NEW YORK SOCIETY FOR GASTROENTEROLOGY & ENDOSCOPY
48th Annual
NEW YORK COURSE
December 12-13, 2024 • New York, NY

NYSGE
New York Society for Gastroenterology and Endoscopy

Updates in Fecal Transplants

48th Annual New York Course
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Division of Gastroenterology and Hepatology – Weill Cornell Medicine
December 12, 2024, NY, NY

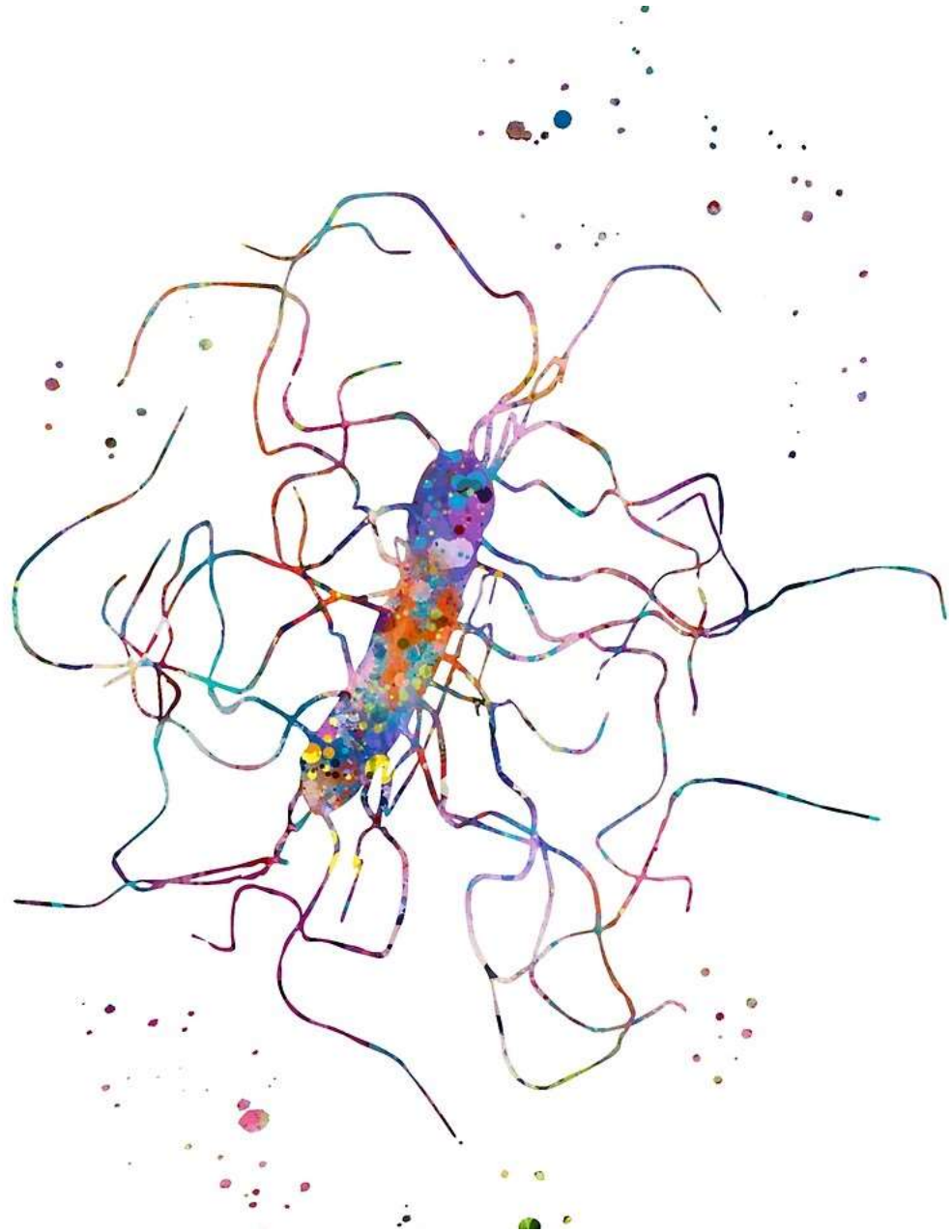
Disclosures

- *Grant/Research Support* from Ferring, and Artugen
- *Consultant* Seres and Ferring
- *Advisory Board* for Seres/Aimmune (Nestle), Ferring

- Carl V. Crawford Jr., MD, does intend to discuss either non–FDA-approved or investigational use for the following products/devices: agents used off-label or in clinical trials for *C. difficile* infection such as metronidazole, fecal microbiota transfer (FMT), fidaxomicin, bezlotoxumab, SER-109, RBX2660, and VE303

Objectives

- Background of *C. difficile* infection (CDI)
- Diagnostic strategies
- Management
- FMT vs Live Bacteriotherapeutic Products (LBP)
- Prevention



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A Brief History of *C. Difficile*

1893- first case of PMC

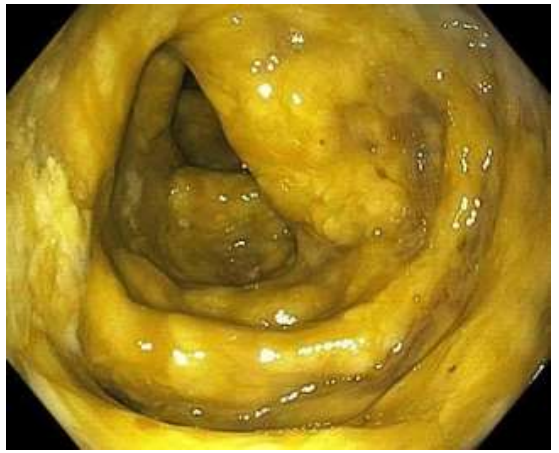
1935 *C. difficile* identified in the stool of neonates by Hall and O'Toole

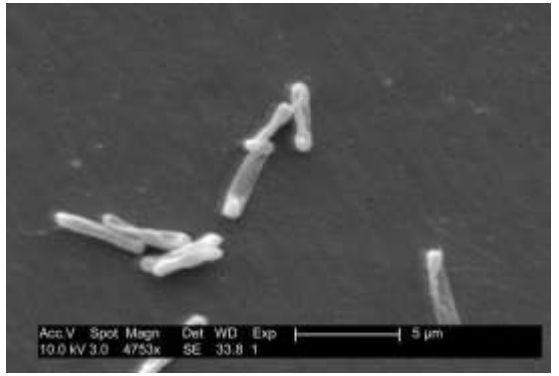
1950's *Staphylococcus aureus* (nosocomial) implicated in abx associated colitis and vancomycin becomes the standard of treatment

1974 : A toxin is implicated in clindamycin-induced PMC via endoscopy by Tedesco *et al*

1977 -1978: *C. difficile* identified as cause of PMC

1977: AGA recommends metronidazole 250 mg po QID over vancomycin for *C. difficile*-associated diarrhea (CDAD)





CDC/ Lois S. Wiggs - http://phil.cdc.gov/phil/

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A Brief History of *C. Difficile*

2001 – An outbreak in Canada

2005 – BI/NAPI/027 strain reported in NEJM

2010 SHEA/IDSA *C. difficile* guidelines

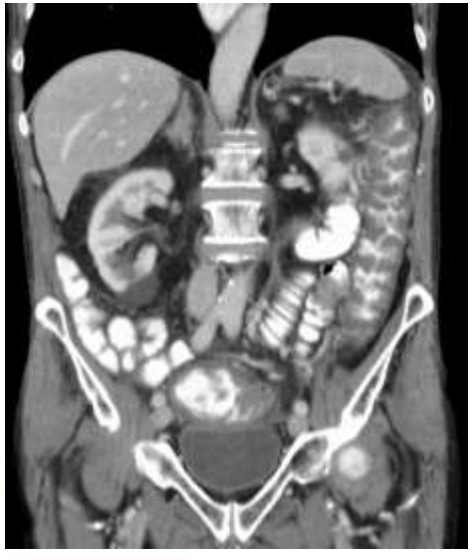
2010 Surpasses MRSA as top HAI

2011 Fidaxomicin approved by FDA

And called an Urgent Public Health Threat by CDC

Present → Importance of the Microbiome ie FMT

AND the immune system



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The microbiome

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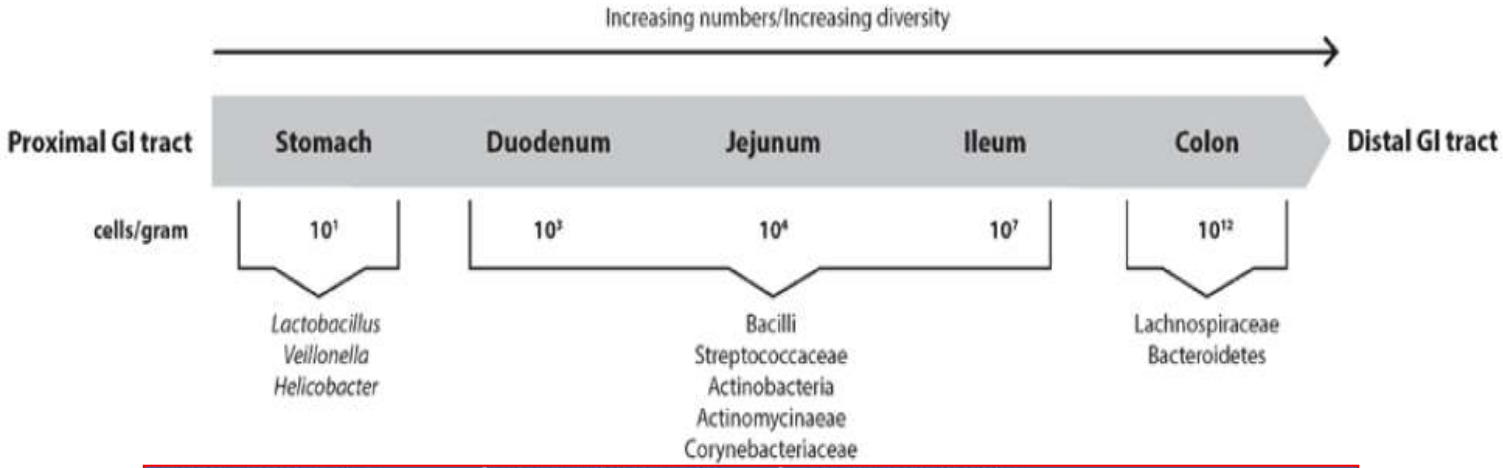
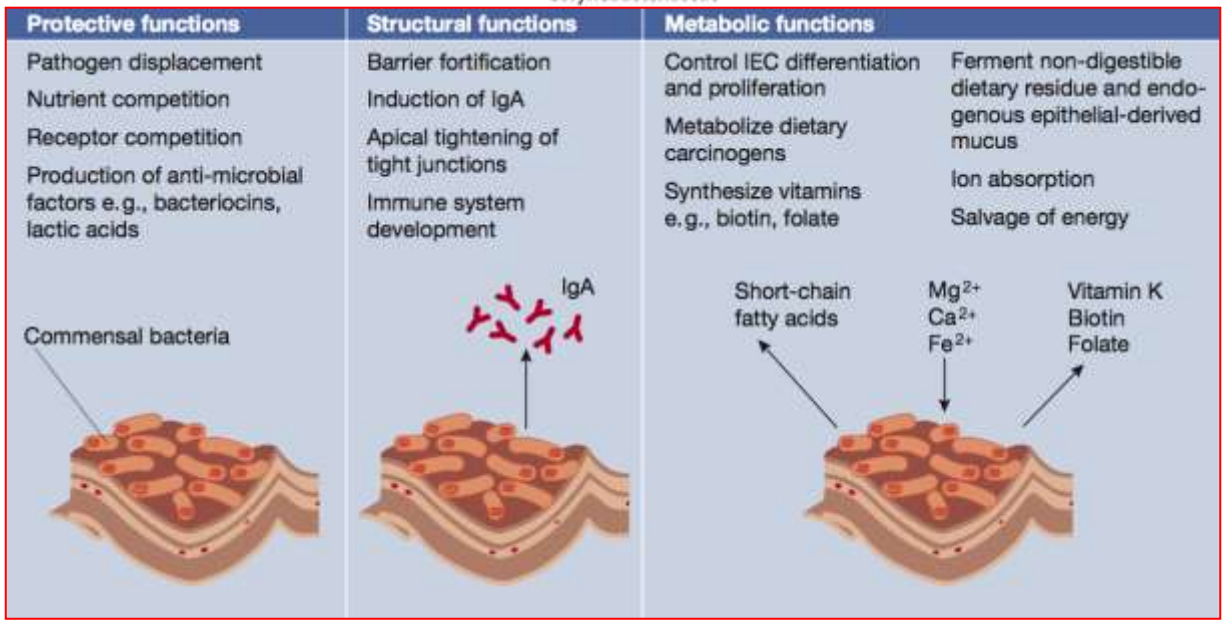
Role of the Gut Microbiome in Human Health

