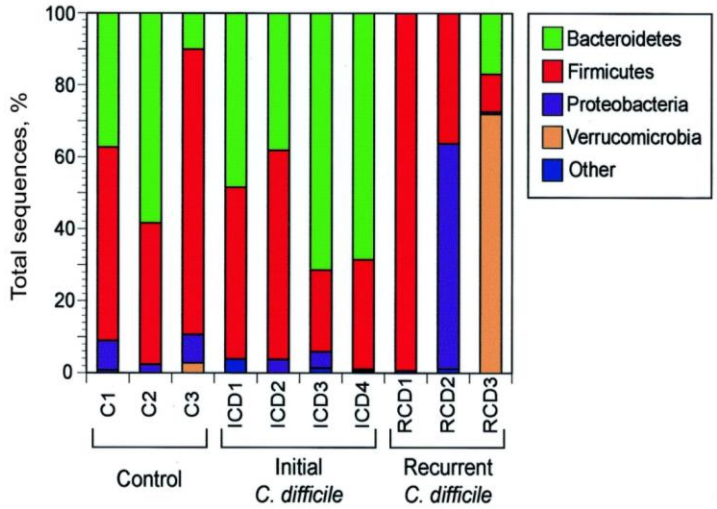


Kyne L, et al. *N Engl J Med*. 2000;342(6):390-397.

Practical Updates in Primary Care

Altered Intestinal Microbiome





- Decreased phylogenetic richness
- Bacteroidetes and Firmicutes are reduced in patients with recurrent CDI, not in patients with just 1 episode

Chang JY, et al. *J Infect Dis*. 2008;197(3):435-438.

- Not just microbial membership, but function

- Antibiotics disturb not only the structure of the microbiome, but also its function
  - Fermentation of SCFA
  - Lipid metabolism
  - Protein digestion
  - Bile salt metabolism

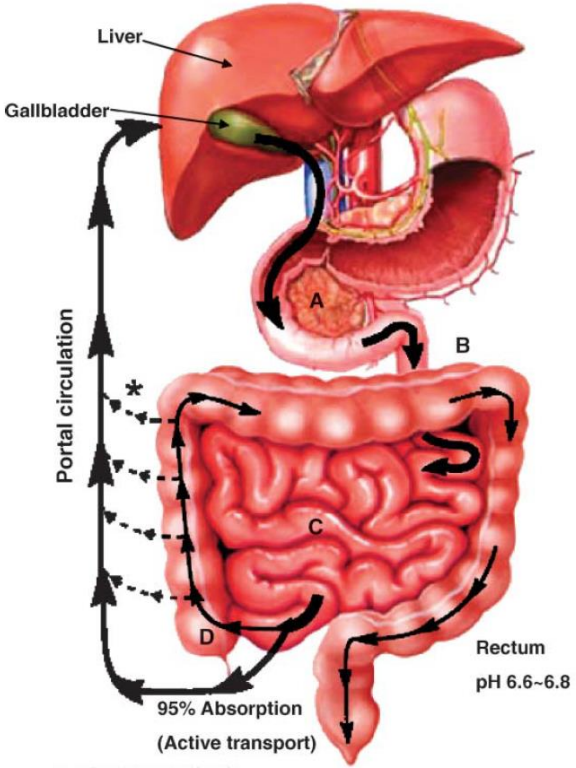
SCFA = short-chain fatty acids.

- CDI is communicated by ingestion of spores

- Spores
  1. Are resistant to heat and antibiotics and are able to survive outside of the colon
  2. Germinate in the GI tract and become vegetative cells, which can produce toxin
  3. Germination is critical to initiate CDI
  4. Bile acids are vital to the germination process

Bartlett JG. *Ann Intern Med*. 2006;145(10):758-764. Ridlon JM, et al. *J Lipid Res*. 2006;47(2):241-259.

Bile Acids



Primary bile acids:
Chenodeoxycholate and cholate

↓

Exposure to colonic flora

↓

Biotransformation via
bile salt hydrolases (BSH) and
7α-dehydroxylation

↓

Secondary bile acids:
Deoxycholate and lithocholate

Ridlon JM, et al. *J Lipid Res*. 2006;47(2):241-259.

