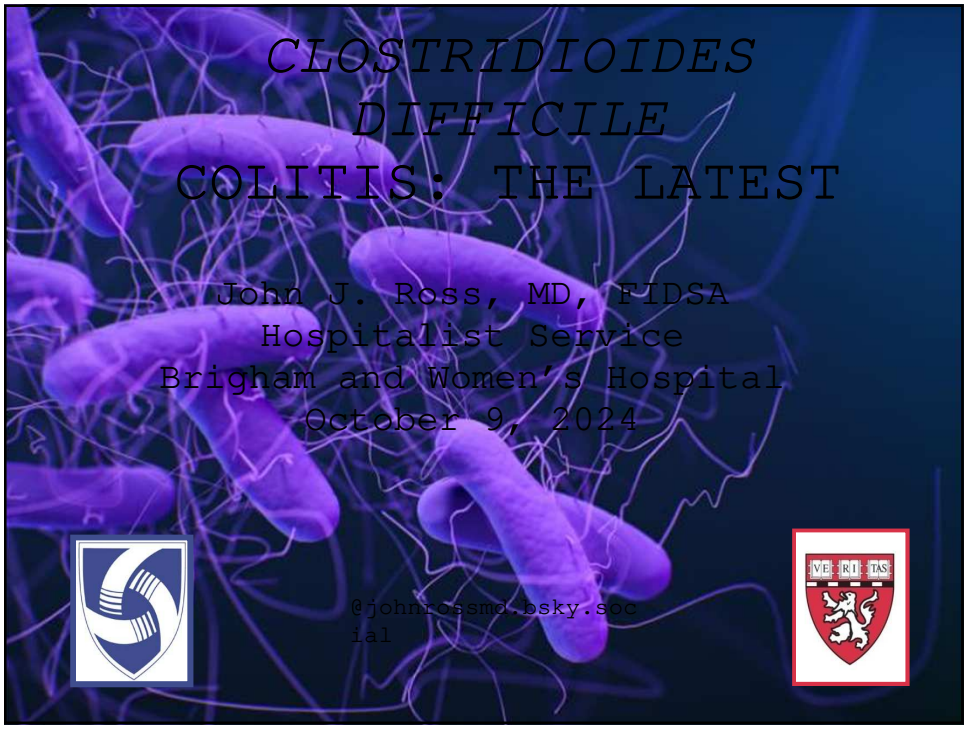


Disclosures

I have no financial relationship with a commercial entity producing health-care related products and/or services.

Risk Factors

- Antibiotics, antibiotics, antibiotics (85%)
- Proton pump inhibitors
- Inflammatory bowel disease
- GI manipulation (surgery, tube feeds)
- Advanced age, poor functional status, many comorbid conditions
- Malnutrition (poor antibody response to toxin)
- Sleeping in a bed previously occupied by a patient who received antibiotics

*Which of the following antibiotics used in the treatment of COPD flares is LEAST likely to cause *C. difficile* colitis?

1. Amoxicillin-clavulanic acid
2. Azithromycin
3. Doxycycline
4. Levofloxacin

Antibiotic Exposure and *C. difficile* Risk

Antibiotic	Adjusted hazard or odds ratio
Clindamycin	22.6
Fluoroquinolones	4.0
3rd- and 4th-generation cephalosporins	3.1
1st- and 2nd-generation cephalosporins	2.4
Beta-lactam and beta-lactamase inhibitor combos	2.3
Macrolides	1.5
TMP-SMX	0.88-0.96
Doxycycline	0.41
Metronidazole	0.3
3 or 4 antibiotics (compared to only 1)	3.3

Clin Infect Dis 2005;41:1254; Infect Control Hosp Epidemiol 2005;26:273; Infect Control Hosp Epidemiol 2008;29:44; Open Forum Infect Dis 2023 ofad413

Doxycycline is Associated with Less *C difficile*, Compared to Azithromycin

- Retrospective study of 156,107 hospitalized patients in the VA system with community-acquired pneumonia
- Treatment with ceftriaxone/doxycycline was associated with a 17% decrease in the risk of *C difficile*, compared to ceftriaxone/azithromycin (P=0.03)
- In patients with prior *C difficile* infection, doxycycline was associated with a 45% lower risk of recurrence (P=0.02)

Am J Infect Control 2024;52:280-3

Household Exposure: An Emerging Risk Factor?