- Composition of the microbiota:
- Human body contains > 100 trillion organisms
- Highest density in GI tract
- Function of the microbiome:
- Key role in metabolism, regulation of gut barrier function, immunity
- Inhibit harmful pathogens through competitive exclusion (colonization resistance)
    - Anaerobic species in the colon produce bactericidal substances that protect host from colonization and infection

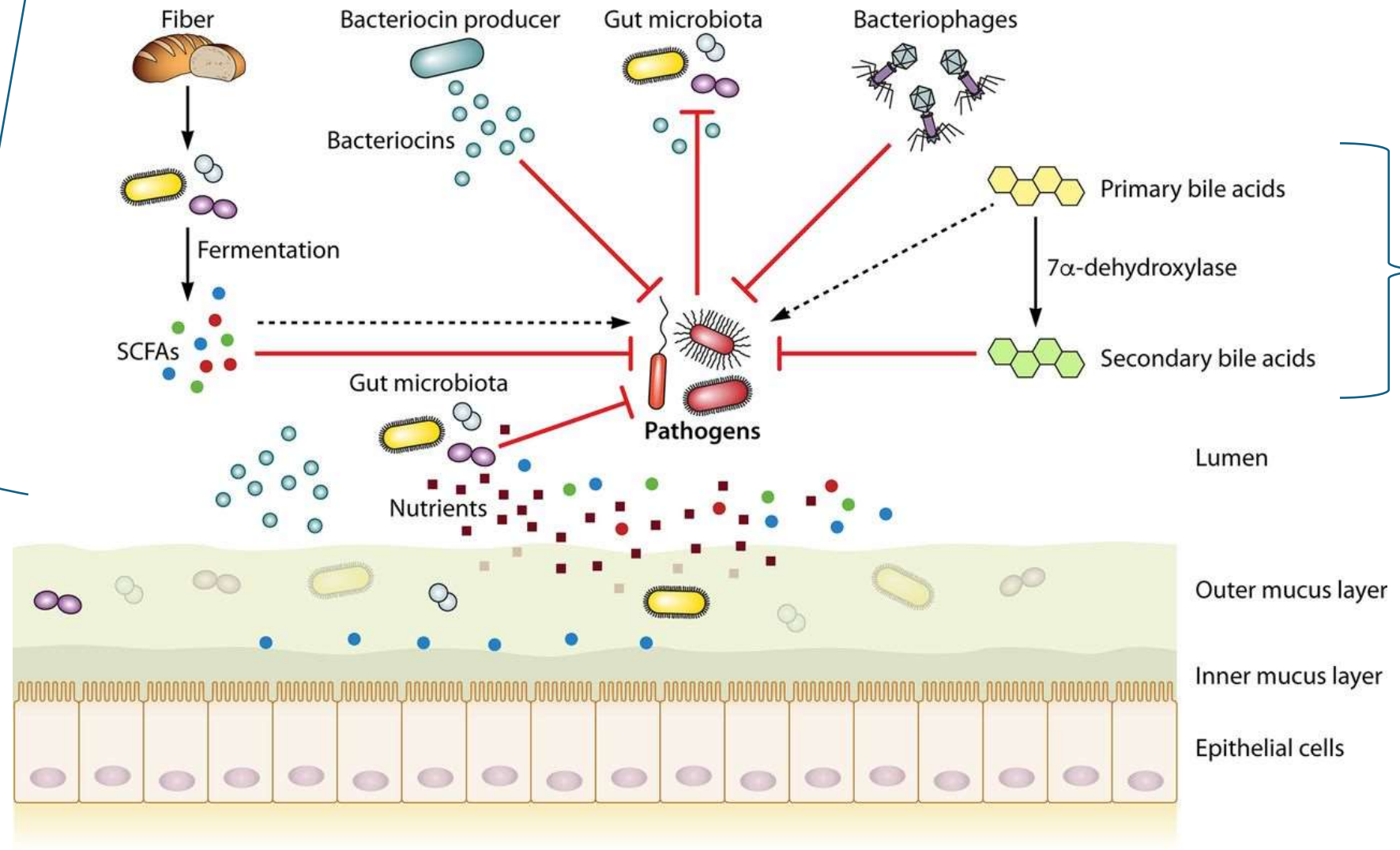




Khanna S, Pardi DS. Expert Rev Gastroenterol Hepatol. 2016;10:1145-1152.
O'Hara & Shanahan 2006. The gut as a forgotten organ. EMBO reports 7:685-693
Khan, I, et al. Front Cell Infect Microbiol. 2021;11:716299. doi: 10.3389/fcimb.2021.716299

Overview of microbiota-mediated colonization resistance

Bacteroidetes



Firmicutes (Bacilotta)

Ducarmon QR, et al. Microbiol Mole Biol Rev. 2019;83:e00007-19.

What is *C. difficile*?

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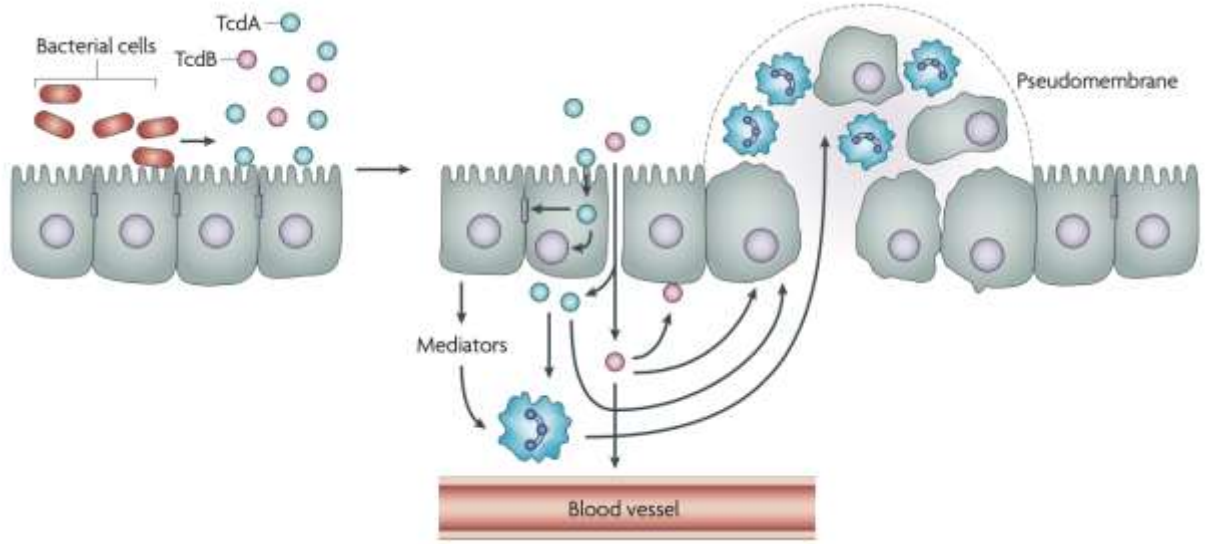
Basic facts about *C. difficile*

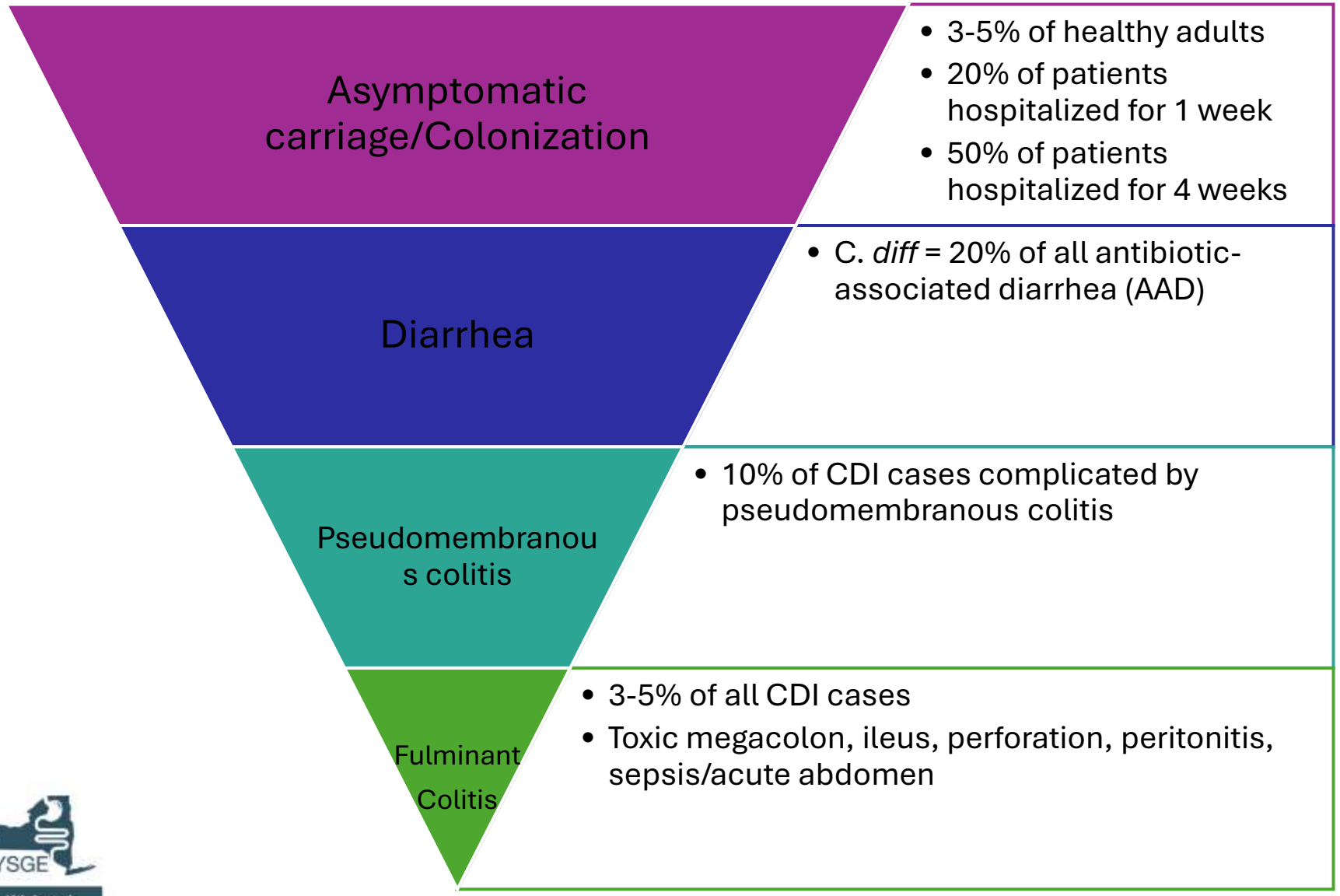
Gram positive, spore-forming, anaerobic bacillus

