Clinical Update on *Clostridioides difficile* Infection

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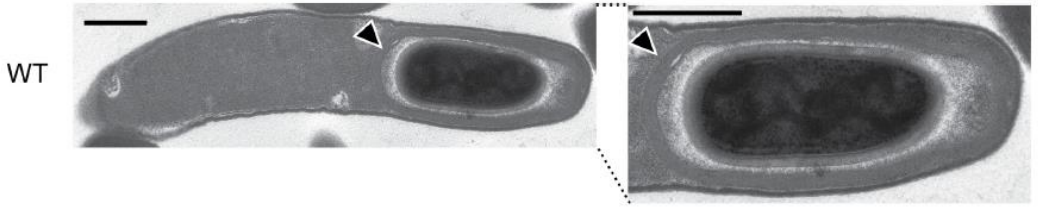
Clostridioides difficile

- Member of *Peptostreptococcaceae* family
- Gram-positive bacillus
- Strict anaerobe
- Spore former
- Protein toxin synthesis (TcdA, TcdB, CDT)
- Sporulation=making the spore in mother cell
- Germination=transition from spore to bacillus

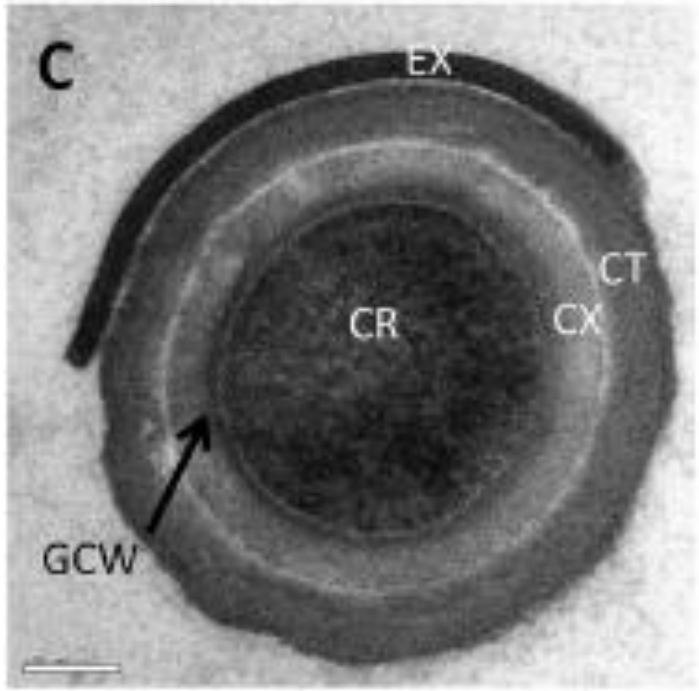
Spore

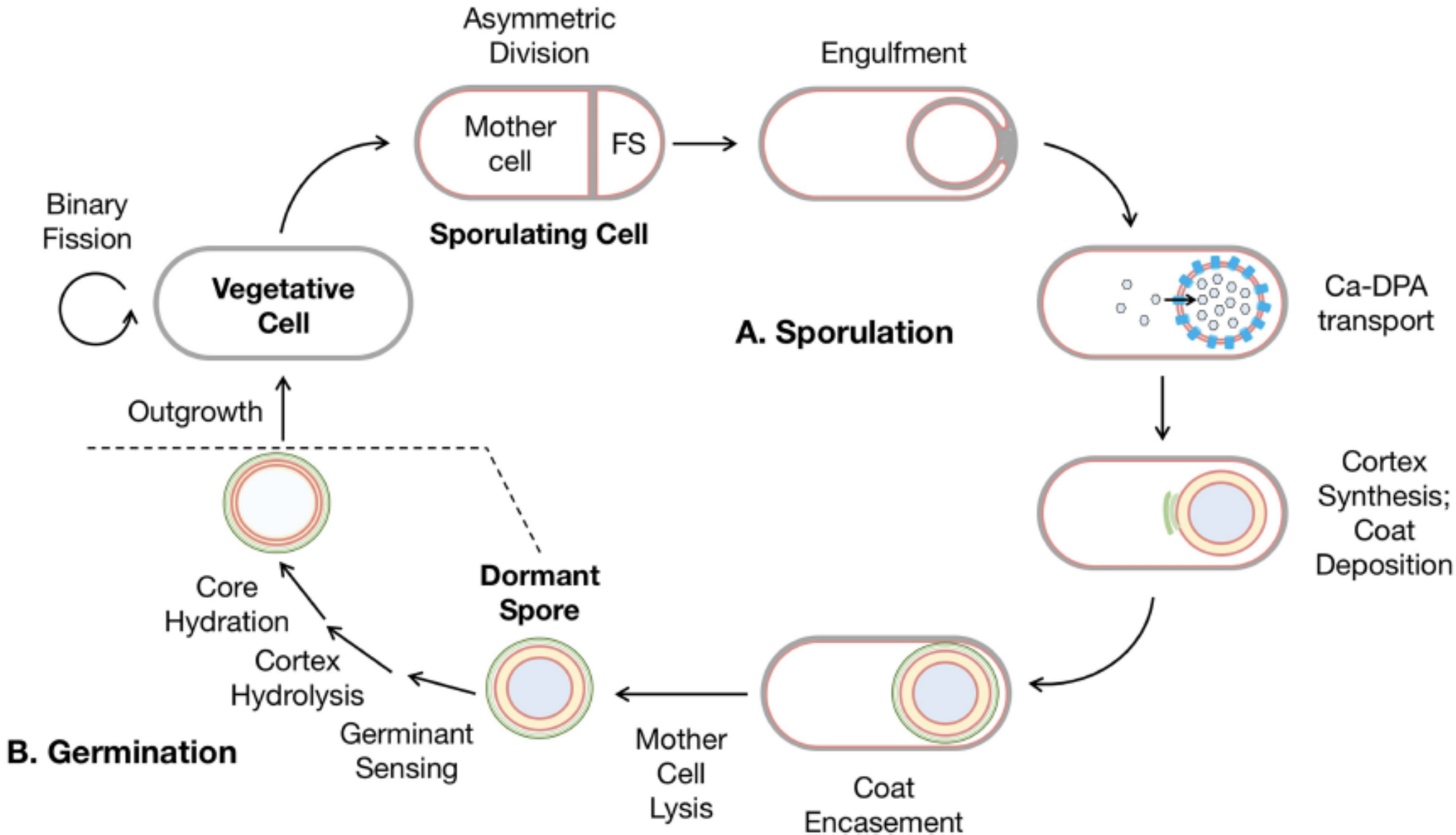
- *Infectious* form
- Survival
- *Resistant* to antibiotics
- *Resistant* to antiseptics, disinfectants



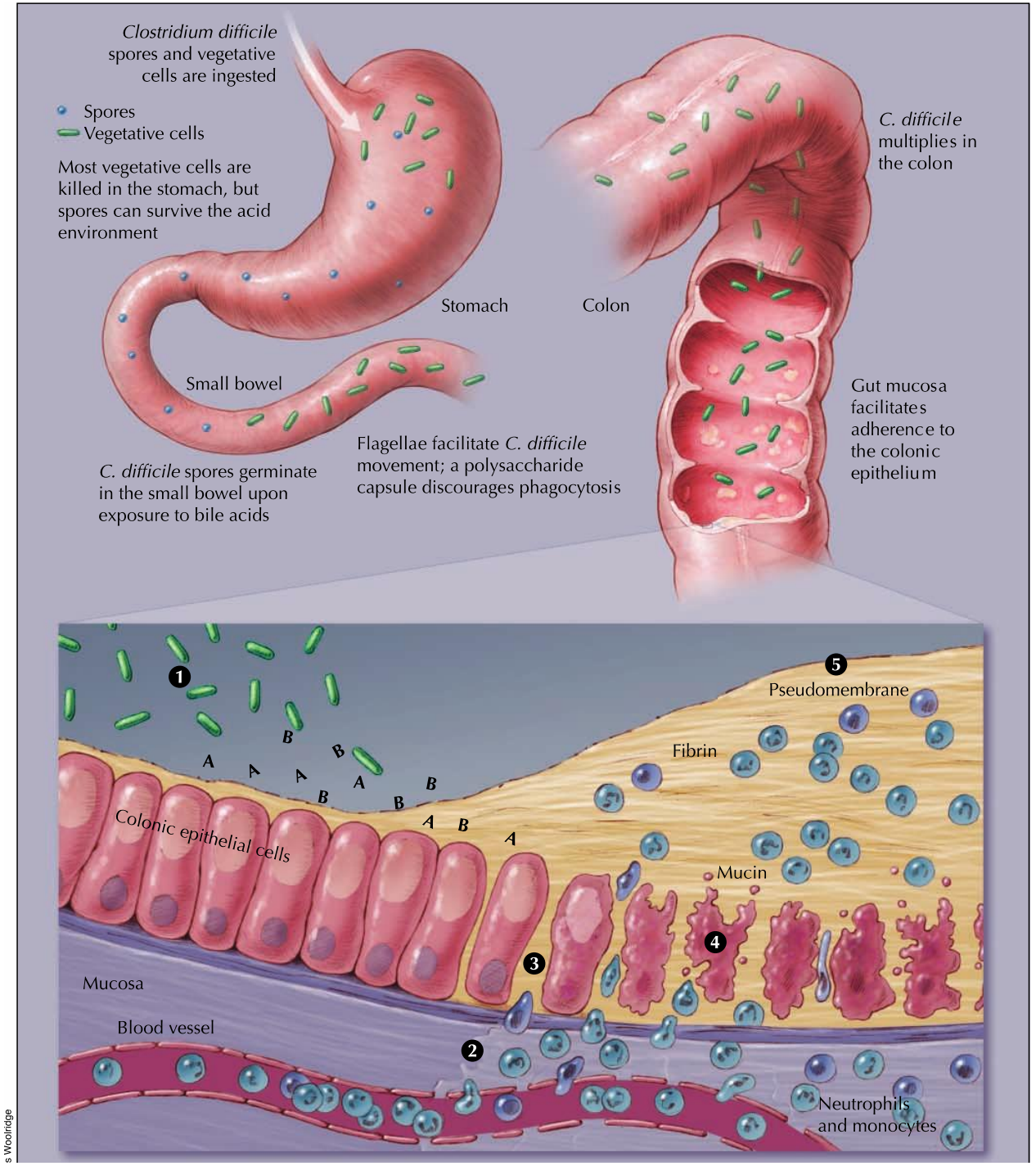
Vegetative bacillus

- *Replication*
- *Disease* causation,
- Adaptation
- *Susceptible* to antibiotics, antiseptics, disinfectants