Practical Updates in Primary Care

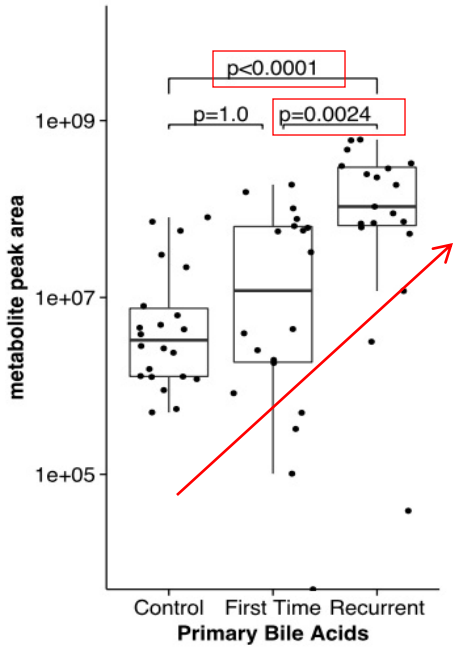
The Relationship between CDI and Bile Acids

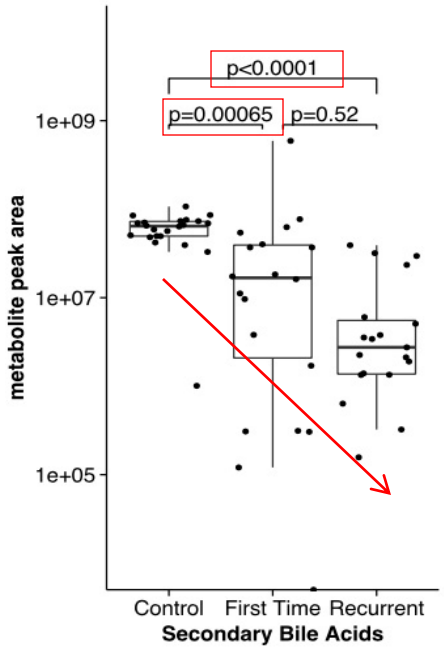
- In vitro primary bile acids can stimulate germination of *C. difficile* spores
- The secondary bile acid deoxycholate can inhibit growth of the vegetative form
- Antibiotic therapy may ablate critical members of the microbiota that generate inhibitory (protective) secondary bile acids
  - Stool extracts from antibiotic-treated mice have higher concentrations of primary bile acids; untreated mice have relatively higher secondary bile acids.
- The relationship between the host microbiome and bile salt metabolism is poorly defined in humans with CDI

Allegretti JR, et al. *Aliment Pharmacol Ther*. 2016;43(11):1142-1153.

