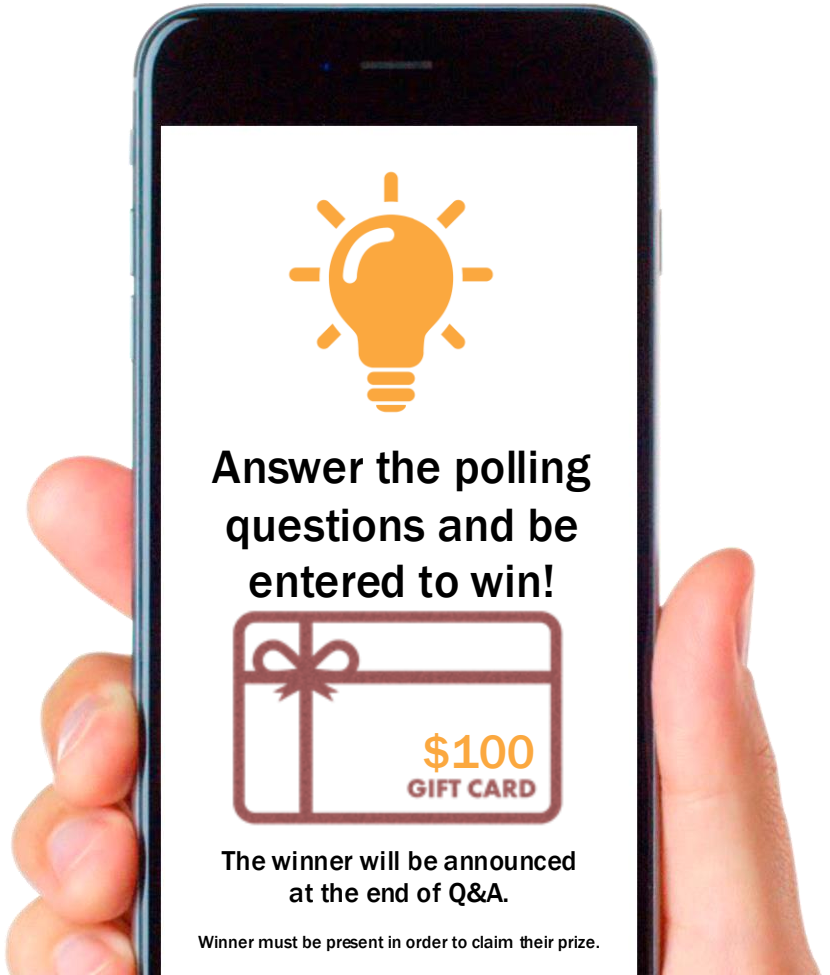

Click on Polling & Questions in the app to participate in this session

NORTHERN HEMISPHERE D

You can also scan this QR code:

WHEN LOW PREVALENCE MASKS HIGH BURDEN:

Identifying and Managing Recurrent *C. difficile* in IBD Through Microbiome-Based Approaches

AIBD

Supported by an independent educational grant from Nestlé Health Science.

Learning Objectives

- Evaluate the role of the gut microbiome in the pathogenesis and prevention of rCDI in patients with IBD
- Apply evidence-based strategies to differentiate CDI/rCDI from IBD flares, facilitating accurate and timely diagnosis in patients with IBD
- Assess the latest clinical data, real-world evidence, and best practices for the appropriate use of LBPs/FMT in the prevention of rCDI

CDIs = *Clostridioides difficile* infections; IBD = inflammatory bowel disease; LBP = live biotherapeutic product; FMT = fecal microbiota transplantation.

Overview of CDI

Miguel Regueiro, MD, FACG

Chief, Digestive Disease Institute
Professor of Medicine
Cleveland Clinic, Cleveland, OH

Disclosures

- **Miguel Regueiro, MD:** Consultant – Abbvie, Allergan, Amgen, BMS, Boehringer Ingelheim, Celgene, Genentech, Gilead, Janssen, Lilly, Organon, Pfizer, Prometheus, Salix, Seres, Takeda, UCB; advisory board – Abbvie, Allergan, Amgen, BMS, Boehringer Ingelheim, Celgene, Genentech, Gilead, Janssen, Lilly, Organon, Pfizer, Prometheus, Salix, Seres, Takeda, UCB; other financial/material support – CMEOutfitters, Cornerstones, GiHF, IBDRemedy, Imedex, UpToDate, Vindico

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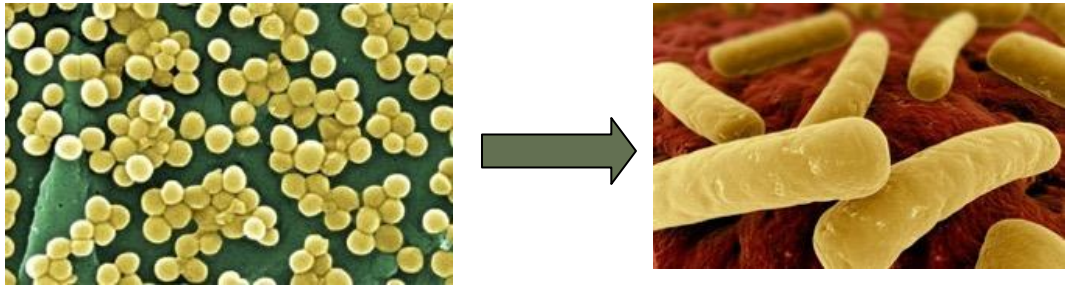
C. difficile Overview

- Anaerobic gram-positive, spore-forming, toxin-producing bacillus
  - Transmission via the fecal-oral route
  - Soil, water, air, human and animal feces, hospital surfaces
  - Ribotype 027
- Two forms: Spore and vegetative



- Spores are resistant to alcohol and can survive at room temperature up to 6 months
- Toxin A causes inflammation leading to intestinal fluid secretion and mucosal injury
- Toxin B is a major factor for virulence and is more potent than toxin A for mediating colonic mucosal

Kuehne SA, et al. *Nature*. 2010;467(7316):711-713. Kuehne SA, et al. *J Infect Dis*. 2014;209(1):83-86. Mada PK, Alam MU. *StatPearls*. 2024. Accessed Nov 10, 2025. https://www.ncbi.nlm.nih.gov/books/NBK431054/.

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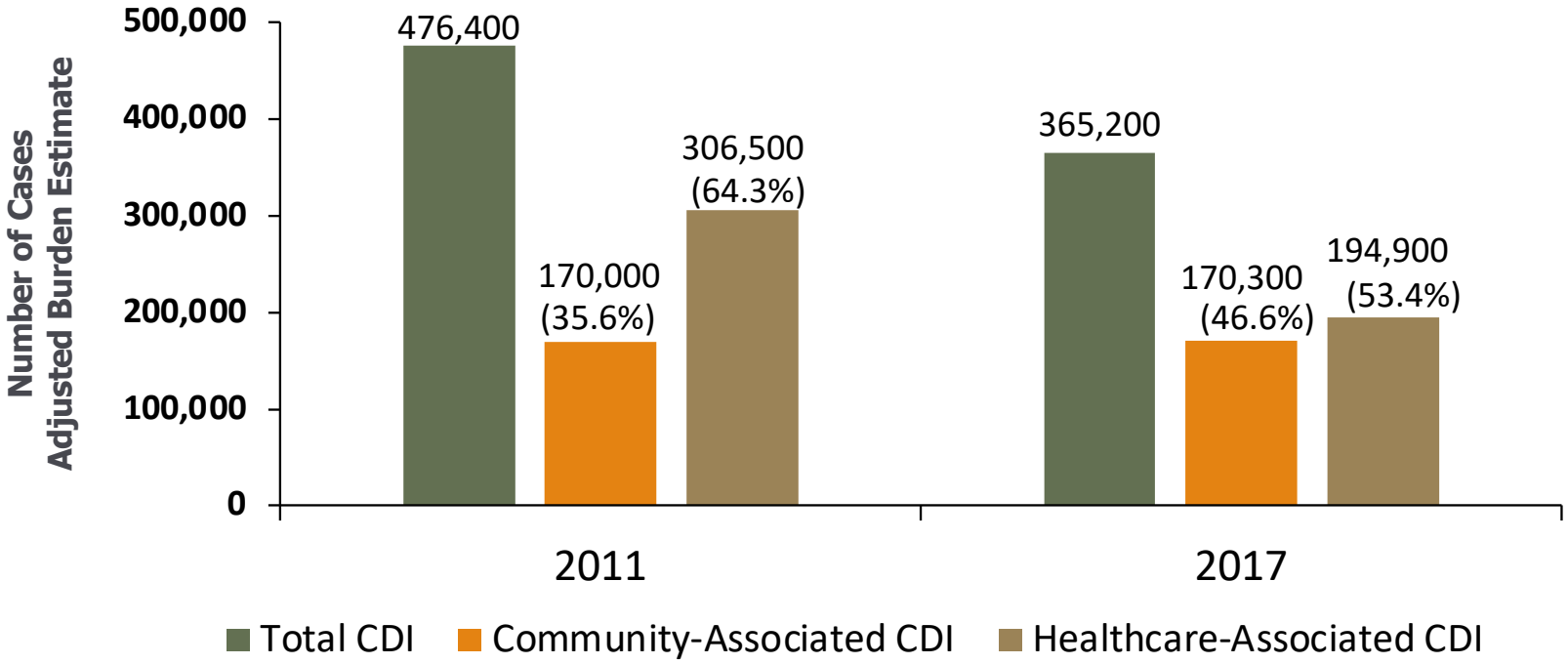
Healthcare- vs Community-Associated *C. difficile* Infection: 2011 vs 2017



Guh AY, et al. *N Engl J Med*. 2020;382(14):1320-1330.