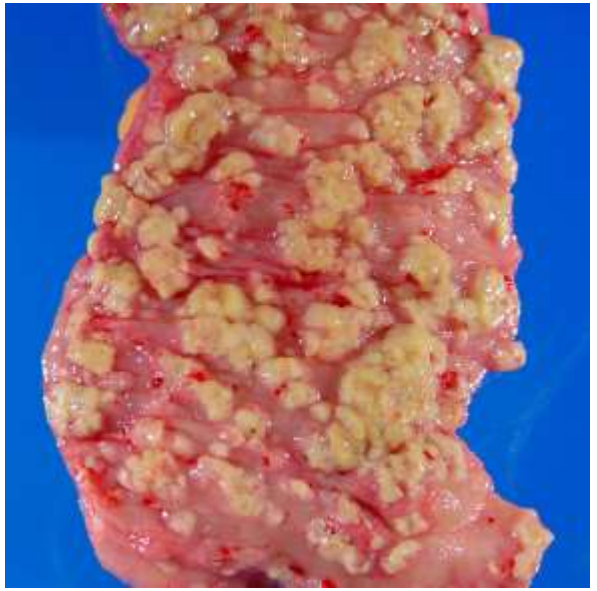
- **Spore Form:**
  - Survives up to 6 months
  - Resistant to disinfectants (e.g., heat, light, alcohol)
- **Vegetative Form**
  - Survives up to 6 hours
  - Easier to kill with most cleansers and oxygen
- Many Strains:
  - > 400 strains of *C. difficile*
  - Main virulence factors are toxins: A and B
  - Epidemic strains produce an additional "binary toxin"
  - Not all strains produce toxins and cause disease

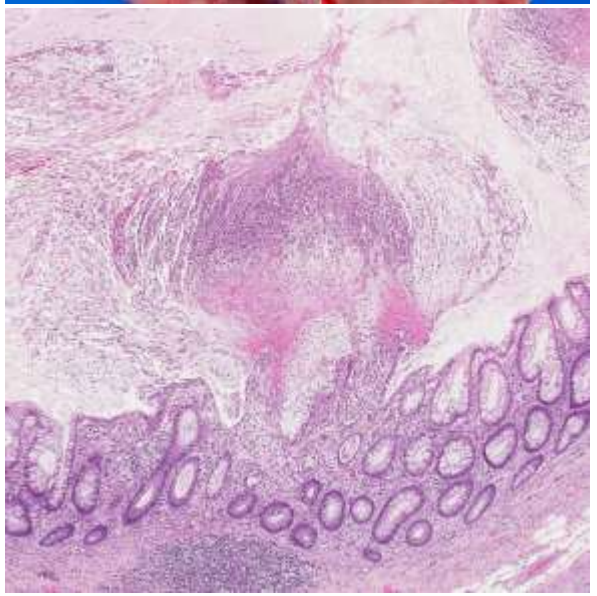


Rupnik M et al. *Nat Rev Microbiol*. 2009;7:526-536

C. diff causes a wide spectrum of disease







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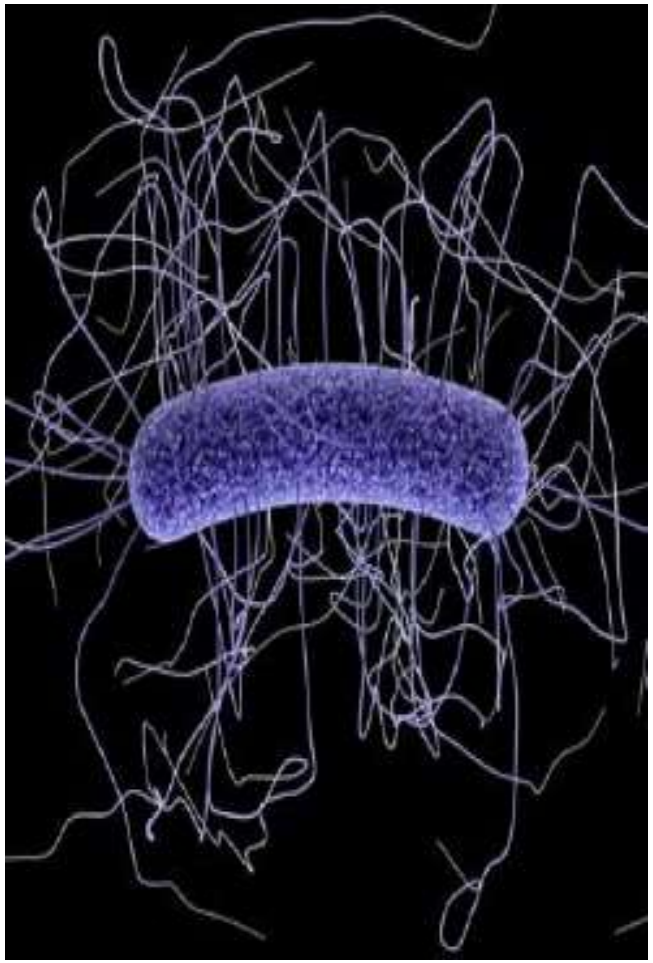
Impact of CDI

Epidemiology

- Approximately 450,000 new cases per year
- 83,000+ recurrences per year in the United States[1]
- 29,000 deaths[1] per year (~80 per day!)

- The most common healthcare-associated infection (HAE) in US hospitals
  - Excess healthcare costs for acute care facilities alone ~$4.8 Billion per year[2-4]



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1. Lessa FC et al. N Engl J Med. 2015;372:825-834. 2. Miller BA et al. *Infect Control Hosp Epidemiol*. 2011;32:387-390.
3. Magill SS et al. *N Engl J Med*. 2014;370:1198-1208. 4. Dubberke ER, Olsen MA. *Clin Infect Dis*. 2012;55(suppl 2):S88-S92.

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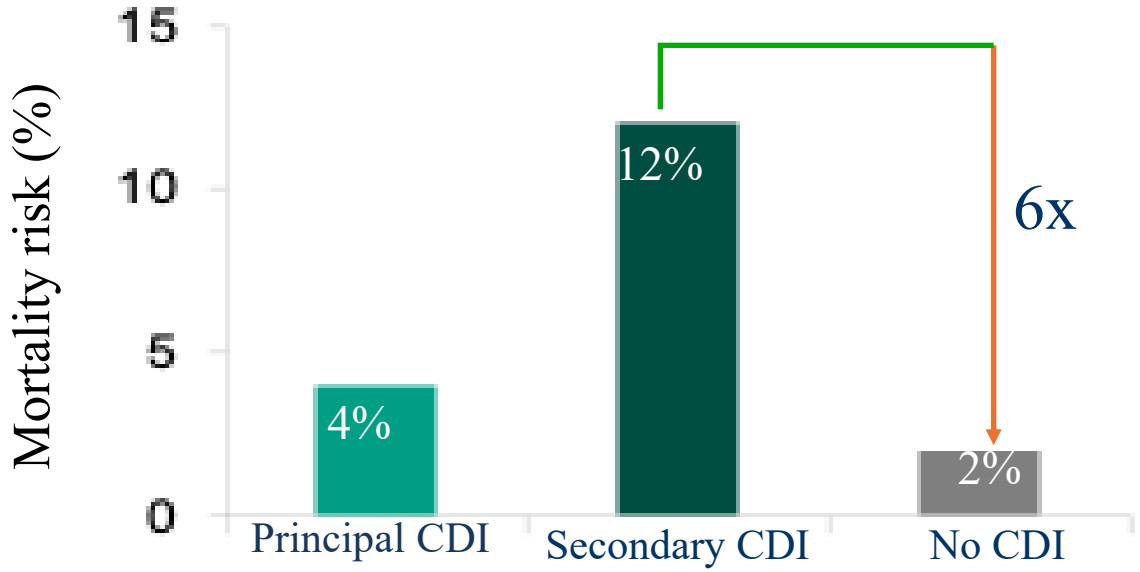
HCUP Analysis 2009: Mortality Risk in Patients With a Secondary Diagnosis of CDI vs No CDI

- Compared to those without CDI, patients with a secondary diagnosis of CDI were
  - 6-times more likely to die (12% vs 2%)
  - 4-times more likely to be at a major or extreme risk of dying (68% vs 17%)



Total Number of Stays

- Non-CDI: 39,098,400
- Principal CDI: 110,600
- Secondary CDI: 226,000

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Lucado J, Gould C, Elixhauser A. Healthcare Cost and Utilization Project (HCUP) Statistical Brief #124. January 2012. 2012;124:1–12.

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Risk Factors

Risk factors for *C. difficile* infection

Advanced age (> 65 years)

Younger people may also have *C difficile* infection

Medications (antibiotics and proton pump inhibitors)

Antibiotic use remains a key modifiable risk factor for infection

Comorbid conditions and immunosuppression

i.e., Inflammatory bowel disease, malignancy, chemotherapy use, kidney disease

Contact with active carriers or those actively infected

Prolonged length of hospital stay

Long-term care facility residence

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Adapted from Ayesha Angelito, RN

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Antibiotics increase the risk of CDI to varying degrees

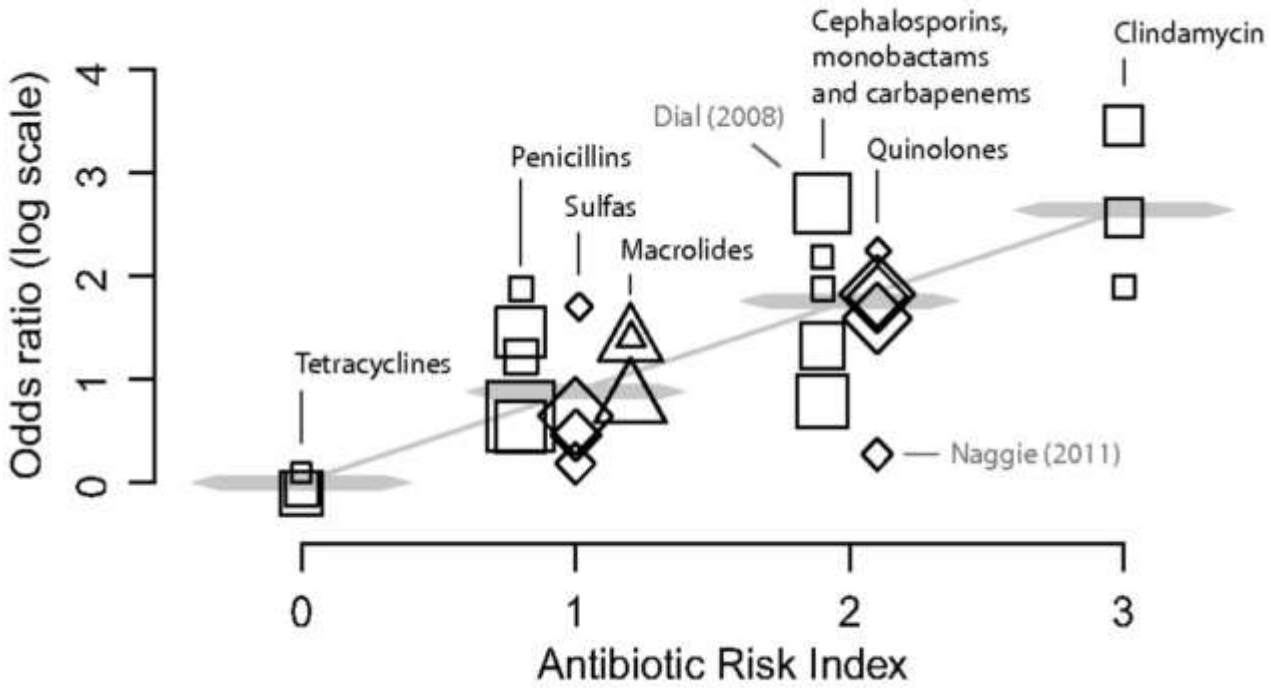

Fig 3 Linear association between a 4-point antibiotic risk index and community-associated CDI risks.