- Case–control study of 224,818 patients with *C. difficile* colitis
- 1,074 patients (4.8%) had a household contact with *C. difficile* in the past 60 days
- Incidence rate ratio 21.74 for community–onset *C. difficile*
- Stronger recommendations for discharged patients to **wash hands**, disinfect bathroom, kitchen

JAMA Netw Open 2020;3(6): e208925

Society Guidelines Currently Do **Not** Recommend Probiotics

- American College of Gastroenterology (2021): not recommended for primary or secondary prevention
- IDSA (2018): insufficient data

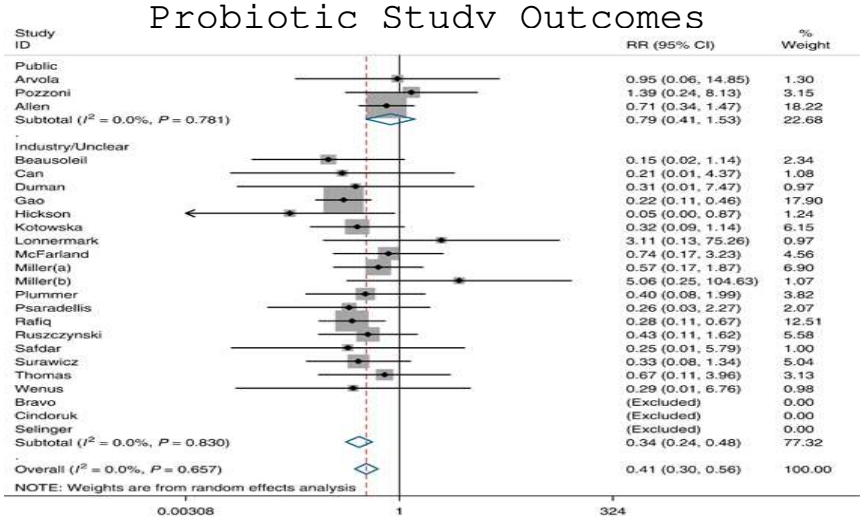
Am J Gastroenterol 2021;116:1124–47; Clin Infect Dis 2018; 66:e1–e48

Cochrane Meta-Analysis: Modest Benefit of Probiotics in High-Risk Patients

- *C difficile* risk 1.5% with probiotics, vs 4% in placebo group (relative risk 0.40, 95% CI 0.30 to 0.52)
- However, many studies suspect: small, poorly-controlled, missing data, and at high risk of bias
- Positive results relied on 5 studies with *C difficile* rates >15% (extraordinarily high!)

Cochrane Database Syst Rev 2017 Dec 19;12:CD006095;
Am J Gastroenterol 2021;116:1124-47

Follow the Money: Public vs Industry Funding Predicts Probiotic Studv Outcomes



Am J Gastroenterol 2014;109:1081-2

PLACIDE: Probiotics Don't Prevent Diarrhea or *C. difficile* in Older Hospitalized Inpatients

- 2,981 patients >65 yrs receiving antibiotics
  - High quality, multicenter double-blinded RCT
  - Seven times larger than next largest study
- Lactobacillus plus bifidobacterium vs. placebo for 21 days
- Antibiotic-associated diarrhea in 10.8% of treatment group, vs. 10.4% placebo (p=0.71)
- *C. difficile* in 0.8% treatment group, 1.2% placebo group (p=0.35)

Lancet 2013;382:1249-57

Failure of a Computer Prompt for Probiotics to Reduce *C difficile* Incidence

- EPIC prompt to prescribe lactobacillus probiotics to high-risk patients on antibiotics at four Maryland hospitals
- Pre-intervention 17,536 patients, post 15,023
- Propensity match scoring for confounders
- No change in *C difficile* risk (OR 1.46, CI 0.87-2.45)

Clin Infect Dis 2021; ciab417

Current Probiotics Are a Paltry Imitation of Our Normal Gut Flora

Some Key Bacterial Species in Successful Fecal Transplants

- *Akkermansia muciniphila*
- *Alistipes putredinis*
- *Phocaeicola dorei*
- *Phascolarctobacterium faecium*
- *Mesosutterella massiliensis*
- *Barnesiella intestinihominis*
- *Faecalibacterium prausnitzii*