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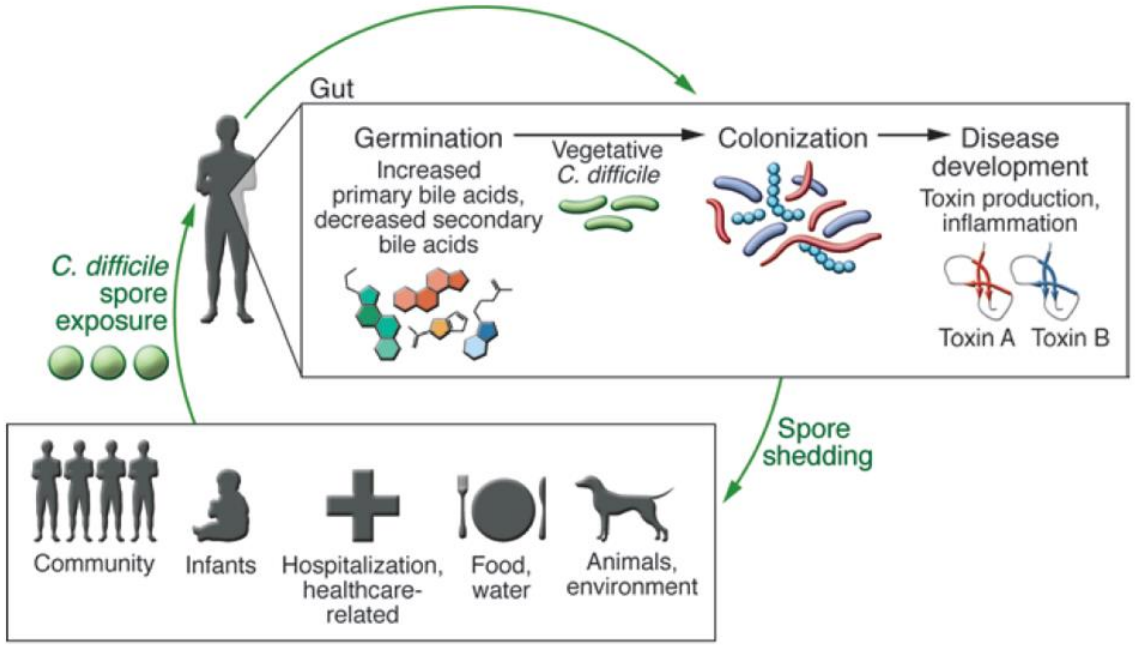
C. difficile Lifecycle

- Main risk factors → lack of colonization resistance
  - Advanced age (>65)
  - Antibiotics
  - Contact with healthcare environment
  - IBD
  - Transplant recipients
  - Gastric acid suppression?



Seekatz AM, et al. *J Clin Invest*. 2014;124(10):4182-4189. Lessa FC, et al. *N Engl J Med*. 2015;372(9):825-834.

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IBD-Specific Risk Factors for *C. difficile*

Immunosuppression

Exposure to corticosteroids

Common use of antibiotics

Antibiotic use remains a key modifiable risk factor for infection

Frequent healthcare facility exposure

Hospitalizations, more frequent ambulatory care visits

Colonic involvement

Similar risk magnitude for UC and CD

Uncontrolled disease/inflammation

***C. difficile* is a marker for disease severity**

Persistent dysbiosis

Diminished colonization resistance

UC = ulcerative colitis; CD = Crohn's disease.
Singh H, et al. *Gastroenterology*. 2017;153(2):430-438.e2.

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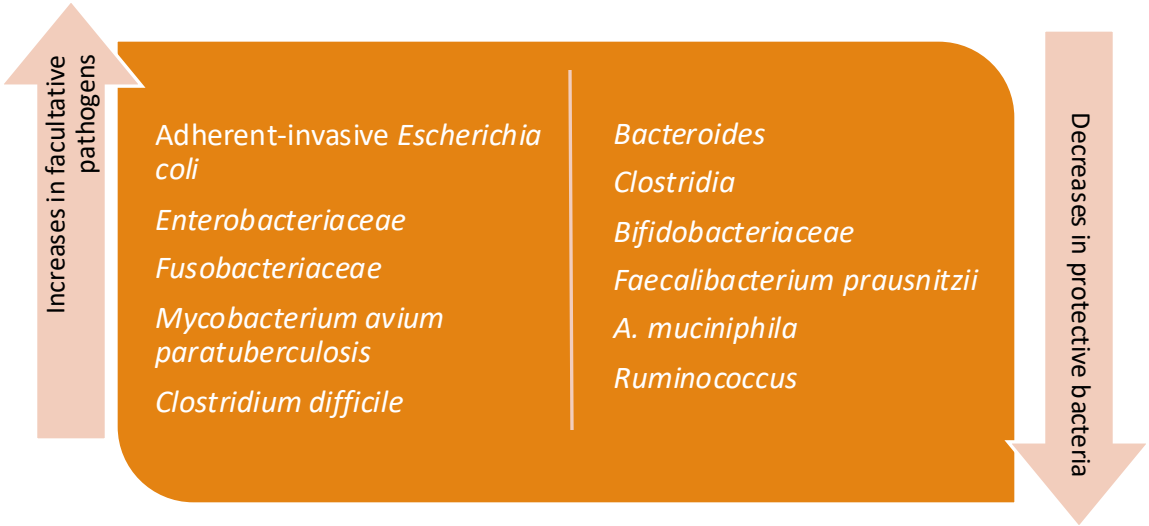
Dysbiosis in IBD: Loss of Colonization Resistance

- Loss of healthy microbiota
- Decreased diversity
- Increased levels of mucosal and luminal facultative pathogens
- Decreased levels of protective bacteria



Sheehan D, et al. *Gastroenterol Clin North Am.* 2017;46(1):143-154.

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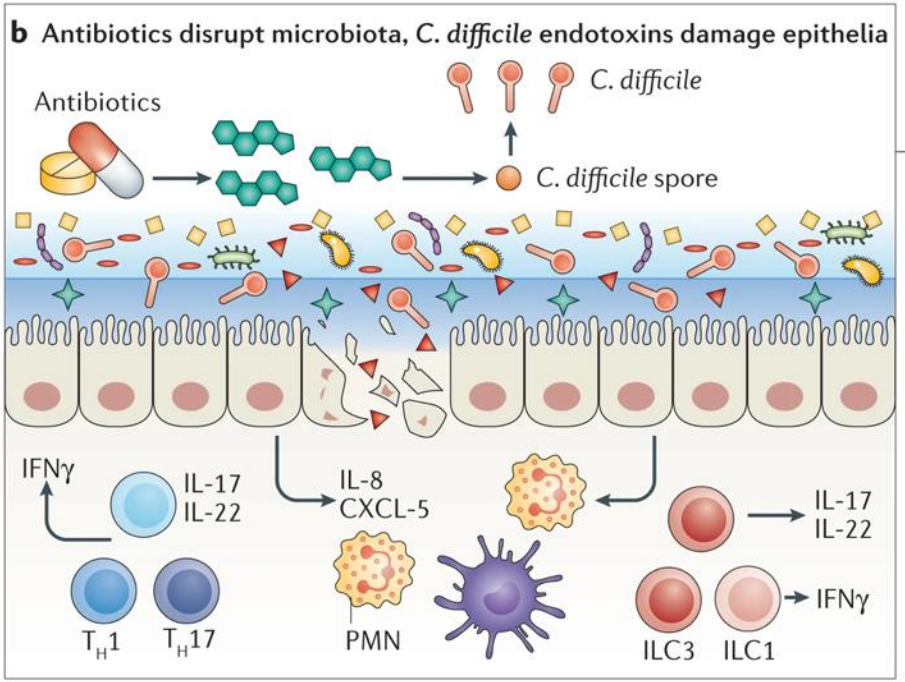
Disrupted Microbiota: Uninhibited Growth of *C. difficile* and Toxins Damage Epithelia



Loss of microbiota
- Decreased mucus
- Loss of AMPs and bacteriocins
- Loss of tight junctions
- IL-8, CXCL5, made by epithelial cells
- ↑ *C. difficile*
- ↑ Sialic acid
- No secondary bile acids

IFN = interferon; IL = interleukin; ILC = innate lymphoid cell; PMN = polymorphonuclear leukocyte; AMPs = antimicrobial peptides.
Khoruts A, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13(9):508-516.

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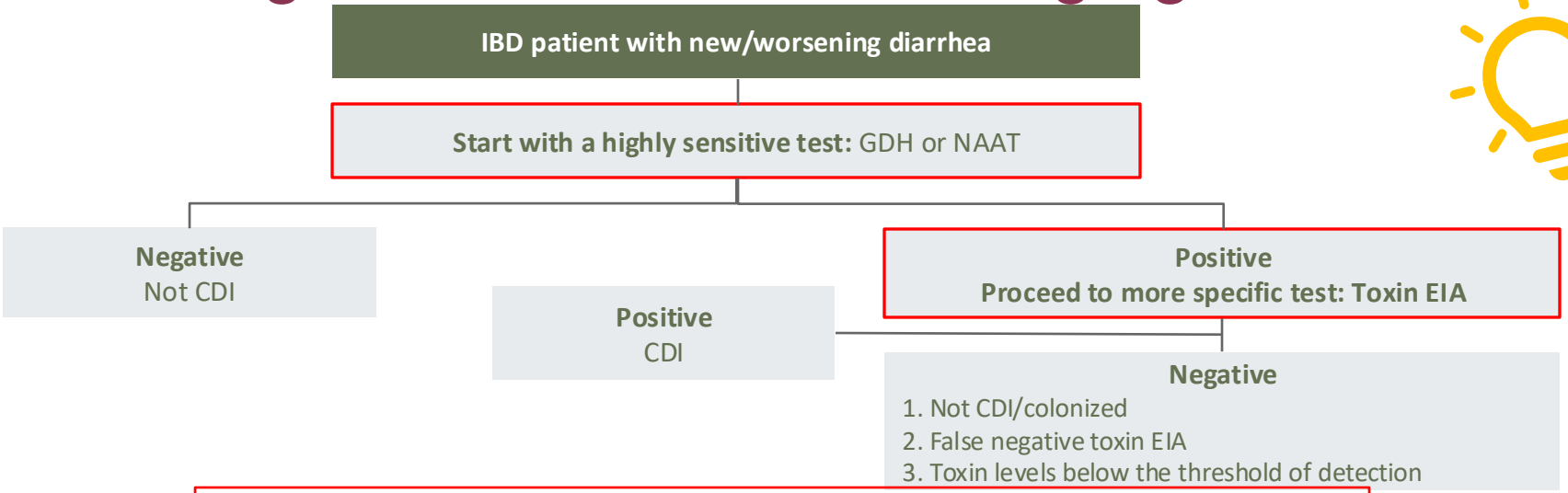
ACG 2021 Guidelines *C. difficile* Testing Algorithm: Diagnosis of CDI Is Challenging in IBD



Testing outcomes

GDH- or PCR-	= Not *C. difficile* infection
GDH+ or PCR+ EIA+	= *C. difficile* infection
GDH+ or PCR+ EIA-	= toxigenic *C. difficile* colonization
GDH+ but PCR- EIA-	= non-toxigenic C. difficile

ACG = American College of Gastroenterology; NAAT = nucleic acid amplification testing; GDH = glutamate dehydrogenase; PCR = polymerase chain reaction; EIA = enzyme immunoassay.