Highly	Moderate	Low
Clindamycin (OR=16.8)	Macrolides (OR=2.65)	Aminoglycosides
Fluoroquinolones (OR=5.50)	Other PCN (OR=2.71)	Metronidazole
2nd & 3rd gen Cephalosporins (OR=5.68)	SMX-TMP (OR=1.81)	Tetracyclines (OR=0.92)
Ampicillin	Sulfonamides	Tigecycline
Amoxicillin		Daptomycin

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Bouza E et al. *Med Clin North Am*. 2006;90:1141-1163; Loo VG et al. *N Engl J Med*. 2005;353:2442-2449; Brown K et al. *Antimicrob Agents Chemother*. 2013 May;57(5):2326-32.

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Treating CDI

Management principles of CDI

1. Stop all nonessential antimicrobials

2. Confirm presence of toxin-producing *C. difficile* in stool

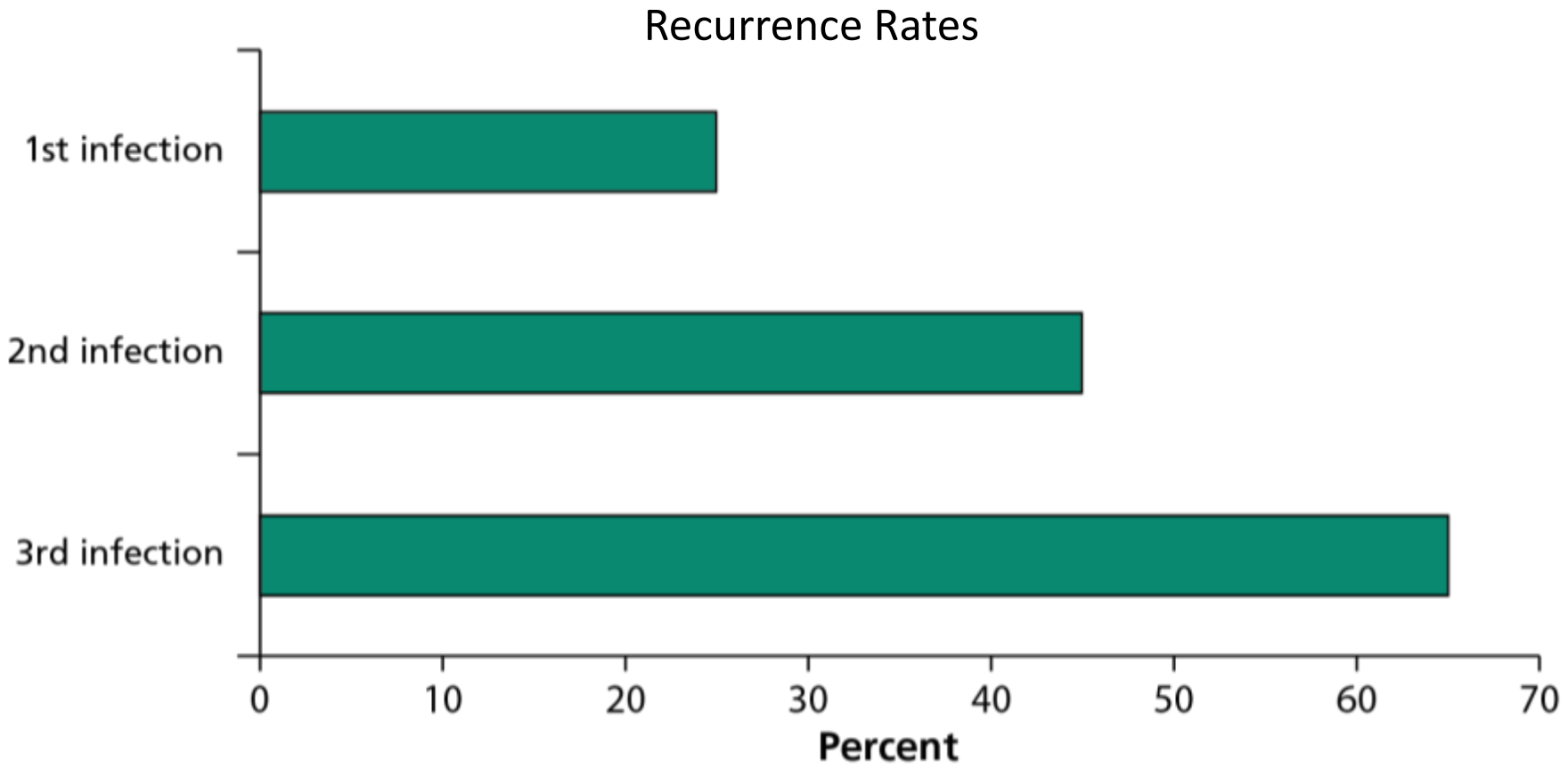
3. Treat with *C. difficile* directed antibiotics

   AVOID treating empirically unless: High clinical index of suspicion, Very sick patient, or Immediate testing will not be available

Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2021 Focused Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

Recurrent CDI

Risk of recurrent CDI increases with each episode



- Although some studies have looked at the causes, there is little consensus on causes of *C. difficile* recurrence
  - Persisting dysbiosis as the root cause?

Recurrent Infections

- One of the most challenging aspects of CDI is Recurrent CDI (rCDI):
  - Complete abatement of CDI symptoms after appropriate treatment, followed by subsequent reappearance of diarrhea and/or other symptoms after completion of that treatment

- Two forms of **RECURRENCES**:
  - **RELAPSE** infection with the same **ENDOGENOUS strain** *C. difficile*
  - **REINFECTION** infection with an **EXOGENOUS strain** of *C. difficile*
  - Relapse and reinfection difficult to distinguish but treated the same

- The treatment for CDI is also a simultaneous and major risk factor for its recurrence:
  - Recurrences are associated with increase mortality, morbidity, length of stay, healthcare utilization and costs; also puts additional strain on the patients' and family's QOL

1. Walters BA et al. *Gut*. 1983;24:206. 2. Young G, McDonald M. *Gastroenterology*. 1986;90:1098. 3. Wilcox MH et al. *J Hosp Infect*. 1998;38:93. 4 LaBarbera FD et al. *J Community Hosp Intern Med Perspect*. 2015;5:26-33. 5. Ghantoji SS et al. *J Hosp Infect*. 2010;74:309-318. 6. Rohlke F, Stollman N. *Therap Adv Gastroenterol*. 2012;5:403-420.

Risk factors for recurrent *C. difficile* infection

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Comorbid conditions and immunosuppression

ie, inflammatory bowel disease, malignancy, chemotherapy use, kidney disease

Contact with active carriers or those actively infected

Prolonged length of hospital stay

Long-term care facility residence

Prior *C difficile* infection

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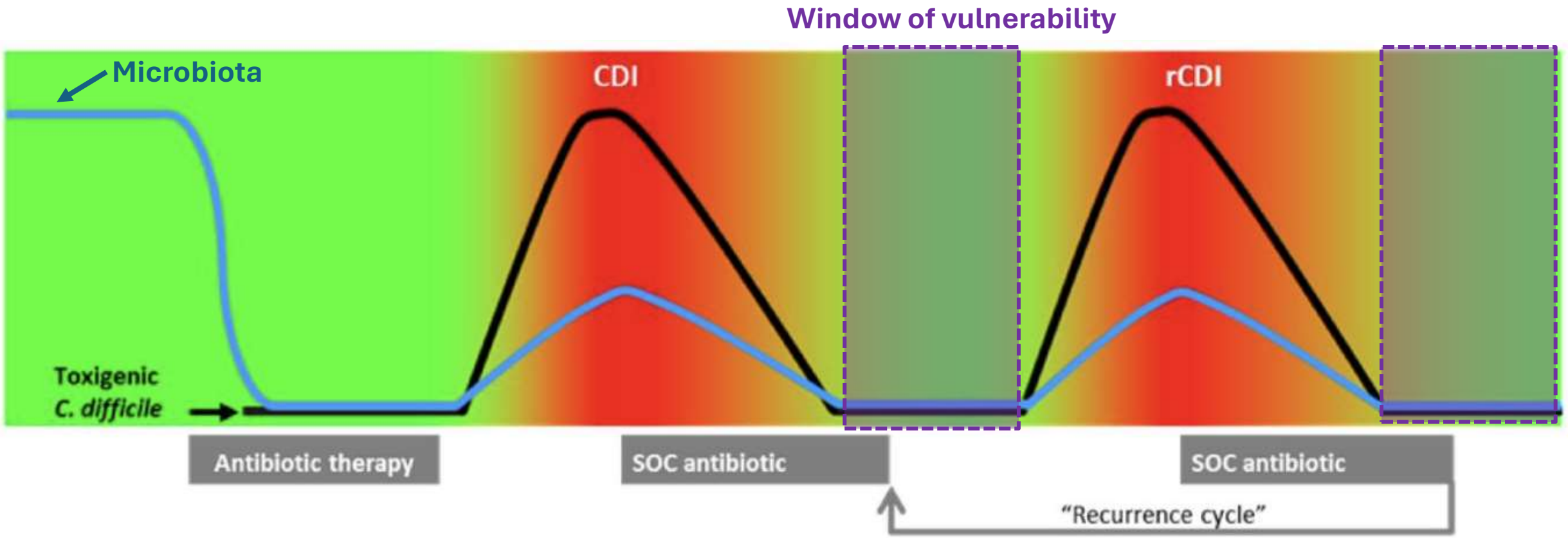
Antibiotic therapy and "the window of vulnerability" for *C. difficile* recurrence



Warn et al Antimicrobial Agents and Chemo Nov 2016 vol 60 no 11

IDSA 2021 Update for Recurrent CDI Infection: Current Recommendations

Clinical Definition	Recommended Treatment

First recurrence	• **Preferred: Fidaxomicin 200 mg PO BID x 10 days OR BID x 5 days then QOD x 20 days (Both 20 pill regimens)**
	• Alternatives:
	  • Vancomycin PO in tapered and pulsed regimen
	  • Vancomycin 125 mg PO QID x 10 days (if metronidazole was used first)
	• Adjunctive treatment:
	  • Bezlotoxumab 10 mg/kg IV x 1 during administration of SOC antibiotics

Second or more recurrence	• Fidaxomicin (same two regimen options as above) • Vancomycin PO in tapered and pulsed regimen • Vancomycin 125 mg PO QID x 10 days followed by rifaximin 400 mg 3 times daily for 20 days • Fecal microbiota transplantation (typically for ≥3 CDI episodes)

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Johnson S et al. *Clin Infect Dis.* 2021;73(5):e1029–44

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Fecal Microbiota Transplant (FMT)
vs
Live Bacteriotherapeutic Products (LBP)

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Brief History of FMT

Ge Hong describes treatment of diarrhea with fecal water

4th Century AD China

"Transfaunation" practices documented in animal husbandry

17th Century

Dr. Borody describes use of bacteriotherapy for common GI diseases

1980s US

First FMT RCT and US guideline recommendation for treatment of recurrent CDI.