Sci Transl Med 2023;15(720):eabo2750

Clinical Features

- Onset typically 5–10 days after antibiotics, but highly variable
- Diarrhea usually watery, bloody in 5–10%
- Fever, abdominal pain/cramping, tenderness with colitis, delirium
- Colonic pseudomembranes ~50%
- Rarely, *C difficile* causes ileitis after total colectomy; similar risk factors to colitis

J Gen Intern Med 2019;34:1392–3, Open Forum Infect Dis 2019; ofz409

Laboratory Features

- Major laboratory abnormality is leukocytosis (average 15K)
- Leukocytosis may proceed onset of diarrhea by 1–2 days
- Magnitude of leukocytosis correlates with severity and risk of relapse
- Fulminant colitis: lactic acidosis
- Procalcitonin not sensitive, except in severe disease

Diagnostic Testing for *C. difficile*

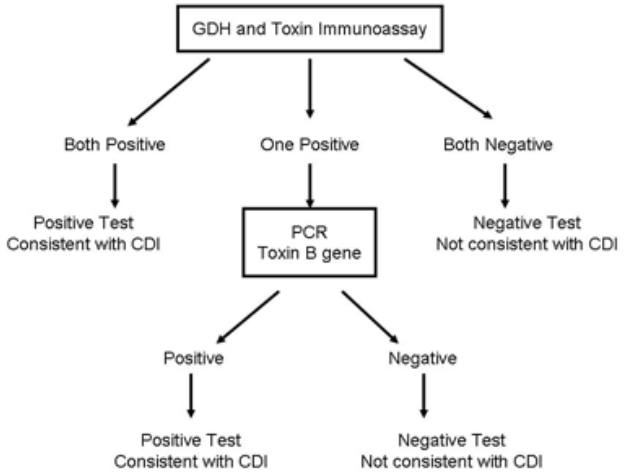
- Test only diarrheal stool (assumes shape of container)
- Do NOT test asymptomatic patients, or patients on laxative regimens
- Gold standard: cytotoxicity assay
  - detects as little as 10 pcg of toxin B
  - expensive, labor-intensive, ≥48 hrs turnaround

Infect Control Hosp Epidemiol 2010;31:431-55

Current Diagnostic Tests

- Toxin enzyme immunoassay (EIA)
  - fast, cheap
  - NOT sensitive: 50-95%
  - NOT recommended as only test
- EIA for glutamate dehydrogenase
  - >90% sensitive
  - 20% false positive rate
  - doesn't distinguish between toxigenic and non-toxigenic strains
- PCR/NAAT testing for toxin B genes
  - rapid; sensitivity 93-97%; expensive
  - not specific (positive in colonization with toxigenic strains); still requires clinical judgment

C. difficile Testing Algorithm



Treatment of Non-Fulminant *C difficile* Colitis

- Fidaxomicin 200 mg twice daily for 10 days (IDSA guidelines) OR either vancomycin 125 mg po q6h or fidaxomicin (ACG guidelines)
- Per IDSA guidelines, oral vancomycin acceptable alternative

Clin Infect Dis 2021 Jun 24; ciab549
Am J Gastroenterol 2021;116:1124-47

Fidaxomicin

- Narrow spectrum macrocyclic antibiotic
- Cure rates similar with 10-day course of fidaxomicin 200 mg q12h vs. vancomycin 125 q6h in initial treatment of *C. difficile* infection
- Relapse rates lower with fidaxomicin (13–15%) vs vanco (25–27%)
- High uric acid, neutropenia, GI bleed, high LFTs more common with fidaxomicin
- Cost: $2800 for 10 days

NEJM 2011;364:422-31; Clin Infect Dis 2011;53:440-7; Lancet Infect Dis 2012;12:281-9; Eur J Clin MicrobiolInfect Dis 2016;35:251-9

EXTEND Trial

- Fidaxomicin 200 mg twice daily for days 1–5, then 200 mg every other day for days 7–25 *vs* vancomycin 125 mg four times daily for ten days
- Sustained cure 70% extended-pulse fidaxomicin *vs* 59% conventional vancomycin (P=0.03)
- Is it the drug, or the regimen?