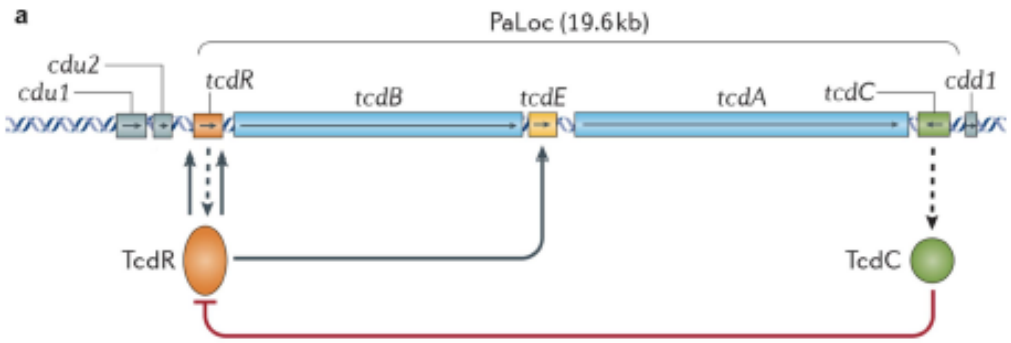
Shen A, et al. Microbiol Spectrum 2019. PMID: 31858953

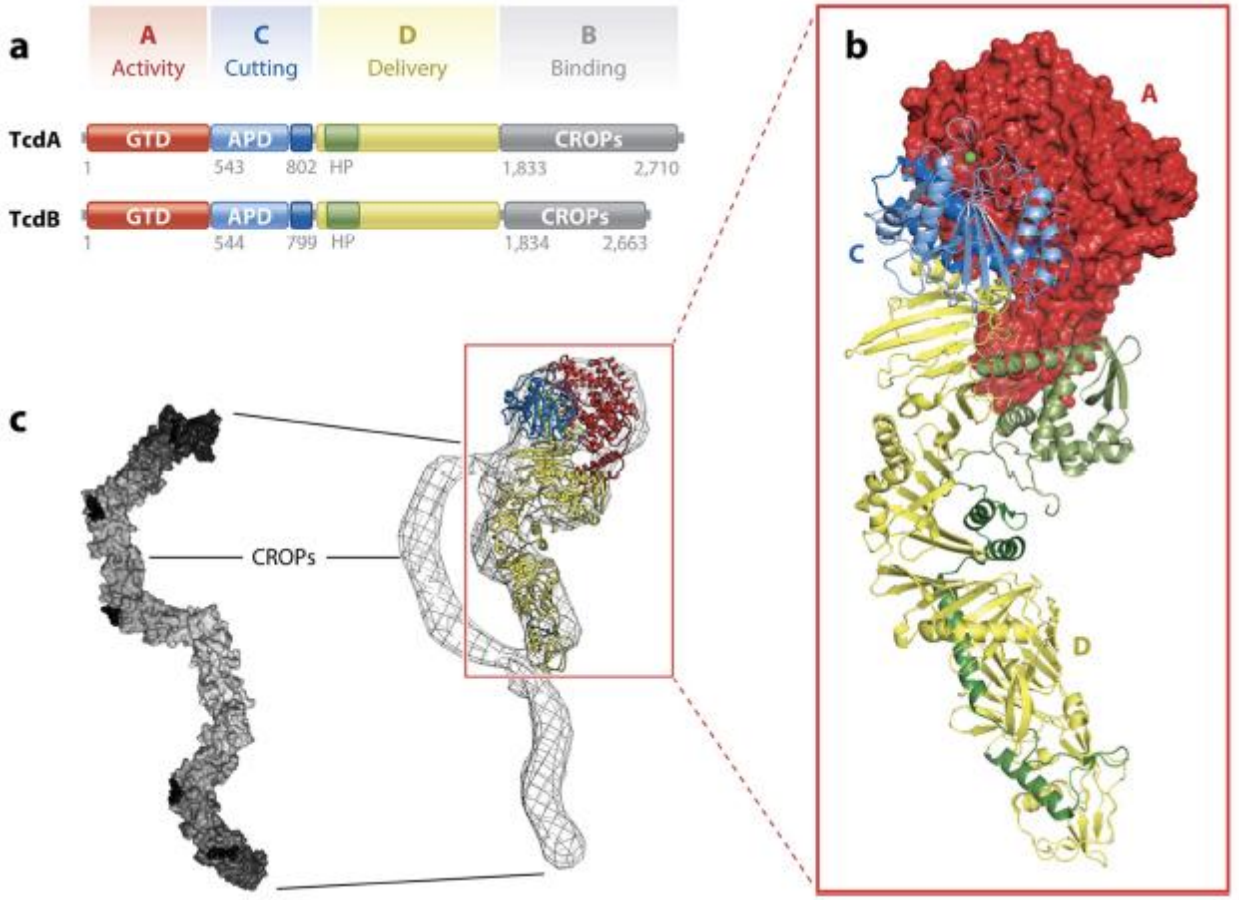


Poutanen SM, Simor AE. CMAJ 2004. 171:51-8.

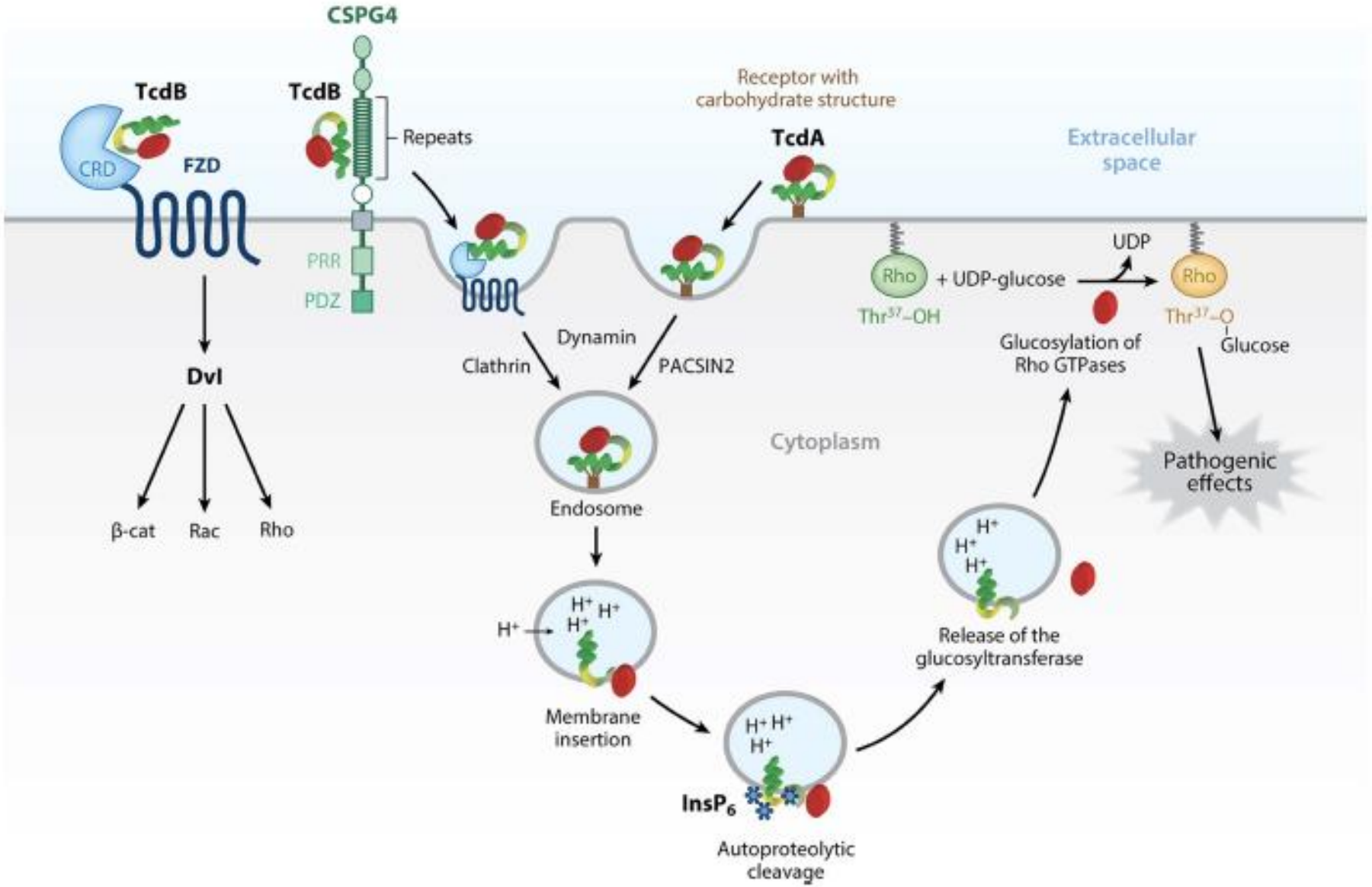
Large glucosylating toxins: TcdA and TcdB

- bacterial AB-type protein toxins
  - A domain is a glucosyltransferase (GTD)
  - B domain responsible for binding, cytosol delivery and autoproteolysis of the A domain
  - Synthesis is regulated via a pathogenicity locus (PaLoc)
  - GTD uses UDP-glucose to enzymatically alter a critical threonine residue in the catalytic site of Rho GTPases





Mileto S, Das A, Lyras D. Microbiol Spectrum 2019. 7(3): GPP3-0015-2018. doi:10.1128/microbiolspec.GPP3-0015-2018.



Intoxication

- Actin cytoskeleton
- Cell rounding, detachment
- Loss of intercellular junctions
- Apoptosis, necrosis
- Inflammasome formation via pyrin (IL-1β, IL-18)
- IL-8, IFN-ɣ, IL-23 production
- ROS generation

Mileto S, Das A, Lyras D. Microbiol Spectrum 2019. 7(3): GPP3-0015-2018. doi:10.1128/microbiolspec.GPP3-0015-2018.