2013

16th Century China

Li Shizhen describes treatment of >20 conditions with fecal water or fermented stool

1958 US

Dr. Eisman publishes successful treatment of pseudomembranous colitis using fecal water enema

2000s US

Dr. Khoruts FMT clinical trials, demonstrates engraftment of donor FMT in CDI patients.

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Courtesy slide of Charlie Buffie, MD PhD

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Donor Screening Exclusion Criteria

- Active infection
- Exposure to antibiotics in prior 3 months
- Recent travel with exposure to epidemic diarrheal disease
- Significant GI history
- Autoimmune or significant allergy history
- Other considerations: CJD, Diabetes, metabolic syndrome, Obesity, Chronic pain syndrome, exposure to medications that may alter the gut microbiome

- Stool testing- Bacteria, viruses, parasites, multi-drug resistant organisms
- Blood testing – Bacteria, Viruses

Delivery Methods

- GI Route: EGD, Nasogastric, Nasojejunal, Nasoduodenal tube, Lower GI (Colonoscopy, Retention enema), Oral capsule
  - EGD or enteroscopy – For patients with severe colitis or can't prep
    - **Suggest Reglan**
  - Colonoscopy – Superiority in recolonizing the entire colon with favorable bacteria
  - Oral Capsule – Less invasive and high acceptance rate from patients

- *FMT may be a one-time therapy or multiple intensive doses- based on patient's condition and response to treatment and efficacy of the therapy

Nursing Responsibilities Pre-Procedure

- Complete patient assessment (medical & surgical history, NPO status, Escort availability)
- Reconcile patient medications
- Confirm that patient took the appropriate preparation (for colonoscopy mode of delivery) **and/or Loperamide**
- Patient need to be off antibiotics for 72 hours prior to procedure
- Verify consent for procedure
- As per Institutional policy, anesthesia team to assess patient
- **Confirm that you have the donated stool** for FMT and plan for thawing

Nursing Shared Responsibilities

Fresh Donor

- Mix 75-100 grams of stool with 150ml non-bacteriostatic saline for goal of 250ml somewhere safe
- Blend
- Filter using gauze
- Inf hours

Frozen FMT

- Inspect label for expiration date
- Confirm Lot number, tracking and storage (ie. -80°C etc.)
- Thawed in 37°C water bath vs room temp
- **Avoid** repetitive thawing and refreezing!!
  - $500-$9,487
- Infuse within 6 hours after thawing
- Do not reuse

Nursing Responsibilities

- Determine that FMT is properly thawed before administration
- Check FMT Lot number
- Patient monitoring by anesthesia team
- Appropriate PPE worn by staff in room (gown, gloves, mask, face shield)
- Prepare FMT in Three to FIVE 60cc syringes
- Position patient according to mode of delivery
- Administer FMT when desired location is reached (i.e. terminal ileum/ ascending colon/whole colon)
- For colonoscopy mode of administration, MD suctions residual stool and fluid on the way to cecum
- **Make sure they don't suction the material on the way out!!!!**

Potential Post-procedural Adverse Events

Minor

- Nausea
- Vomiting
- Abdominal discomfort
- Bloating
- Flatulence
- Diarrhea / Constipation
- Low-grade Fever

Severe

- Sedation related
- Endoscopy related
- Infection ± sepsis
- Inflammatory bowel disease flare
- Post infectious irritable bowel syndrome

Adverse events reported after FMT

Long-Term Effects of Fecal Transplant are Unknown

Transient constipation, diarrhea, discomfort	New medical conditions reported: single case reports	Infectious transmission
▪ Post-infectious irritable bowel syndrome	▪ Peripheral neuropathy ▪ Sjogren syndrome ▪ Idiopathic thrombocytopenic purpura ▪ Rheumatoid arthritis ▪ Obesity ▪ Microscopic colitis	▪ ESBL-producing *E coli* ▪ Shiga-toxin-producing *E coli*

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- ESBL, extended spectrum beta-lactamase; *E coli, Escherichia coli*.
- Brandt LJ, et al, Am J Gastroenterol. 2012;107:1079-87; Saha S, et al. Gastroenterology. 2021;160:1961-1969.e3.

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ACG Guideline 2021 Guidelines

Indications for FMT in CDI

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)

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)

We suggest FMT be considered for patients with severe or fulminant CDI refractory to antimicrobial therapy, particularly, when patients are deemed poor surgical candidates

(Strong recommendation, low quality of evidence)

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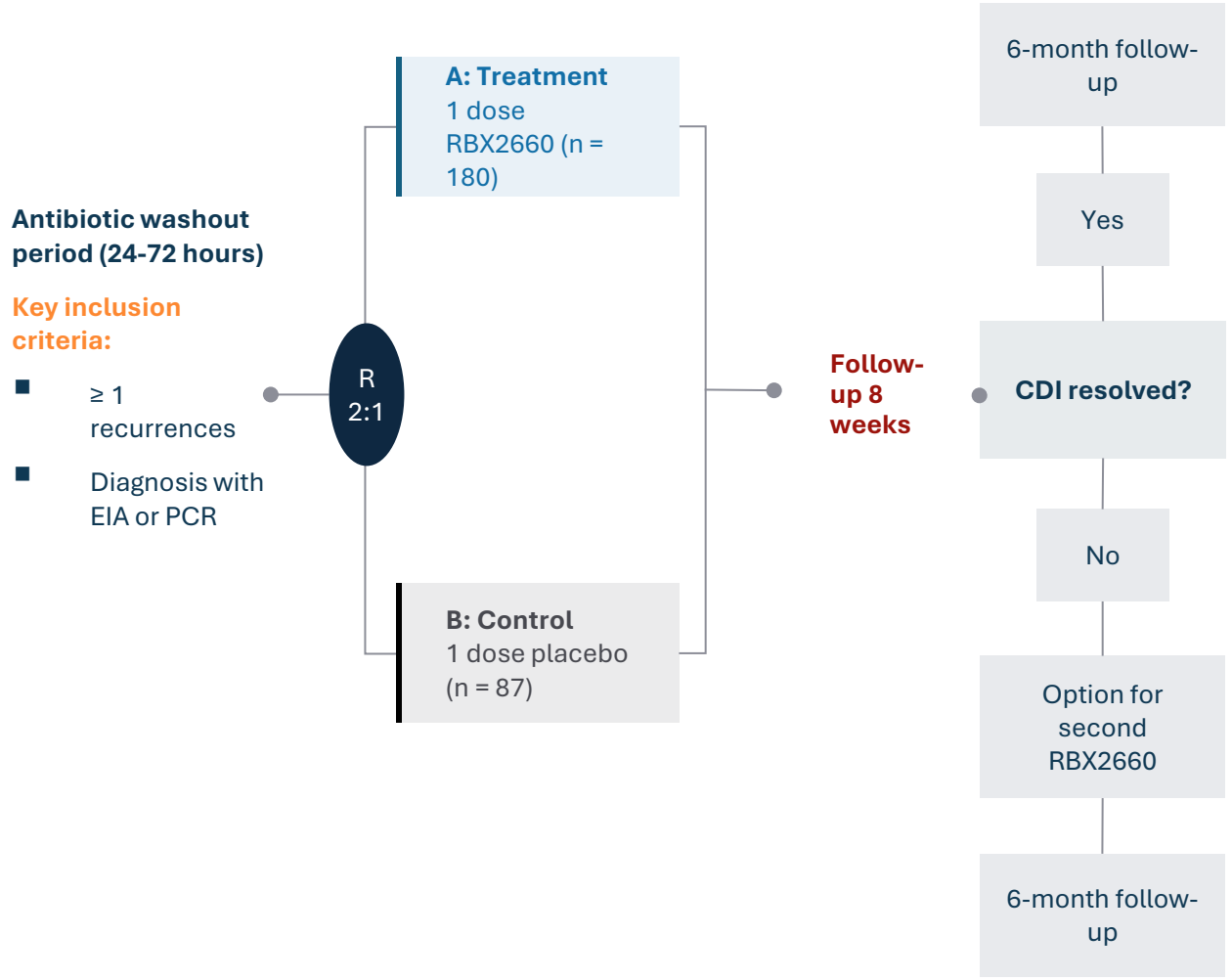
- Kelly CR, et al. Am J Gastroenterol. 2021;116:1124-1147.

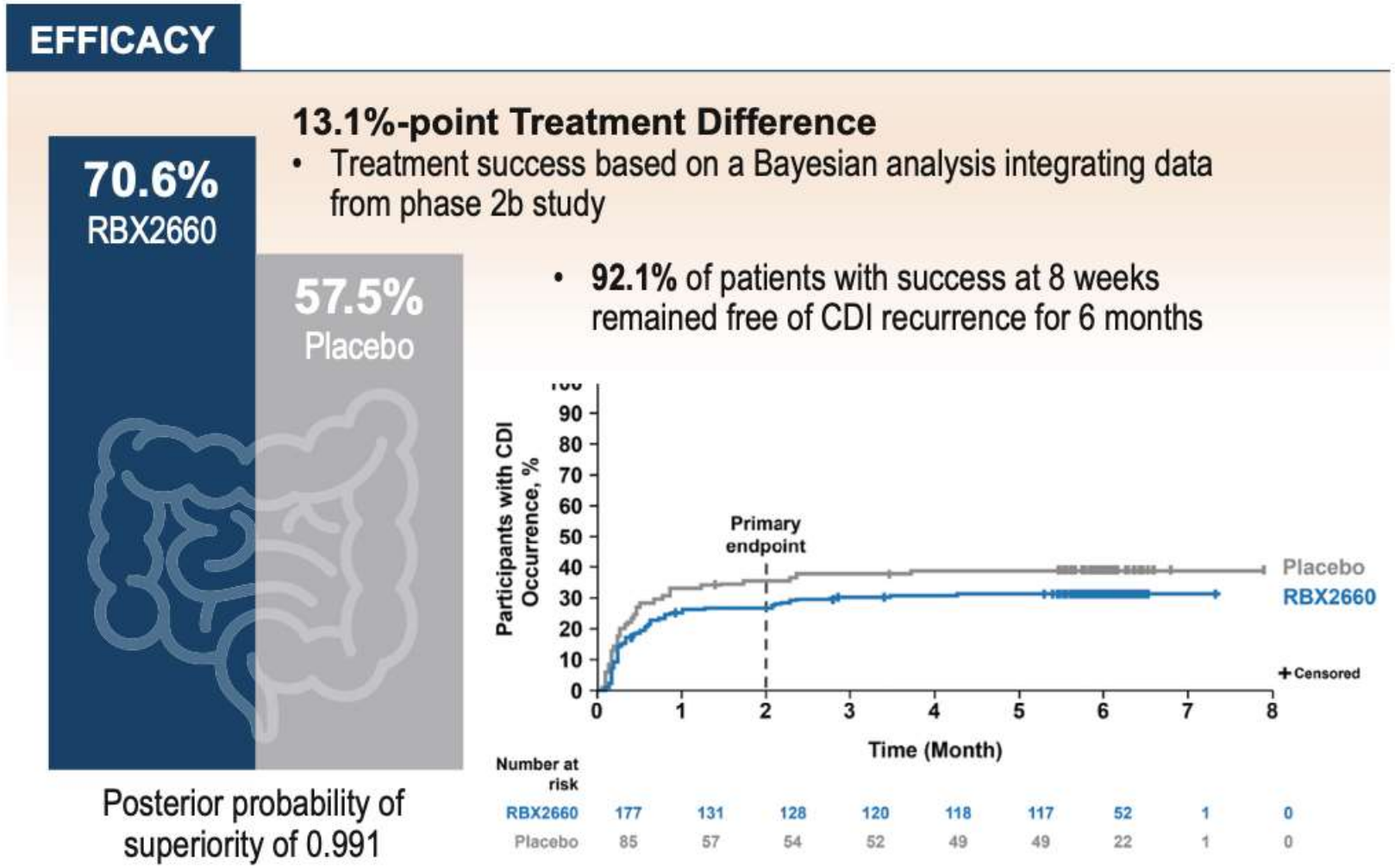
RBX2660 (Full-spectrum) – PUNCH Study

- **Analysis**: 5 prospective clinical trials (n = 723)
  - 3 Phase II and 2 Phase III
- **Intervention**: 150 ml, rectally instilled suspension of human sourced intestinal microbiota (RBX2660)
- **Study population**: ≥ 1 recurrence of CDI and completion of ≥1 standard-of-care (SoC) oral antibiotic course, or ≥2 episodes of severe CDI requiring hospitalization
- **Primary outcome**: Absence of recurrent CDI at 8 weeks following treatment



1. Bancke L, Su X. Presented at: IDWeek 2021;
2. Microbiota Restoration Therapy for Recurrent CDI (PUNCHCD3). https://clinicaltrials.gov/ct2/show/NCT03244644

Punch CD3 efficacy and durability results



FDA approved:

1st recurrence or more

Khanna et al. Drugs (2022) 82:1527–1538

How does RBX2660 differ from FMT?