Lancet Infect Dis 2018;18:296

C difficile Isolates with Reduced Susceptibility to Vancomycin

- Susceptibility testing for *C difficile* is not obtained in clinical practice (expense, lack of standardization)
- Study from Houston, Texas, in which minimum inhibitory concentrations to vancomycin were calculated for 300 isolates
- 34% of isolates showed reduced vancomycin susceptibility
- Reduced vancomycin sensitivity was associated with:
  - Lower rates of cure at 14 days (89% vs 96%), P=0.04
  - Lower rates of sustained clinical

Clin Infect Dis 2024;79:15-21

Fulminant *C. difficile* (Kitchen Sink Approach)

Clinical definition	Supportive clinical data	Recommended treatment	Strength of recommendation
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg four times/day by mouth or NG tube, plus metronidazole 500 mg IV every 8 hours. If ileus, consider rectal vancomycin ****ACG: strongly consider fecal microbiota transplant if failing antibiotic Rx**	Strong for oral vancomycin and IV metronidazole, weak for rectal vancomycin

Clin Infect Dis 2018;66:987-94; Am J Gastroenterol 2021;116:1124-47

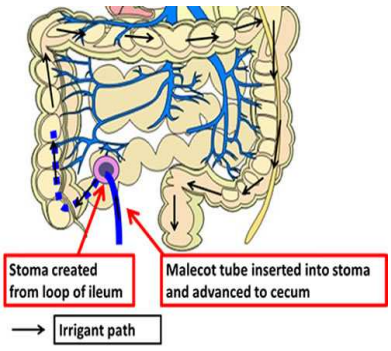
Is IV Metronidazole Useless?

- Dual therapy with po vancomycin and IV metronidazole common in both fulminant and non-fulminant *C. difficile*
- Use in non-fulminant disease **not** supported by guidelines
- Possible harms: anorexia, further depletion of gut flora
- Retrospective study of 2,114 patients
- IV metronidazole was not associated with lower risk of death, colostomy, or relapse after adjusted analysis

Clin Infect Dis 2019 Nov 12;ciz1115

Loop Ileostomy with Colonic Vanco Lavage for Fulminant *C. difficile*

- Loop ileostomy 26% mortality (vs 31% mortality for total colectomy)
- Loop ileostomy patients younger, less severely ill, earlier operation
- Only 14% require conversion to total colectomy



JAMA Surg 2019;154:899-906; J Trauma Acute Care Surg 2017;83:36-40

*What is the most effective therapy to prevent *C difficile* relapse?

1. Bezlotoxumab (monoclonal antibody to toxin B)
2. Fecal transplantation
3. Fidaxomycin (extended-pulse regimen)
4. Vancomycin treatment with taper

Treatment of *C. difficile* Relapse

Clinical definition	Recommended treatment
First recurrence	IDSA: Preferred regimen: fidaxomicin (standard or pulsed-dose regimen) + bezlotoxumab; alternatively, vanco taper + bezlotoxumab ACG: Vanco taper (preferred) or fidaxomicin AGA: Fecal microbiota therapy in patients at high risk
Second or subsequent recurrence	IDSA: Vanco taper OR vanco + rifaximin chaser OR fecal microbiota transplantation ACG, AGA: Fecal microbiota therapy

Clin Infect Dis 2021 Jun 24; ciab549; Am J Gastroenterol 2021;116:1124-47; Gastroenterology 2024;166:409-34

Sample Vancomycin Taper

- Vancomycin 125 mg po 4 times daily for 10-14 days, then
- Vancomycin 125 mg twice daily for a week, then
- Vancomycin 125 mg daily for a week, then
- Vancomycin 125 mg every 2 or 3 days for 2-8 weeks

Bezlotoxumab: Monoclonal Antibody to Toxin B

- FDA-approved in 2016 for prevention of relapse in patients at high risk
- Recurrence rate 17% with usual care + bezlotoxumab, vs 27% with usual care + placebo
- All-cause mortality similar
- Excess deaths in CHF patients (19.5% with bezlotoxumab, vs 12.5% with placebo
- Cost $4000/vial
- Now recommended for recurrent *C difficile* episodes by IDSA but not ACG