Practical Updates in Primary Care

Bile Salt Analysis in Stool

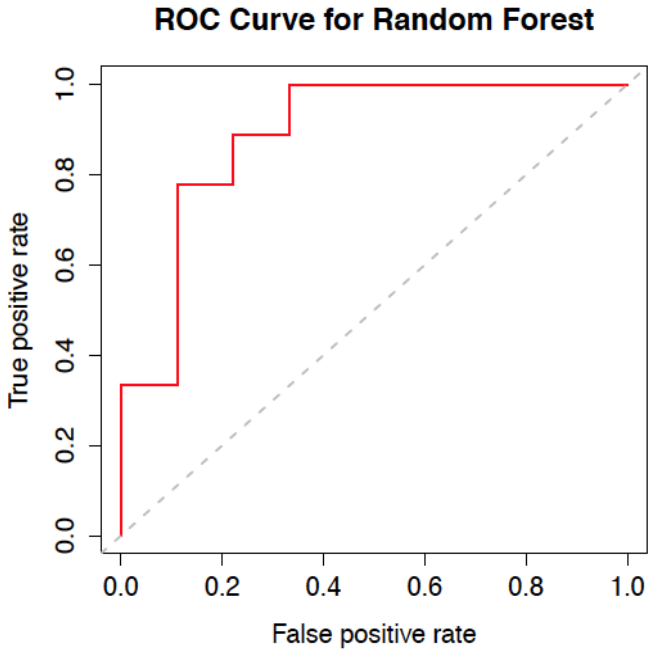


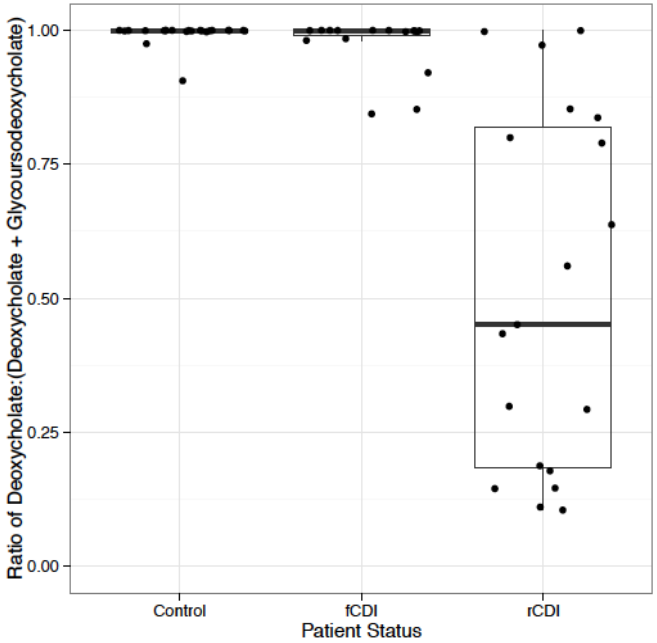


Allegretti JR, et al. *Aliment Pharmacol Ther*. 2016;43(11):1142-1153.

Practical Updates in Primary Care

Accuracy of Bile Salts as Predictors





Allegretti JR, et al. *Aliment Pharmacol Ther*. 2016;43(11):1142-1153.

Recurrent CDI: Treatment Options

Practical Updates in Primary Care

Treatment of Recurrent CDI: Summary from IDSA

- First recurrence: DO SOMETHING DIFFERENT
  - Vancomycin 125 mg QID x 10 days if metronidazole was used initially
  - Prolonged taper if standard vancomycin was used
    - 125 mg orally 4 times daily for 14 days
    - 125 mg orally twice daily for 7 days
    - 125 mg orally once daily for 7 days
    - 125 mg orally every 2-3 days for 2-8 weeks
  - Fidaxomicin 200 mg BID x 10 days
- Second or further recurrence: Treatment and prevention
  - Vancomycin taper
  - Fidaxomicin
  - FMT
  - Previously, bezlotoxumab

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Prevention of Recurrence

Prevention of Recurrence	
FMT	14. We recommend patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences (strong recommendation, moderate quality of evidence).
	15. We recommend FMT be delivered via colonoscopy (strong recommendation, moderate quality of evidence) or capsules (strong recommendation, moderate quality of evidence) for treatment of rCDI; we suggest delivery by enema if other methods are unavailable (conditional recommendation, low quality of evidence).
	16. We suggest repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT (conditional recommendation, very low quality of evidence).
Suppressive Vanco	17. For patients with rCDI who are not candidates for FMT, or who relapsed after FMT or require ongoing or frequent courses of antibiotics, suppressive oral vancomycin may be used to prevent further recurrences (conditional recommendation/very low quality of evidence).
	18. Oral vancomycin prophylaxis may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence (conditional recommendation, very low quality of evidence).
*Bezlotoxumab	19. We suggest bezlotoxumab be considered for prevention of CDI recurrence in patients who are at high risk of recurrence (conditional recommendation, moderate quality of evidence).
	20. We suggest against discontinuation of antisecretory therapy in patients with CDI, provided there is an appropriate indication for their use (strong recommendation, very low quality of evidence).

***Discontinued 1/31/25.**

Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Bezlotoxumab

- A fully humanized monoclonal antibody that binds to *C. difficile* toxin B
- Single IV Infusion
- Indicated to prevent recurrence of CDI
- To be used with a course of antibiotics
- Discontinued Jan 31, 2025 – no longer in production

Wilcox MH, et al. *N Engl J Med*. 2017;376(4):305-317.

Non-FDA Approved Fecal Microbiota Transplantation

- Instillation of minimally manipulated microbial communities from stool of a healthy donor into a patient's GI tract
- FMT is distinguished from a defined consortia of microorganisms, highlighting the degree of complexity and functionality of the microbiome
- It is considered to be both a "drug" and a "biologic or tissue"

GI = gastrointestinal.