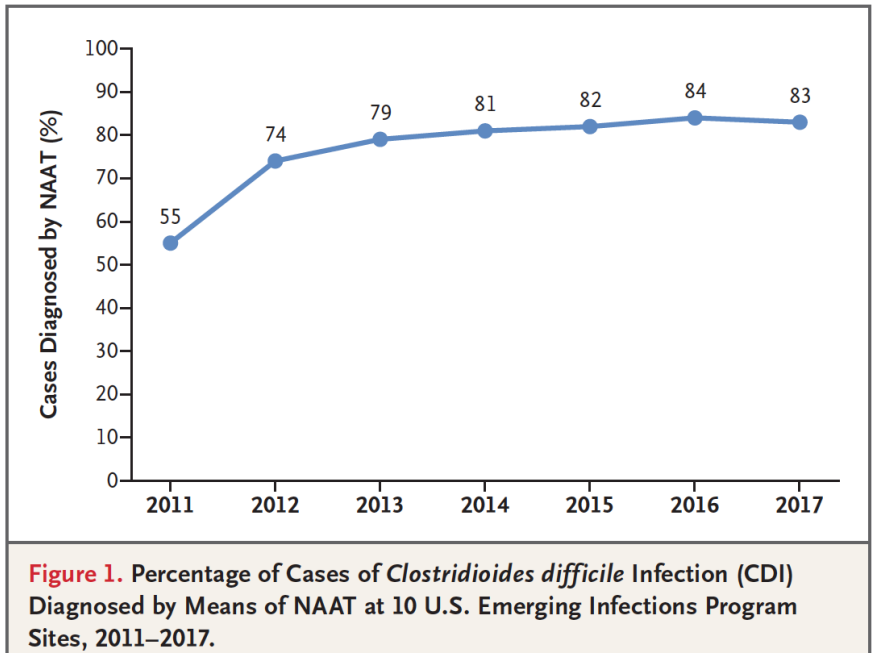
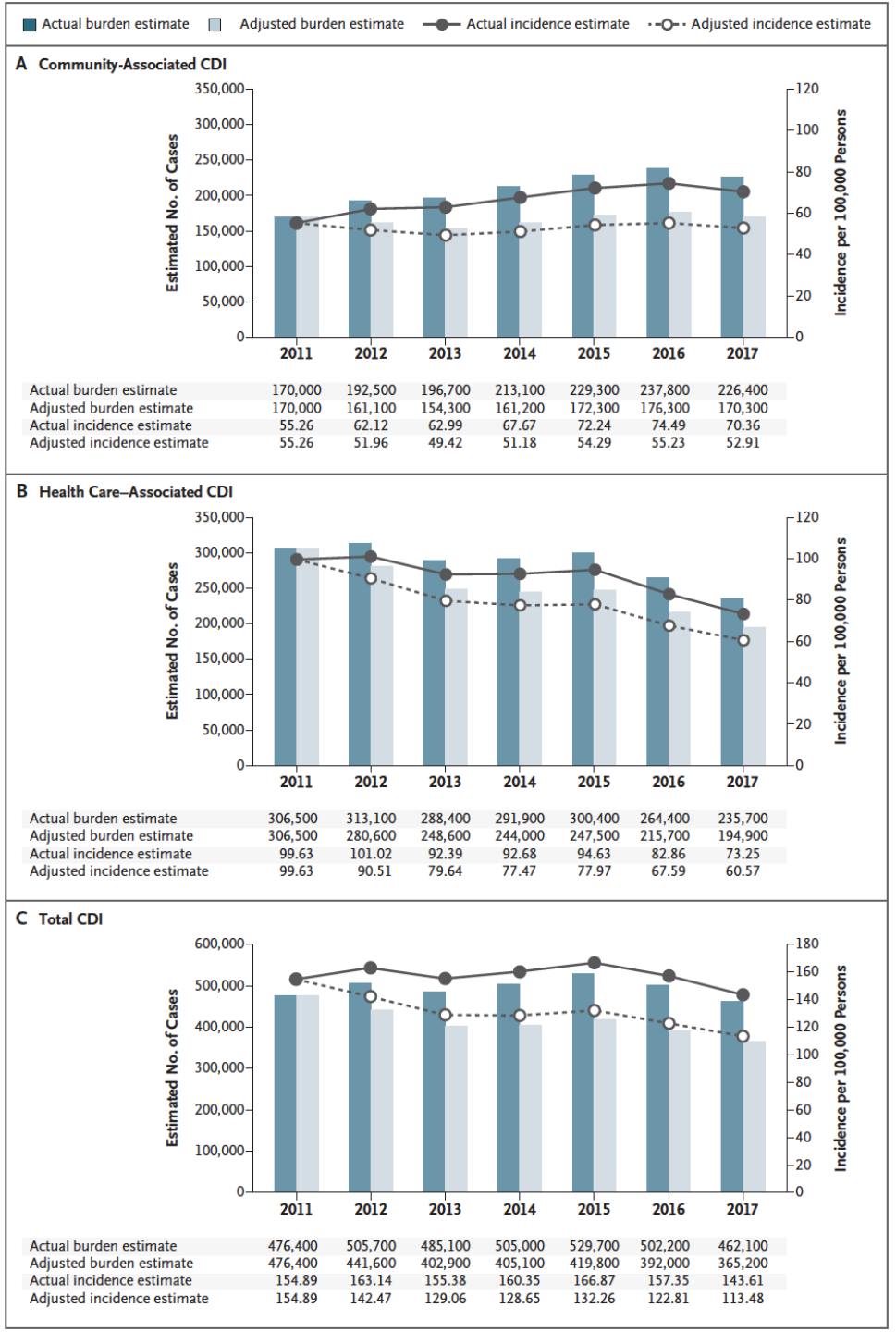


Figure 1. Percentage of Cases of *Clostridioides difficile* Infection (CDI) Diagnosed by Means of NAAT at 10 U.S. Emerging Infections Program Sites, 2011–2017.

Guh A, et al. N Engl J Med 2020. 382:1320-30.



Quantifying CDI Disease Severity

CDC criteria for severe CDI (any, 30-days of CDI diagnosis):

1. ICU admission due to CDI,
2. Required surgery for CDI,
3. Attributable CDI death.

TABLE 4. Concordance of Severity Score Indices for Severe *Clostridium difficile* Infection

Index	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Kappa score (95% CI)
Beth Israel	63.2	87.3	36.4	95.4	0.38 (0.24–0.52)
UPMC version 1	68.4	93.9	56.5	96.3	0.57 (0.43–0.71)
University of Calgary version 1	68.4	90.3	44.8	96.1	0.48 (0.34–0.62)
Hines VA	73.7	93.4	70.0	97.0	0.69 (0.54–0.83)
Modified University of Illinois	84.2	59.4	19.3	97.3	0.18 (0.08–0.27)
University of Calgary version 2	73.7	72.7	23.7	96.0	0.24 (0.13–0.36)
UPMC version 2	73.7	88.5	42.4	96.7	0.47 (0.33–0.61)
University of Temple	68.4	71.5	21.7	95.2	0.20 (0.09–0.32)

NOTE. CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; UPMC, University of Pittsburgh Medical Center.

TABLE 3. Significant Risk Factors for *Clostridium difficile* Infection by Multivariate Analysis (Stepwise Logistic Regression Test)

Factor	Severe cases (n = 19)	Nonsevere cases (n = 165)	P	OR (95% CI)
Abdominal distension	16 (84.2)	27 (16.4)	.007	12.74 (2.91–55.79)
Fever (temperature, >38.0°C)	10 (52.6)	33 (20.0)	.042	4.70 (1.05–20.95)
WBC count ≥20,000 cells/mm^3	12 (63.2)	36 (21.8)	.035	4.42 (1.11–17.65)
Hypoalbuminemia (serum albumin level <3 mg/dL)	17/18 (94.4)	74/136 (54.4)	.029	13.69 (1.30–143.8)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Some denominators differ from the population total because of missing data. CI, confidence interval; OR, odds ratio; PPI, proton pump inhibitor; WBC, white blood cell.

Fujitani S, George L, Murthy R. Infect Control Hosp Epidemiol 2011. 32:220-8.

Table 1 *Clostridium difficile* disease score

Variable	Points
Fever (38.0 °C)	1
Ileus[a]	1
Systolic blood pressure < 100 mmHg[b]	1
Leukocytosis	
WBC < 15,000/mm^3	0
WBC ≥ 15,000/mm^3, <30,000/mm^3	1
WBC > 30,000/mm^3	2
CT scan findings (thickened colonic wall, colonic dilatation, ascites)	
No findings	0
1 Finding	1
≥2 Findings	2

[a] Ileus diagnosed by clinical or radiographic findings.
[b] Any single reading within 3 days of CDD diagnosis.

Belmares J, et al. J Infect 2007. 55:495-501.

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)

McDonald LC, et al. Clin Infect Dis 2018. 66:987-94.

How Recurrent is CDI?

Table 2 Treatment response of vancomycin and metronidazole for *Clostridium difficile* infections

Patients enrolled	*N*	Followed up (days)	Treatment failures (%)	Recurred (%)	Reference
Vancomycin					
1982–1991	122	30	1	10	Olson *et al.* [59]
1993–1995	31	30	6	16	Wenisch *et al.* [60]
1994–2002	71	21	3	7	Zar *et al.* [61••]
2006	80	56	9	19	Louie *et al.* [62]
2006–2007	18	60	16	11	Al-Nassir *et al.* [63•]
Metronidazole					
1982–1991	632	30	2	6	Olson *et al.* [59]
1991–2002	688	60	10	21	Pepin *et al.* [64]
1993–1995	31	30	6	16	Wenisch *et al.* [60]
1994–2002	79	21	16	14	Zar *et al.* [61••]
1999–2002	50	40	7	29	Wullt and Odenholt [65]
2003–2004	27	56	26	20	Modena *et al.* [66]
2003–2004	435	60	26	47	Pepin *et al.* [64]
2003–2004	119	56	34	33	Musher *et al.* [67•]
2004–2005	20	40	35	38	Lagrotteria *et al.* [68]
2006–2007	34	60	12	12	Al-Nassier *et al.* [63•]

6-47%

McFarland LV. Curr Opin Gastroenterol 2008. 25:24-35.

Risk Factors for Recurrent CDI

Systematic review and meta-analysis of risk factors for rCDI

- 33 studies, n=18530
- Random effects model; pooled RR calculations

Independent Risk Factor	RR (95% CI)
Age ≥65 years	1.63 (1.24-2.14)
Additional antibiotics during follow-up	1.76 (1.52-2.05)
Renal insufficiency	1.59 (1.14-2.23)
Proton pump inhibitor use	1.58 (1.13-2.21)
Prior fluoroquinolone use	1.42 (1.28-1.57)

Deshpande A, et al. Infect Control Hosp Epidemiol 2015. 36:452-60.