N Engl J Med 2017; 376:305-317

Clin Infect Dis 2021 Jun 24; ciab549

Am J Gastroenterol 2021;116:1124-47

Secondary Prophylaxis to Prevent *C. difficile* Relapses

- Randomized controlled trial of secondary prophylaxis for patients requiring antibiotics who had prior *C difficile*
- Vancomycin 125 mg po once daily while on antibiotics, and for five days thereafter
- *C. difficile* relapses: 0/50 patients on prophylaxis, 6/50 on placebo (P = 0.03)

Clin Infect Dis 2020;71:1133-9

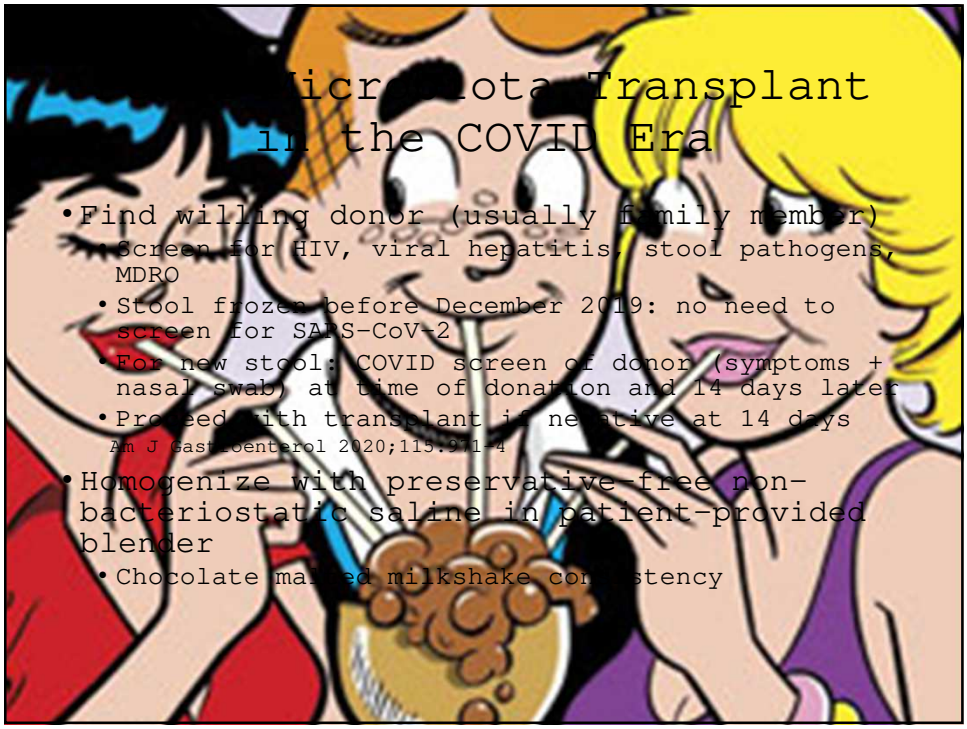
Stool transplant

Fecal microbiota therapy

C. difficile Colitis As a Deficiency of Normal Gut Flora

- Stool transplants may be most effective Rx for *C. difficile* ("brown standard"?)
  - Colonization resistance
  - Bile acid transformation (kills *C. diff* spores)
  - Bacteriocins
  - Modulation of innate immunity via TLRs
  - 80–90% cure rates in patients with multiple relapses (vs 20–30% conventional Rx)
  - Less likely to have antibiotic-resistant gut flora

Britton and Young, Trends Microbiol 2012; NEJM 2013;368:407-15; Clin Infect Dis 2016;62:1479-86



Microbiota Transplant in the COVID Era

- Find willing donor (usually family member)
  - Screen for HIV, viral hepatitis, stool pathogens, MDRO
  - Stool frozen before December 2019: no need to screen for SARS-CoV-2
  - For new stool: COVID screen of donor (symptoms + nasal swab) at time of donation and 14 days later
  - Proceed with transplant if negative at 14 days

  Am J Gastroenterol 2020;115:971-4
- Homogenize with preservative-free non-bacteriostatic saline in patient-provided blender
  - Chocolate malted milkshake consistency

Colonoscopic Delivery

- Taper down vancomycin prior to "transpoosion"
- Strain through gauze to catch particulates
  - Target volume 250-700 cc
- Bowel prep
- Stool delivered to right colon, terminal ileum
- Post-procedure:
  - Patient lays on right side
  - Consider loperamide to help retain stool