Regulations: USA (FDA)

- **May 2013: Investigational New Drug application (IND) requirement announced**
  - Fecal microbiota = drug/biologic product
  - Considered investigational
  - Requires randomized controlled trials, safety/efficacy data
- **July 2013: May administer FMT to treat *C. difficile* infection not responding to standard therapies**
  - Must provide informed consent
    - State that FMT is investigational
    - Discuss potential risks
  - All other applications outside of CDI require an IND
- **March 2016: <u>Draft</u> guidance would require directed donors; limit material from stool banks**
  - Public comments were elicited
  - April 2019 “update to the policy is imminent,” and human stool does not meet definition of human tissue

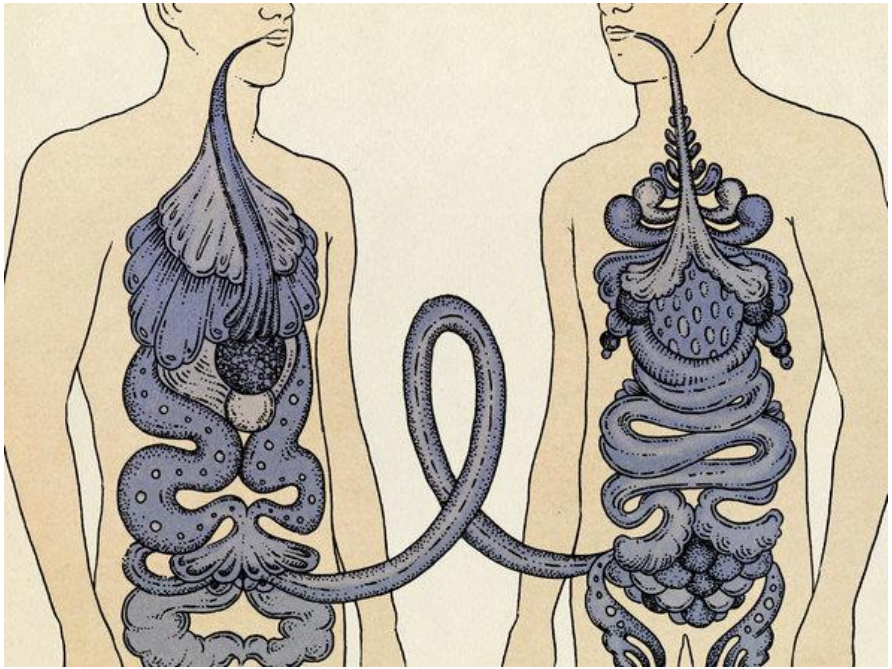
FDA. Accessed July 11, 2025. https://www.fda.gov/media/86440/download.

Regulations: USA

- **Update in 2022**
  - IND is required for stool-banked material
- Unclear if/when enforcement discretion will be rescinded
- OpenBiome no longer able to ship material as of 12/2024

FDA. Accessed July 11, 2025. https://www.fda.gov/media/86440/download. OpenBiome. Accessed July 11, 2025. https://openbiome.org/fmt-update-future-directions/.

What Concerns Have Been Raised about FMT?



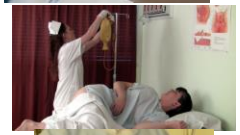
Challenges with Non-FDA-Approved FMT

- Cost – still not covered by most payors, so need to cover cost
- Storage on site (-80 °C freezer)
- Will your hospital still allow you to offer this with FDA-approved products available?
- What about safety concerns?
- Now lack of centralized supply

Procedural Risk: Mode of Delivery

The administration of FMT is not technically difficult and has variable delivery modalities (colonoscopy, enema, naso-enteric tube), allowing access to a variety of physicians/hcps with differing training

- Nasogastric or nasoduodenal tube
  - Uncomfortable
  - Requires radiology
- Retention enemas
  - Variable patient ability to tolerate
- Lower endoscopy
  - Enables examination of mucosa
- Encapsulation
  - Decreased procedure related risk and cost



Aas JA, et al. *Clin Infect Dis*. 2003;36(5):580-585. Rubin TA, et al. *Anaerobe*. 2013;19:22-26. van Nood E, et al. N Engl J Med. 2013;368(5):407-415. Silverman MS, et al. *Clin Gastroenterol Hepatol*. 2010;8(5):471-473. Kassam Z, et al. *Am J Gastroenterol*. 2013;108(4):500-508. Lee CH, et al. *JAMA*. 2016;315(2):142-149.

Procedural Risk: Inherent Risk of FMT

1. Aspiration with upper GI delivery
   - A case of feculent aspiration after FMT via upper endoscopy was subsequently fatal

   **Large-volume FMT should not be administered into the upper GI tract by nasogastric tube or upper endoscopy

2. Bowel perforation after a colonoscopy
   - 1 study reported a case of a superficial mucosal tear due to colonoscopy
   - Few cases of perforation in the setting of fulminant CDI

Benefits and alternatives should be communicated to patients undergoing FMT, and a shared decision-making process should be utilized to identify the most appropriate FMT delivery modality for each patient

Baxter M, et al. *Clin. Infect. Dis*. 2015;61(1):136-137. Link A, et al. *Dig Liver Dis*. 2016;48(11):1336-1339. Seekatz AM, et al. *mBio*. 2014;5(3):e00893-e00914. Tixier EN, et al. *Aliment Pharmacol Ther*. 2019;50(10):1094-1099.

