CHI Memorial

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Clostridium Difficile Infection

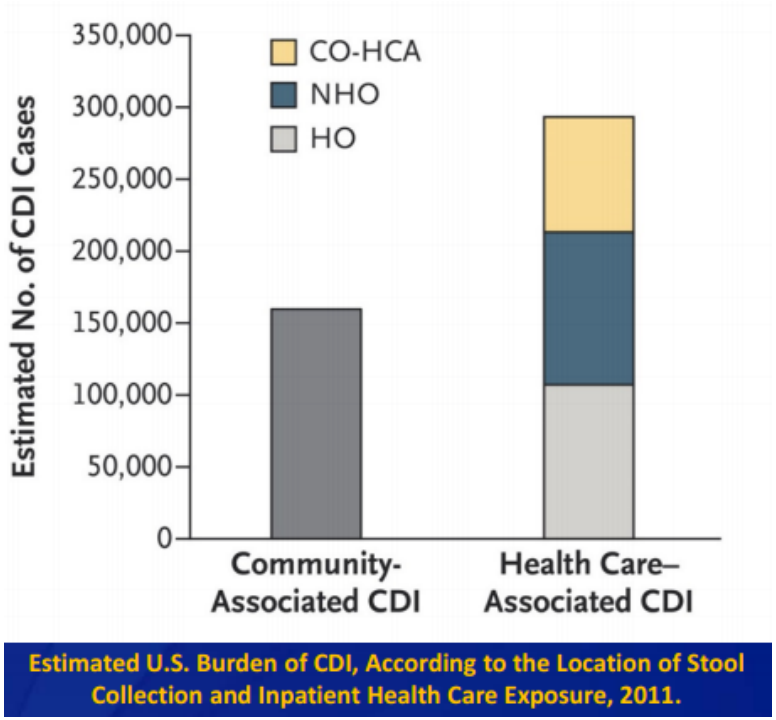
March 23, 2017

Objectives

- Pharmacists:
  - Discuss epidemiology and pathogenesis of *C. difficile* infection
  - Describe *C. difficile* prevention strategies
  - Evaluate the diagnosis of *C. difficile* (utilize CDI decision tree)
  - Recommend management strategies for initial and recurrent episodes of *C. difficile* infection

- Technicians:
  - Discuss epidemiology and pathogenesis of *C. difficile* infection
  - Describe *C. difficile* prevention strategies
  - List the principles of *C. difficile* infection management

Estimated Annual US Burden



Estimated U.S. Burden of CDI, According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.

- 453,000 CDI cases
  - 293,000 healthcare associated
  - 160,000 community-associated
    - 82% associated with outpatient healthcare exposure
- 29,000 death
- $4.8 billion in excess health care costs

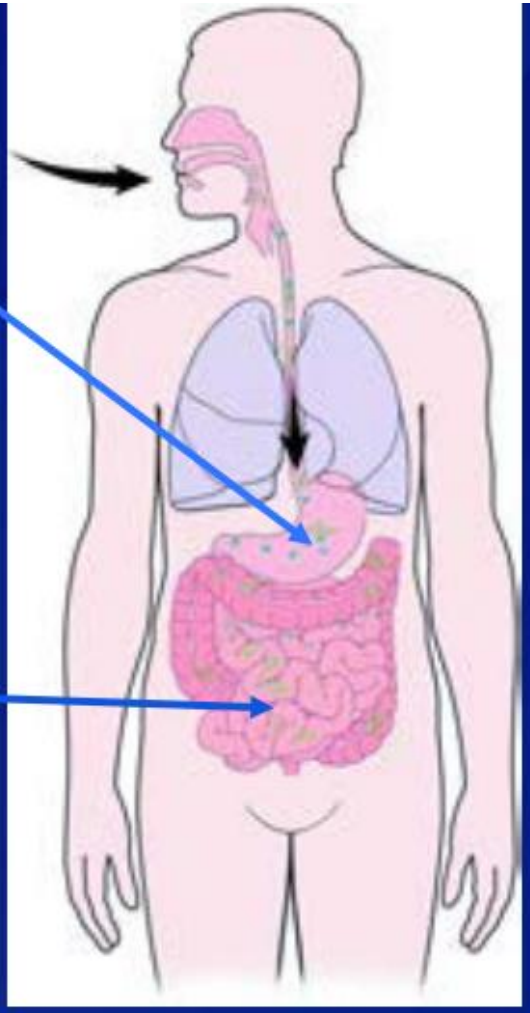
Lessa et al. N Engl J Med 2015; 372(9):825-834
Dubberke et al. Clin Infect Dis 2012; 55:S88-92

Adapted from CDCs CDI Prevention Primer (3/16)

Pathogenesis of CDI

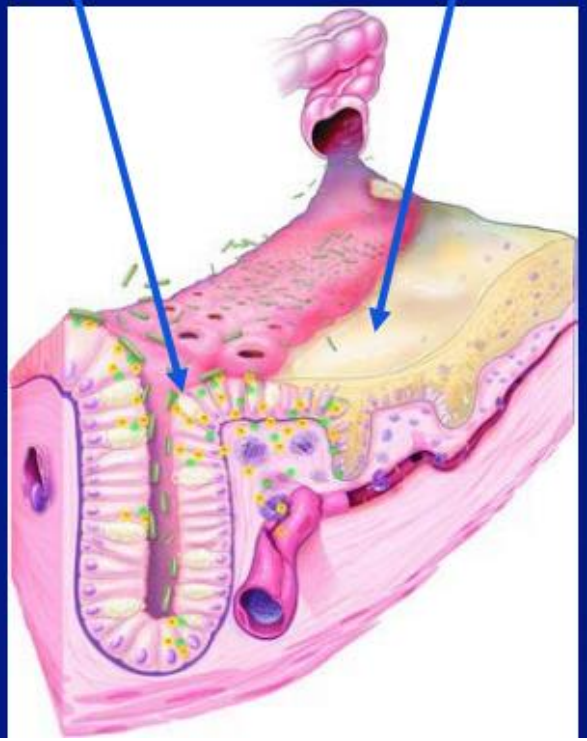
1. CDI spores survive in the environment for long periods of time. Following ingestion, they traverse the acidic environment of the stomach.

2. Spores germinate within the intestine.



3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon.

4. Toxin A & B Production leads to colon damage +/- pseudomembrane.



Sunenshine & McDonald Cleve Clin J Med 2006; 73(2):187-197

Adapted from CDCs CDI Prevention Primer (3/16)

DEADLY DIARRHEA:
C. DIFFICILE CAUSES IMMENSE SUFFERING, DEATH

IMPACT

Caused close to half a million illnesses in one year.

Comes back at least once in about 1 in 5 patients who get *C. difficile*.

1 in 11 people 65 and older died within a month of *C. difficile* infection diagnosis.

Adapted from CDCs CDI Prevention Primer (3/16)

Epidemiology: Host Factors

- Advanced Age
  - Incidence higher among females, whites, and persons >65 y
  - Deaths more common in persons >65 y

- Underlying illness and medical history

- Immunosuppression
  - Inflammatory bowel disease
  - Immune-suppressive treatment
  - Hematological malignancy/stem cell transplant

Lessa et al. N Engl J Med 2015; 372(9):825-834
See et al. Clin Infect Dis 2014; 58(10):1394-1400
Bliss et al. Ann Intern Med 1998; 129:1012-1019
Kombuj et al. Infect Control Hosp Epidemiol 2016; 37:8-15

Adapted from CDCs CDI Prevention Primer (3/16)

Epidemiology: Modifiable Risk Factors

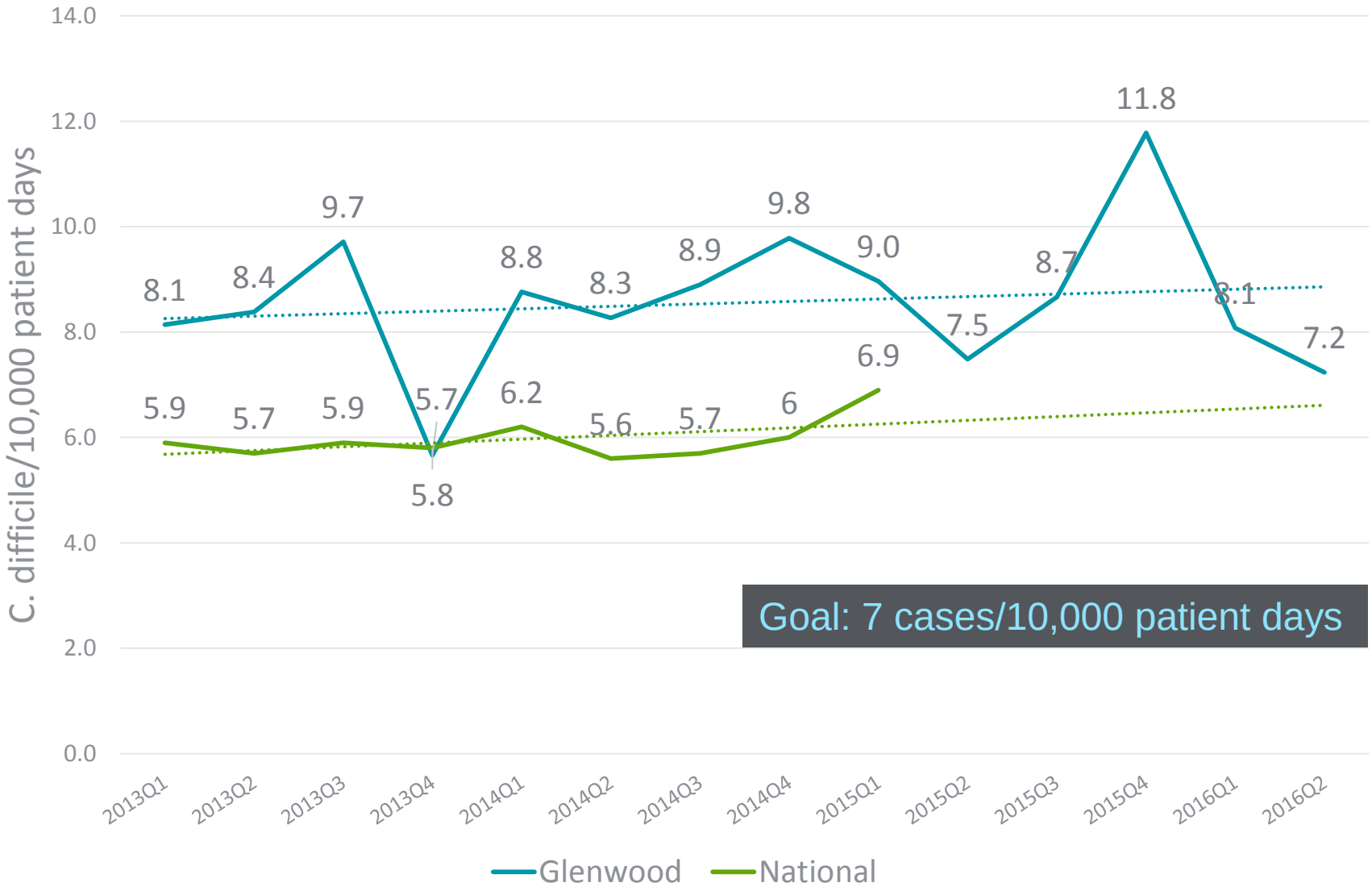
- Exposure to C. difficile spores
  - Spores can remain viable for months
  - Contamination is increased in rooms of patients with active CDI
  - Hands of patients and personnel are easily contaminated

