CLOSTRIDIOIDES DIFFICILE COLITIS: THE LATEST

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Disclosure

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

Risk Factors

- Antibiotics, antibiotics, antibiotics (85%)
- Sleeping in a bed previously occupied by a patient who received antibiotics
- Proton pump inhibitors
- GI manipulation (surgery, tube feeds)
- Advanced age, poor functional status, many comorbid conditions
- Malnutrition (poor antibody response to toxin)
- Inflammatory bowel disease
- ?GABAergics (benzodiazepines, gabapentin)
  - Open Forum Infect Dis 2020; ofaa353

Antibiotic Exposure and *C. difficile* Risk

Antibiotic	Adjusted hazard ratio
Quinolones	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 total antibiotics (compared to only 1)	3.3
5 or more (compared to only 1)	9.6
8-18 days (compared to <4 days)	3.0
>18 days (compared to <4 days)	7.8

Clin Infect Dis 2005;41:1254-60; Infect Control Hosp Epidemiol 2005;26:273-80; Infect Control Hosp Epidemiol 2008;29:44-50

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

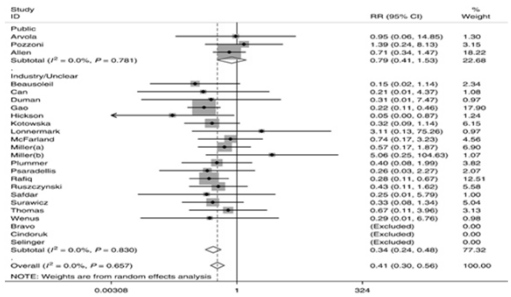
Am J Gastroenterol 2021;116:1124-47; Clin Infect Dis 2018; 66:e1–e48

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 Study 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)

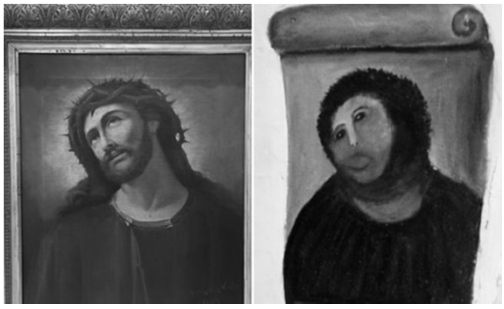
Lancet 2013;382:1249-57

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

- 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



If You Must Use Probiotics, Try *Saccharomyces boulardii*

- Probiotic yeast with direct inhibitory effects on *C. difficile* (has protease which binds to *C. difficile* toxin A receptor)
- Retrospective cohort, n = 8,763 patients
- *Saccharomyces* 250 mg bid reduced *C. difficile* adjusted odds ratio to 0.57
- Most effective early?: aOR 0.47 when started within 24 hours of antibiotics vs >24 hours

Clin Infect Dis 2020; ciaa808

Clinical Features

- Onset on average 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%
- *C difficile* enteritis
  - 5.1% of total colectomy cases (44/855 patients); 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*

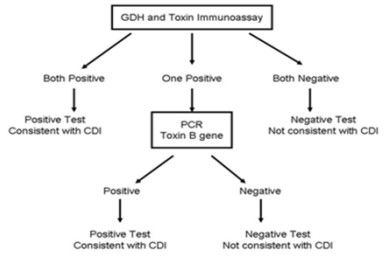
- Test only diarrheal stool (assumes shape of container)
- Testing of stool from asymptomatic patients or those on laxatives discouraged
- Gold standard: cytotoxicity assay
  - detects as little as 10 pcg of toxin B
  - expensive, laborious

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
- PCR/NAAT testing for toxin B genes
  - rapid; sensitivity 93-97%; expensive
  - NOT specific (i.e., positive in colonization)

Sample Multistep *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 (AGC 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

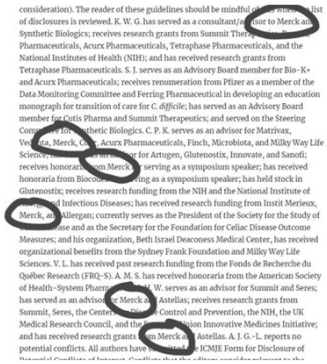
NEJM 2011;364:422-31; Clin Infect Dis 2011;53:440-7; Lancet Infect Dis 2012;12:281-9; Eur J Clin MicrobiolInfect Dis 2016;35:251-9

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

IDSA guidelines and conflict of interest


consideration). The reader of these guidelines should be mindful of [illegible] list of disclosures is reviewed. K. W. G. has served as a consultant/advisor to Merck and Synthetic Biologics; receives research grants from Summit Therapeutics, Pharmaceuticals, Acurx Pharmaceuticals, Tetraphase Pharmaceuticals, and the National Institutes of Health (NIH); and has received research grants from Tetraphase Pharmaceuticals. S. J. serves as an Advisory Board member for Bio-K+ and Acurx Pharmaceuticals; receives renumeration from Pfizer as a member of the Data Monitoring Committee and Ferring Pharmaceutical in developing an education monograph for transition of care for *C. difficile*; has served as an Advisory Board member for Cutis Pharma and Summit Therapeutics; and served on the Steering Committee for Synthetic Biologics. C. P. K. serves as an advisor for Matrivax, Vedanta, Merck, Da[illegible], Acurx Pharmaceuticals, Finch, Microbiota, and Milky Way Life Sciences; has served as an advisor for Artugen, Glutenostix, Innovate, and Sanofi; receives honoraria from Merck for serving as a symposium speaker; has received honoraria from Biocodex for serving as a symposium speaker; has held stock in Glutenostix; receives research funding from the NIH and the National Institute of Allergy and Infectious Diseases; has received research funding from Institut Merieux, Merck, and Allergan; currently serves as the President of the Society for the Study of Celiac Disease and as the Secretary for the Foundation for Celiac Disease Outcome Measures; and his organization, Beth Israel Deaconess Medical Center, has received organizational benefits from the Sydney Frank Foundation and Milky Way Life Sciences. V. L. has received past research funding from the Fonds de Recherche du Québec Research (FRQ-S). A. M. S. has received honoraria from the American Society of Health-System Pharmacists. D. W. serves as an advisor for Summit and Seres; has served as an advisor for Merck and Astellas; receives research grants from Summit, Seres, the Centers for Disease Control and Prevention, the NIH, the UK Medical Research Council, and the European Union Innovative Medicines Initiative; and has received research grants from Merck and Astellas. A. J. G.-L. reports no potential conflicts. All authors have completed the ICMJE Form for Disclosure of