Practical Updates in Primary Care

MDRO Transmission

- The FDA reported 2 patients with immunocompromise developing systemic infection with extended-spectrum beta-lactamase-producing *Escherichia coli* after FMT
  - 1 of whom died

- The donor had not been tested for ESBL prior to the FMT (IND-approved protocol)
  - But it was confirmed as ESBL colonized subsequently

- This type of scenario has emphasized the importance of meticulous attention to donor testing for potential pathogens, as supported by guidelines

MDRO = multi-drug resistant organism; ESBL = extended-spectrum beta-lactamase.

Minimal Screening Requirements per the FDA

Stool testing:

- *Clostridium difficile*
- *Salmonella* spp.
- *E. coli* 0157
- *Shigella* spp.
- *Vibrio* spp.
- *Yersinia* spp.
- *Campylobacter* spp.
- *Plesiomonas* spp.
- Giardia
- Cryptosporidium
- Cyclospora
- Isospora
- Microsporidia
- Entamoeba histolytica
- Ova and parasites
- Rotavirus
- Norovirus
- Adenovirus
- Enterovirus
- Multi-drug resistant organisms (MDROs)
  - Extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*
  - Vancomycin-resistant enterococci (VRE)
  - Carbapenem-resistant *Enterobacteriaceae* (CRE)
  - Methicillin-resistant Staphylococcus aureus (MRSA)[1]

Serological testing:

- Hepatitis A
- Hepatitis B
- Hepatitis C
- HIV 1/2
- HTLV 1/2
- Syphilis
- Strongyloides
- EBV
- CMV

Carlson PE Jr. *Cell Host Microbe*. 2020;27(2):173-175.

Other Infections of Concern

- EPEC and STEC
  - Stool is screened for: Enterohemorrhagic *E. coli* (EHEC) and Shiga toxin-producing *E. coli* (STEC) via enzyme immunoassay
  - Enteropathogenic *E. coli* (EPEC) is not screened for (generally not considered a pathogen)

- 4 cases of STEC and 2 cases of EPEC were reported post-FMT

- New guidance from FDA is STEC and EPEC testing via PCR

PCR = polymerase chain reaction.
Carlson PE Jr. *Cell Host Microbe*. 2020;27(2):173-175.

Common Symptoms

- Mild gastrointestinal symptoms may develop following FMT and are typically self-limiting

- Symptoms reported have included
  - Diarrhea
  - Constipation
  - Abdominal discomfort
  - Cramping
  - Fever
  - Belching
  - Bloating
  - Flatulence
  - Nausea
  - Vomiting
  - Borborygmus

Are We Still Doing FMT?

The Pandemic Effect

- Initially material produced after Dec 1, 2019 was not eligible for use per FDA

- OpenBiome implemented SARS-CoV-2 screening in asymptomatic donors with NP swabs
  - Stool testing was eventually done on all banked samples
  - No reports of transmission of SARS-CoV-2 via FMT to date

- Many centers halted or stopped their programs

NP = nasopharyngeal.

FDA. Accessed July 11, 2025. https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-new-safety-information-regarding-additional-protections-screening.

SO, ARE WE STILL DOING FMT?

- FDA policy is still in place
- Previously: “OpenBiome distributes investigational FMT preparations manufactured by the University of Minnesota under an IND application. Registered physicians may request investigation FMT preparations for the treatment of recurrent CDI not responsive to standard therapies.”