- Exposure to antibiotics and gastric acid suppression
  - High risk: fluoroquinolones, cephalosporins, clindamycin, Carbapenems
  - PPI use has been linked to increased CDI incidence

Pepin et al. Clin Infect Dis 2005; 41(9):1254-1260
Weber & Rutala Infect Control Hosp Epidemiol 2011;32:207-209
Dubberke et al. Am J Infect Control 2007;35:315-318
Linney et al. Can J Hosp Pharm 2010; 63(1):31-37

Adapted from CDCs CDI Prevention Primer (3/16)

Clostridium Difficile Rates

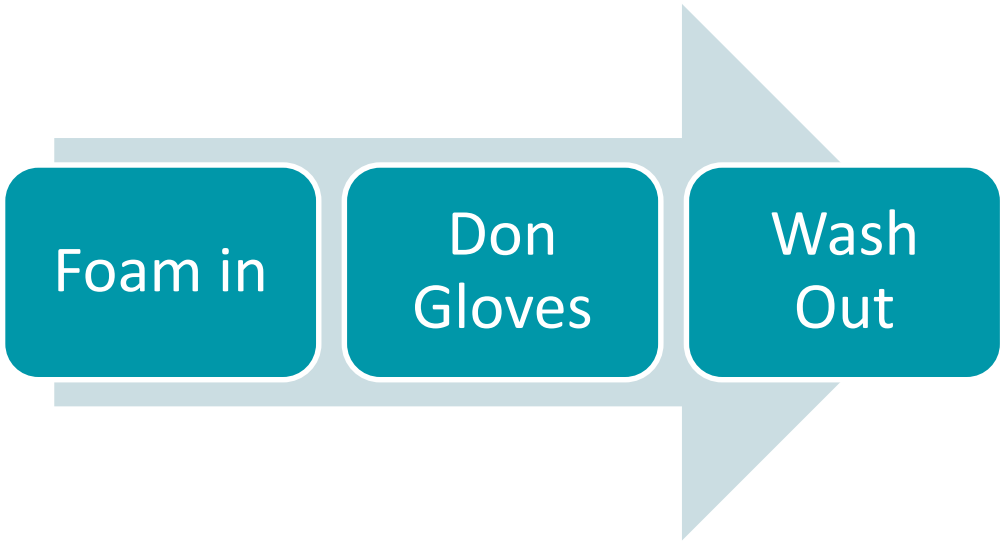


Clostridium Difficile Prevention

- Hand Hygiene
- Environmental Cleaning
- Antimicrobial Stewardship

Hand Hygiene

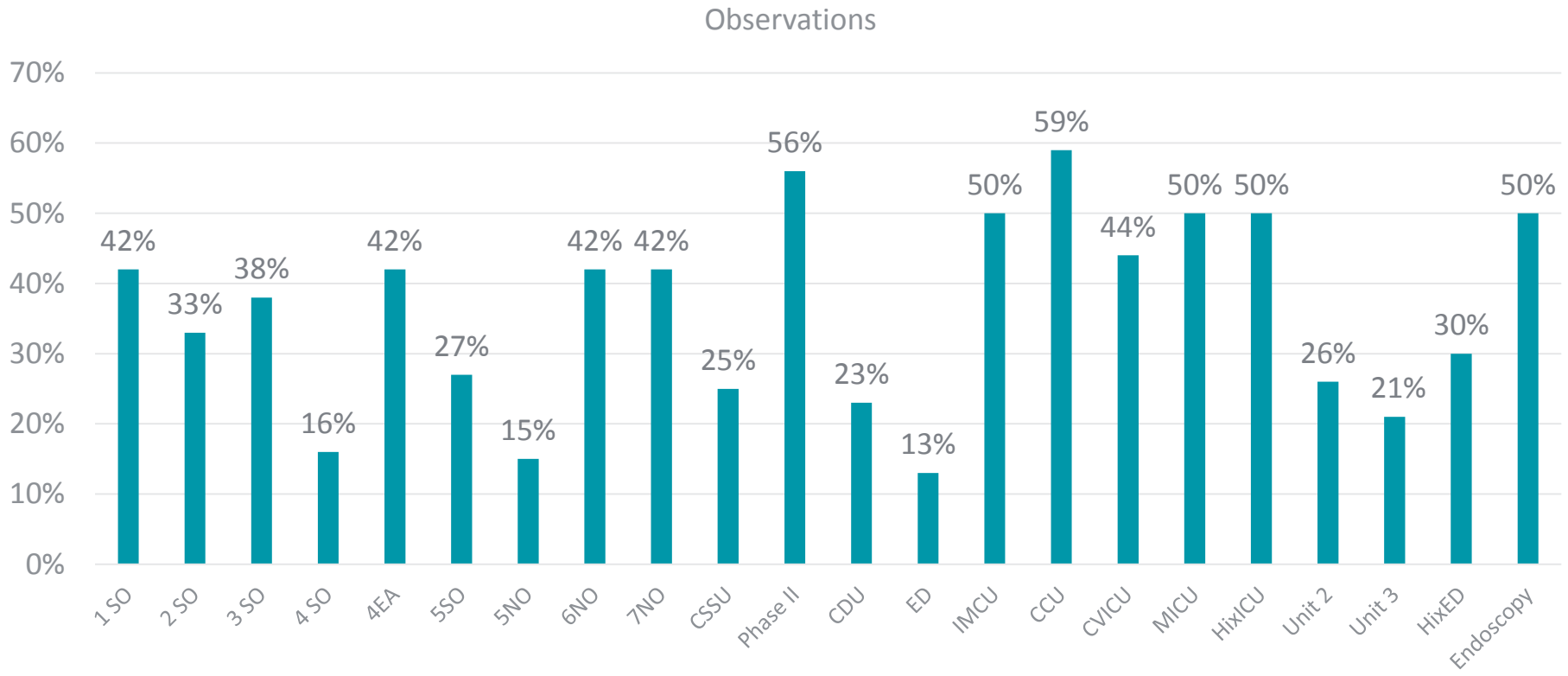
- Strict adherence to glove use is the most effective means of preventing hand contamination w/ C. difficile spores
- Spores are not killed by alcohol-based hand rub and may be difficult to remove even through hand washing



Riggs et al. Clin Infect Dis 2007; 45(8):992-998
Isaacson et al. Am J Infect Control 2015;43:530-532
Oughton et al. Infect Control Hosp Epidemiol 2009;30(10):939-944

Adapted from CDCs CDI Prevention Primer (3/16)

Hand Hygiene Observations



Environmental Cleaning

- Meticulous cleaning reduces spores in environment
- Use sporicidal disinfectants

Technique	Reduction in Spores	Dry Time
Wiping with any disinfectant	> 2.9 $\log_{10}$	2-6 minutes
Spraying (no wipe) with sporicide	3.4 $\log_{10}$	28-40 minutes
Wiping with sporicide	3.9 $\log_{10}$	2-6 minutes

- Monitoring and feedback of cleaning performance

Rutala et al. Infect Control Hosp Epidemiol 2012;33(12):1255-1258
Gonzalez et al. Am J Infect Control 2015; 43:1331-1335

Adapted from CDCs CDI Prevention Primer (3/16)