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

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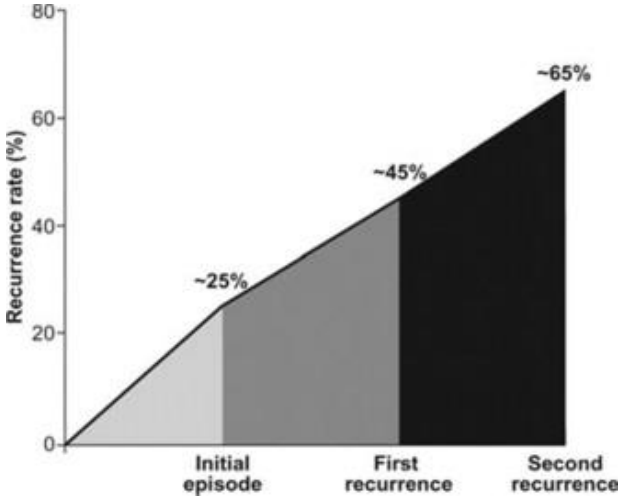
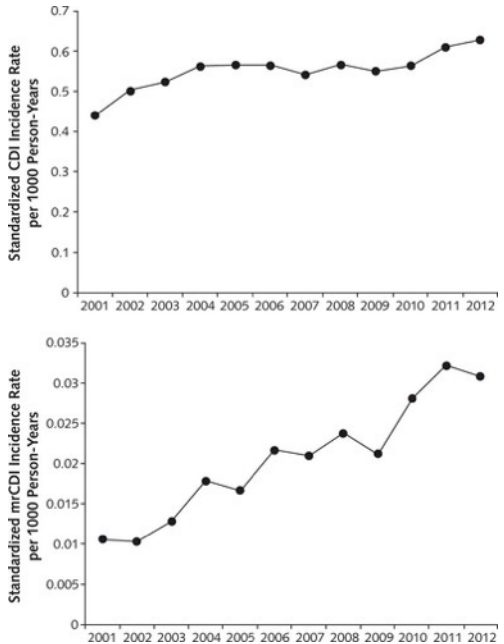
Recurrent *C. difficile* Infection

- Recurrence of symptoms after **<u>successful therapy</u>** for *C. difficile*
- Recurrence = another episode of CDI within **<u>8 weeks</u>**
  - Symptoms must have resolved from the previous episode





mrCDI = multiply recurrent CDI.

Ma GK, et al. *Ann Intern Med*. 2017;167(3):152-158. Kelly CP. *Clin Microbiol Infect*. 2012;18(Suppl 6):21-27.

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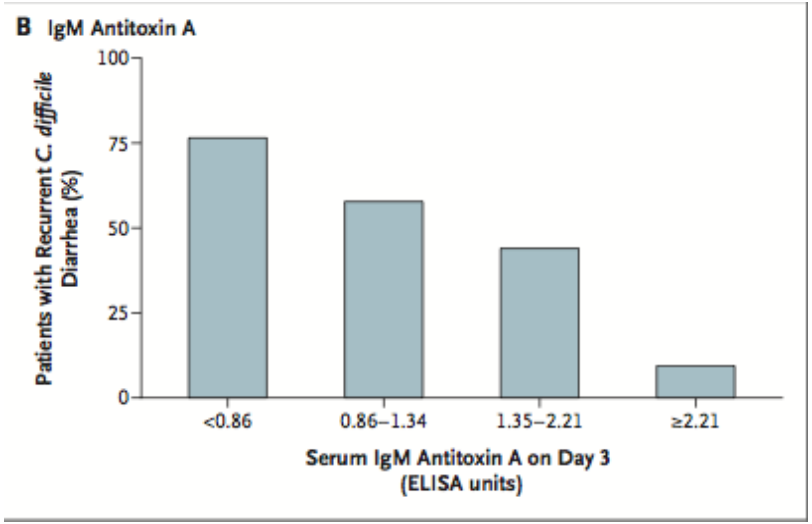
Risk Factors for Recurrent *C. difficile* infection

- **Patient characteristics**
  - Advancing age
  - Prior recurrence
  - Recurrent antibiotic exposure
  - More virulent strain
  - **IBD**
    - Up to 40% of patients with IBD will experience recurrence after first CDI
    - Over 50% recur after first recurrence with IBD

- **Host immune response**
  - Low serum antitoxin A IgM



ELISA = enzyme-linked immunosorbent assay; IgM = immunoglobulin M.

Kyne L, et al. *N Engl J Med*. 2000;342(6):390-397. Khanna S, et al. *Clin Gastroenterol Hepatol*. 2017;15(2):166-174. Kelly CP. *Clin Microbiol Infect*. 2012;18(Suppl 6):21-27. Kyne L, et al. *Lancet*. 2001;357(9251):189-93.

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Key Take-Aways

- *C. difficile* is a highly transmissible, nosocomial pathogen and can cause both health-care associated and community-associated infection
- Dysbiosis leads to decreased colonization resistance and increased risk of pathogens like *C. difficile*
- The most common risk factors for *C. difficile* infection include antibiotic use, advanced age, hospitalization, IBD, and severe comorbid illness
- A diagnosis of *C. difficile* should be based on the clinical picture and preferentially 2-step testing with GDH or NAAT (like PCR) as the first screening test
- Up to 25% of patients experience recurrent *C. difficile* infection within 30 days of treatment

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CDI and IBD: Challenges and Burden

Jessica R. Allegretti, MD, MPH

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
Boston, MA

Disclosures

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

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C. difficile Epidemiology in IBD

- At ~5-fold increased risk of getting CDI
  - Manitoba cohort: 8433 patients with IBD (50.3% UC, 49.7% CD) and 76,510 without
  - *C. diff* occurred in 84 patients with CD, 107 with UC, and 385 without IBD
    - ~4% of all patients with IBD developing CDI in the first 6 years after IBD diagnosis
- More likely to have community-onset CDI
- Younger at the time of CDI diagnosis
- More likely to have recurrent CDI (rCDI)
- In a retrospective study of 503 patients (RECIDIVISM), rCDI occurred in 32% of patients with IBD compared to 24% of patients without IBD (P<0.01); patients with IBD are **33% more likely** to experience rCDI

Singh H, et al. *Gastroenterology*. 2017;153(2):430-438.e2. Razik R, et al. *Am J Gastroenterol*. 2016;111(8):1141-1146.

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A Patient with IBD and *C. difficile*

- Often needs escalation of IBD therapy
- Visits the emergency room (ER) more often
- When hospitalized, the mortality risk is
  - ~4-fold higher than patients admitted for IBD alone
  - ~2-fold higher than patients admitted for CDI alone
- Has a higher risk for colectomy in IBD long-term (>3 months)
- Has a more refractory and complicated CDI
- Challenging diagnosis

Tariq R, et al. *J Clin Gastroenterol*. 2019;53(2):127-133. Nguyen GC, et al. *Am J Gastroenterol*. 2008;103(6):1443-1450. Law CCY, et al. *Aliment Pharmacol Ther*. 2017;45(8):1011-1020. Issa M, et al. *Clin Gastroenterol Hepatol*. 2007;5(3):345-351.

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Diagnosis of CDI Is Challenging in IBD

- Similar symptomatology
- High colonization rate (5-10%)
- Pitfalls of standalone CDI tests

ACG & ISDA Recommendations

1. All patients with IBD hospitalized with disease flare should undergo CDI testing
2. Ambulatory patients who develop diarrhea in setting of quiescent disease or presence of risk factors should be tested for CDI

	Advantages	Pitfalls
PCR	• High sensitivity • Rapid • Inexpensive	• Does not distinguish cases from carriers • May lead to overdiagnosis
GDH/ EIA (toxin)	• Able to detect active toxin production • Rapid • Inexpensive	• Low sensitivity of the toxin EIA • May lead to missed cases

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48. Surawicz C, et al. *Am J Gastroenterol*. 2013;108:478-498. Khanna S, et al. *Clin Gastroenterol Hepatol*. 2017;15(2):166-174; Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

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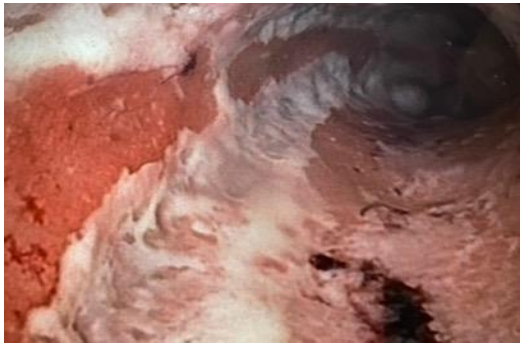
Distinguishing CDI in Quiescent IBD from *C. difficile* Colonization in Active IBD

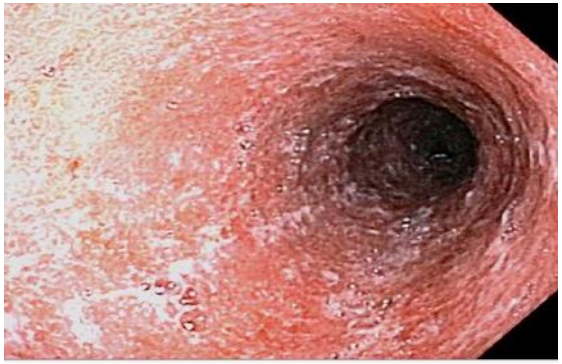
- **Inactive IBD with CDI**
  - Patients with inactive IBD may develop CDI, which resolves with vancomycin, as in a patient without IBD
  - Often, endoscopic evaluation can help distinguish between these 2 scenarios
  - Anti-CDI antibiotic therapy should be initiated and maintenance therapy for IBD continued
- **Active IBD with *C. difficile* colonization**
  - Inadequately controlled IBD is more likely to develop CDI as a consequence of the inflammation and disturbed microbiota contributing to symptoms of disease flare
  - If no improvement in clinical symptoms after 3 days, immunosuppressive therapy should be escalated
  - Treat the flare because anti-CDI therapy alone is unlikely to change the outcome

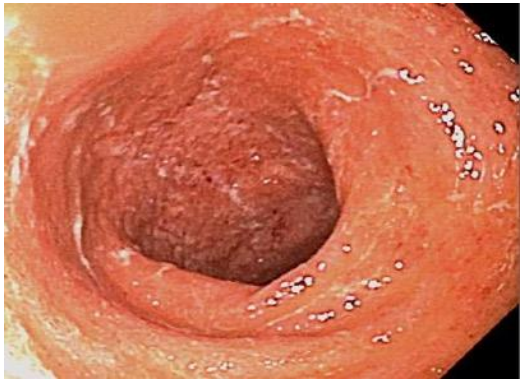
Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

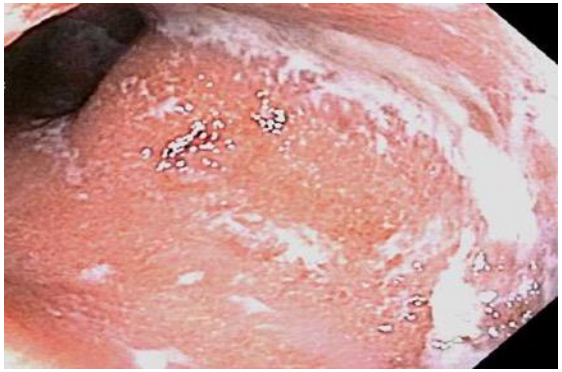
AIBD

Pseudomembranes Are Rare in IBD









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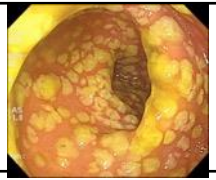
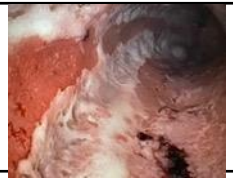
Classification of CDI Severity Can Be Tricky in IBD…

Classification	Definition
Non-severe	Leukocytosis with a WBC count <15,000 cells/µL and a serum creatinine level ≤1.5 mg/dL
Severe  	Leukocytosis with a WBC count ≥15,000 cells/µL or a serum creatinine level >1.5 mg/dL
Fulminant	Criteria for severe infection, plus hypotension or shock, ileus, or megacolon

WBC = white blood cell.