Item	Description	Price	Quantity	Subtotal
MTP-101LR	35mL Investigational FMT for recurrent *C. difficile* infection not responsive to standard therapies.	$1695		
MTP-101LF	35mL Investigational FMT for **fulminant** *C. difficile* infection not responsive to standard therapies.	$1695		

- BUT, OpenBiome is no longer open and shipping treatments

Fecal Microbiota, Live-jslm: Indications for Use

- Broad-consortium microbiota-based therapy
- Administered as a single rectal installation following SOC antibiotic for recurrent CDI
- FDA indication: Prevention of recurrent CDI in individuals ≥18 years of age following antibiotic treatment for recurrent CDI

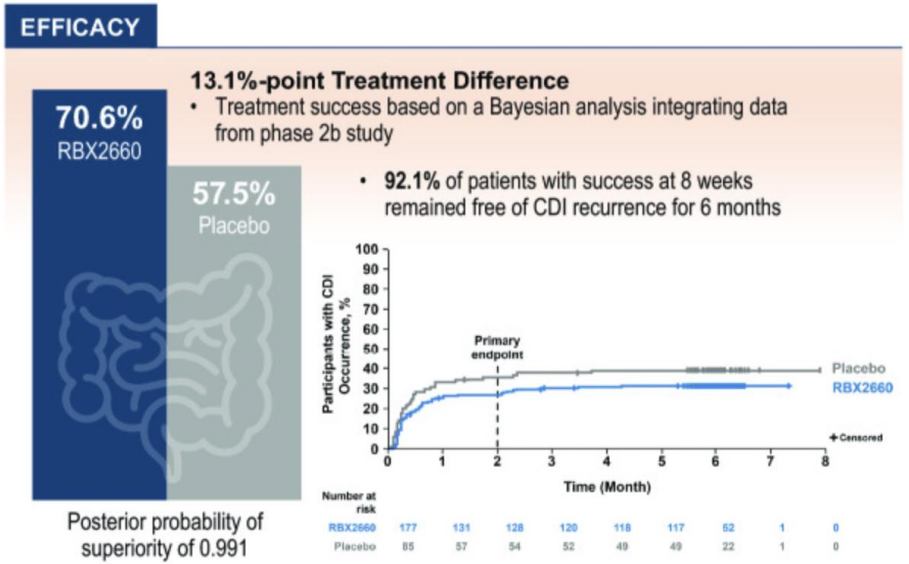
Indications*
Second recurrence (third episode) following standard-of-care antimicrobial
First recurrence in patients that are at high risk for future recurrences
Age >65
Chronic proton pump inhibitor usage
Immunocompromised (eg, chronic kidney disease, diabetes mellitus, active chemotherapy)
Likely future concomitant antimicrobial usage
Lives in skilled nursing facility
Severe underlying illness
Spends significant amount of time as an inpatient at the hospital
Lives in skilled nursing facility
Recurs within 8 weeks of receiving an initial treatment
FDA Indication: Fecal microbiota, live-jslm 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

***The indications from this chart are based upon expert opinion and not data supporting these specific risk factors.**

Feuerstadt P, et al. *Am J Gastroenterol*. 2023;118(8):1303-1306. FDA. Accessed July 11, 2025. https://www.fda.gov/media/163587/download?attachment.

PUNCH CD3 Study

- **Composition:** 50 g stool in 150 mL diluent
  - $>10^7$ organisms
- **Administration:** Enema placebo after SOC antibiotics
- **Study design:** Randomized double-blind with 2:1
- **Key inclusions**
  - 2 or more episodes
  - Diagnosis with toxin EIA or PCR allowed
- **Key exclusion**
  - Inflammatory bowel disease (IBD)
  - Irritable bowel syndrome (IBS)
  - Immunocompromised
- **Primary endpoint**
  - Lack of recurrence of CDI at 8 weeks
  - Bayesian analysis



SOC = standard of care.

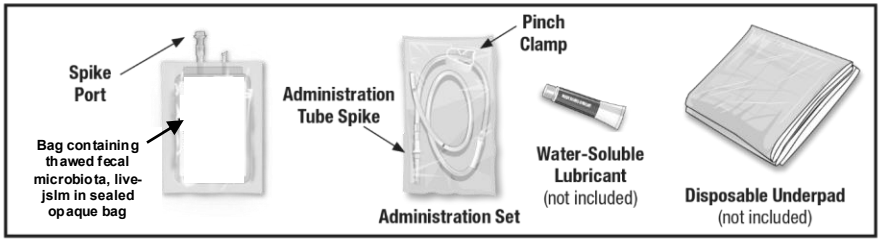
Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

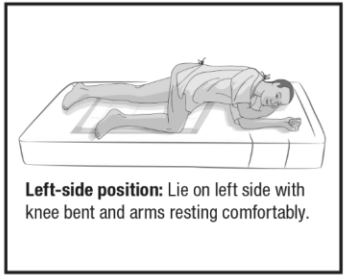
Fecal Microbiota, Live-jslm: Safety

- Contraindicated in patients with history of severe allergic reaction (eg, anaphylaxis) to any known components
- Potential to cause adverse reactions due to food allergens is unknown