Antimicrobial Stewardship

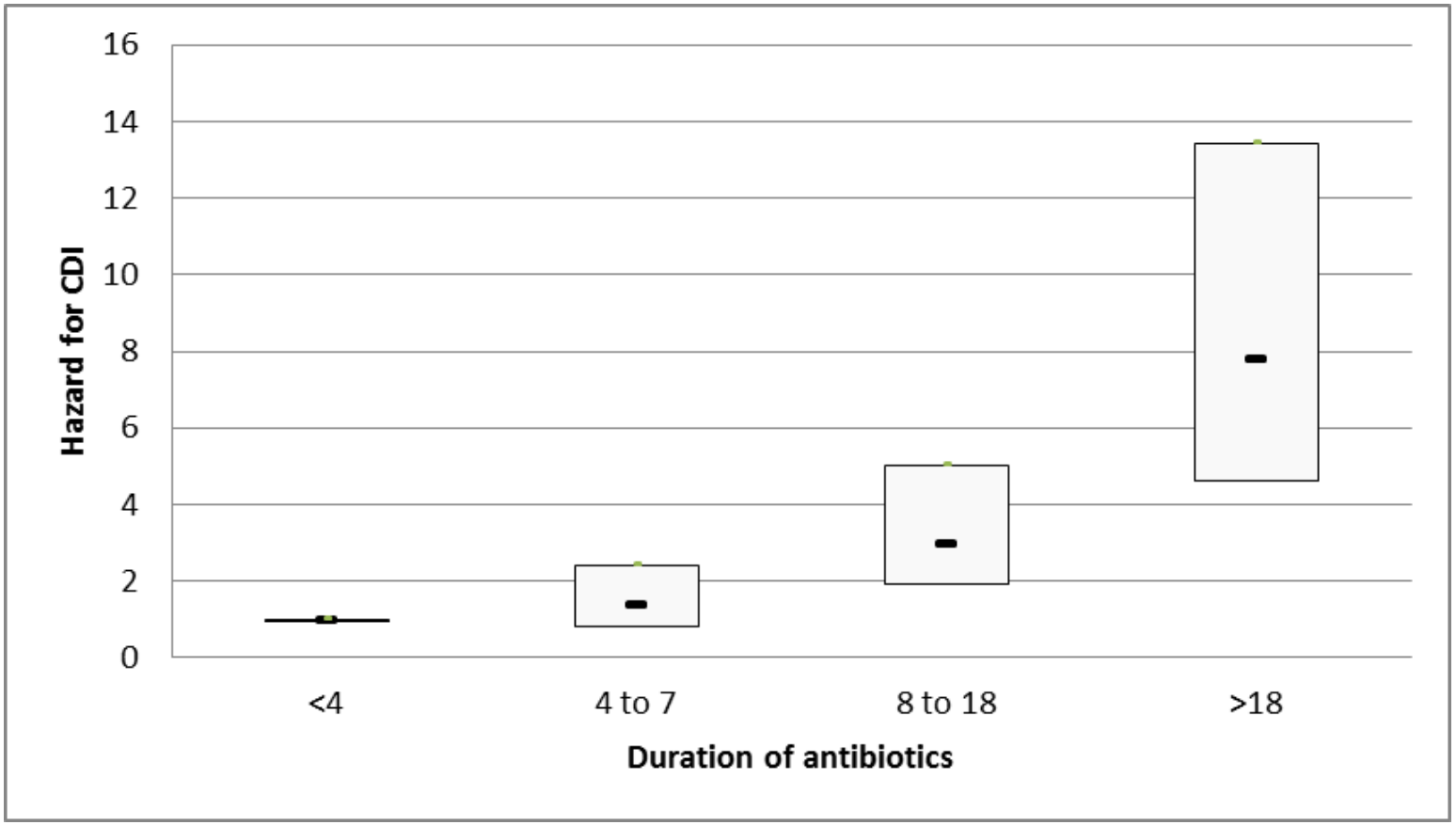
Host

- Advanced age
  - >65
- Underlying illness and medical history
- Immunosuppression
  - Inflammatory bowel disease
  - Immune-suppressive treatment
  - Hematological malignancy/stem cell transplant

Modifiable

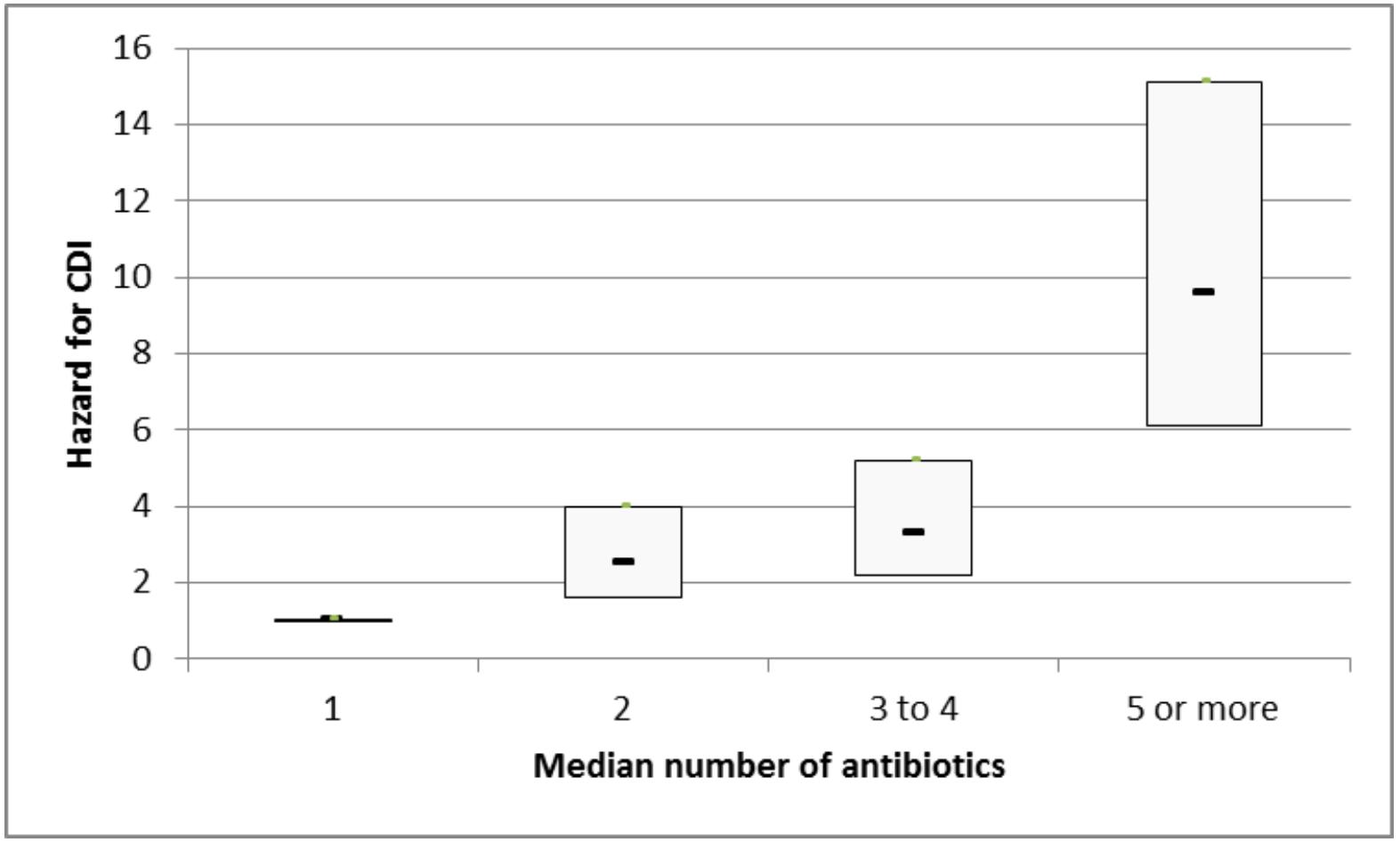
- Exposure to *C. difficile* spores
- Exposure to antibiotics and gastric acid suppression

Duration, #, and intensity of abx affect CDI risk



 / Stevens V, et al. Clin Infect Dis 2011; 53: 42-48.

Duration, #, and intensity of abx affect CDI risk



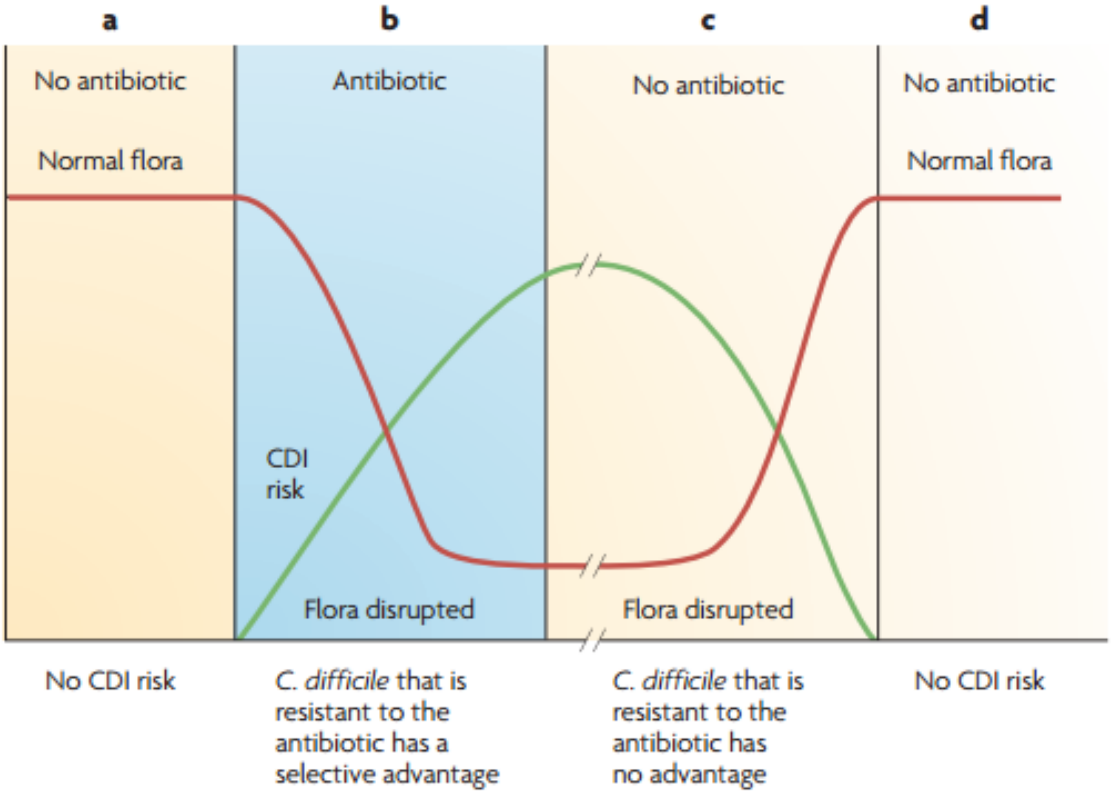
 / Stevens V, et al. Clin Infect Dis 2011; 53: 42-48.

Antibiotics and CDI Risk

Very Commonly Related	Less Commonly Related	Uncommonly Related
Clindamycin Ampicillin Amoxicillin Cephalosporins Fluoroquinolones	Beta-lactam inhibitors Macrolides Carbapenems Tigecycline	Aminoglycosides Metronidazole Rifampin Tetracyclines Daptomycin Sulfonamides Trimethoprim