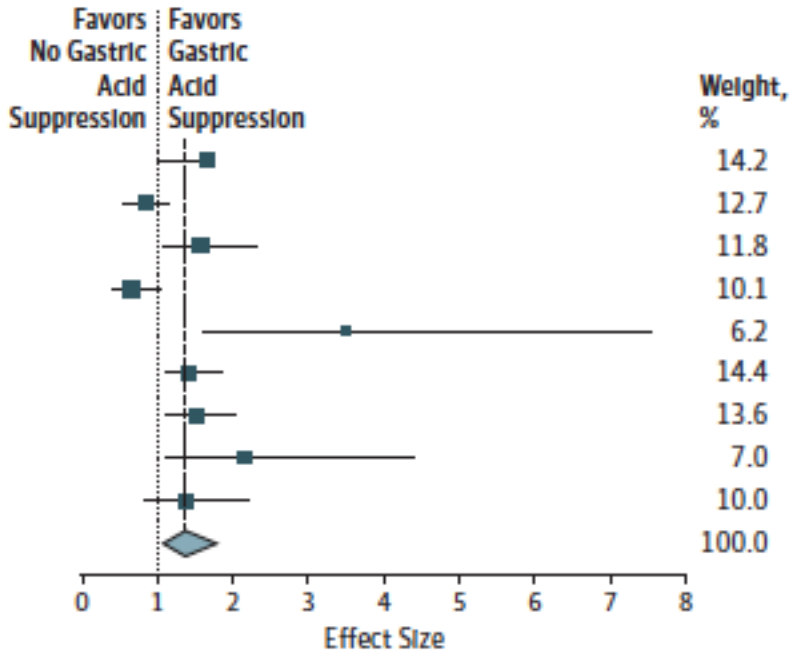
JAMA Internal Medicine | Original Investigation

Association of Gastric Acid Suppression With Recurrent *Clostridium difficile* Infection

A Systematic Review and Meta-analysis

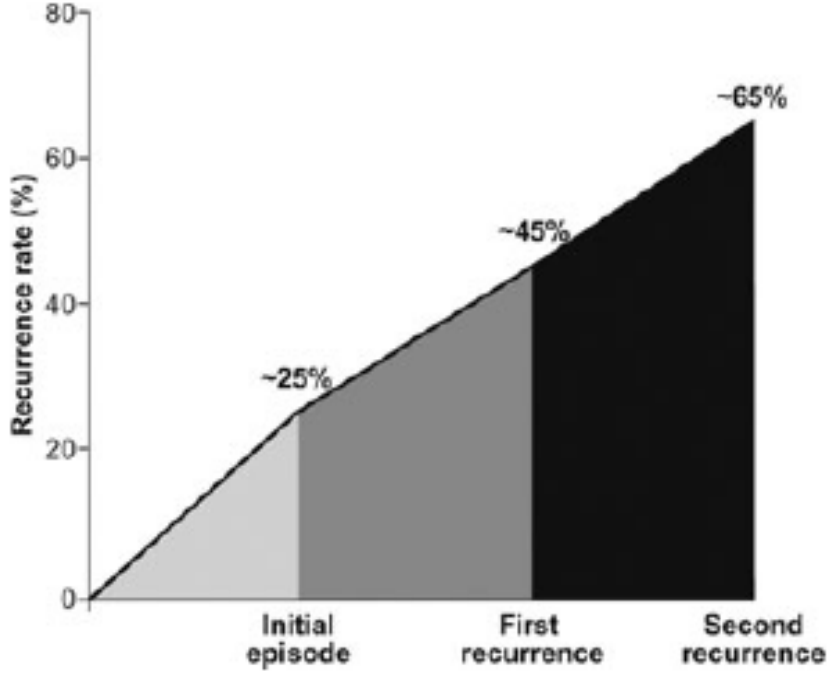
Figure 4. Nine Studies That Controlled for Potential Confounders

Source	Effect Size (95% CI)
Abdelfatah et al,[16] 2015	1.65 (1.00-1.70)
Freedberg et al,[30] 2013	0.82 (0.58-1.16)
Hebert et al,[31] 2013	1.55 (1.05-2.29)
Khanna et al,[18] 2012	0.65 (0.40-1.06)
Kim et al,[25] 2010	3.48 (1.61-7.54)
Linsky et al,[33] 2010	1.42 (1.10-1.83)
McDonald et al,[17] 2015	1.50 (1.10-2.00)
Rodríguez-Pardo et al,[34] 2013	2.17 (1.08-4.35)
Weiss et al,[36] 2015	1.35 (0.83-2.21)
Overall: $Q=27.40$; $P=.02$; $I^2=71\%$	



Plot demonstrates increased risk of recurrent *Clostridium difficile* infection with gastric acid suppressants by the random-effects model (odds ratio, 1.38; 95% CI, 1.08-1.76).

Tariq R, et al. JAMA Intern Med 2017. 177:784-91.



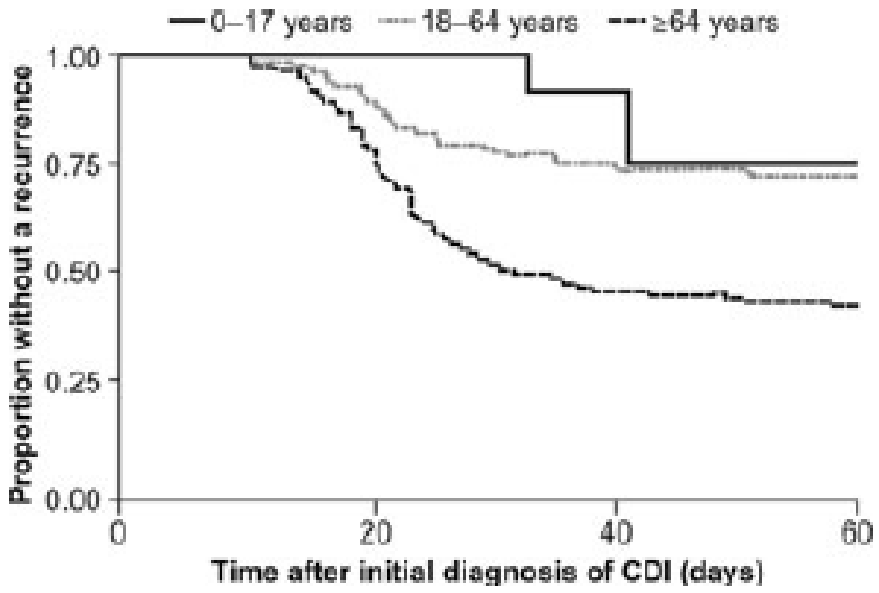


TABLE 1. Clinical prediction rule for recurrent *Clostridium difficile* infection [34]

Risk factor	Score
Age >65 years	1
Severe underlying disease (Horn index score of 3 or 4)[a]	1
Additional antibiotic use	1
Add one point for each risk factor present to determine score (range 0–3)	

[a]The Horn index rates the severity of underlying disease into one of four categories on the basis of clinical judgement: 1 = mild (single mild illness); 2 = moderate (more severe illness but uncomplicated recovery expected); 3 = severe (major complications or multiple conditions requiring treatment); 4 = fulminant (catastrophic life-threatening illness).

TABLE 2. Risk of recurrent *Clostridium difficile* infection (CDI) in comparison with score on the clinical prediction rule [34]

	Recurrence			
	Derivation cohort *n* = 44; 50% recurrence		Validation cohort *n* = 64; 20% recurrence	
Score	*n*	%	*n*	%
0	0/7	0	0/9	0
1	5/15	33.3	6/36	16.7
2	10/14	71.4	5/16	31.3
3	7/8	87.5	2/3	66.7

Patients with scores ≥2 were classified as being at high risk of recurrent CDI. The point estimate of the accuracy of a score ≥2 for predicting recurrence is 71.9% (95% CI 59.2–82.4%) [34]. Other point estimates of performance include a sensitivity of 53.8%, a specificity of 76.5%, a positive predictive value of 36.8%, and a negative predictive value of 86.7% [34].

Kelley CP. Clin Microbiol Infect 2012. 18(Suppl 6):21-7.

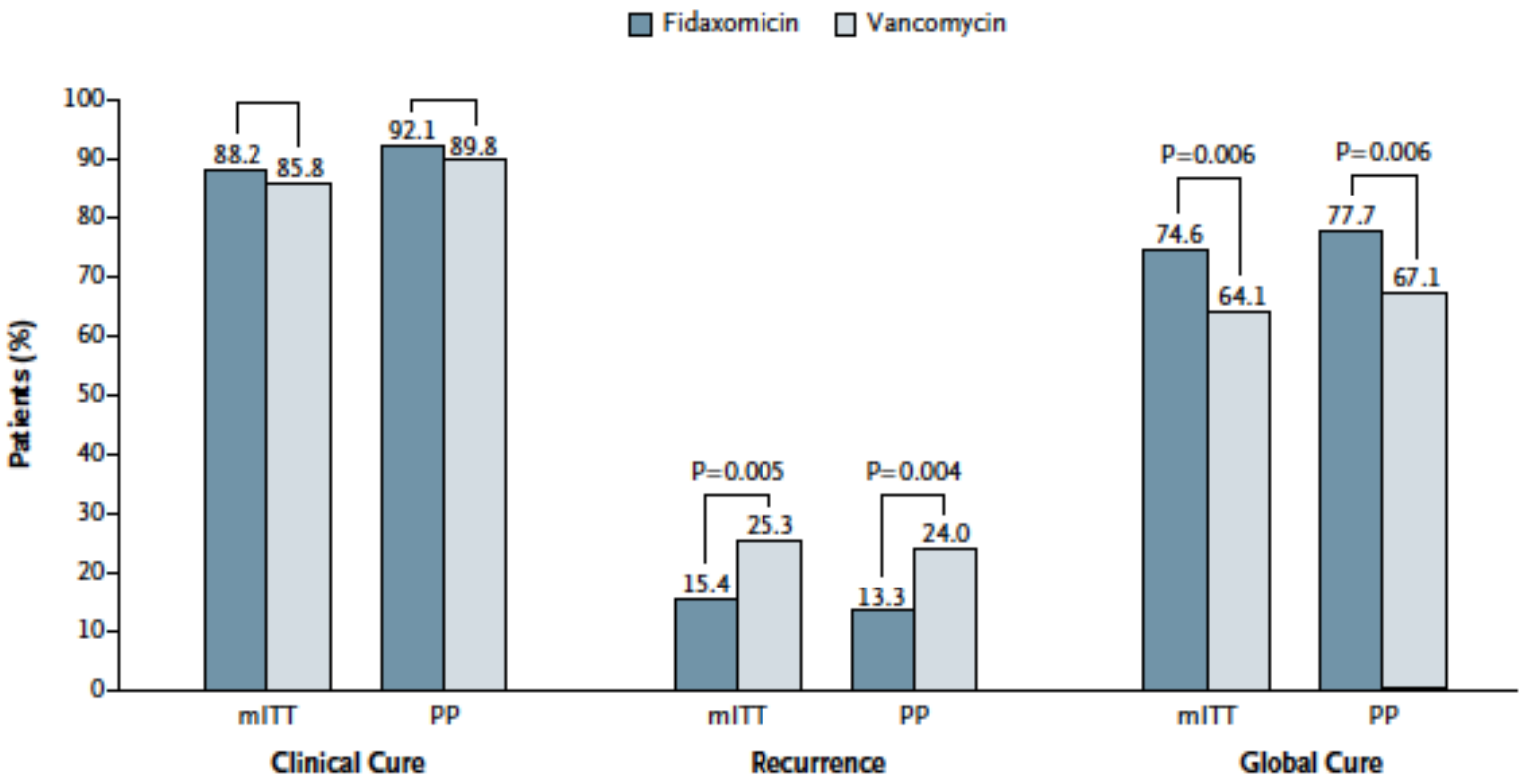
What about Treating Recurrent CDI (rCDI)?