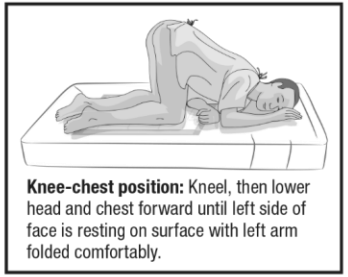
Adverse Reaction	Fecal Microbiota, Live-jslm (N=180) **N (%)**	Placebo (N=87) **N (%)**
Abdominal pain	16 (8.9)	6 (6.9)
Diarrhea	13 (7.2)	3 (3.4)
Abdominal distension	7 (3.9)	2 (2.3)
Flatulence	6 (3.3)	0
Nausea	6 (3.3)	1 (1.1)

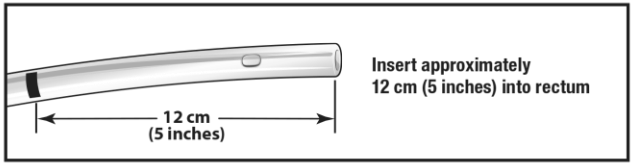
FDA. Accessed July 11, 2025. https://www.fda.gov/media/163587/download?attachment.

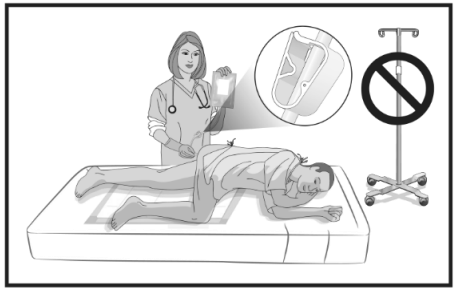




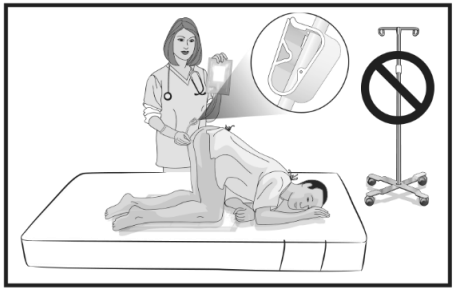
OR







OR



FDA. Accessed July 11, 2025. https://www.fda.gov/media/163587/download?attachment.

Fecal Microbiota Spores, Live-brpk Capsules: Indications for Use

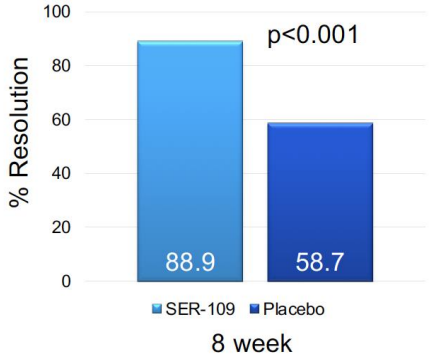
- Narrow consortium composed of live purified *Firmicutes* spores
- FDA indication: Prevention of recurrent CDI in individuals ≥18 years of age following antibiotic treatment for recurrent CDI
- Dosage: 4 capsules taken orally once daily for 3 consecutive days
  - Antibiotic treatment for recurrent CDI should be completed 2 to 4 days before initiating therapy with FMS, live-brpk capsules

FMS = fecal microbiota spores.

FDA. Accessed July 11, 2025.
https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert-VOWST.pdf.

Fecal Microbiota Spores, Live-brpk Capsules: ECOSPOR III Study

- **Composition:** Higher dose of *Firmicutes* spores, derived from donor stool
  - Treated with ethanol
- **Administration:** Oral dose (over 3 days) or placebo after SOC antibiotics
  - With bowel prep
- **Study design:** Randomized double-blind (1:1)



- **Key inclusions**
  - 3 or more episodes within 12 months
  - Diagnosis with toxin EIA
- **Key exclusion**
  - IBD
  - Immunocompromised
- **Primary endpoint**
  - Lack of recurrence of CDI at 8 weeks

No serious or treatment-related AEs

AEs = adverse events.

Feuerstadt P, et al. *N Engl J Med*. 2022;386(3):220-229.