Bouza E, et al. Med Clin North Am. 2006;90:1141-1163

Microbiota disruption, antibiotics, C. difficile



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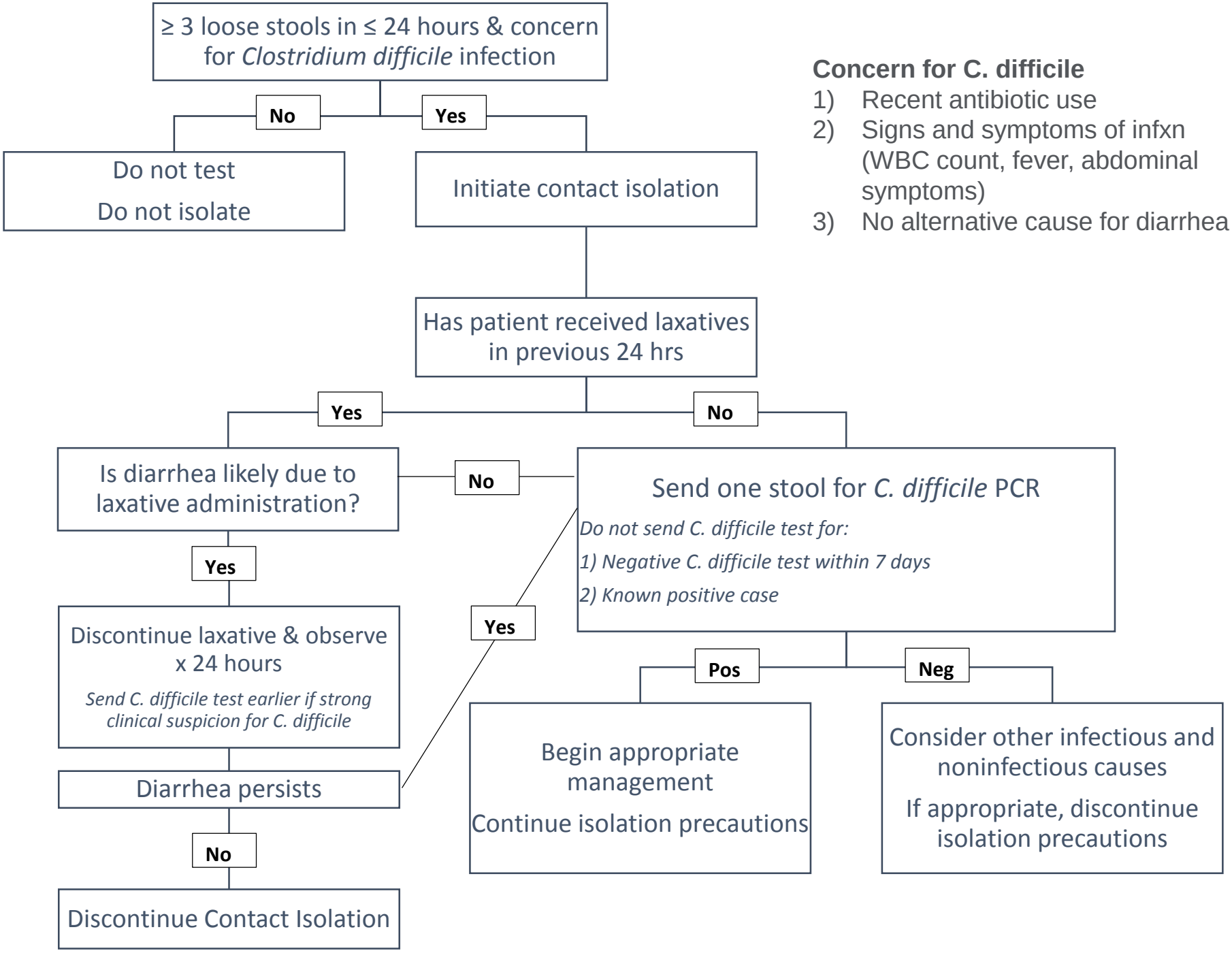
- Due to activity against *C. difficile*
- Risk increases once the antibiotic is stopped


≥ 3 loose stools in ≤ 24 hours & concern for *Clostridium difficile* infection
No
Yes
Do not test
Do not isolate
Initiate contact isolation
Has patient received laxatives in previous 24 hrs
Yes
No
Is diarrhea likely due to laxative administration?
No
Yes
Discontinue laxative & observe x 24 hours
Send C. difficile test earlier if strong clinical suspicion for C. difficile
Diarrhea persists
No
Discontinue Contact Isolation
Yes
Send one stool for *C. difficile* PCR
Do not send C. difficile test for:
1) Negative C. difficile test within 7 days
2) Known positive case
Pos
Neg
Begin appropriate management
Continue isolation precautions
Consider other infectious and noninfectious causes
If appropriate, discontinue isolation precautions
Concern for C. difficile
1) Recent antibiotic use
2) Signs and symptoms of infxn (WBC count, fever, abdominal symptoms)
3) No alternative cause for diarrhea

Principles of CDI Management

1. Stop all unnecessary antibiotics
2. Narrow the spectrum of antibiotic activity when possible
3. Shorten antibiotic courses
4. Stop acid suppressive medication when possible
5. Discontinue all anti-motility agents

CDI Treatment (IDSA 2010 Guidelines)

Clinical definition	Criteria	Treatment
Mild to moderate	Not meeting criteria for severe	Metronidazole 500mg PO TID for 10-14 days
Severe	WBC ≥ 15 OR Cr ≥ 1.5x baseline	Vancomycin 125 mg po q6h x 10-14 days
Severe, complicated	Hypotension, shock, ileus, and/or megacolon	Vancomycin 500 mg po/ng q6h + metronidazole 500 mg IV q8h

Metronidazole vs vancomycin

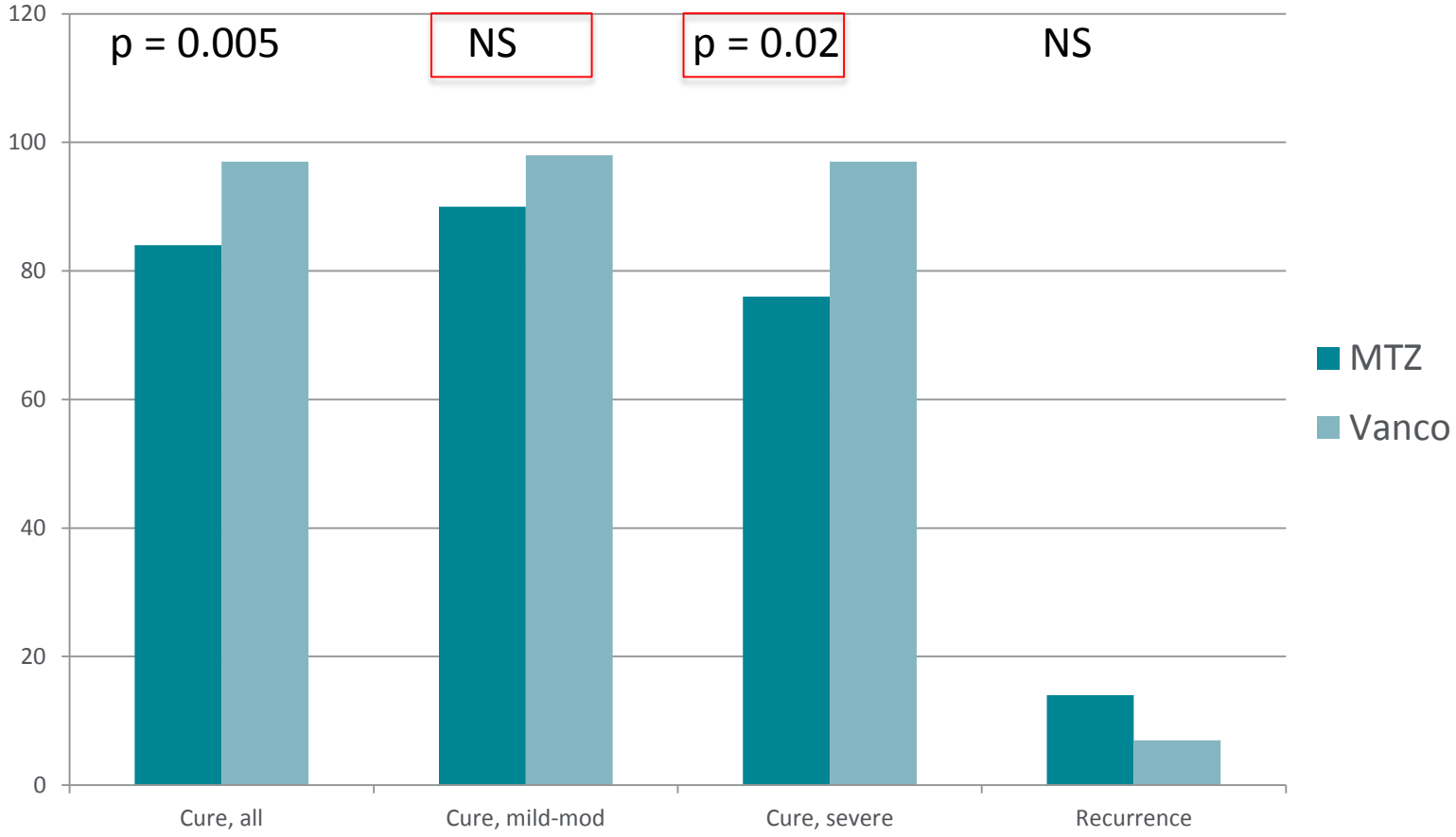
Metronidazole

- 95% absorbed, re-excreted into colon when inflamed
- *C. difficile* MIC_{50}=0.5mcg/mL
  MIC_{90}=2.0mcg/mL
- Stool concentration: 1.9-77.3 mcg/gm, 40% <10 mcg/gm, 30% <5 mcg/gm
- ADRs: Metallic taste, N/V, peripheral neuropathy with long-term exposure
- DDIs: Inhibitor of CYP2C9 & 3A4 (Coumadin)

Vancomycin

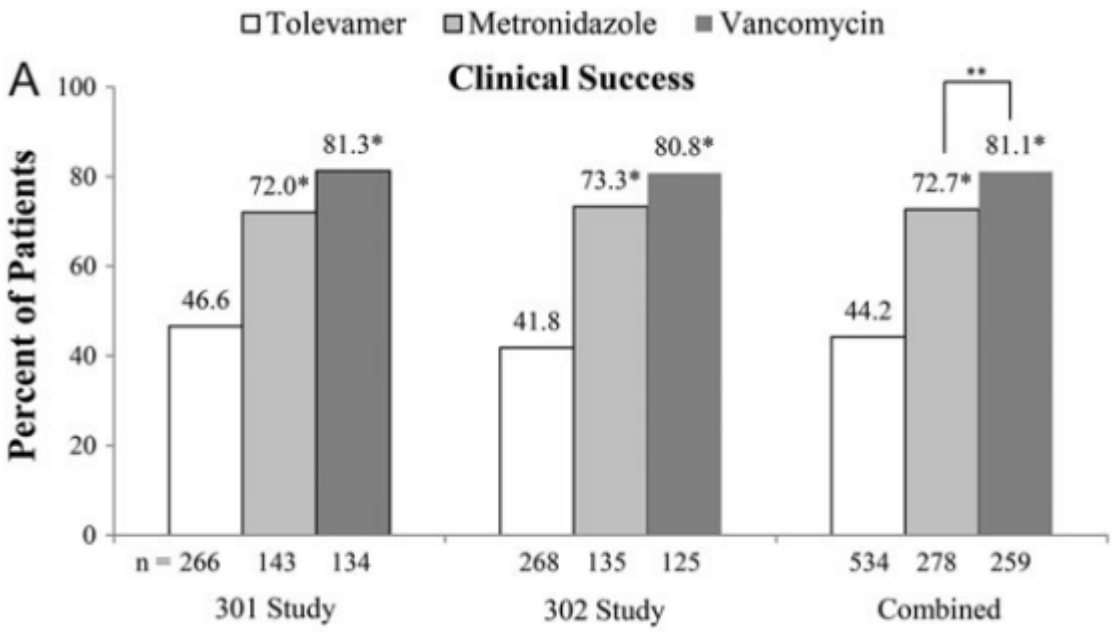
- Undetectable serum concentrations. Oral doses mostly excreted in feces
- *C. difficile* MIC_{90}=2.0mcg/mL
- Stool concentration: 357 mcg/gm
- ADRs: Abdominal pain, N/V
- DDIs: Cholestyramine/colestipol can bind PO vancomycin and reduce effectiveness