Measured potency Consistent number of colony-forming units (CFU) in each dose	**CFU GUARANTEED** per 150-mL dose
Live fecal microbes Composition includes *Bacteroidia* and *Clostridia* classes	15 billion to 7.5 trillion CFU
Quality Control *Bacteroides* (fragile; viability can be profoundly affected by external forces during processing)	>15 million CFU

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Khanna et al. Drugs (2022) 82:1527–1538
Blount et al. Frontiers in Microbiol. January 2022

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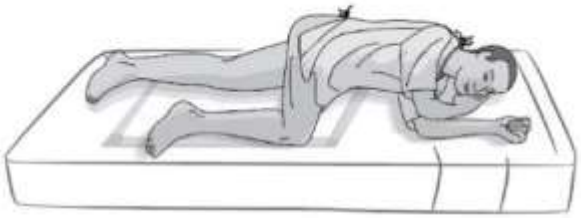
Difference in delivery from FMT?



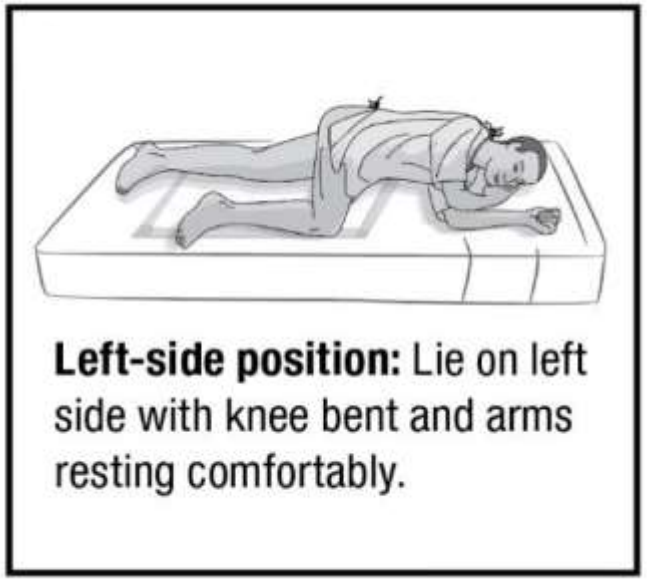
Left-side position: Lie on left side with knee bent and arms resting comfortably.

OR

Knee-chest position: Kneel, then lower head and chest forward until left side of face is resting on surface with left arm folded comfortably.

Package insert FDA approved

Difference in delivery from traditional FMT?



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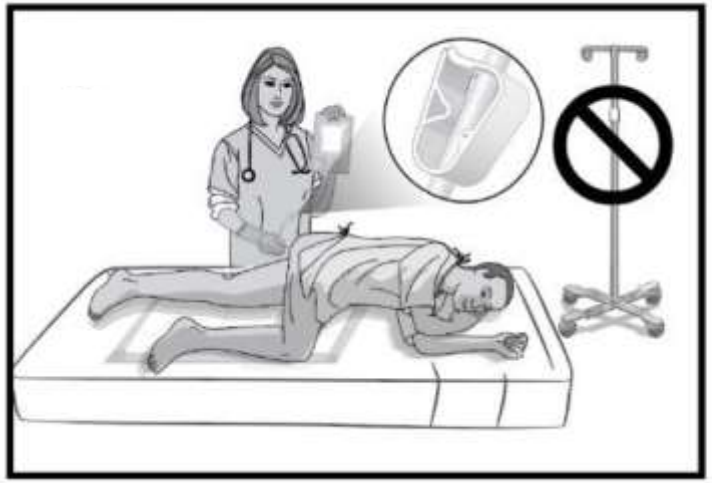

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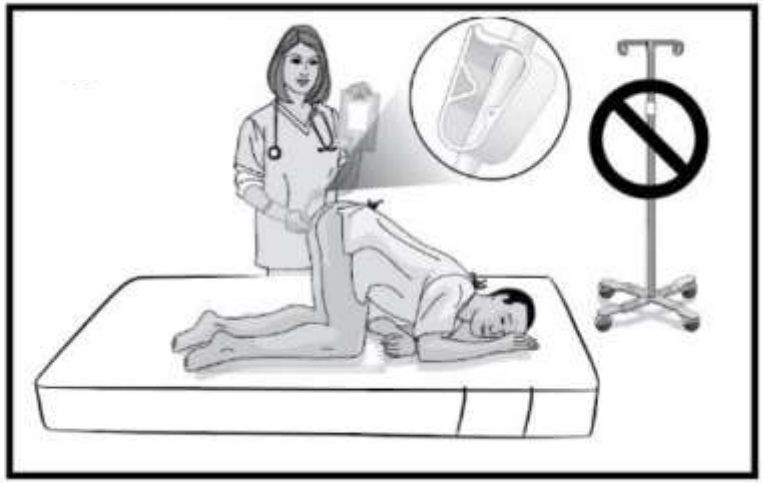

Now in Suite or the Office

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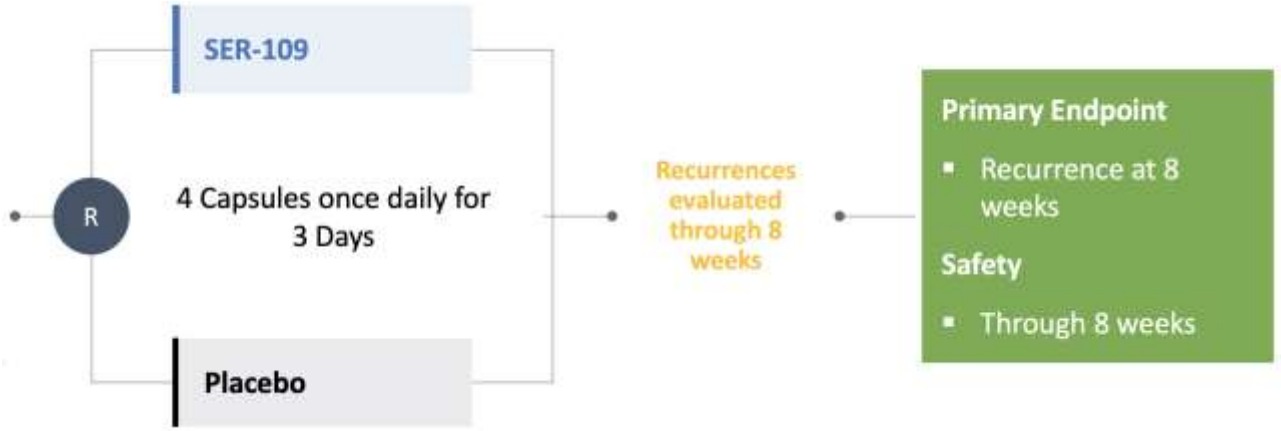
SER-109 (Consortia) - ECOSPOR

- SER-109 is a consortia of ~50 species of only live Firmicutes spores derived from stool specimens from healthy donors and alcohol purified
- ECOSPOR-III: Phase III, double-blind, randomized, placebo-controlled trial
  - N=281 pts; (182 patients with 3 or more EIA toxin + CDI)
  - Given after SoC Abx for CDI
  - Magnesium citrate 1 day prior to capsules
  - Primary efficacy endpoint – rate of recurrence after 8 weeks and safety at 24 wks



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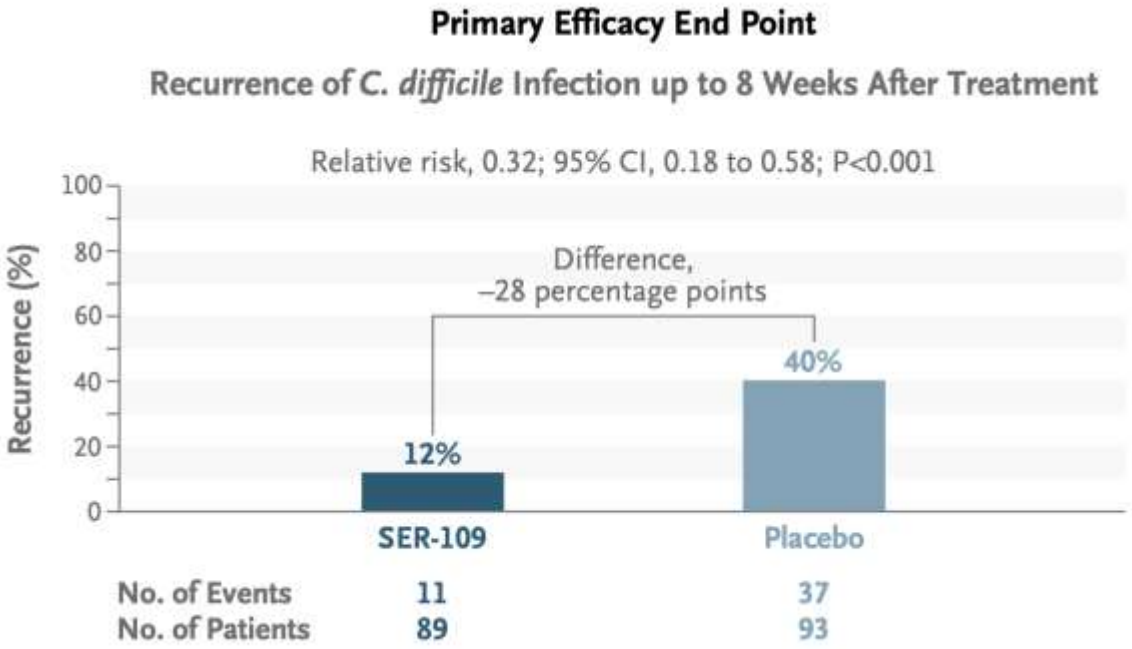
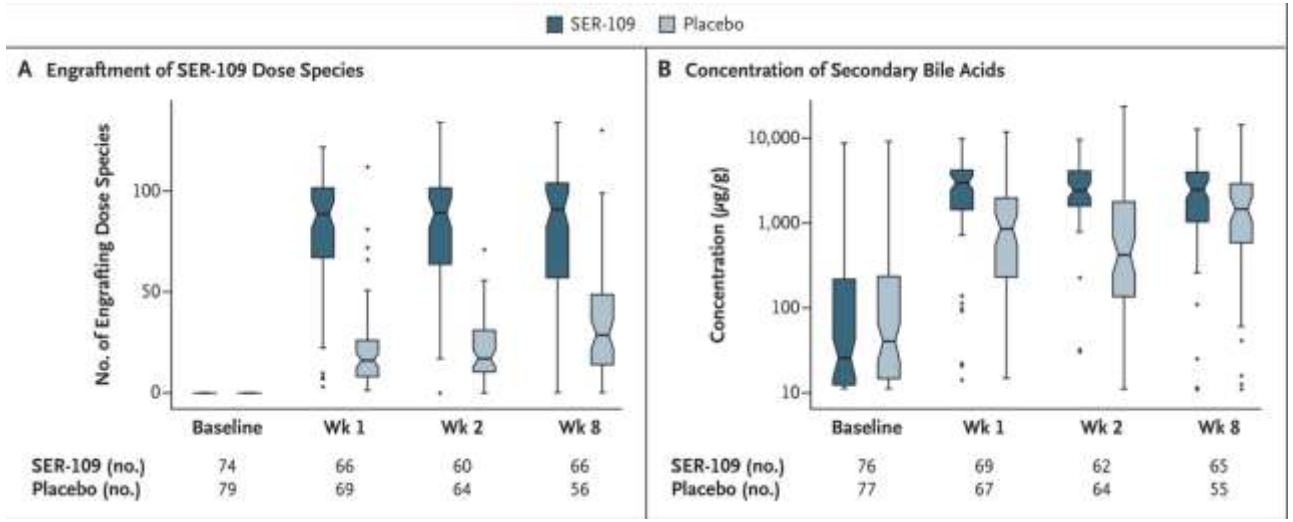
Feuerstadt et al. NEJM 2022;386:220-9