Fecal Microbiota Spores, Live-brpk Capsules: Safety

- Contraindications: None
- Potential to cause adverse reactions due to food allergens is unknown

Adverse Reaction	FMS, Live-brpk N=90 (%)	Placebo N=92 (%)
Abdominal distention*	31	29
Fatigue*	22	22
Constipation*	14	11
Chills*	11	8
Diarrhea†	10	4

***Solicited adverse events: AEs that were recorded by participants in a diary for 7 days after completion of the 3-day regimen of FMS, live-brpk or placebo. Participants were monitored for unsolicited events by queries during visits for a period of 8 weeks after the first dose of study drug; †Unsolicited.**

FDA. Accessed July 11, 2025. https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert-VOWST.pdf.

Practical Use of FDA-Approved Live Biotherapeutic Products

Fecal Microbiota, Live-jslm

- Single-dose rectal installation
- In-office administration by anyone trained in its administration (depending on state regulations)
- Refrigerate for ≥24 h to 5 d
  - Thaw at room temperature 1 h before patient arrives
- Administer 24 to 72 h after completion of SOC antibiotics for recurrent CDI

Fecal Microbiota Spores, Live-brpk Capsules

- 4 capsules taken orally once daily for 3 consecutive days
- Taken 2 to 4 days after completion of SOC antibiotics for recurrent CDI
- Drink 296 mL (10 oz) of magnesium citrate on day before and ≥8 h before taking first dose of FMS, live-brpk capsules

FDA. Accessed July 11, 2025. https://www.fda.gov/media/163587/download?attachment; https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert-VOWST.pdf.

How Do You Choose What Is Appropriate for Your Patient?

Upper vs lower administration?

- Ability to swallow capsules
- Contraindication to a colonoscopy, or rectal administration
- Need for a mucosal assessment

Location of patient

- Is the patient traveling very far for this?
  - FMS will get shipped to the patient's house for administration
- FMT is done in the office
  - Is this an inpatient procedure?

Speed

- How fast do you need to get product?
- Insurance approval can often take weeks

FMS = fecal microbiota suspension.

Challenges with Current Approved Products

- Insurance coverage and cost are variable

- Denials can occur
  - Prior bezlotoxumab use
  - No attempted bezlotoxumab
  - Mandatory pass-throughs of other treatments

- Patient assistance programs exist, but require paper forms to be filled out by the patient
  - Difficult with virtual visits

Key Learning Points

- Incidence of CDI is still increasing at an alarming rate
- Metronidazole is no longer a good option for first episodes of CDI
- Counseling about post-infectious IBS is crucial
- FMT is an effective therapy for recurrent CDI infections – but there is no longer a stool bank supply in the US
- Fecal microbiota, live-jslm and FMS, live-brpk are approved for use; more agents coming

Comprehensive Strategies for Follow-Up

- Recommend timely follow-up for surveillance with PCP
- Ongoing assessment of symptoms
- Consider need for re-testing early
  - May indicate recurrent infection or inadequately treated infection
- Consult with GI for refractory cases

A 35 y/o female with no significant past medical history was given a course of clindamycin 3 weeks ago for a tooth abscess. Shortly after completing her course of antibiotics, she began having loose stools that progressed to 5 watery bowel movements daily over the last 3 days. She presents to the office and on exam, she has a mildly tender abdomen diffusely. Her white blood cell count was 15,000/uL. You confirm *C. difficile* infection, and she is treated with a standard vancomycin course. Diarrhea recurs 4 weeks after completion of the vancomycin course. The stool testing, using a 2-step method, returns positive and confirms a recurrent infection. For this patient's initial recurrence of CDI, what is the best treatment course?

a) Vancomycin taper

b) Metronidazole 500 mg TID x 10 days

c) Fecal microbiota transplantation

d) Watchful waiting

Acknowledgements

BWH

J. Allegretti Lab

Jonathan Hurtado
Jenna Marcus
Jessica Sitko
Sanchit Gupta, MD
Hannah Goodrick
Emma McClure
Madeline Carrellas
Margaret Storm
Jordan Pruce
Rahul Dalal, MD
Jen Mitri

Research Collaborators

- Monika Fischer
- Colleen Kelly
- Ari Grinspan
- Zain Kassam
- Benjamin Mullish
- Julian Marchesi
- Julie A.K. McDonald

Imperial College London

BROWN Alpert Medical School

Mount Sinai

Indiana University

Funding

- Crohn's and Colitis Foundation
- Harvard Digest Disease Center
- NIDDK
- American College of Gastroenterology

OpenBiome

Practical Updates in Primary Care