Metronidazole vs. vancomycin



Metronidazole Inferior for Non-Severe CDI

*P<0.001, T vs.M and T vs. V
**P=0.020, M vs. V



Vancomycin superior to metronidazole on multivariable analysis, including controlling for clinical severity (p=0.013)

Johnson S, et al. *Clin Infect Dis*. 2014;59:345-354

CDI Treatment

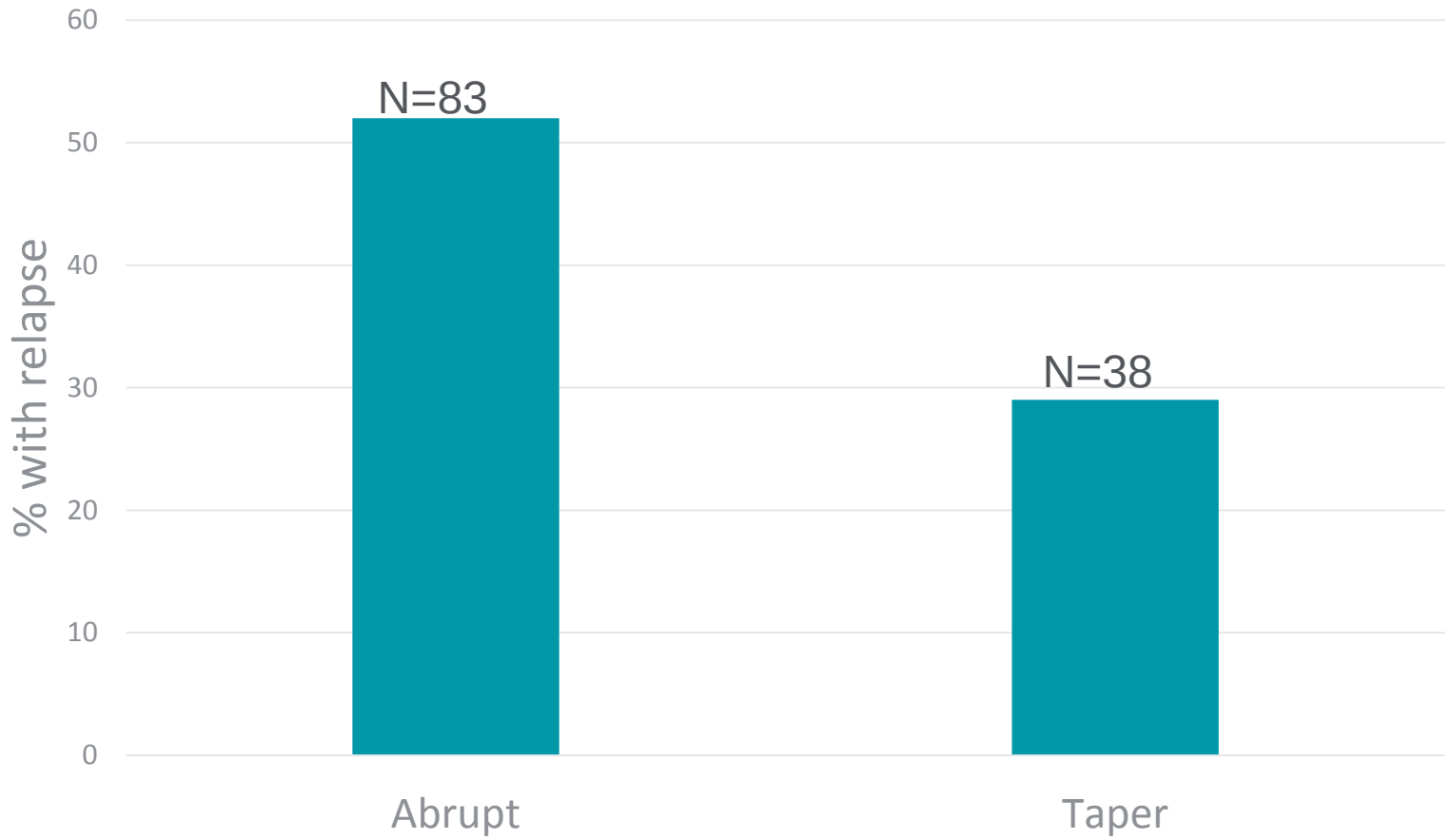
Clinical definition	Criteria	Treatment
~~Mild to moderate~~	~~Not meeting criteria for severe~~	~~Metronidazole 500mg PO TID for 10-14 days~~
Severe	WBC ≥ 15 OR Cr ≥ 1.5x baseline	Vancomycin 125 mg po q6h x 10-14 days
Severe, complicated	Hypotension, shock, ileus, and/or megacolon	Vancomycin 500 mg po/ng q6h + metronidazole 500 mg IV q8h

- If metronidazole is inferior mild/moderate CDI , no need to select treatment based on severity
- Considerations: Risk of recurrence

Risk Factors Associated with CDI Recurrence

- Increased Age: >65
- Immunosuppression
- Concomitant antibiotics
- NAP1/BI/027 strain

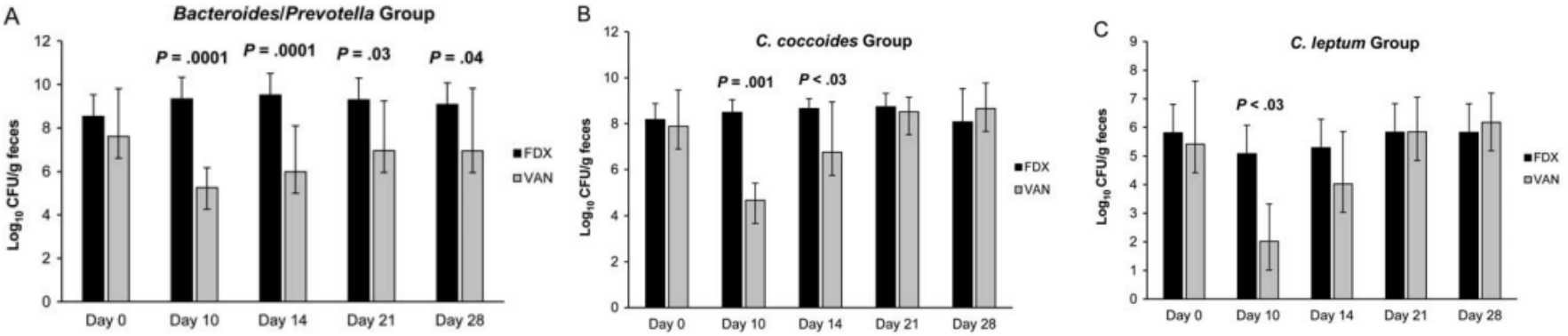
Abrupt stop vs. taper or pulse of vancomycin



- Mean number of CDI episodes: 3 ± 2.1 (range 1-14)
- Relative risk of relapse = 0.51 (95% CI, 0.29-0.90)

Fidaxomicin for CDI

- FDA approved: 5/27/2011
- Narrow spectrum
  - Sparing of bacteroides spp., bifidobacterium, clostridium clusters IV and XIV
- Decrease in recurrences
  - Studies included patients with first and second CDI episodes
  - Intestinal dysbiosis?



Fidaxomicin vs. PO vancomycin

- Bottom line vs. vanco: Similar cure (~88%), lower recurrence (13-15% vs. 25-27%)
- Unclear role in multiply recurrent or severe disease: excluded these

	Cure	Relapse
Strain		
Epidemic	Same	Same
Non-epidemic	Same	↓
Concomitant abx	↑	↓
Prior CDI	Same	=/↓

Fidaxomicin
$2800

CHI Memorial /

Louie TJ, et al. NEJM 2011;364:422-431; Cornely et al, Lancet Infect Dis 2012;12:281-8 ; Petrella LA, et al. Clin Infect Dis 2012;55(3):351-7; Mullane et al., CID 2011;53(5):440-7; Corneley et al., CID 2012;55:s154-s161.; Bartsch SM et al., CID 2013; 57(4): 555-561; Konijeti GG et al., CID 2014; 58:1507-1514.

Prevention of recurrence: FMT

Study	1st dose	2nd dose
Youngster (n=20)	70%	90%
Hirsch (n=19)	68%	89%
Orenstein (n=34)	52%	79%
Van Nood (n=16)	81%	94%
Lee (n=178)	62%	84%
Khanna (n=30)	87%	97%

Bezlotoxumab (Zinplava™)

Manufacturer: Merck and Co.