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

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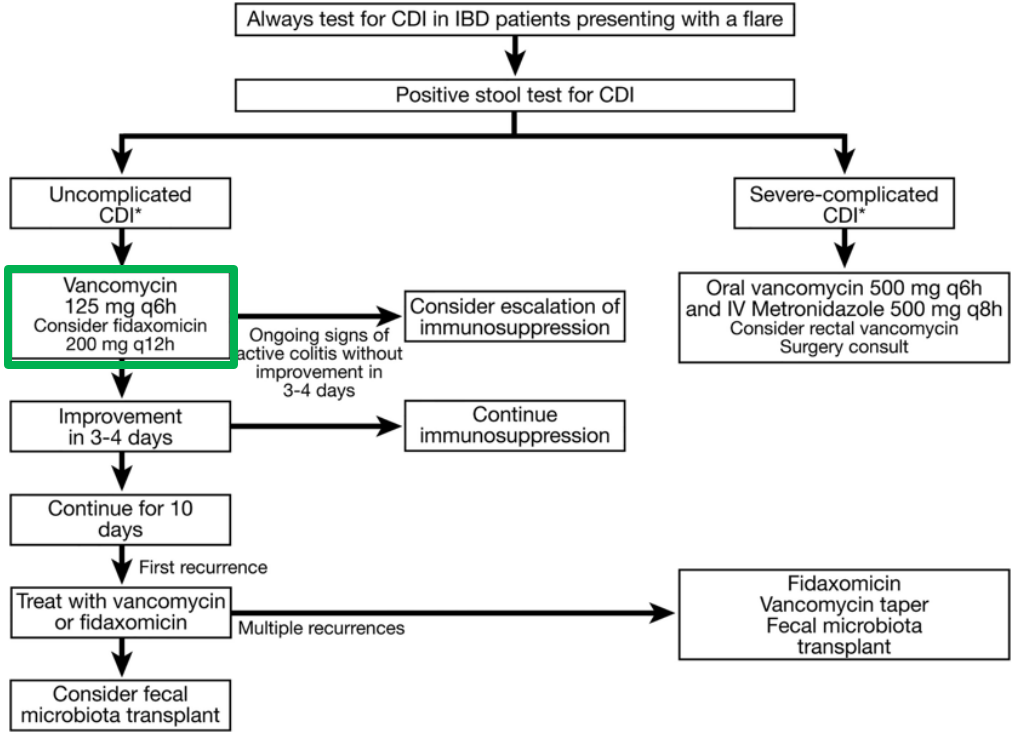
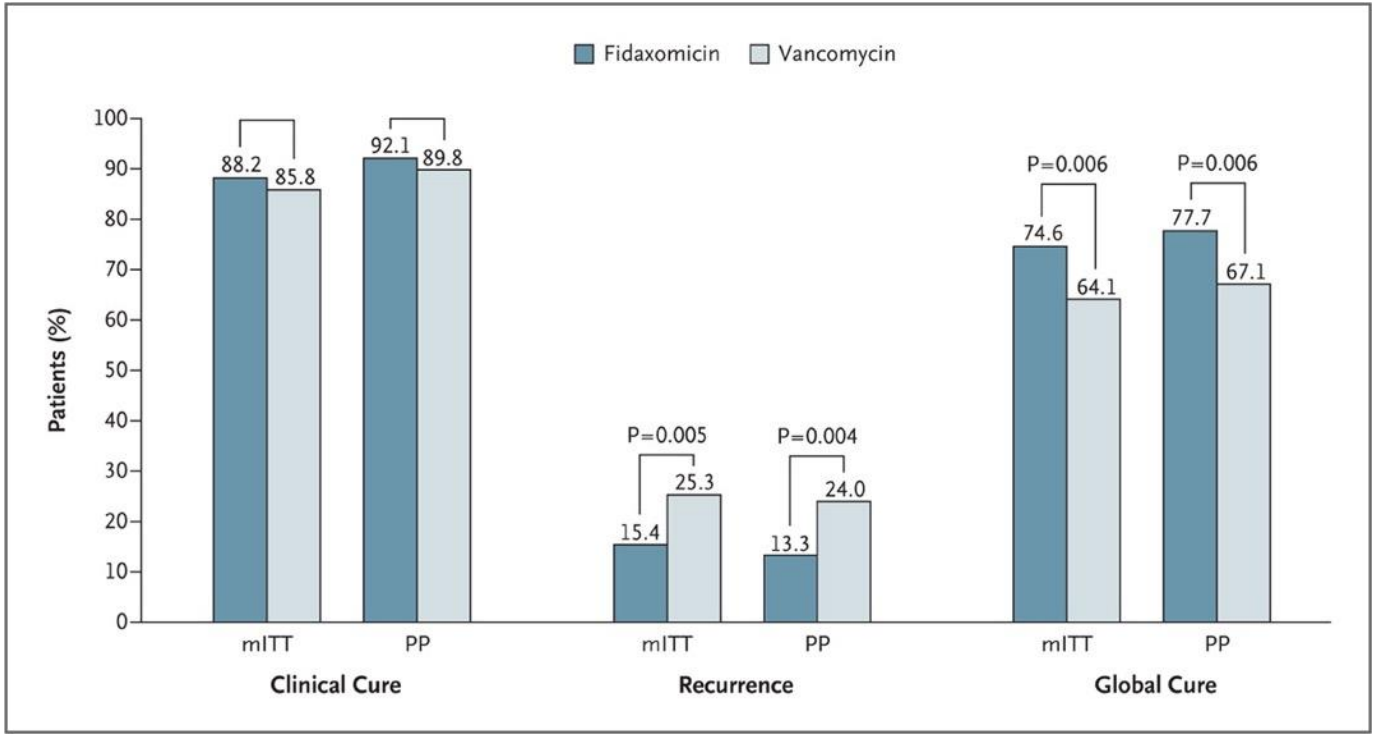
Management of *C. diff* in IBD



Khanna S, et al. *Clin Gastroenterol Hepatol*. 2017;15(2):166-174.

Fidaxomicin vs Vancomycin

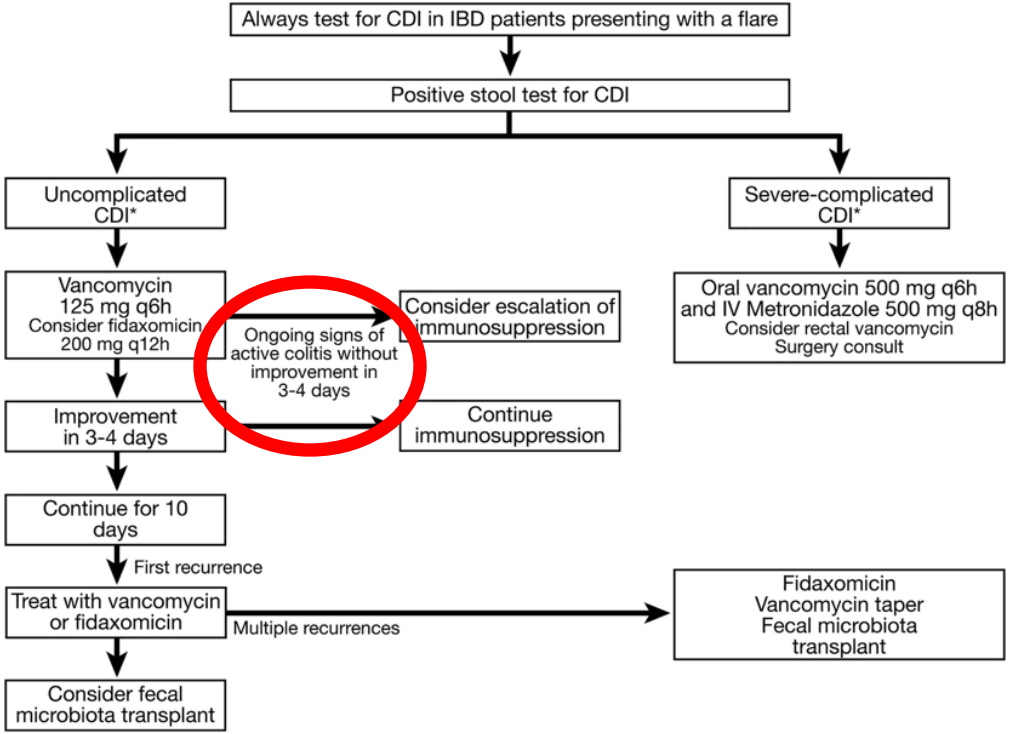


Fidaxomicin is better than vanco (90% vs 80%) in patients with concurrent systemic antibiotic use with CDI treatment

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

AIBD

Management of *C. diff* in IBD



Khanna S, et al. *Clin Gastroenterol Hepatol*. 2017;15(2):166-174.

2021 ACG Guidelines on Immunosuppression in Patients with CDI and IBD

"Immunosuppressive IBD therapy should not be held during anti-CDI therapy in the setting of disease flare, and escalation of therapy may be considered if there is no symptomatic improvement with treatment of CDI."

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

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How to Manage IBD during/after CDI: Escalation Is Safe!

Outcome within 90 d	No Escalation (n = 142)	Escalation (n = 62)	*P*-value
Death	7 (5.2%)	0	0.10
Sepsis	15 (11.2%)	1 (1.8%)	0.04
Colectomy	9 (6.8%)	1 (1.7%)	0.29
Composite endpoint	21 (15.6%)	1 (1.8%)	<0.01

Lukin DJ, et al. *Inflamm Bowel Dis.* 2019;25(4):775-781.

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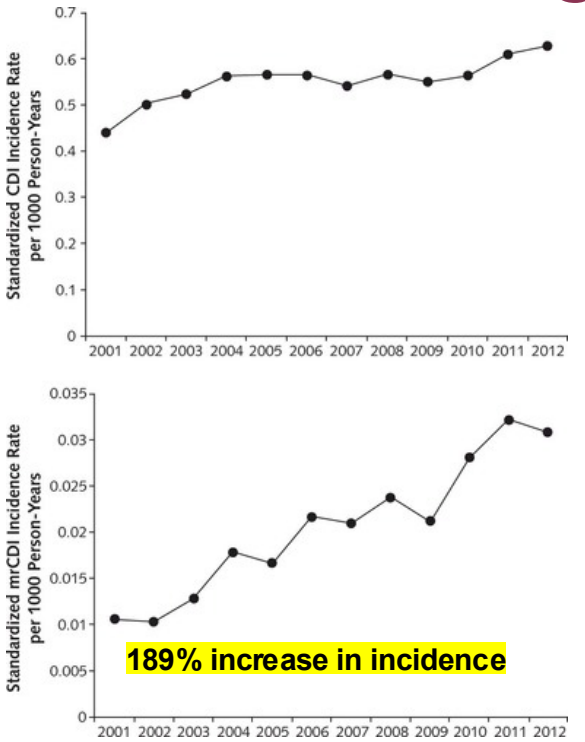
The Focus of Newer CDI Guidelines Is on Preventing CDI Recurrence



- 32-40% of patients with IBD will experience recurrence after first CDI
- **Over 50% recur after first recurrence with IBD**
- Recurrence accounts for 75,000 to 175,000 additional cases of CDI per year in the US

Razik R, et al. *Am J Gastroenterol*. 2016:111(8):1141-1146. Khanna S, et al. *Clin Gastroenterol Hepatol*. 2017;15(2):166-174. Ma GK, et al. *Ann Intern Med*. 2017;167(3):152-158.