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 complete ileus, consider rectal vancomycin	Strong for oral vancomycin and IV metronidazole, weak for rectal vancomycin

Clin Infect Dis 2018;66:987-94

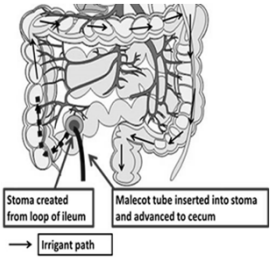
Is IV Metronidazole Useless?

- 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

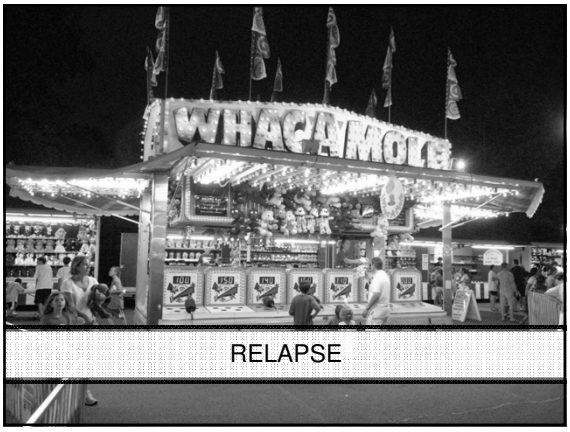
Clin Infect Dis 2019 Nov 12;ciz1115

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 OR
- Only 14% require conversion to total colectomy



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



Treatment of *C. difficile* Relapse

Clinical definition	Recommended treatment
First recurrence	IDSA: Preferred regimen: fidaxomicin (standard or pulsed-dose regimen) + bezlotoxumab; alternatively, can give vanco taper + bezlotoxumab AGC: Vanco taper (preferred) or fidaxomicin
Second or subsequent recurrence	IDSA: Vanco taper OR vanco + rifaximin chaser OR fecal microbiota transplantation AGC: Fecal microbiota transplantation

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

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 (Zinplava): 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 *C. difficile* in the past
- 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

Ursodiol

- Secondary bile acids inhibit germination of *C difficile* spores
- Ursodiol 300 mg tid given as salvage therapy to 16 chronically ill patients with contraindications to FMT
- Observed relapse rate 12.5% (expected 50%)
- Median duration 107 days; cost ~ $1/day

Clin Infect Dis 2019;68:498-500

Treatments with Limited Evidence to Support Use

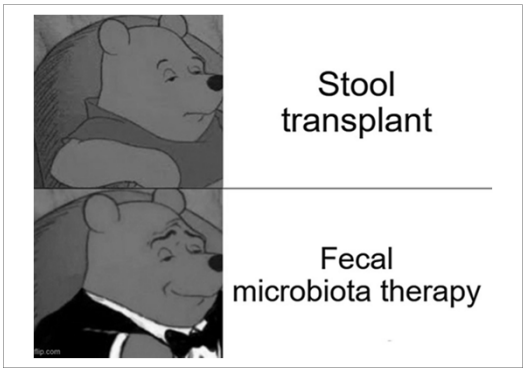
Rifaximin

- Underpowered trials to prevent relapse did not achieve statistical significance
- Resistance rates as high as 50%

Tigecycline

- Observational data only, no randomized trials
- FDA black box warning in 2013 for excess mortality

Gut 2019;68:1224-31; Anaerobe 2019;55:35-39; Eur J Clin Microbiol Infect Dis 2020;39:1053-8



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

Fecal 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 transplant
- 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

Oral Encapsulated vs Colonoscopic Stool Transplant

- 116 patients in an unblinded randomized trial of stool transplant, either:
  - colonoscopy (360 mL fecal slurry), or
  - 40 capsules swallowed under direct observation
- Cure rates 96.2% in each arm at 12 weeks post-transplant
- Capsule group more likely to view their experience as "not at all unpleasant" (66%, vs 44% in the colonoscopy arm)

JAMA 2017;318:1985-93

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

Clin Infect Dis 2017;65:1745-7; Clin Microbiol Infect 2019;25:958-63

"Microbial cocktails"

- Industrially processed feces
- Farthest along in pipeline: SER-109
- Stool donations refined to reduce solid matter, kill off vegetative bacteria, viruses, fungi, and parasites, and enrich spore-forming *Firmicutes* bacteria (which regulate bile acids and inhibit *C difficile*)
- Mean 86 species per lot (single donor per lot), dose 4 capsules

Clin Infect Dis 2021;72:2132-40

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
- First relapse: oral vanco taper OR fidaxomicin; IDSA guidelines also recommend IV bezlotoxumab
- Two or more relapses: fecal bacteriotherapy
- Stool transplant options: colonoscopy, enema, frozen capsules
- New options: ursodiol
- Secondary *C difficile* prophylaxis: vanco 125 mg once daily while on antibiotics and for five days afterward