Date FDA Approved: 10/21/16

Class: Human monoclonal antibody

Indication: Reduction of CDI recurrence in patient ≥ 18 y.o., who are receiving antibacterial drug tx for CDI & are at high risk for recurrence

Bezlotoxumab

- 10mg/kg infusion x 1 dose at any time during CDI antibacterial therapy (no dose adjustments necessary)
  - Supplied as: 1,000/40mL solution (25mg/mL)
  - Diluted in NS or D5W with a final concentration 1mg/mL to 10mg/mL

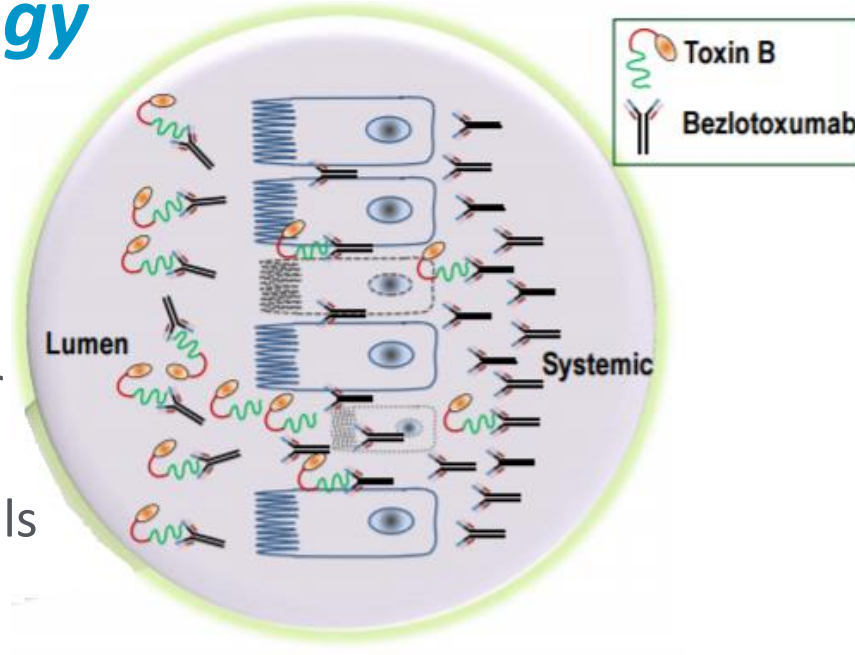
- Infuse over 60 mins using a filter

- T½: 19 Days
  - Eliminated by protein catabolism: low DDI potential

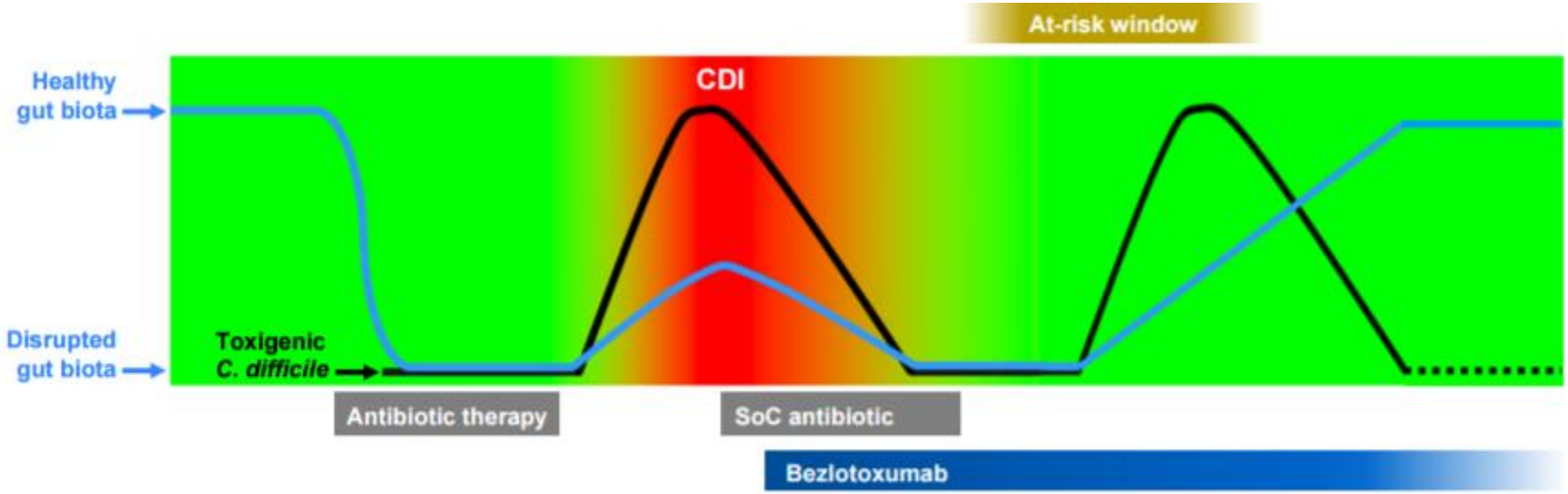
- Low potential for immunogenicity

Bezlotoxumab: Pharmacology

- Human monoclonal antibody directed against C. difficile toxin B
- BEZLO enters gut lumen via paracellular transport
  - Blocks toxin binding to mucosal cells prevents gut wall damage
- Long t½ allows sustained toxin neutralization
- Gut microbiota recovers



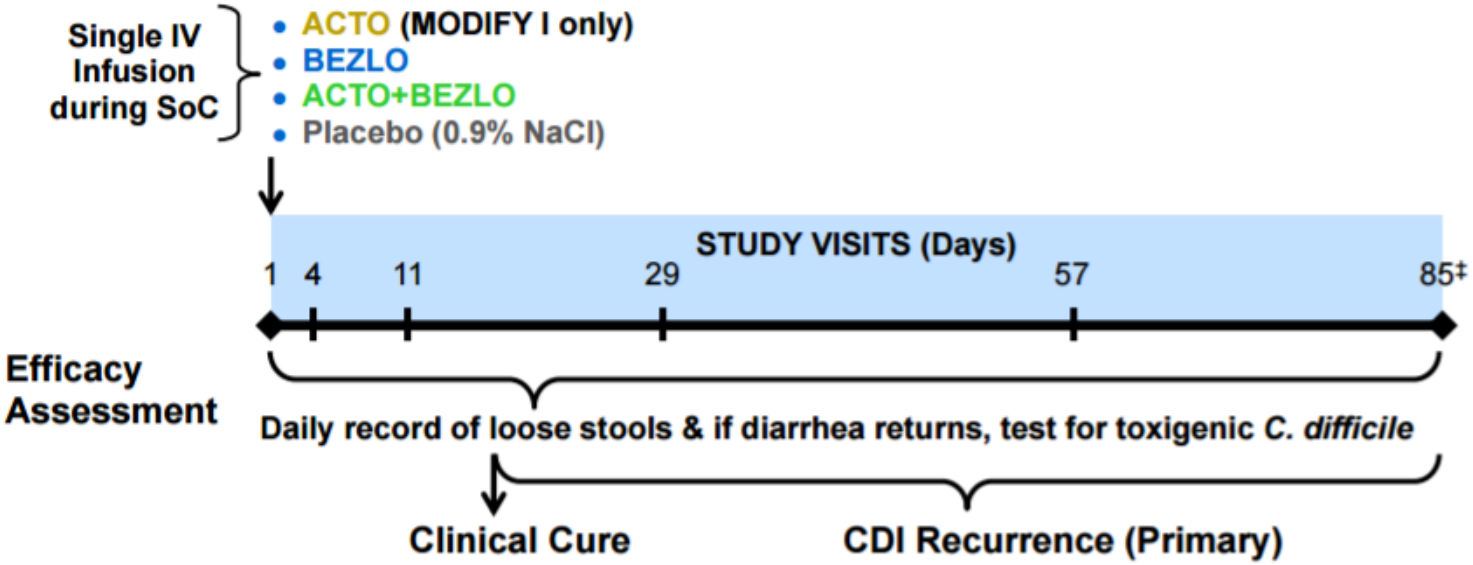
Bezlotoxumab: MOA



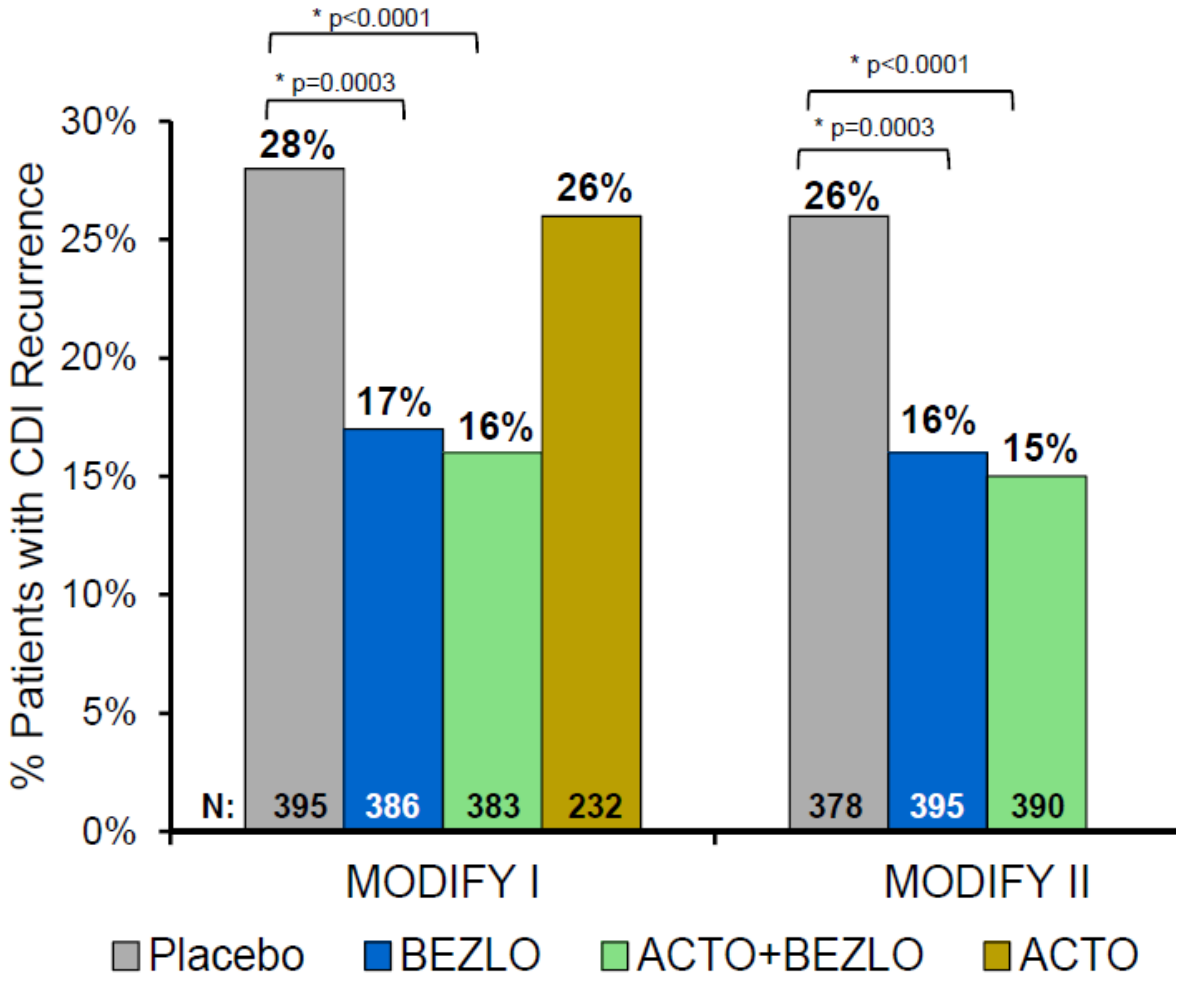
Bezlotoxumab prevents clinical manifestation of CDI during at-risk window and allows microbiota to recover, leading to clearance of *C. difficile*