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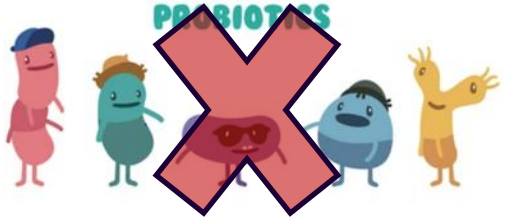
No Role for Probiotics in CDI



- PLACIDE trial (primary prevention)
  - 2981 hospitalized elderly pts in UK; probiotics (4 strains) vs placebo
  - No difference in rate of AAD or CDI occurrence between groups
- Recent systemwide multicenter US study (primary prevention)
  - A 13-month-long intervention of prescribing a 3-strain probiotic mixture to hospitalized pts age >50 years on systemic antibiotics showed no impact in CDI incidence
- PICO trial (secondary prevention)
  - Initial mild-to-moderate CDI on anti-CDI therapy randomized 33 pts to 4-strain probiotics or placebo; no difference in rates of CDI recurrence
- Not tightly regulated/not risk-free
  - Infections in immunocompromised pts
  - May impede normal recolonization after antibiotics
  - Expensive
- 2021 ACG Guidelines: Recommend AGAINST the use of probiotics for both primary and secondary prevention of CDI

AAD = antibiotic-associated diarrhea.

Allen SJ, et al. *Health Technol Assess*. 2013;17(57):1-140. Heil EL, et al. *Clin Infect Dis*. 2021;73(8):1330-1337. Barker AK, et al. *J Antimicrob Chemother*. 2017;72(11):3177-3180. Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

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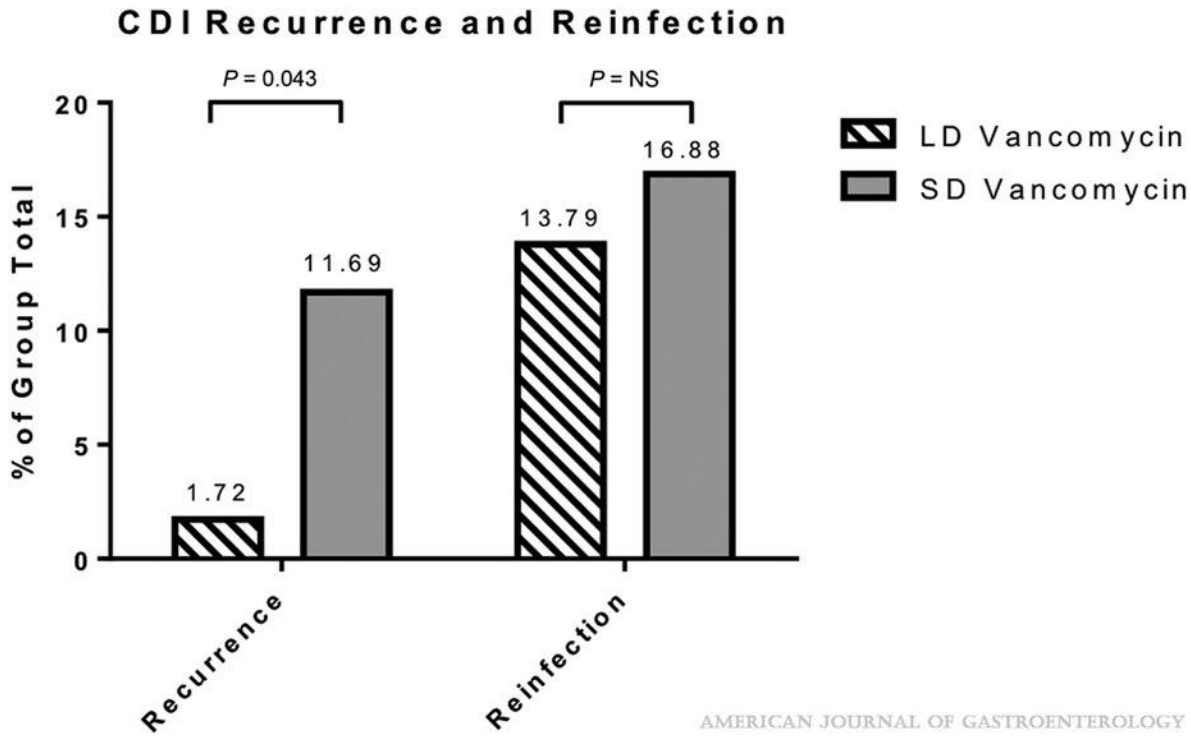
Long-Duration Vancomycin for CDI in IBD



Lei DK, et al. *Am J Gastroenterol*. 2019;114(12):1904-1908.

AIBD

Case 1

- 30 y/o F with moderate left-sided ulcerative colitis maintained on infliximab. She had been doing well but recently she is having increasing diarrhea and abdominal pain. Infliximab trough was checked and is 4.5, no abs and you send a *C. diff* PCR and it comes back positive

- What are the next steps? Any additional work up?

Case 1

- Would you consider any of the following?
  - Start vancomycin? (What dose/duration?)
  - Hold infliximab? (For how long?)
  - Start steroids? (What dose/duration?)
  - Dose escalated infliximab?
  - Offer FMT or an LBP? (Which one and why?)

Key Take-Aways

- CDI leads to significant morbidity in IBD patients and recurrence is 33% more common than in patients without IBD
- Initial therapy of CDI should be vancomycin 125 mg q6h x 10 days or fidaxomicin 200 mg q12h x 10 days
- Longer duration of vancomycin or fidaxomicin may be beneficial in recurrent CDI
- IBD therapy should not be held during anti-CDI therapy in the setting of disease flare, and escalation of therapy may be considered if there is no symptomatic improvement with treatment of CDI within 3-4 days

AIBD

Current and Emerging Agents for rCDI

Jordan Axelrad, MD, MPH, FACG, FCCF

Co-director, Inflammatory Bowel Disease Center, NYU Langone Health
Associate Professor of Medicine , NYU Grossman School of Medicine
New York, NY

Disclosures

- **Jordan Axelrad, MD, MPH, FACG, FCCF:** Research/grant support – BioFire, Biomerieux, Diagnostics, Genentech, Johnson & Johnson, Janssen, Takeda; consultant – AbbVie, Adiso, Biomerieux, Bristol-Meyers Squibb, Celltrion, Ferring, Johnson & Johnson, Pfizer, Takeda, Vedanta; advisory board – AbbVie, Abivax, Adiso, Biomerieux, Bristol-Meyers Squibb, Ferring, Fresenius Kabi, Johnson & Johnson, Pfizer, Vedanta

AIBD

Prevention of Recurrence: What Are the Options?

- Antibiotics (taper and prolonged suppressive therapy)
- Bezlotoxumab: NO LONGER AVAILABLE
- Fecal microbiota-based therapies
  - Fecal microbiota transplantation: INVESTIGATIONAL
  - Live biotherapeutic products: FDA-APPROVED DRUGS
    - Fecal microbiota live-jslm
    - Fecal microbiota spores live-brpk

Min H, et al. *J Microbiol Biotechnol.* 2025;35:e2410054.

AIBD

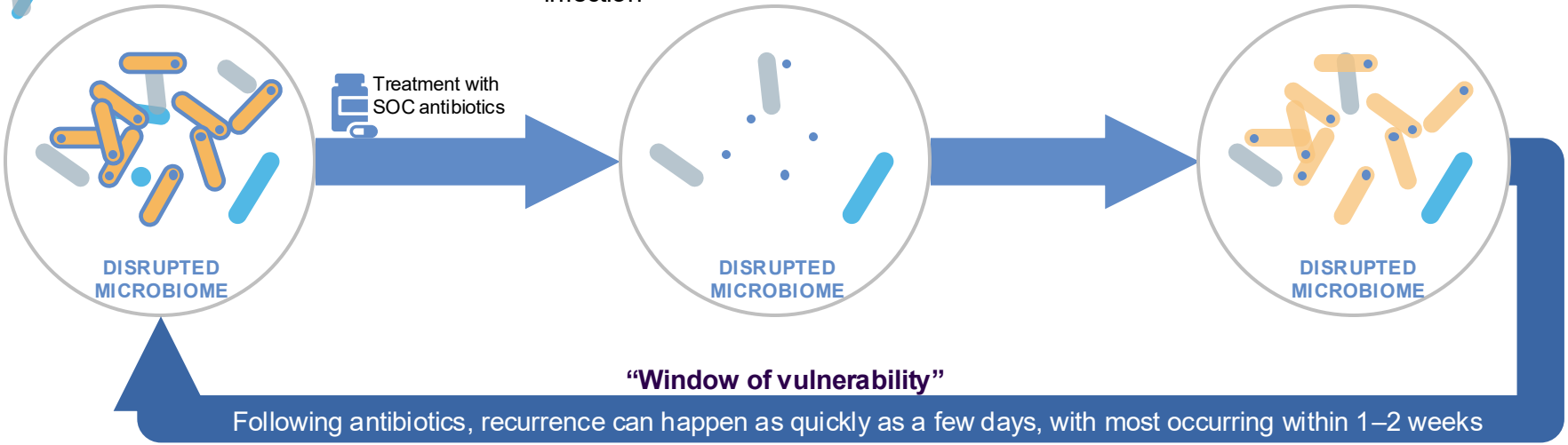
Antibiotics Do Not Address the Underlying Microbiome Disruption

Toxin-producing vegetative *C. difficile* causes symptoms

Antibiotic-resistant *C. difficile* spores
Other bacteria species

Antibiotics **resolve symptoms** by eliminating the vegetative *C. difficile* but **do not directly affect the *C. difficile* spores;** antibiotics also disrupt the microbiome, priming for recurrent infection

C. difficile spores germinate and grow without competition in the disrupted microbiome



SOC = standard of care.