SER-109 Phase 3 Trial: ECOSPOR-III Efficacy Results





Quality control: Each capsule contains $1x10^6$ and $3x10^7$ Firmicutes spore colony forming units

FDA approved: **1ST RECURENCE or more** based on ECOSPOR III and IV results

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

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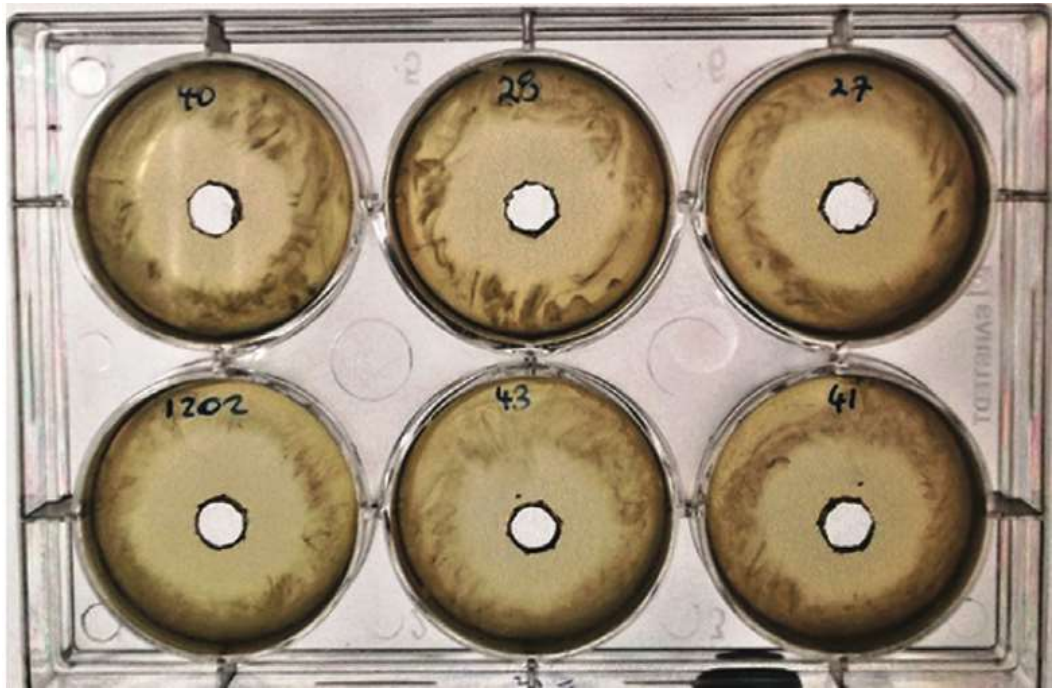
ADS024 (ART24; Single Species)

- ADS024 is a naturally occurring, non-colonizing, pure bacterial strain of a *Bacillus velezensis* with potent and selective *in vitro* and *in vivo* activity against a broad range of clinically relevant *C. difficile* ribotypes
  - ADS024 has bactericidal activity against *C. difficile*, with minimal impact on other common members of the gut microbiota
  - Produces proteases that can degrade both TcdA and TcdB

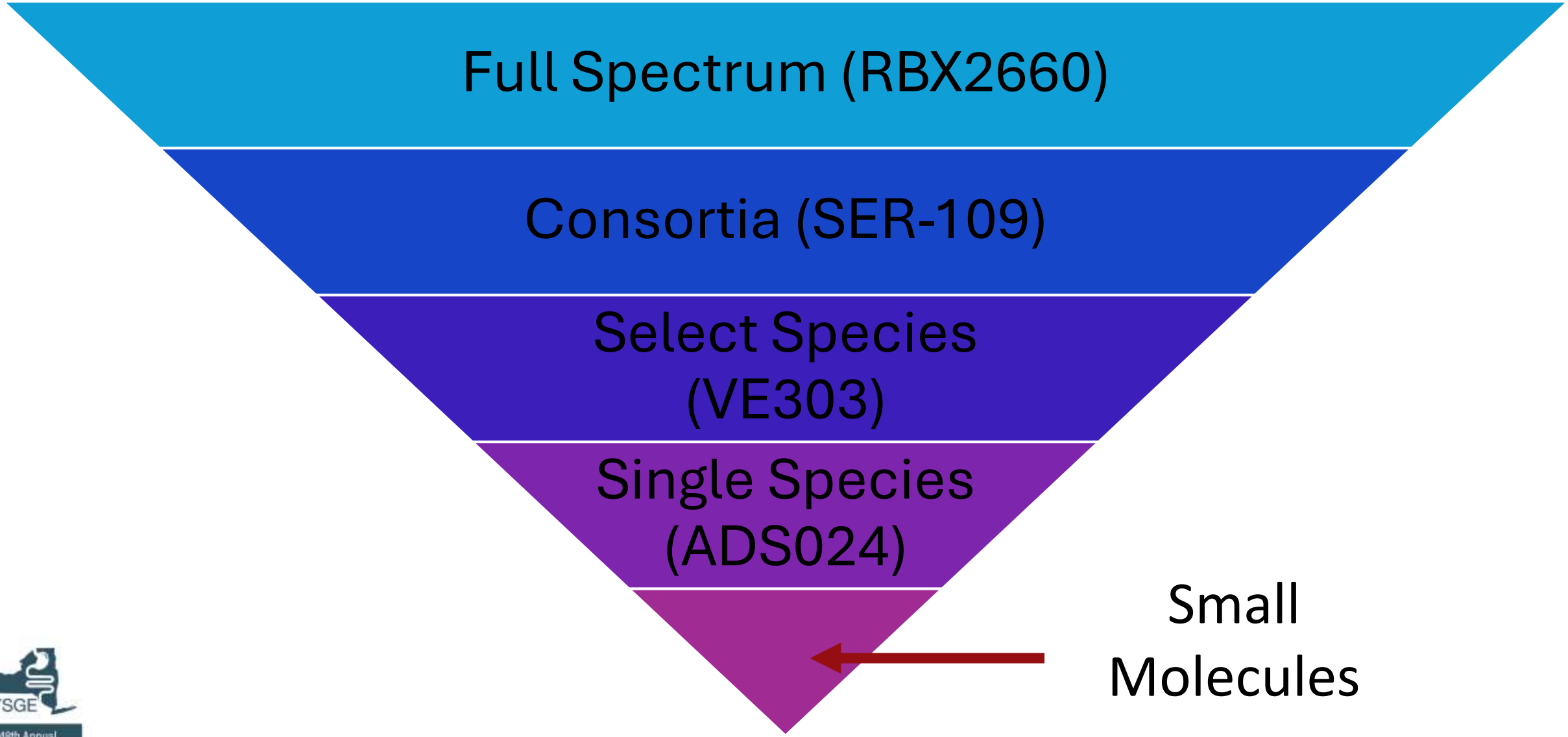
- Phase I randomized, double blind, placebo-controlled study in 36 participants with with a recent CDI who have completed a SoC course of antibiotics and have achieved clinical cure based on signs and symptoms
- Patients will be followed for 6 months



Zone of Inhibition of cell free extract of ART 24

O'Donnell M et al. Artugen Therapeutics Abstract 2020

Summary of Future CDI Therapies



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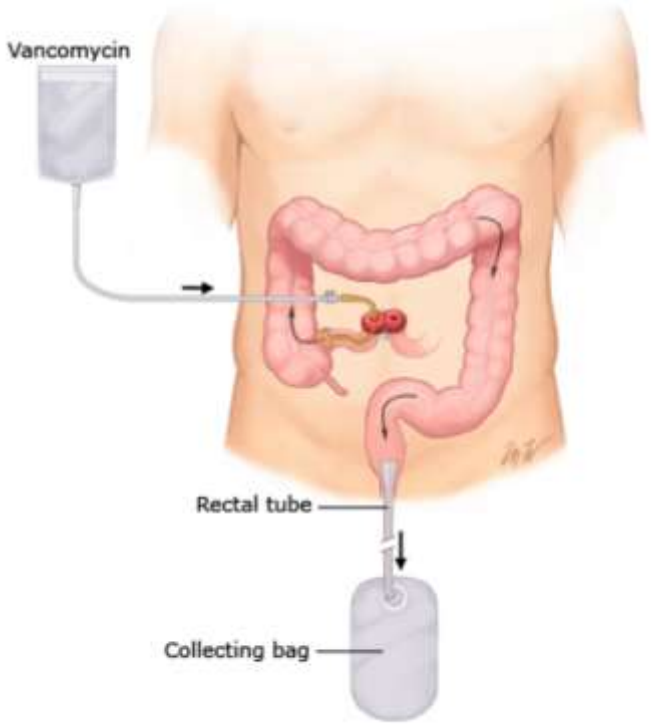
Surgical management of refractory CDI

Colectomy: standard surgical approach

High morbidity and mortality (80%)



Diverting loop ileostomy: Alternative approach

- Loop ileostomy
- Intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte via the ileostomy
- Post-op antegrade vancomycin instillation via ileostomy

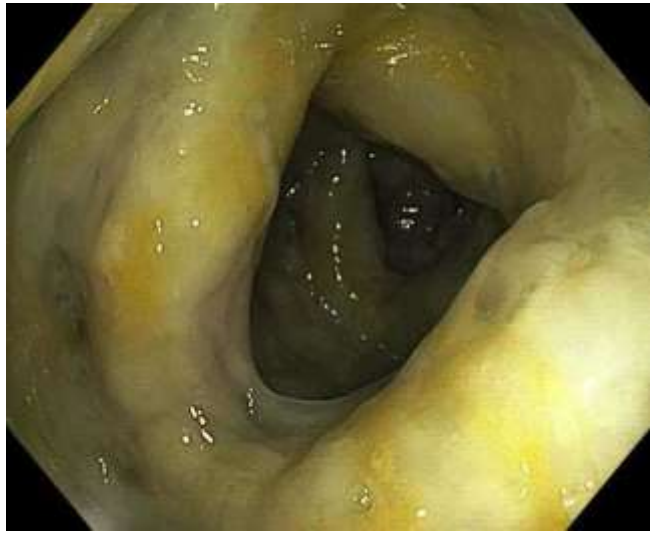
N = 42

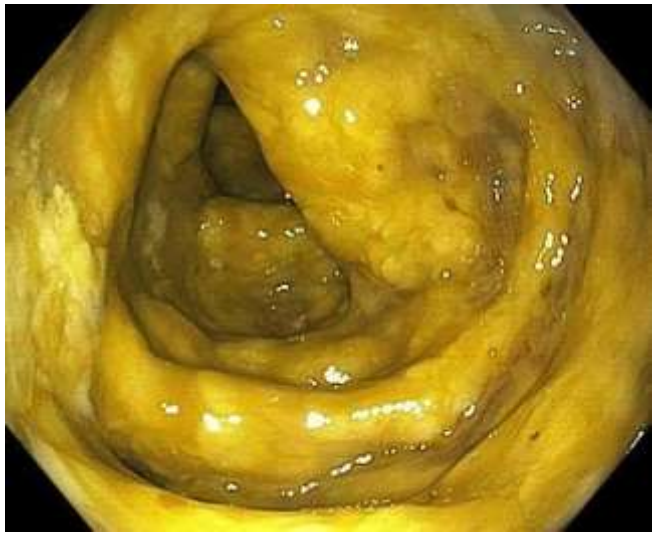
- 83% by laparoscopy
- 93% colon preserved
- 19% mortality vs 50% mortality in historical controls (odds ratio, 0.24; *P* =.006)

Cohen SH et al. *Infect Control Hosp Epidemiol*. 2010;31:431-455. 2. Neal MD et al. *Ann Surg.* 2011;254:423-429.