MODIFY I and II

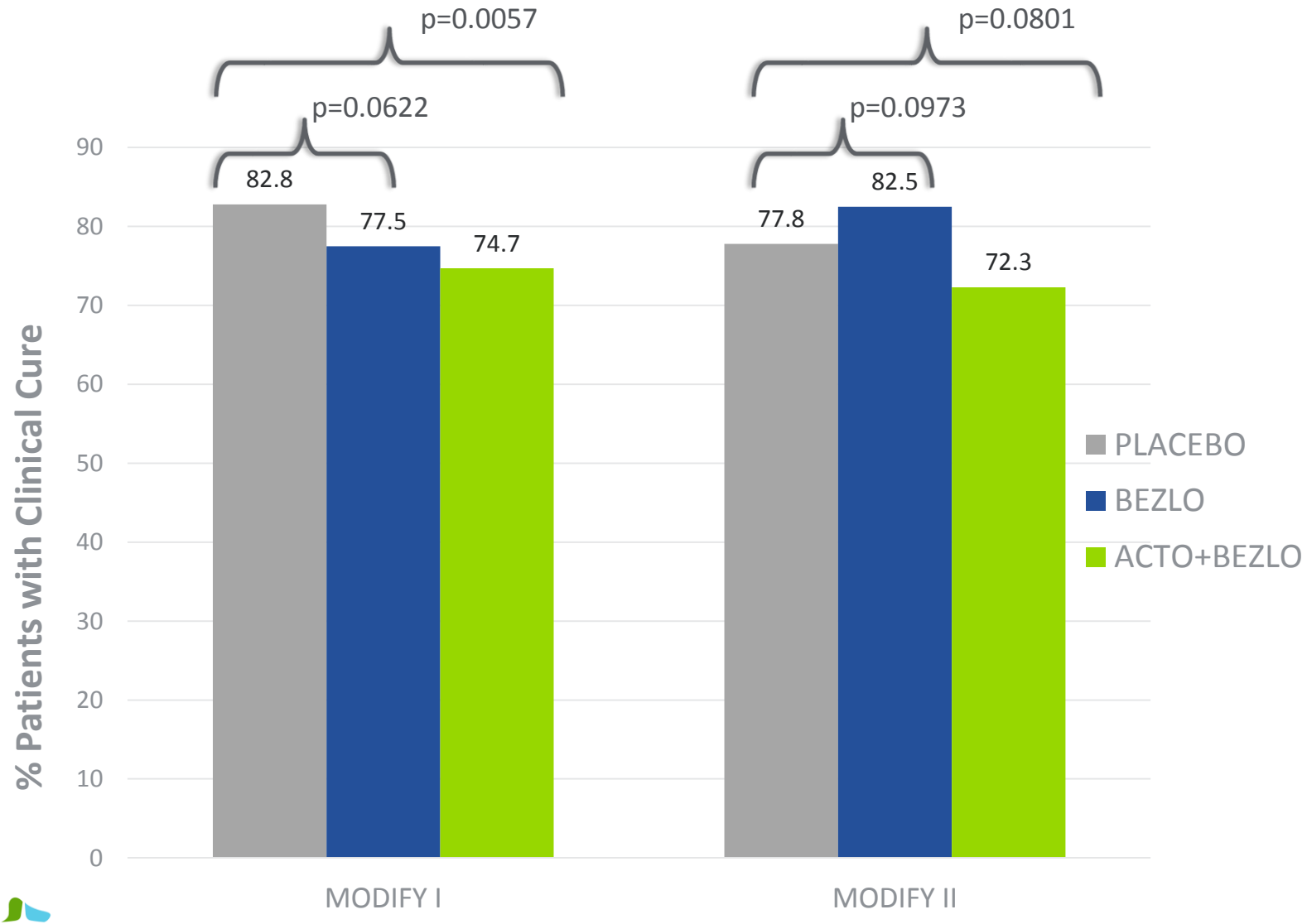
- Adult patients with confirmed CDI
  - Diarrhea (≥ 3 loose stools in ≤ 24 hours) AND
  - Positive stool test for toxigenic *C. difficile*
  - Receiving SOC antibiotic therapy for CDI (10-14 day regimen)
    - Oral metronidazole
    - Oral vancomycin (± IV metronidazole)
    - Oral fidaxomicin (± IV metronidazole)



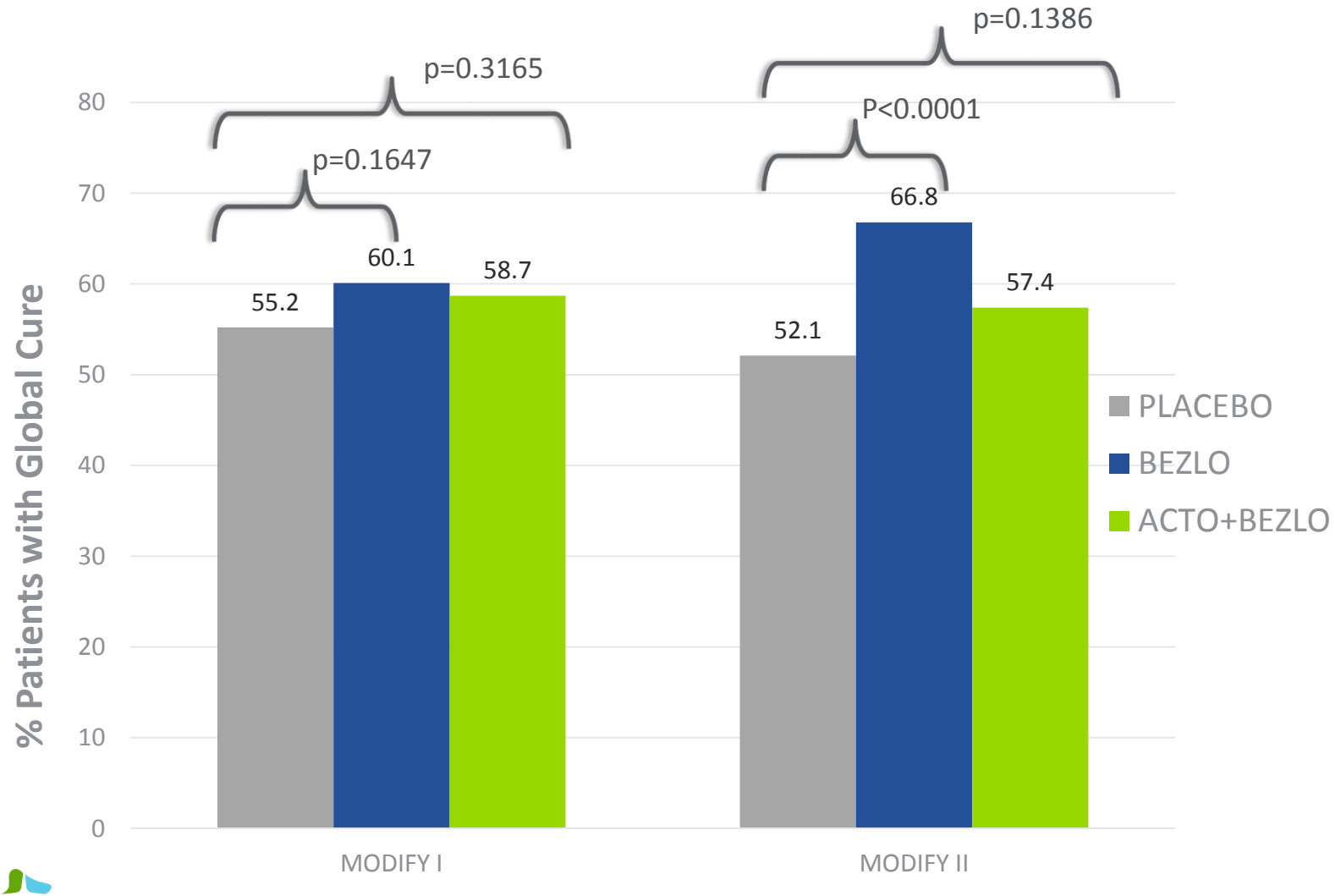
Efficacy: CDI Recurrence



Efficacy: Clinical Cure



Efficacy: Global Cure



Safety

- Adverse effects (reported in ≥ 4% of Bezlotoxumab-treated patients and at a greater frequency than placebo):

	Bezlotoxumab (N=786)	Placebo (N=781)
Nausea (%)	7	5
Pyrexia (%)	5	3
Headache (%)	4	3

- Serious adverse reactions:
  - Heart failure (2.3% bezlotoxumab vs. 1% placebo)
  - One discontinuation due to ventricular tachyarrhythmia 30 mins after start of infusion
  - Mortality rates (7.1% bezlotoxumab and 7.6% placebo)

Summary

- Decrease in CDI recurrence with the use of bezlotoxumab
- Concern for negative effect in clinical cure
- Global Cure – only significant for one of the 2 trials and the significance in Modify II needs to be interpreted with caution
  - Non-significant result of acto + bezlo vs. placebo
- Safety: CHF (not fluid related) (Median observation: Day 30) – Maybe immune-mediated – unclear mechanism
- Cost: Not yet available for purchase

IVIG in severe disease

- No RCTs
- Retrospective review of 14 patients who received IVIG at one institution
  - 6 refractory
  - 6 recurrent
  - 2 severe failing to respond to therapy
- Dose 150 to 400 mg/kg x 1-2
- 9 (64%) responded fully
  - Of these, 3 (33%) had subsequent recurrences