McGovern BH, et al. *Clin Infect Dis.* 2021;72(12):2132-2140. Khanna S, et al. *Antibiotics (Basel).* 2022;11(9):1234. Louie TJ, et al. *Clin Infect Dis*. 2012;55 (suppl 2):S132-42. McDonald LC, et al. *Clin Infect Dis.* 2018; 66(7):e1-e48. Gerding D, et al. *Clin Infect Dis.* 2018;67(5):649-56; Abujamel T, et al. *PloS One.* 2013;8(10)e76269.

AIBD

AGA Clinical Practice Guideline on Fecal Microbiota-Based Therapies for Select GI Diseases

- Consider after the 2nd recurrence (3rd episode) or in select patients at high risk of recurrence or a morbid recurrence
- Careful consideration in patients who require frequent antibiotics or long-term antibiotic prophylaxis
- In severely immunocompromised adults, the AGA suggests against the use of fecal microbiota-based therapies
- Severely immunocompromised: Active cytotoxic, CAR T-cell therapy, neutropenia, severe primary immunodeficiency, advanced or untreated HIV infection (CD4 counts <200/mm3, AIDS-defining illness)

CAR = chimeric antigen receptor.

Peery AF, et al. *Gastroenterology*. 2024;166(3):409-434.

AIBD

Logistics of Microbial Therapies

- Performed after completion of a course of SOC antibiotics
- Suppressive antibiotics should be used to bridge SOC antibiotics to fecal microbiota-based therapy
- Antibiotics should be stopped 1-4 days prior to fecal microbiota-based therapy to allow adequate time for antibiotics to wash-out (bowel prep is a washout)
- Patients recognize the inherently unappealing nature of FMT, but they are nonetheless open to considering it as a treatment alternative for recurrent CDI, especially when recommended by a physician

Peery AF, et al. *Gastroenterology*. 2024;166(3):409-434. Zipursky JS, et al. *Clin Infect Dis*. 2012;55(12):1652-8.

AIBD

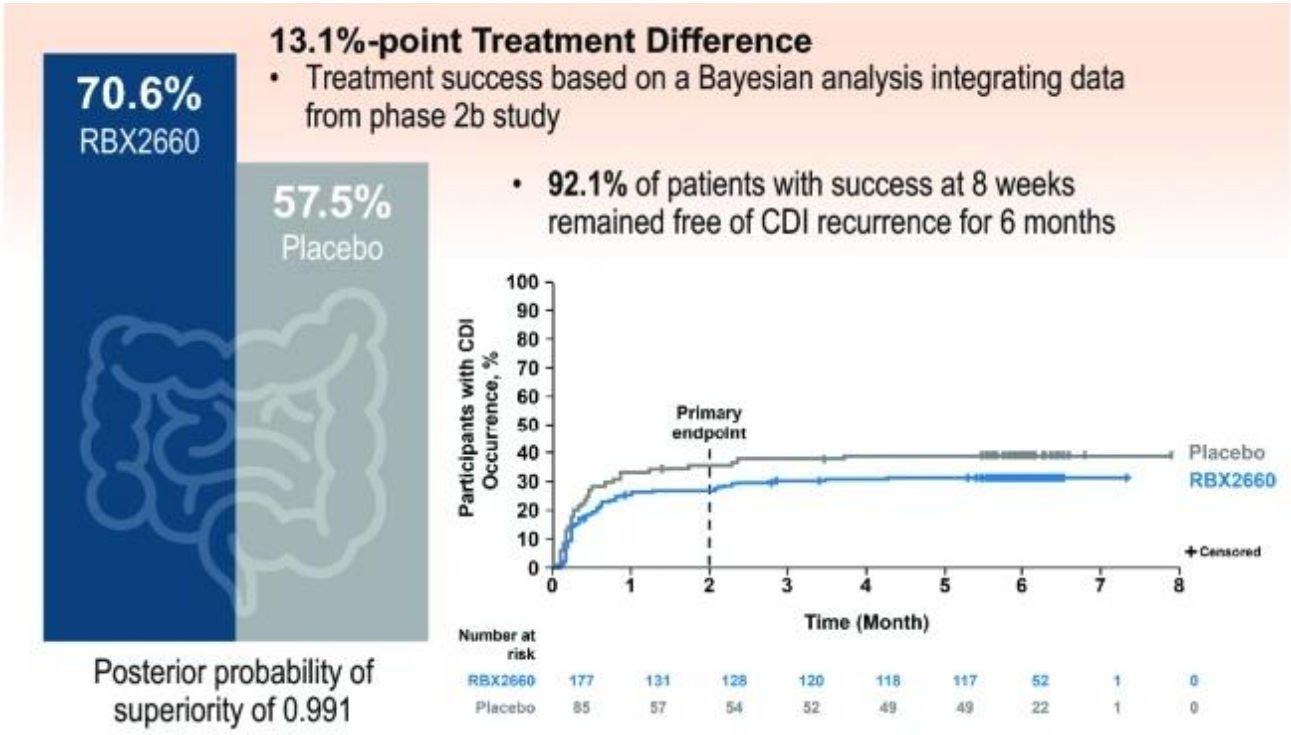
Fecal Microbiota, live-jslm

- First FDA-approved microbiome-based treatment to prevent recurrent *C. diff* infection
- Single dose of 150mL of liquid, full spectrum FM
- Enema (or colonoscopy)
- PUNCH trials (PCR+) via

Drugs@FDA: FDA-Approved Drugs. Accessed Nov 10, 2025. https://www.fda.gov/media/163587/download?attachment.

AIBD

Fecal Microbiota live-jslm in PUNCH CD3 for the Prevention of Recurrent *C. difficile* Infection

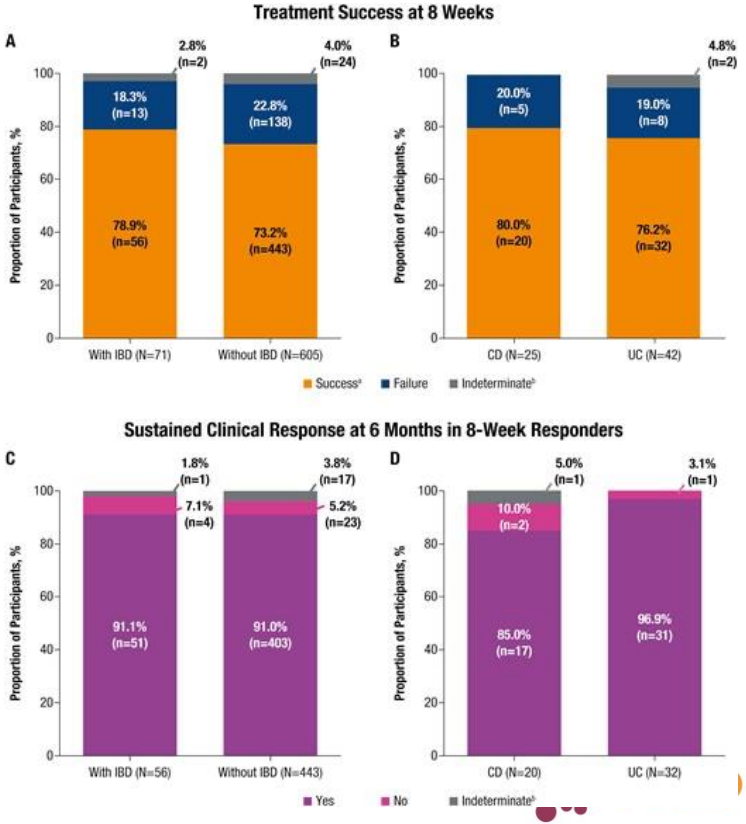


Feuerstadt P, et al. *N Engl J Med*. 2022;386(3):220-229. Khanna S, et al. *Drugs*. 2022;82(15):1527-1538. Feuerstadt P, et al. *Clin Infect Dis*. 2025;80(1):43-51.

AIBD

Efficacy of Fecal Microbiota, live-jslm, in Patients with IBD in PUNCH CD3-OLS

- Of 697 participants who received RBL, 74 had IBD (UC = 45; CD = 25; IBD-U = 4)
- Treatment success was achieved in 78.9% (56/71) of participants with IBD and 73.2% (443/605) without IBD
- Serious TEAEs reported in 1.4% (1/74) with IBD and 4.2% (26/623) without IBD within 8 weeks of RBL
- One participant with UC experienced a flare, classified as a serious TEAE, which was assessed as definitely related to a preexisting condition and possibly related to RBL



Allegretti JR, et al. *Inflamm Bowel Dis*. 2025;31(8):2112-2122.

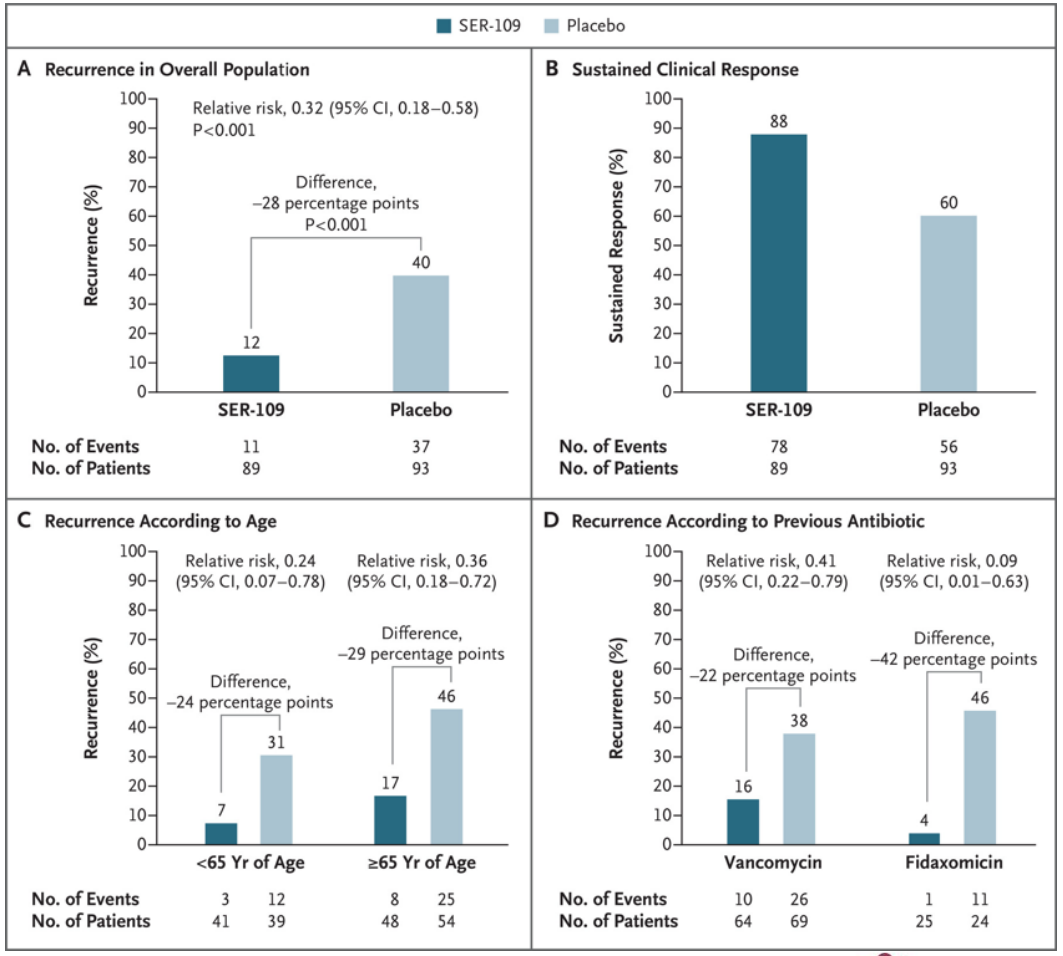
Fecal Microbiota Spores, live-brpk

- Second FDA approved microbiome-based treatment to prevent recurrent *C. diff* infection
- Live purified Firmicutes bacterial spores (4 oral capsules once daily for 3 days after bowel purge)
- ECOSPOR trials (toxin +)