First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

McDonald LC, et al. Clin Infect Dis 2018. 66:987-94.

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

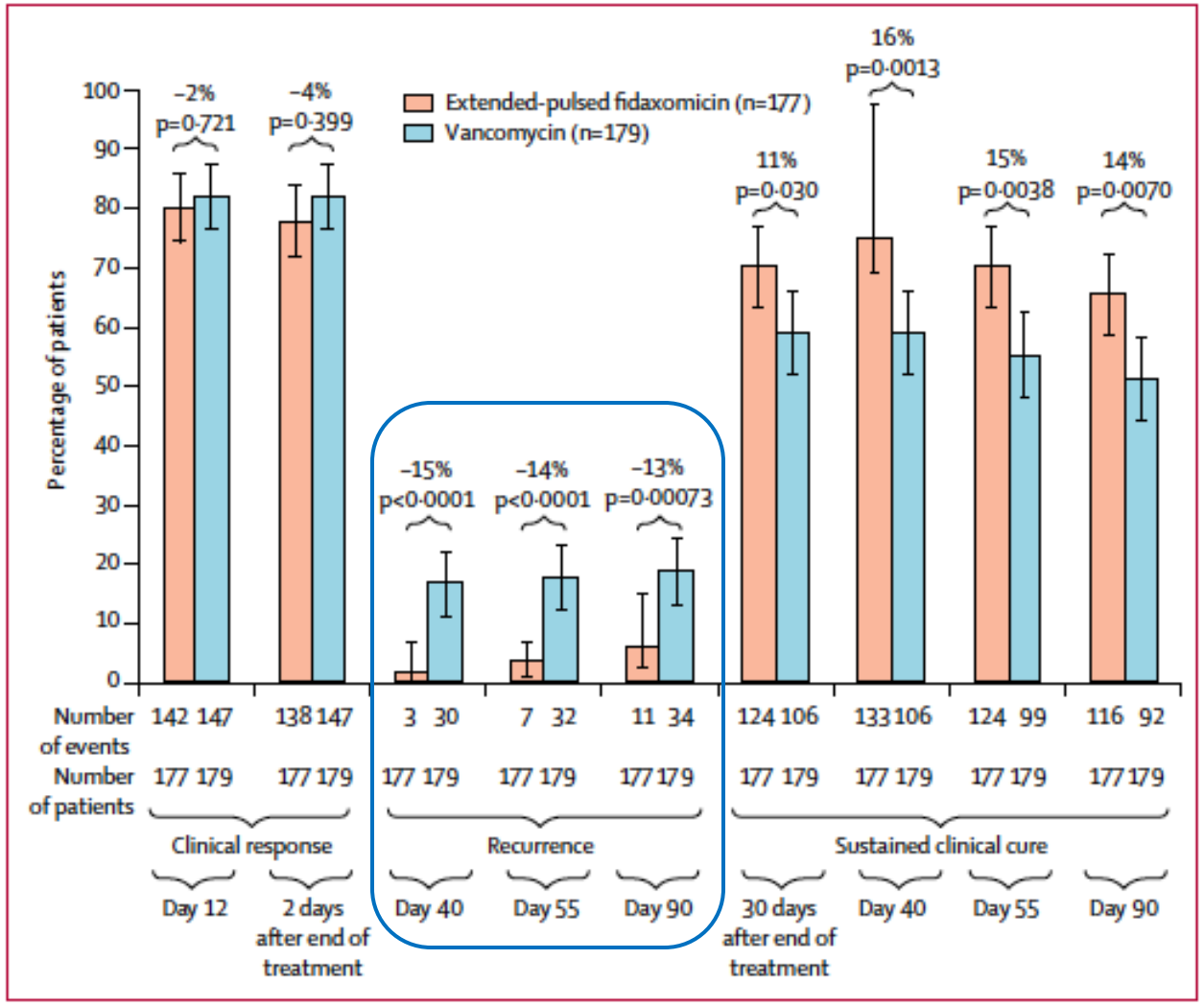
- PRCT, multiple sites, double-blinded, active comparator
- Adults with CDI (+ toxin, 1st or 2nd episode in 3mos)
- 10 days: Oral vancomycin 125mg PO q6hrs; fidaxomicin 200mg PO q12hrs
- Primary outcome: rate of clinical cure at EOT/withdrawal in both mITT and PP populations.
- Recurrence: within 4 weeks of cessation of initial therapy, CDI symptoms, toxin +, required treatment.



Louie TJ, et al. N Engl J Med 2011. 364:422-31.

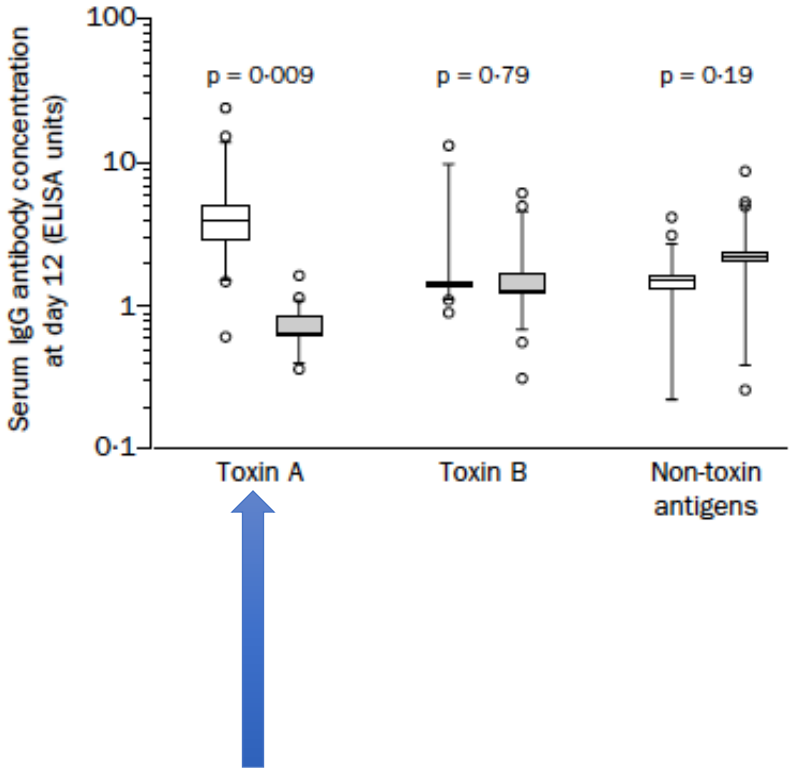
Making the Most of Fidaxomicin-the EXTEND trial

- Confirmed CDI, age>60yrs; excluded any with >2 CDI episodes past 3mos.
- 86 European hospitals
- ~36-37% severe CDI in each group
- Open-label RCT, superiority design
- Fidaxomicin 200mg tabs (total of 20 tabs)
  - BID on days 1-5
  - One tab Q48hrs on days 7-25
- OR vancomycin 125mg PO q6hrs days 1-10
- Primary outcome: sustained clinical cure at 30 days after EOT
- Secondary outcomes included sustained clinical cure and recurrent CDI, both at days 40, 55, 90 after EOT



Guery B, et al. Lancet Infect Dis 2018. 18:296-307.

44 patients with incident CDI followed for 60 days



Kyne L, et al. Lancet 2001. 357:189-93.

What about the host response?

Phase 2 trial of actoxumab and bezlotoxumab (n=99 in placebo group)

Table 2. Multivariate Analysis of Clinical and Immunological Risk Factors for Recurrent *Clostridium difficile* Infection

Variable Name	Odds Ratio	Univariate *P* Value	Odds Ratio	Multivariable *P* Value
Age	1.04	.038		
Age (<65 y/≥65 y)	3.93	.009	3.76	.024
Female vs male sex	1.02	.971		
"Other" race vs white race	0.70	.613		
Horn index 3 vs Horn index 1	3.12	.176		
Horn index 2 vs Horn index 1	4.20	.077		
Metronidazole vs vancomycin	0.65	.424		
Additional antibiotic use	2.20	.095	2.06	.19
Antacid/antiulcer use	0.92	.870		
Prior episodes of CDI (yes/no)	2.7	.041	2.58	.09
Inpatient vs outpatient	0.97	.952		
MassBiologics assay				
Presence of toxin A antibodies (yes/no)	0.40	.401		
Presence of toxin B antibodies (yes/no)	0.12	.045	0.11	.05
Presence of toxin A or toxin B antibodies (yes/no)	0.23	.064		

Gupta SB, et al. Clin Infect Dis 2016. 63:730-4.

MODIFY I and II: Bezlotoxumab for Prevention of Recurrent CDI

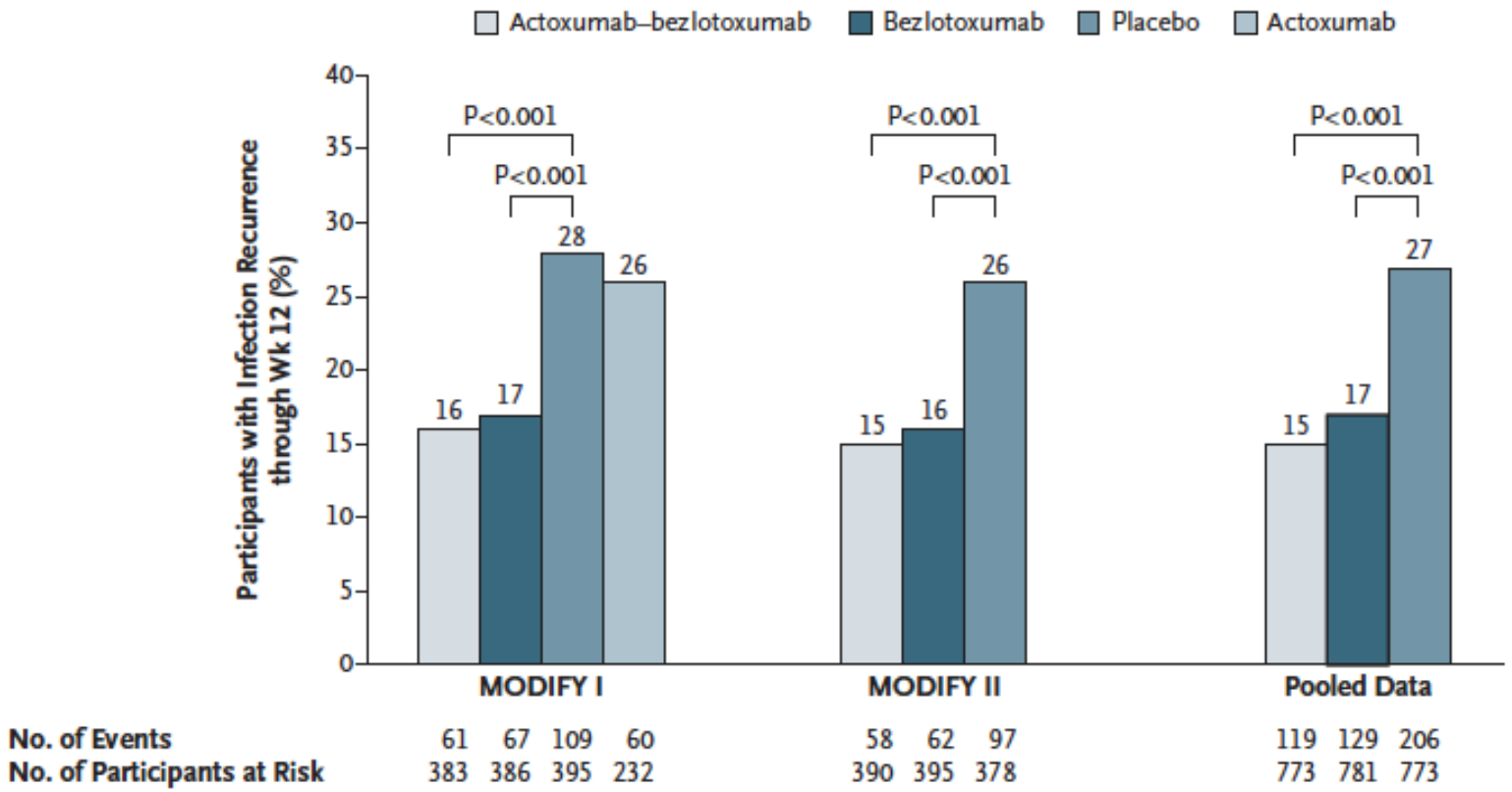
- Two double-blind, placebo-controlled RCTs, confirmed CDI, total n=2655, 322 sites in 30 countries
- Standard-of-care antibacterials for CDI based on treating physician
- Bezlotoxumab 10mg/kg IV once, OR actoxumab* plus bezlotoxumab (same doses), or placebo (* MODIFY 1 included an arm receiving actoxumab alone; stopped after interim analysis)
- Primary outcome: recurrences within 12 weeks of infusion