Stool Transplants Reduce Colonization & Infection with MDR Bacteria

- In 8 patients who received FMT for recurrent *C difficile*, there was:
  - decrease in UTI from 4x/year to once a year
  - UTIs that occurred were highly antibiotic-sensitive (previously R to cipro, TMP-SMX)
- Meta-analysis of 21 studies with 192 patients: FMT associated with 37.5-87.5% eradication rate of MDR bacteria
- Eliminated MDRO bacteria in 8/9 renal transplant recipients

Clin Infect Dis 2017;65:1745-7; Clin Microbiol Infect 2019;25:958-63; Sci Transl Med 2023;15(720):eabo2750

Oral Microbiome Therapy ("Microbial Cocktails")

- Processed feces
- Single donor per dose (trackable)
- Donor blood/stool screened for infectious agents (e.g. HIV, viral hepatitis, GI pathogens, antibiotic-resistant bacteria)
- Given after vancomycin or fidaxomicin to prevent relapse in patients at high risk
- Well-tolerated in small trials
  - abdominal pain, nausea, transient diarrhea

Oral Microbiome Therapy

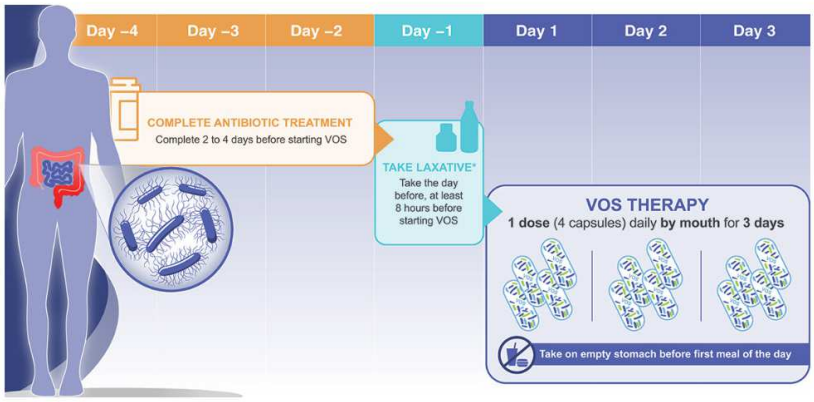
- Two recently approved products
- live-jslm (Rebyota): filtered, suspended in saline/polyethylene glycol, frozen
- live-brpk (Vowst): suspended in ethanol (kills everything except Gram positive spores), then filtered to remove solids and ethanol

Fecal Microbiota live-brpk (Vowst)

- Phase 3 randomized, double-blind trial
- Population: 182 adults with ≥3 episodes of *C difficile* infection, 1:1 randomization
- Recurrence at 8 weeks: 12% treatment, 40% placebo (relative risk 0.32, $p<0.001$)
- Similar efficacy in subgroups (older patients, vancomycin Rx, fidaxomicin Rx)
- Cost $17,500

NEJM 2022;386:220-9

Dosing Regimen for Fecal Microbiota live-brpk (Vowst)



Fecal Microbiota live-jslm (Rebyota)

- Phase 3 randomized double-blind trial in 267 patients with at least one *C difficile* relapse (180 treatment arm, 87 placebo)
- Single 150 mL enema, 1-3 days after antibiotics for *C difficile*; no bowel prep
- Success rate at 8 weeks (no relapse): live-jslm 70.6%, placebo 57.5%
- Cost $9000

Drugs 2022; 82:1527-38

Take-Home Messages

- First episode: fidaxomicin (IDSA guidelines) OR either oral vancomycin or fidaxomicin (ACG guidelines)
- Fulminant: high-dose oral or NGT vancomycin + IV metronidazole; consider fecal microbiota transplant
- First relapse: oral vanco taper OR fidaxomicin; IDSA guidelines also recommend IV bezlotoxumab
- Two or more relapses: fecal bacteriotherapy
- Fecal microbiota therapy includes "conventional" fecal transplant, plus two FDA-approved therapies: fecal microbiota live-jslm (Rebyota) and live-brpk (Vowst)
- Secondary *C difficile* prophylaxis: vanco 125 mg once daily while on antibiotics and for five days afterward