Drugs@FDA: FDA-Approved Drugs. Accessed Nov 10, 2025. https://www.fda.gov/media/167579/download?attachment

AIBD

Fecal Microbiota Spores live-brpk in ECOSPOR III for Prevention of Recurrent *C. difficile* Infection



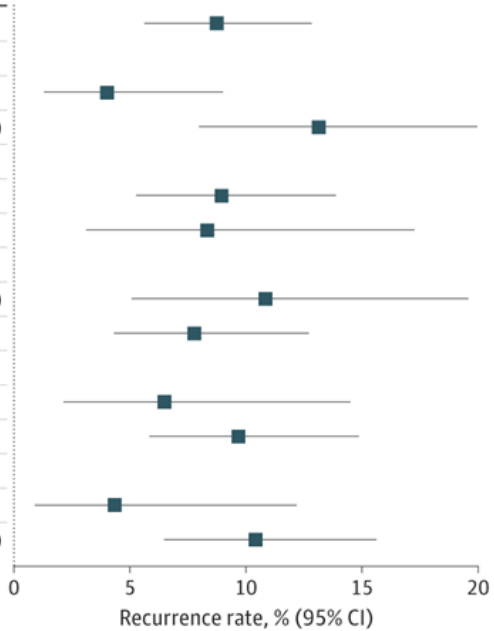
Feuerstadt P, et al. *N Engl J Med.* 2022;386(3):220-229.

AIBD

Fecal Microbiota Spores, live-brpk, in ECOSPOR IV for Prevention of Recurrent *C. difficile* Infection

- Rollover patients from ECOSPOR III who had rCDI by toxin EIA + patients with at least 1 rCDI by PCR or toxin EIA
- 23 (8.7%) had CDI recurrence by toxin EIA up to week 8

Baseline characteristic	Patients, No./ total No.	Recurrence rate, % (95% CI)
Overall	23/263	8.7 (5.6-12.8)
Age, y		
<65	5/126	4.0 (1.3-9.0)
≥65	18/137	13.1 (8.0-20.0)
Antibiotic regimen		
Vancomycin	17/191	8.9 (5.3-13.9)
Fidaxomicin	6/72	8.3 (3.1-17.3)
Sex		
Male	9/83	10.8 (5.1-19.6)
Female	14/180	7.8 (4.3-12.7)
Prior CDI episodes (including qualifying), No.		
2	5/77	6.5 (2.1-14.5)
≥3	18/186	9.7 (5.8-14.9)
Qualifying episode definition		
PCR alone	3/69	4.3 (0.9-12.2)
Toxin with or without PCR	20/192	10.4 (6.5-15.6)



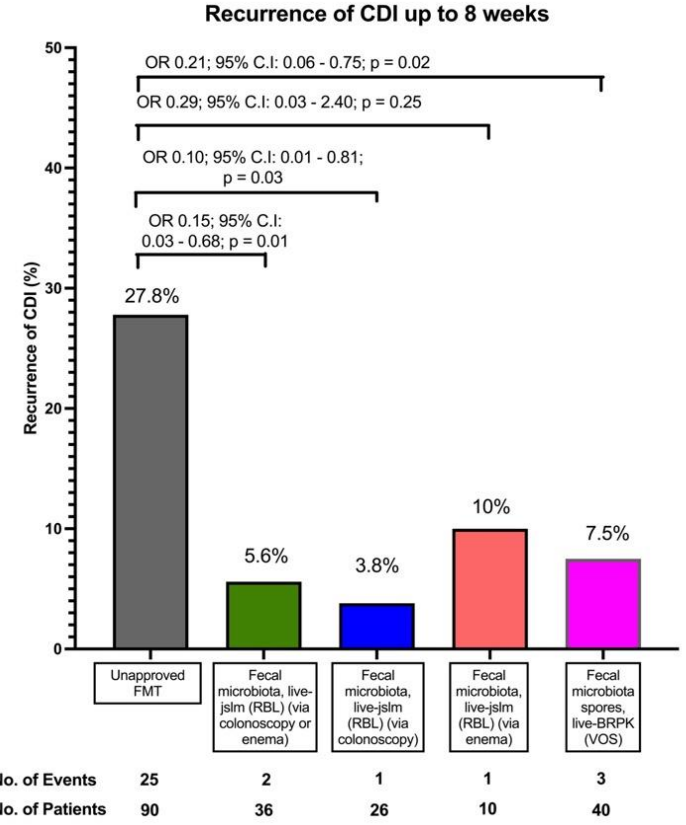
Sims MD, et al. *JAMA Netw Open*. 2023;6(2):e2255758.

AIBD

Fecal Microbiota-Based Therapies Compared to Unapproved FMT in Preventing Recurrent *C. difficile* Infection

- Patients treated with fecal microbiota, live-jslm (via colonoscopy) and fecal microbiota spores, live-brpk had significantly lower recurrent *C. difficile* infection compared to FMT

- Patients treated with fecal microbiota, live-jslm (via enema) had a non-significant trend for reduction in recurrent *C. difficile* infection

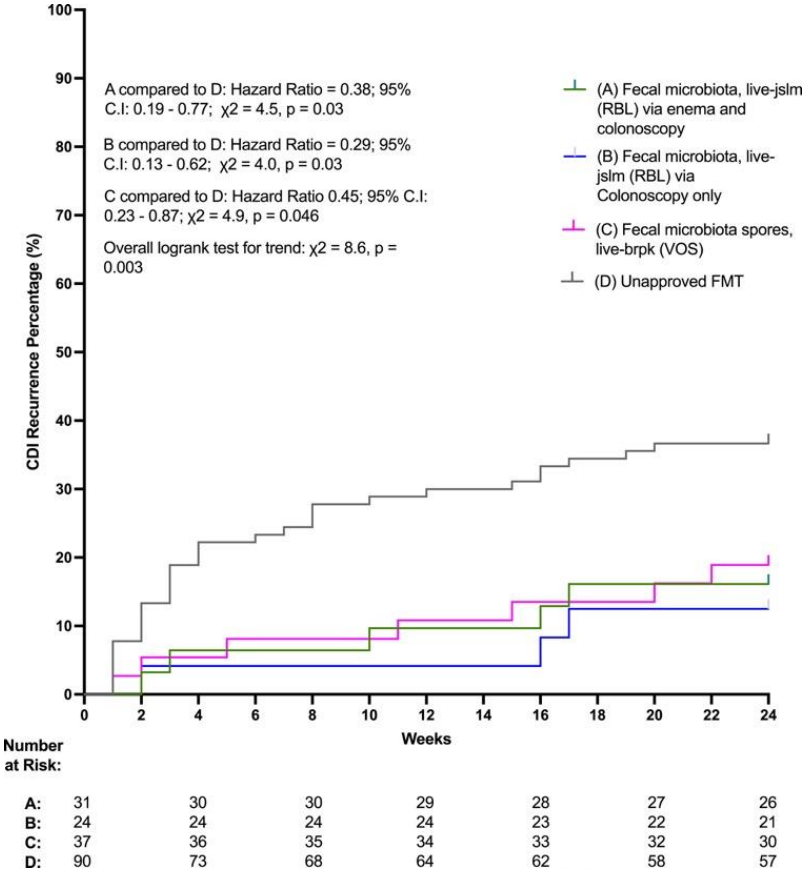


Nguyen L, et al. *Clin Gastroenterol Hepatol*. 2025:S1542-3565(25)00749-9.

Efficacy Outcomes Up to 24 Weeks

- Recurrence over time
  - **RBL (via enema and colonoscopy): 16.1%**
  - **RBL (via colonoscopy only): 12.5**
  - **VOS: 18.9%**
  - **FMT: 36.7%**

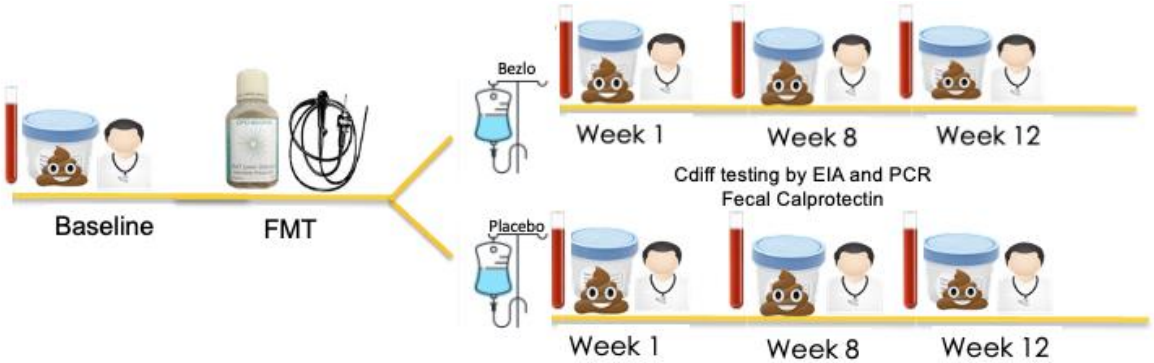
- Sustained clinical response
  - **RBL (via enema and colonoscopy): 89.7%**
  - **RBL (via colonoscopy only): 91.3%**
  - **VOS: 88.2%**
  - **FMT: 87.7%**



RBL = fecal microbiota, live-jslm; VOS = fecal microbiota spores, live-brpk.
Nguyen L, et al. *Clin Gastroenterol Hepatol*. 2025:S1542-3565(25)00749-9.

ICON-2: FMT and Bezlotoxumab Compared to FMT and Placebo for Patients with IBD and CDI

- Multicenter randomized placebo-controlled trial
- Patients with IBD and 2 or more episodes of CDI received a single colonoscopic FMT
- Patients were randomized 1:1 to receive a single bezlotoxumab infusion or placebo prior to the FMT
- *C. difficile* testing (GDH/EIA toxin and PCR) was performed pre-FMT, and at 1, 8, and 12 weeks post-FMT
- Fecal calprotectin and IBD clinical scores were also collected at every visit



Allegretti JR, Axelrad J, et al. *Am J Gastroenterol*. 2024;119(7):1433-1436.