Additional antibiotics

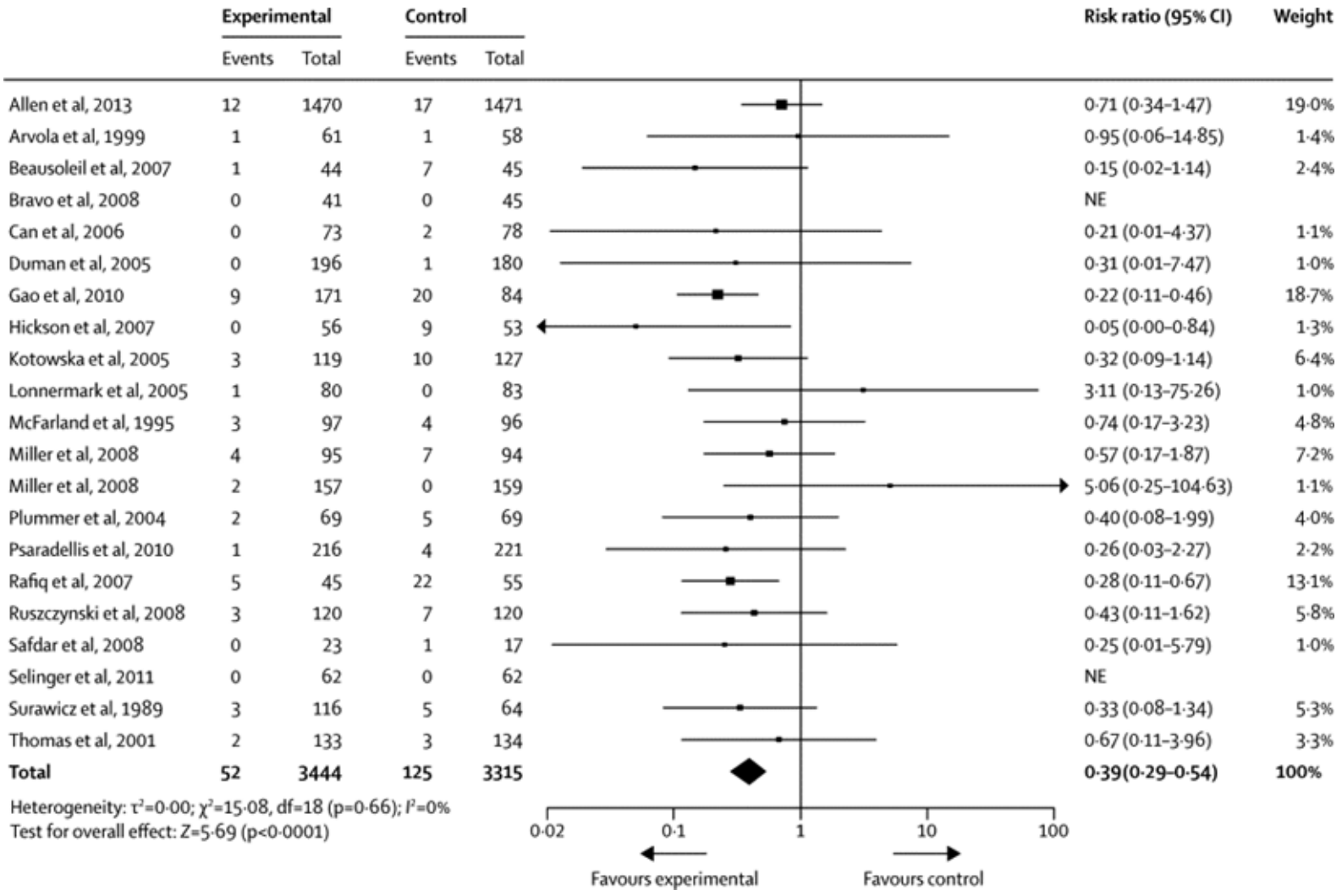
- Data limited to uncontrolled case reports and series
- Nitazoxanide
- Rifaximin: High rates of recurrence, used as a “chaser”
- Tigecycline: Used in intractable disease

Probiotics

Diarrhea class	Probiotic	Placebo	OR
AAD	159/1470 (11%)	153/1471 (10%)	1.04 (0.83–1.32)
CDI	12/1470 (0.9%)	17/1471 (1.2%)	0.70 (0.34–1.48)

- No benefit for probiotic
- Very low rates of CDI in this population
- Majority of patients were receiving amoxicillin/ampicillin or second-generation cephalosoporins (UK study)
- Likely underpowered for the CDI outcome

Probiotics (Meta-analysis)



	Experimental		Control		Risk ratio (95% CI)	Weight
	Events	Total	Events	Total		
Allen et al, 2013	12	1470	17	1471	0·71 (0·34–1·47)	19·0%
Arvola et al, 1999	1	61	1	58	0·95 (0·06–14·85)	1·4%
Beausoleil et al, 2007	1	44	7	45	0·15 (0·02–1·14)	2·4%
Bravo et al, 2008	0	41	0	45	NE	
Can et al, 2006	0	73	2	78	0·21 (0·01–4·37)	1·1%
Duman et al, 2005	0	196	1	180	0·31 (0·01–7·47)	1·0%
Gao et al, 2010	9	171	20	84	0·22 (0·11–0·46)	18·7%
Hickson et al, 2007	0	56	9	53	0·05 (0·00–0·84)	1·3%
Kotowska et al, 2005	3	119	10	127	0·32 (0·09–1·14)	6·4%
Lonnermark et al, 2005	1	80	0	83	3·11 (0·13–75·26)	1·0%
McFarland et al, 1995	3	97	4	96	0·74 (0·17–3·23)	4·8%
Miller et al, 2008	4	95	7	94	0·57 (0·17–1·87)	7·2%
Miller et al, 2008	2	157	0	159	5·06 (0·25–104·63)	1·1%
Plummer et al, 2004	2	69	5	69	0·40 (0·08–1·99)	4·0%
Psaradellis et al, 2010	1	216	4	221	0·26 (0·03–2·27)	2·2%
Rafiq et al, 2007	5	45	22	55	0·28 (0·11–0·67)	13·1%
Ruszczynski et al, 2008	3	120	7	120	0·43 (0·11–1·62)	5·8%
Safdar et al, 2008	0	23	1	17	0·25 (0·01–5·79)	1·0%
Selinger et al, 2011	0	62	0	62	NE	
Surawicz et al, 1989	3	116	5	64	0·33 (0·08–1·34)	5·3%
Thomas et al, 2001	2	133	3	134	0·67 (0·11–3·96)	3·3%
Total	**52**	**3444**	**125**	**3315**	**0·39(0·29–0·54)**	**100%**

Heterogeneity: τ^2=0·00; χ^2=15·08, df=18 (p=0·66); I^2=0%
Test for overall effect: Z=5·69 (p<0·0001)

CHI Memorial / Daneman N, Lancet 2013.

Secondary antibiotic prophylaxis for CDI

- Mixed data – all retrospective data
- Van Hise et al.
  - N=203; Hx of CDI and meeting criteria as high risk; PO vanco
    - Absolute difference in rate of CDI within 1st 4 weeks following completion of abx therapy w/ & w/o PO vanco
    - Reduction in CDI recurrence (1% vs 37%; P=0.0001)
- King et al.
  - N=339; Hx of CDI and receiving broad-spectrum antibiotics; PO vanco and metronidazole
    - Absolute difference in rate of CDI: 1.8% (prophylaxis) vs. 5.7% (control)
    - Not statistically significant

Concern: Further disruption of microbiome

Principles of CDI Management

- Stop all unnecessary antibiotics
- Narrow the spectrum of antibiotic activity when possible.
  - Consider discussion with ID Physician or ASP Pharmacist (x7536)
- Shorten antibiotic courses
- Stop acid suppressive medication when possible
- Discontinue all anti-motility agents

Treatment Recommendations

Initial episode
-AND-
No risk factors for recurrent infection
Vancomycin 125 mg PO Q 6 hours x 14 days

Initial episode
-AND-
Risk factors for recurrent infection
Vancomycin 125 mg PO Q 6 hours x 14 days
+
Vancomycin taper (see below)

Recurrent Episode
Vancomycin 125 mg PO Q 6 hours x 14 days
+
Vancomycin taper (see below)

Consider discussing with ID physician for therapeutic options to prevent further recurrence

Vancomycin taper
Vancomycin 125 mg PO Q 6 hours x 14 days, then
125 mg Q 8 hours x 7 days
125 mg Q 12 hours x 7 days
125 mg Daily x 7 days
125 mg Q2D x 7 days

Initial episode, severe complicated
CDI is confirmed/suspected with hypotension and/or shock, ileus or megacolon

Consider infectious disease and surgical consults

Severe, complicated no ileus:
Vancomycin 500 mg PO/NG Q 6 hours x 14 days + Flagyl 500 mg IV Q 8 hours

Severe, complicated + ileus or megacolon:
Same as above PLUS Vancomycin 500 mg in 100 mL of normal saline Q 6 hours x 14 days via retention enema (retain each dose for 1 hour)

Symptoms worsening: Consider ID consultation

Risk Factors for recurrent infection

- Age ≥ 65
- Immunosuppression
- Concomitant antibiotic
- NAP1/BI/027 strain (+) – associated with increased severity of infection and chance of recurrence

Comments

- There is no evidence to support dual therapy with ORAL Flagyl & ORAL Vancomycin (only IV Flagyl + PO Vanco)
- No need to repeat *Clostridium difficile* testing for test of cure
- Probiotics: Mixed data exist regarding use of probiotics for primary prevention of CDI. There is insufficient data to support use for secondary prophylaxis. Can consider use based on patient and provider preference
- Secondary prophylaxis: Routine use of secondary CDI prophylaxis in patients at high risk of CDI recurrence is not recommended as there is a lack of strong evidence for this practice. Secondary prophylaxis places the patient at unnecessary risk for drug-related toxicities and promotes further disruption of the microbiome

Which of the following are key strategies to prevent the spread of C. difficile infection?

A. Hand hygiene
B. Environmental cleaning with a sporicidal agent
C. Antimicrobial Stewardship
D. All of the above

MG is a 55 y.o. F admitted to the hospital with abdominal pain, dysuria and self-reported history of diarrhea. Her vitals are WNL. MD has ordered labs, a CT of the abdomen and cultures (blood, urine, and stool).
All labs are WNL, CT was negative, blood cultures were negative, and urinalysis was positive with a reflex to culture growing >100,000 CFUs of pan-sensitive E. coli. She was empirically started on rocephin which was narrowed quickly to PO Bactrim. Her abdominal symptoms improved but she has not been stooling.
After a day of docusate and senna, a semi-formed stool sample was collected and sent to the lab by patient's nurse (Day 4). The PCR test resulted as C. difficile positive. MD calls you for a recommendation:

A. D/C Bactrim, begin PO vancomycin 125mg PO q6h for 14 days
B. D/C Bactrim, begin PO vancomycin 125mg PO q6h w/ a prolonged taper
C. Continue Bactrim for a short 5 day course and do not start *C. diff* Tx
D. Continue Bactrim for a short 5 day course and give PO vancomycin 125mg PO q6h for 14 days

Which of the following is not a strategy to prevent C. difficile recurrence?

A. PO vancomycin taper
B. IVIG
C. Fidaxomicin
D. FMT

Thank You!