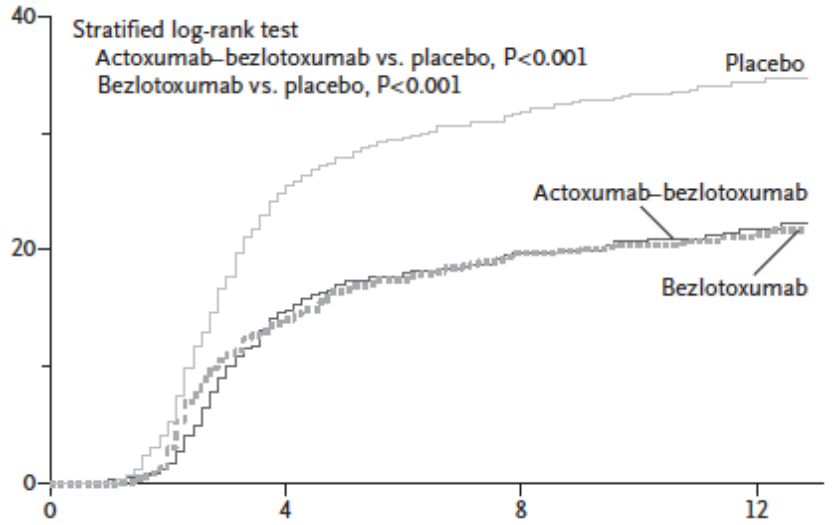
Wilcox MH, et al. N Engl J Med 2017. 376:305-17.

Table 1. Clinical and Demographic Characteristics of Participants in the Modified Intention-to-Treat Population in Both Trials.

Characteristic	Actoxumab plus Bezlotoxumab (N=773)	Bezlotoxumab (N=781)	Actoxumab (N=232)	Placebo (N=773)	All Participants (N=2559)
	number of participants (percent)				
Standard-of-care antibiotic					
Metronidazole	366 (47.3)	365 (46.7)	112 (48.3)	353 (45.7)	1196 (46.7)
Vancomycin	366 (47.3)	370 (47.4)	113 (48.7)	372 (48.1)	1221 (47.7)
Fidaxomicin	25 (3.2)	30 (3.8)	7 (3.0)	30 (3.9)	92 (3.6)
Inpatient	523 (67.7)	530 (67.9)	158 (68.1)	520 (67.3)	1731 (67.6)
Female sex	423 (54.7)	442 (56.6)	130 (56.0)	449 (58.1)	1444 (56.4)
Age ≥65 years	441 (57.1)	390 (49.9)	122 (52.6)	405 (52.4)	1358 (53.1)
≥1 Episodes of *C. difficile* infection in previous 6 mo	200 (25.9)	216 (27.7)	69 (29.7)	219 (28.3)	704 (27.5)
≥2 Previous *C. difficile* infection episodes ever	103 (13.3)	100 (12.8)	34 (14.7)	126 (16.3)	363 (14.2)
Severe *C. difficile* infection*	142 (18.4)	122 (15.6)	31 (13.4)	125 (16.2)	420 (16.4)
Immunocompromised†	163 (21.1)	178 (22.8)	55 (23.7)	153 (19.8)	549 (21.5)
Other antibiotic use during standard-of-care therapy‡	333 (43.1)	292 (37.4)	86 (37.1)	317 (41.0)	1028 (40.2)
Other antibiotic use after standard-of-care therapy‡	274 (35.4)	273 (35.0)	83 (35.8)	275 (35.6)	908 (35.5)
Renal impairment§	96 (12.4)	123 (15.7)	37 (15.9)	110 (14.2)	366 (14.3)
Hepatic impairment¶	56 (7.2)	49 (6.3)	14 (6.0)	44 (5.7)	163 (6.4)
Region of enrollment‖					
Africa	2 (0.3)	5 (0.6)	1 (0.4)	2 (0.3)	10 (0.4)
Asia–Pacific	80 (10.3)	79 (10.1)	10 (4.3)	77 (10.0)	246 (9.6)
Latin America	37 (4.8)	30 (3.8)	9 (3.9)	35 (4.5)	111 (4.3)
Europe	292 (37.8)	313 (40.1)	80 (34.5)	293 (37.9)	978 (38.2)
North America	362 (46.8)	354 (45.3)	132 (56.9)	366 (47.3)	1214 (47.4)
PCR ribotype					
Participants with positive culture	477 (61.7)	490 (62.7)	144 (62.1)	486 (62.9)	1597 (62.4)
Most common strains**††	222 (46.5)	210 (42.9)	57 (39.6)	233 (47.9)	722 (45.2)
027, 078, or 244 strain††	90 (18.9)	102 (20.8)	30 (20.8)	115 (23.7)	337 (21.1)
027 strain††	76 (15.9)	89 (18.2)	24 (16.7)	100 (20.6)	289 (18.1)

MODIFY I and II: Bezlotoxumab for Prevention of Recurrent CDI





ARR for bezlotoxumab vs placebo=0.10

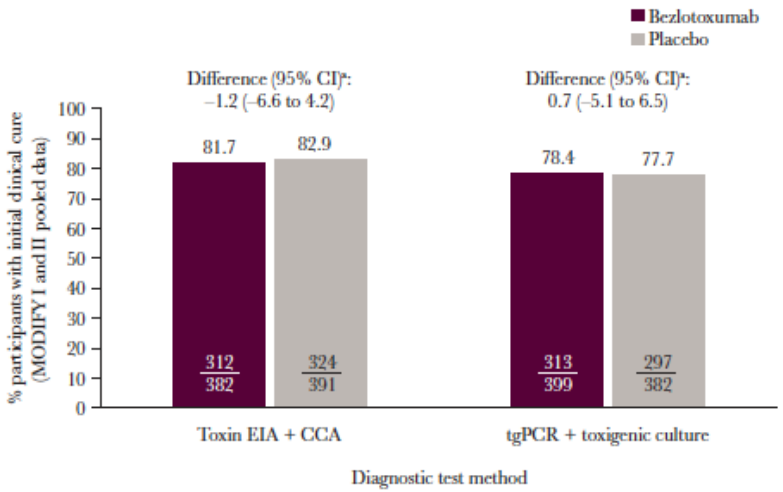
NNT=10

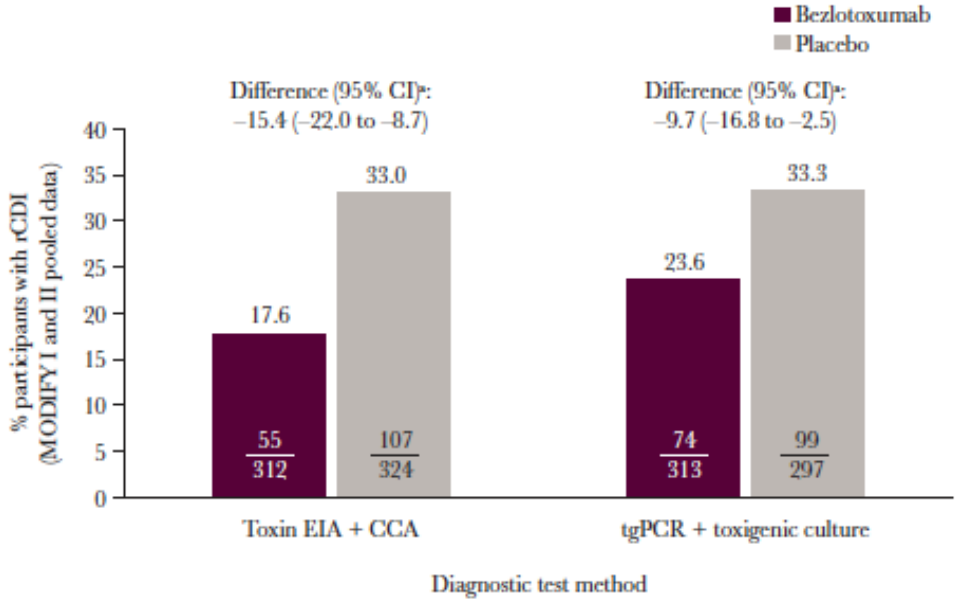
Wilcox MH, et al. N Engl J Med 2017. 376:305-17.