Results

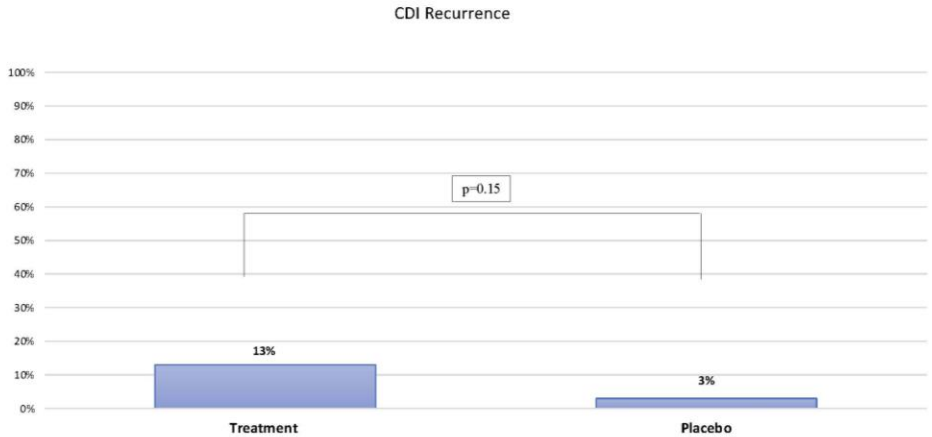
- 61 participants were enrolled
  - Median age of 38 (IQR 28,54)
  - 54% were male (n=33)
  - 20 with CD (mean HBI = 7.2)
  - 41 with UC (mean partial Mayo Score = 3.2).
  - Median baseline fecal calprotectin was 635 (IQR 150, 2615)
- 30 in the treatment arm and 31 in the placebo arm
- Notable differences between groups

Characteristic	Placebo (n=31)	Bezlotoxumab (n=30)
Female sex	14 (45%)	14 (47%)
Age, median (IQR)	34 (28, 54)	38.5 (29, 60)
Race		
White	27 (87%)	27 (90%)
Black	2 (6%)	1 (3%)
Asian	0 (0%)	1 (3%)
IBD type		
Crohn's disease	14 (45%)	6 (20%)
Ulcerative colitis	17 (55%)	24 (80%)
Qualifying CDI test type		
PCR only	15 (54%)	22 (73%)
GHD/EIA toxin	16 (52%)	8 (27%)
Number of prior CDI episodes		
2	18 (58%)	13 (43%)
3	8 (26%)	9 (30%)
4	5 (16%)	8 (27%)
Current Prednisone	8 (26%)	12 (40%)
Current advanced therapy		
None	13 (42%)	10 (33%)
Infliximab	4 (13%)	9 (30%)
Adalimumab	0 (0%)	4 (13%)
Vedolizumab or natalizumab	9 (29%)	3 (10%)
Ustekinumab	5 (16%)	4 (13%)
Number prior advanced therapies		
0	18 (58%)	8 (27%)
1	5 (16%)	13 (43%)
2	6 (19%)	5 (17%)
>2	2 (6%)	4 (13%)
Mayo endoscopic subscore		
0	7 (44%)	3 (13%)
1	2 (12%)	8 (35%)
2	4 (25%)	6 (26%)
3	3 (19%)	6 (26%)
SES-CD, median (IQR)	1.5 (0, 19)	19.5 (15, 23)
Baseline Fecal Calprotectin, median (IQR)	241 (100, 1615)	930 (241, 2950)
Baseline HBI, median (IQR)	6.5 (3, 11)	7 (2, 11)
Baseline Partial Mayo, median (IQR)	2 (0, 4)	3.5 (2, 5.5)

SES-CD = Simple Endoscopic Score for Crohn's Disease; IQR = interquartile range.
Allegretti JR, Axelrad J, et al. *Am J Gastroenterol*. 2024;119(7):1433-1436.

CDI Recurrence Rates

- 5 participants (8%) experienced a CDI recurrence with confirmed EIA toxin+ stool
  - 4 were in the treatment arm and 1 was in the placebo arm
- Participants in the treatment arm had a higher odds of CDI recurrence, though this was not statistically significant (OR 4.6, 95% CI 0.5-43.9)

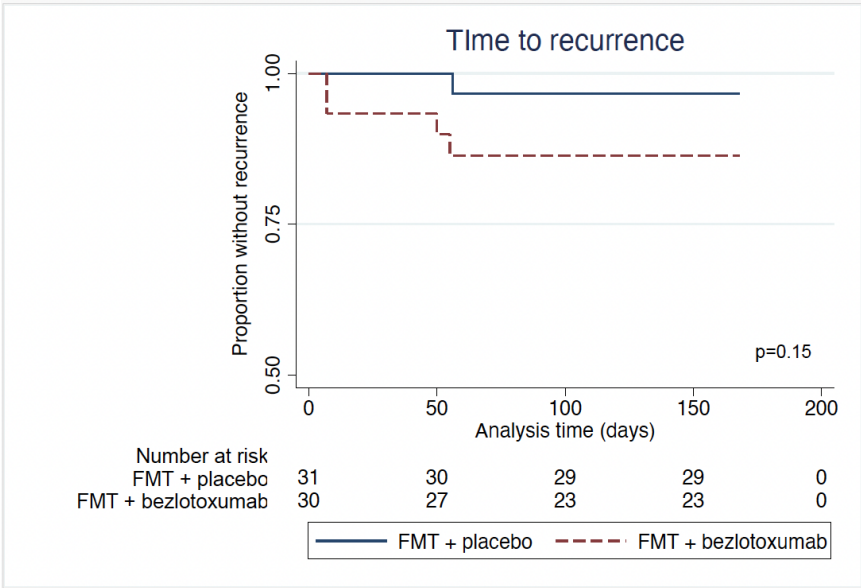


Allegretti JR, Axelrad J, et al. *Am J Gastroenterol*. 2024;119(7):1433-1436.

C. difficile De-Colonization in ICON-2

- More patients in the treatment arm were decolonized compared to placebo at week 1 (82% vs 68%, *p*=0.22) and at week 12 (83% vs 72%, *p*=0.34)

- Steroid use at the time of FMT led to a significant increased risk of ongoing colonization of *C. diff* at week 12 post FMT (OR: 4.90, 95% CI: 1.18-20.37, *p*=0.03)



Allegretti JR, Axelrad J, et al. *Am J Gastroenterol*. 2024;119(7):1433-1436.

Prevention of RECURRENCE: Suppressive and Prophylactic Vancomycin

- Long-term suppressive oral vancomycin may be used to prevent further recurrences in patients who are not candidates for microbial therapies
  - *Conditional recommendation, very low quality of evidence*
  - Suggested dose: 125 mg PO QD (may be increased to BID or TID if needed)

- Oral vancomycin prophylaxis (OVP) 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, low quality of evidence*
  - Age > 65 or immunocompromised and hospitalized with CDI in past 3 months

Allen SJ, et al. *Lancet*. 2013;382(9900):1249-1257. Heil EL, et al. C*lin Infect Dis*. 2021;73(8):1330-1337. Barker AK, et al. *J Antimicrob Chemother*. 2017;72(11):3177-3180. Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

AIBD

Case 2

- 91-year-old male with ulcerative proctitis managed with mesalamine suppositories as needed

- He had hip surgery this year and he was given an IV antibiotic pre-op. He developed diarrhea in the hospital and was *C. diff* PCR positive
- He was treated with vancomycin 125mg q6 hours for 10 days and did recover
- Two weeks later diarrhea resumed and he was again tested and was GDH/EIA toxin positive

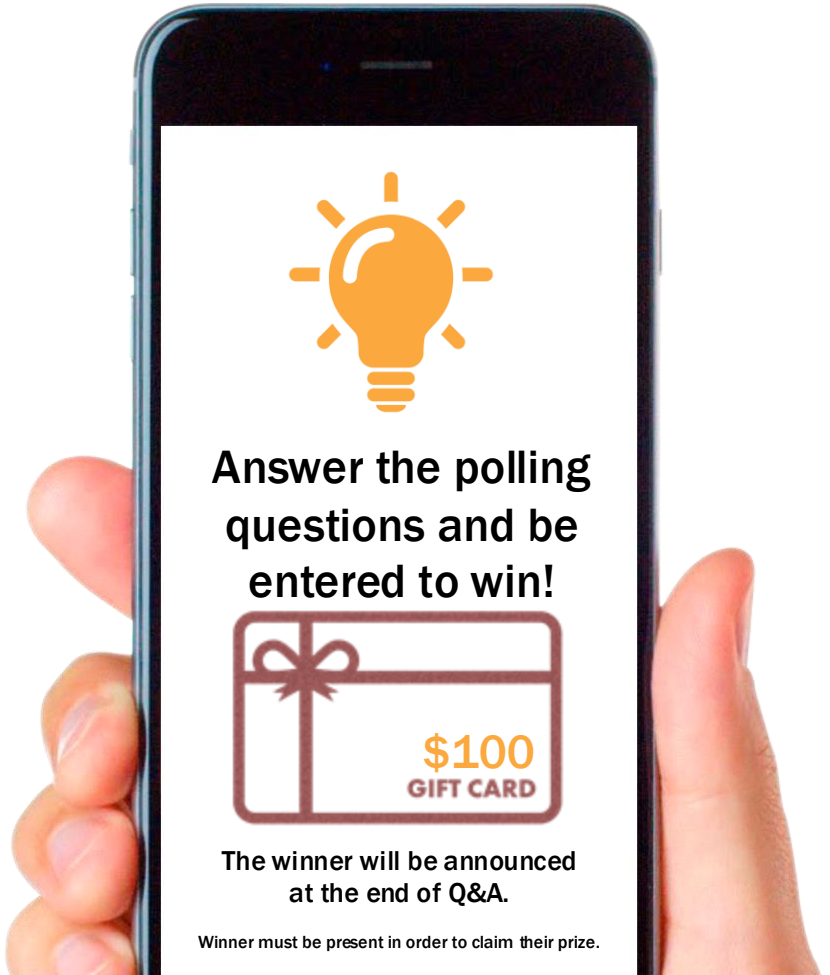
- What are the next steps?

Case 2

- What treatment course is most appropriate?
- What preventative strategy would you consider?
  - Bezlotoxumab
  - Standing vancomycin
  - FMT
  - LBP
- Are you concerned about his IBD worsening post-FMT?
- Would you escalate his IBD therapy? Are you concerned about his age?

Key Take-Aways

- FMT is safe and effective in patients with IBD and recurrent and should be offered
- Two safe and effective LBPs have been recently approved for the prevention of rCDI
  - Phase 3 trial data for fecal microbiota, live-jslm resulted in a treatment success rate of 70.6% compared to 57.5% in the placebo arm
  - Phase 3 trial data of fecal microbiota spore, live-brpk resulted in a treatment success rate of 88.9% compared to 58.7% in the placebo arm
  - Additional data on use of these agents specifically in IBD populations are needed



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