FMT for Severe Complicated CDI

- 74 yo male with seizure disorder, CAD s/p CABG, CVA, Parkinson's was admitted for seizures.
- He developed CDI after PEG placement and required antibiotics for other infections.
- His CDI progressed to severe complicated.





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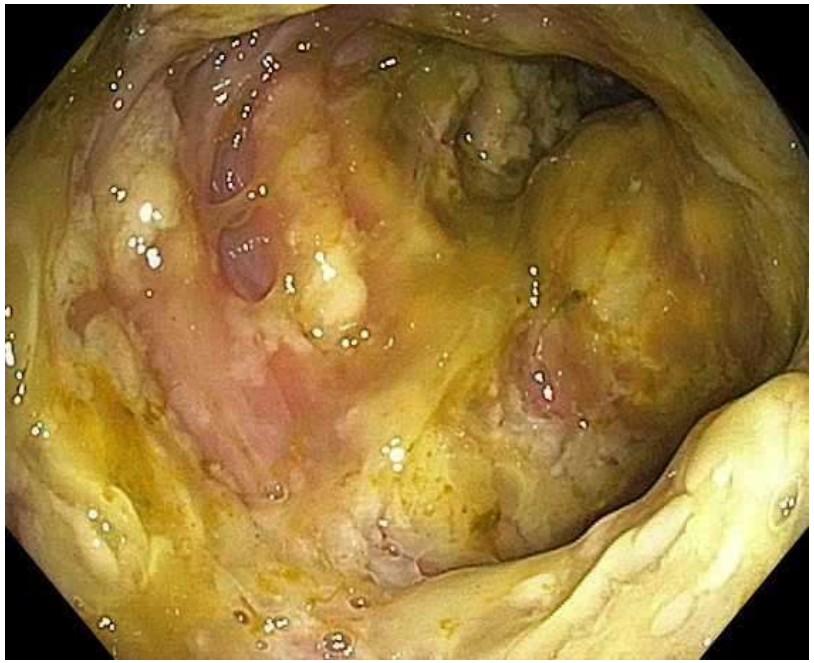
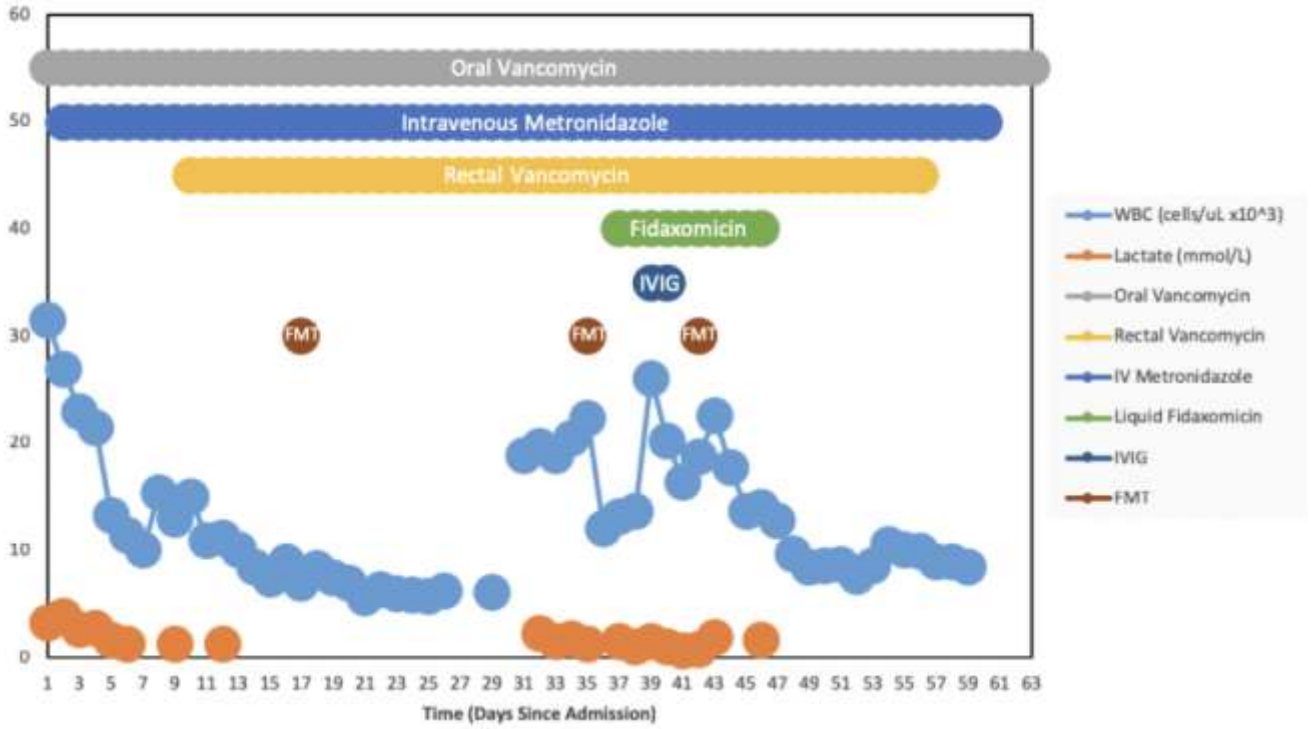
FMT for Severe Complicated CDI

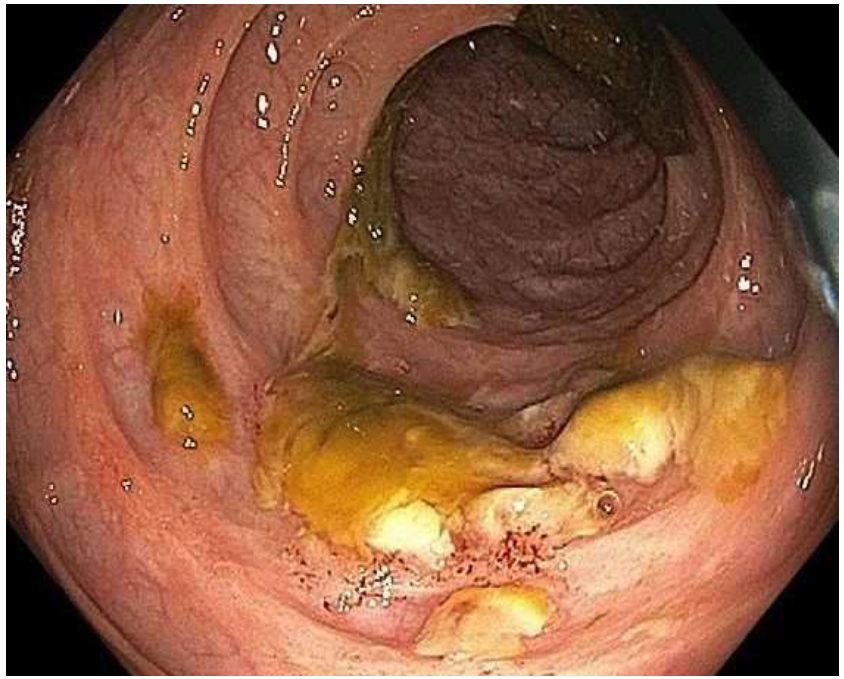
- 74 yo male with seizure disorder, CAD s/p CABG, CVA, Parkinson's was admitted for seizures.
- He developed CDI after PEG placement and required antibiotics for other infections.
- His CDI progressed to severe complicated.
- S/p FMT x1



FMT for Severe Complicated CDI



- S/p FMT x2



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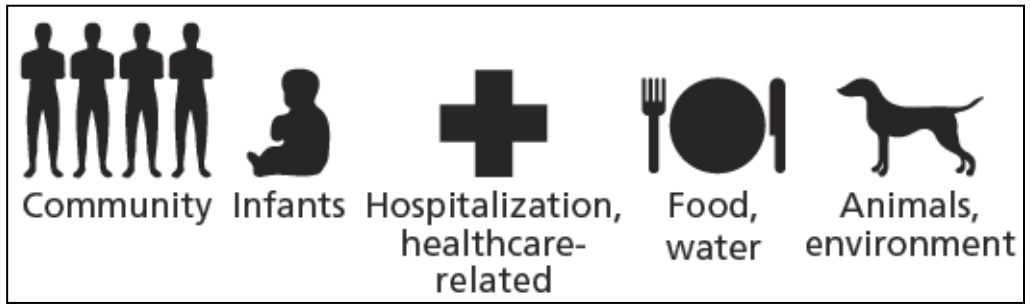
CDI: Strategies for Prevention[1,2]

1. Judicious antibiotic use
2. Education

1. Rapid Diagnosis
2. Isolation/barrier precautions for patients with CDI
3. Universal precautions including hand hygiene with soap and water
4. Environmental cleaning (chlorine)

Exposure to *Clostridium difficile*



1. Rupnik M et al. *Nat Rev Microbiol*. 2009;7:526-536
2. Lessa FC et al. *N Engl J Med*. 2015;372:825-834.

Overview of current management: Prevention

Antibiotic stewardship

◆(Strong recommendation, high quality evidence)

Hand hygiene: soap vs 4% chlorhexidine

◆(Strong recommendation, moderate quality evidence)

Single-use equipment (thermometers, stethoscopes)

◆(Strong recommendation, moderate quality evidence)

Barrier precautions (gloves/gowns)

◆(Strong recommendation, moderate quality evidence)

Contact precautions for 48 hours after resolution of diarrhea or duration of stay

◆(Strong recommendation, high quality evidence)

Overview of current management: Prevention

Environmental Protection Agency (EPA)-registered disinfectant with sporicidal label claim

- (Strong recommendation, high quality evidence)

Several minutes of 5,000 p.p.m. chlorine containing cleaning agent

- (Strong recommendation, high quality evidence)

ACG/IDSA 2013; WHO

Conclusion

- Microbial diversity is important in maintaining overall health and preventing CDI
- CDI has a tremendous impact on patients and the health care system
- Adherence to management testing and treatment guidelines can help reduce CDI and rCDI
  - Antibiotic strategies: Fidaxomicin> vancomycin > metronidazole
  - Passive Immunity – bezlotoxumab
  - Surgery for fulminant cases (diverting loop ileostomy vs total colectomy)
  - FMT in rCDI or to prevent/treat fulminant dz
  - Multiple routes of FMT delivery
- FMT products have evolved into live bacteriotherapeutic products (LBP)
  - 2 products are FDA approved starting as soon as the 1st recurrence
- Prevention strategies and education help decrease spread