Bezlotoxumab for Prevention of Recurrent CDI in Patients with Toxin + Stools

Direct Methods: toxin EIA, cell cytotoxicity assay (CCA)

Indirect Methods: toxin gene PCR, toxigenic culture

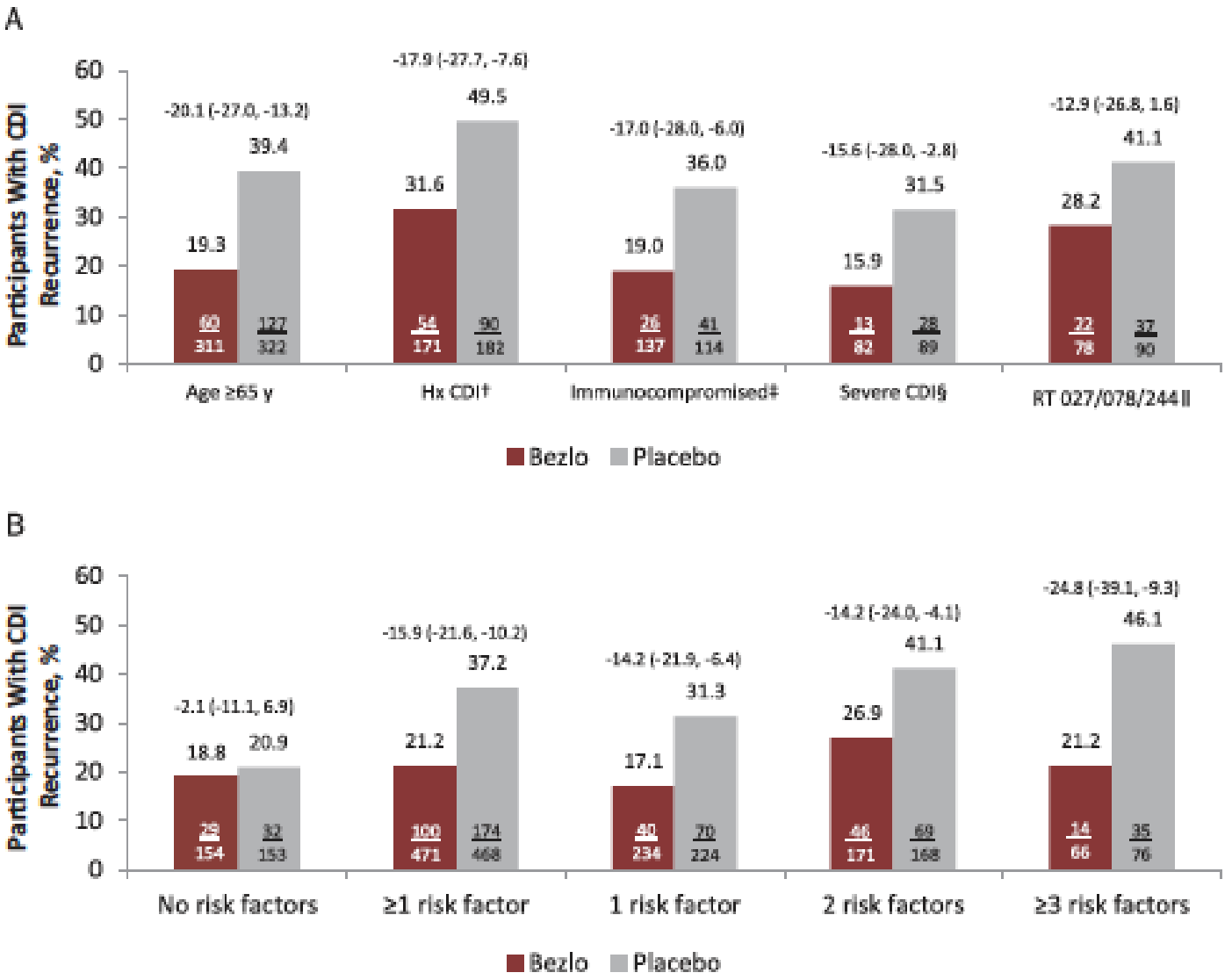




Toxin EIA+CCA NNT=6.5

tgPCR+toxigenic culture NNT=10.3

Wilcox MH, et al. Open Forum Infect Dis 2019.



Gerding DN, et al. Clin Infect Dis 2018. 67:649-56

ID physicians finally have their own CPT code: 5T00L

Fecal Microbiota Transplantation (FMT): Practical Aspects

Box 1 Key issues to select potential donors at the preliminary interview

INFECTIOUS DISEASES
- History of, or known exposure to, HIV, HBV or HCV, syphilis, human T-lymphotropic virus I and II, malaria, trypanosomiasis, tuberculosis
- Known systemic infection not controlled at the time of donation
- Use of illegal drugs
- Risky sexual behaviour (anonymous sexual contacts; sexual contacts with prostitutes, drug addicts, individuals with HIV, viral hepatitis, syphilis; work as prostitute; history of sexually transmittable disease)
- Previous reception of tissue/organ transplant
- Previous (<12 months) reception of blood products
- Recent (<6 months) needle stick accident
- Recent (<6 months) body tattoo, piercing, earring, acupuncture
- Recent medical treatment in poorly hygienic conditions
- Risk of transmission of diseases caused by prions
- Recent parasitosis or infection from rotavirus, *Giardia lamblia* and other microbes with GI involvement
- Recent (<6 months) travel in tropical countries, countries at high risk of communicable diseases or traveller's diarrhoea
- Recent (<6 months) history of vaccination with a live attenuated virus, if there is a possible risk of transmission
- Healthcare workers (to exclude the risk of transmission of multidrug-resistant organisms)
- Individual working with animals (to exclude the risk of transmission of zoonotic infections)

GI, METABOLIC AND NEUROLOGICAL DISORDERS
- History of IBS, IBD, functional chronic constipation, coeliac disease, other chronic GI disorders
- History of chronic, systemic autoimmune disorders with GI involvement
- History of, or high risk for, GI cancer or polyposis
- Recent appearance of diarrhoea, hematochezia
- History of neurological/neurodegenerative disorders
- History of psychiatric conditions
- Overweight and obesity (body mass index >25)

DRUGS THAT CAN IMPAIR GUT MICROBIOTA COMPOSITION
- Recent (<3 months) exposure to antibiotics, immunosuppressants, chemotherapy
- Chronic therapy with proton pump inhibitors

Box 3 Blood and stool testing to check donors for any potentially transmittable disease

GENERAL BLOOD TESTING
- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis A
- HBV
- HCV
- Hepatitis E virus
- Syphilis
- HIV-1 and HIV-2
- *Entamoeba histolytica*
- Complete blood cell count with differential
- C-reactive protein and erythrocyte sedimentation rate
- Albumin
- Creatinine and electrolytes
- Aminotransferases, bilirubin, gamma-glutamyltransferase, alkaline phosphatase

BLOOD TESTING IN SPECIFIC SITUATIONS
- Human T-lymphotropic virus types I and II antibodies
- *Strongyloides stercoralis*

GENERAL STOOL TESTING
- Detection of *Clostridium difficile*
- Detection of enteric pathogens, including *Salmonella*, *Shigella*
- *Campylobacter*, *Escherichia coli O157 H7*, *Yersinia*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, Gram-negative multidrug-resistant bacteria
- Norovirus
- Antigens and/or acid fast staining for *Giardia lamblia* and *Criptosporidium parvum*
- Protozoa (including *Blastocystis hominis*) and helminths
- Faecal occult blood testing

STOOL TESTING IN SPECIFIC SITUATIONS
- Detection of *Vibrio cholera* and *Listeria monocytogenes*
- Antigens and/or acid fast staining for *Isospora* and *Microsporidia*
- Calprotectin
- *Helicobacter pylori* faecal antigen
- Rotavirus

Cammarota G, et al. Gut 2017. 66:569-80.

Table 3. Cost of Screening a Single Donor for Fecal Transplant[a]

Screening Tests	Cost per Person in Canada (USD)	Cost per Person in United States (USD)
Stool Tests		
Ova, cysts, and parasites	$21.00	$138.84
Microscopy and culture	$13.50	NA[b]
Rotavirus	NA[c]	$97.94
Norovirus	NA[c]	$108.70
Adenovirus	NA[c]	$78.02
Clostridium difficile toxin GDH and toxin	$30	$100.09
Vancomycin-resistant *Enterococcus*	$2.63	NA[b]
Fecal *Giardia* antigen	$10.88	$88.15
Fecal *Cryptosporidium* antigen	$10.88	$86.10
Helicobacter pylori	NA[c]	$169.69
Extended spectrum β-lactamase-producing *Enterobacteriaceae*	NA[c]	$77.49
Microsporidia	NA[c]	$72.11
Blood Tests		
Complete blood count	$6.20	$42.18
Electrolytes	$7.77	$39.69
Urea	$1.94	$49.04
Creatinine	$1.94	$46.64
Alanine aminotransferase	$1.94	$19.03
Alkaline phosphatase	$1.94	$49.04
Total bilirubin	$1.94	$19.03
Albumin	$1.94	$41.16
Fasting lipids	$10.48	$147.35
HbA1c	NA[c]	$71.39
Glucose	$1.94	$34.80
Anti-TTG antibody (for celiac disease)	$11.95	$156.68
HIV type 1 and 2	NA[c]	$110.85
Hepatitis A virus IgM	$15.00	$96.86
Hepatitis B virus surface antigen	$17.25	$398.44
Hepatitis B virus core antibody IgM and IgG	$14.42	$107.63[d]
Hepatitis B virus surface antibody	$15.46	$52.28
Hepatitis C virus antibody	$15.14	$66.73
Human T-cell lymphotropic virus 1 and 2	NA[c]	$110.85
Epstein-Barr virus IgM	$26.25	$75.34
Cytomegalovirus IgM	$30.00	$76.41
Strongyloides stercoralis serology	NA[c]	$145.29
Entamoeba histolytic serology	NA[c]	$96.86
H pylori serology	NA[c]	NA[b]
Treponema pallidum screening cascade	NA[c]	$75.78
Listeria	NA[c]	$127.00
Swabs		
Gonorrhea	NA[c]	$150.68
Chlamydia	NA[c]	$75.24
MRSA	$15.00	$159.60
Carbapenem-resistant *Enterobacteriaceae*	NA[c]	$171.12
Total per person (laboratory testing)	**$287.39**	**$3772.49**
Other Costs		
Administrative fee	$56.25	NA
Doctor's visit	$90.00	NA
Advertising	$4.88	NA
Total per person	**$438.52**	NA

Craven LJ, et al. Open Forum Infect Dis 2017. doi:10.1093/ofid/ofx243

Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant

Zachariah DeFilipp, M.D., Patricia P. Bloom, M.D., Mariam Torres Soto, M.A., Michael K. Mansour, M.D., Ph.D., Mohamad R.A. Sater, Ph.D., Miriam H. Huntley, Ph.D., Sarah Turbett, M.D., Raymond T. Chung, M.D., Yi-Bin Chen, M.D., and Elizabeth L. Hohmann, M.D.

Fecal microbiota transplantation (FMT) is an emerging therapy for recurrent or refractory *Clostridioides difficile* infection and is being actively investigated for other conditions. We describe two patients in whom extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* bacteremia occurred after they had undergone FMT in two independent clinical trials; both cases were linked to the same stool donor by means of genomic sequencing. One of the patients died. Enhanced donor screening to limit the transmission of microorganisms that could lead to adverse infectious events and continued vigilance to define the benefits and risks of FMT across different patient populations are warranted.

DeFilipp Z, et al. N Engl J Med 2019. doi:10.1056/NEJMoa1910437

E. ORDER INFORMATION

ITEM	DESCRIPTION	UNIT PRICE *Effective as of March 16, 2020*	QUANTITY	TOTAL
FMP250	FMT Lower Delivery (for colonoscopy, sigmoidoscopy, or enema)	$1695		$
FMP30	FMT Upper Delivery (for naso-enteric tube or EGD)	$1695		$
FMPCapDE	FMT Capsule DE (physician orientation required before first order) Requesting Physician: _____ Patient(s) Scheduled? Y__ N__	$2050		$
Standard Delivery	Flat Shipping & Handling fee per shipment, approximate **10:30AM** delivery time. Delivered in 2-3 business days. Waived on orders of 10 units or more.	$150	☐	$
UPS Early AM Fee	Fee assessed for orders requiring approximate **8AM** delivery, as compared to standard estimated 10:30AM. Delivered in 2-3 business days.	Additional $100	☐	$
Next-Day Delivery Fee	Fee assessed for orders requiring next-day delivery. Orders must be received before 3PM ET Mon-Thur. Availability not guaranteed.	Additional $50	☐	$
*Sales tax will be applied to customers located in the Commonwealth of Massachusetts unless Form ST-12 is on file for the account			**SUM TOTAL***	$

Is Fecal Microbiota Transplantation Effective for Preventing Recurrent CDI?

Table 1 Summary of randomized controlled trials of fecal microbiota transplantation for recurrent *Clostridium difficile* infection

Publication	# of patients	Donor	Preparation	Mode	Overall resolution rate (%)	Follow-up duration
Van Nood *et al* 2013 [23]	16	UR	Fresh	NDT	94	10 weeks
Youngster *et al* 2014 [24]	20	UR	Frozen	NGT, colonoscopy	90	6 months
Cammarota *et al* 2015 [25]	20	R & UR	Fresh	Colonoscopy	90	10 weeks or longer
Kelly *et al* 2016 [26]	22	R & UR	Fresh	Colonoscopy	90.9	6 months
Lee *et al* 2016 [5]	178	R & UR	Fresh, frozen	Enema	96.1	13 weeks - 1 year
Hota *et al* 2017 [29]	16	R & UR	Fresh	Enema	43.8	4 months
Kao *et al* 2017 [27]	105	UR	Frozen	Colonoscopy, capsule	96.2	3 months or longer
Jiang *et al* 2017 [28]	72	UR	Fresh, frozen, lyophilized	Colonoscopy	87	5 months

UR, unrelated; R, related; NDT, nasoduodenal tube; NGT, nasogastric tube

YES!!

Ramai D, et al. Ann Gastroenterol 2019. 32:30-8.

Can FMT be given as a pill?

JAMA | Original Investigation

Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection A Randomized Clinical Trial

- Unblinded RCT, 3 sites
- Adults with ≥3 prior CDI episodes
- Oral capsule FMT (40) vs FMT via colonoscopy (360mL in cecum)
- Primary outcome: proportion with no rCDI 12 weeks after FMT

Primary Outcome	
Oral Capsule	Colonoscopy
51/53 (96%)	50/52 (96%)

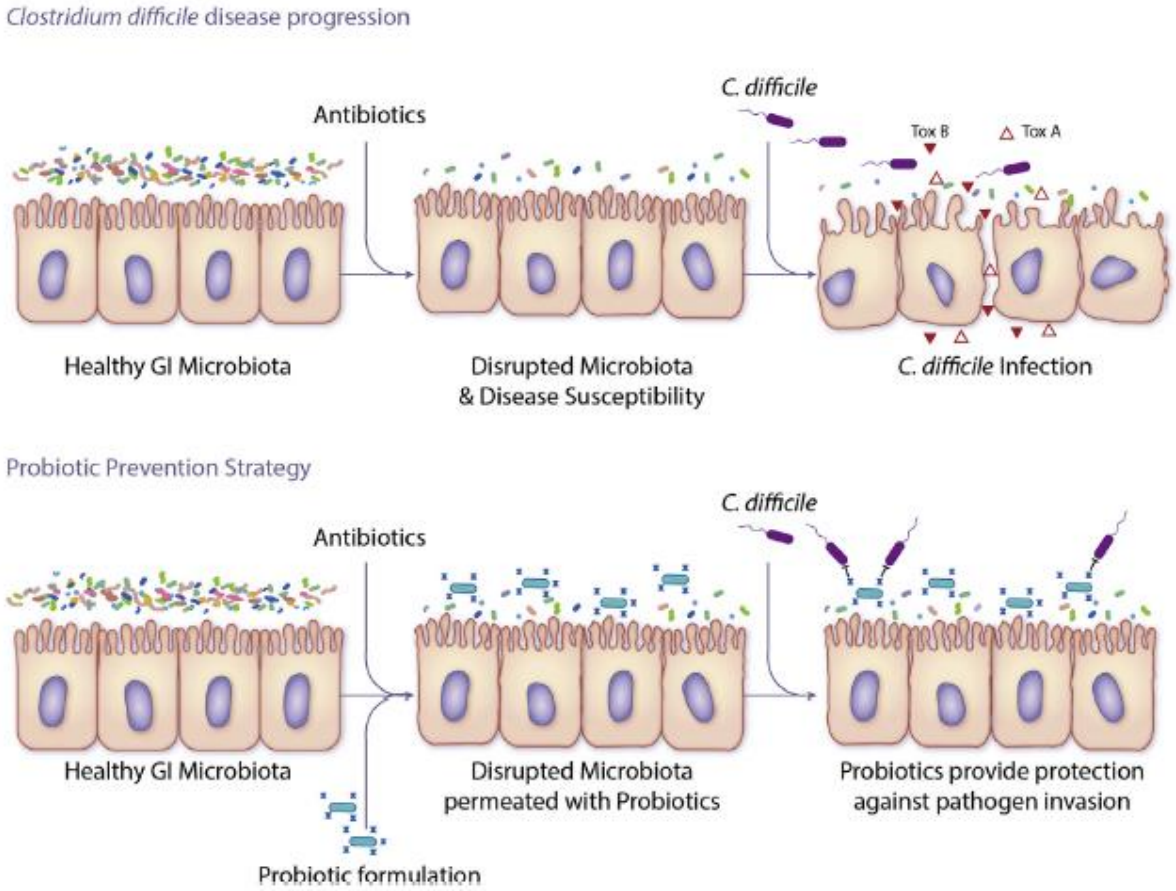
Kao D, et al. JAMA 2017. 318:1985-93.

Probiotics, Prebiotics, Synbiotics, Oh My!!

Probiotic: single or multiple living micro-organisms, administered to promote microbiome diversity and enhance colonization resistance.

Prebiotics: nutrients administered to enhance specific populations of the microbiome.

Synbiotics: mixtures of probiotics and prebiotics.



Spinler JK, Ross CL, Savidge TC. Anaerobe 2016. 41:51-7.

PLACIDE Trial: Probiotic RCT

- Multicenter RCT, double-blind, placebo-controlled
- Lactobacilli and Bifidobacteria
- Inpatients ≥65yrs exposed to parenteral antibiotics; randomized to either probiotic ($6x10^{10}$ cfu once daily x 21 days) or placebo
- Screened 17420, randomized 2981
- Primary outcomes: Antibiotic-associated diarrhea within 8 weeks; CDI within 12 weeks

	Microbial preparation	Placebo	OR (95% CI)	p value
Antibiotic-associated diarrhoea				
Antibiotic-associated diarrhoea*	159/1470 (10·8%)	153/1471 (10·4%)	1·04 (0·83–1·32)	0·72
Clostridium difficile diarrhoea	12/1470 (0·8%)	17/1471 (1·2%)	0·70 (0·34–1·48)	0·35

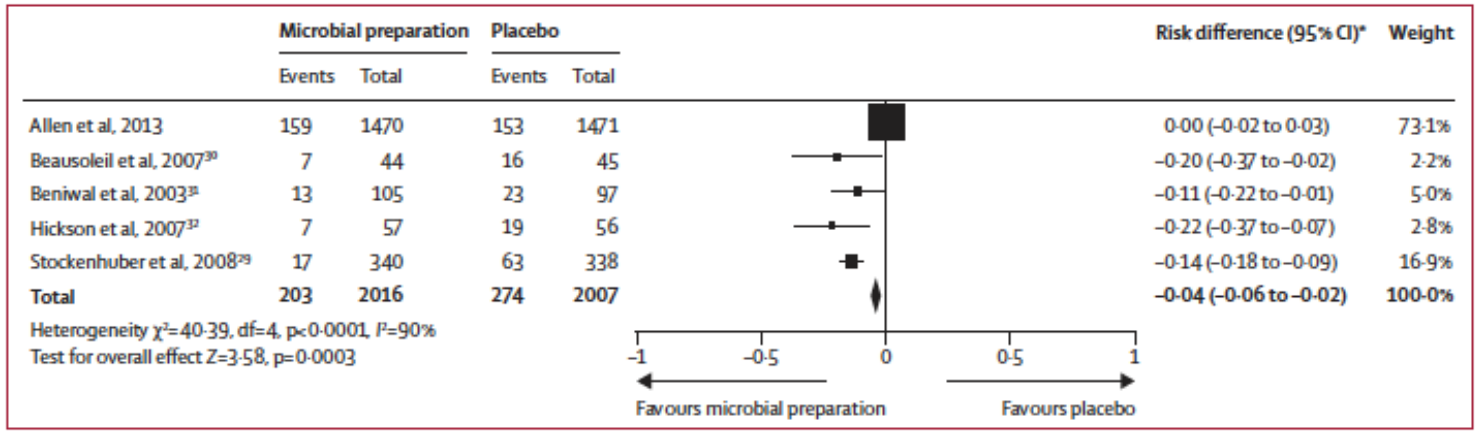


Figure 4: **Meta-analysis of trials of lactobacilli or bifidobacteria, or both, in the prevention of antibiotic-associated diarrhoea in older inpatients**
*From Mantel-Haenszel fixed effects analysis.

Allen SJ, et al. Lancet 2013. 382:1249-57.

What Do I Do?

- **General**
  - Avoid antibacterials (if possible)
  - Hygiene (soap and water)
  - Dilute bleach (10%)
  - Probiotics (live culture yogurts, kefir, OTC products)-optional, advise against in immunocompromised patients.
- **First Recurrence** (within 3 months)
  - EXTEND trial fidaxomicin
  - Vancomycin pulse-taper course
  - Evaluate PPI use
- **Second Recurrence** (within 3 months)
  - Bezlotoxumab (age>65, immunocompromised)
- **Three or more recurrences** (within a year)
  - Bezlotoxumab
  - FMT