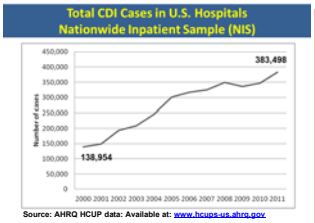
C. difficile Infection (CDI): Rising Incidence and Fatalities



Source: AHRQ HCUP data: Available at: www.hcups-us.ahrq.gov

CDC estimate from 2015:

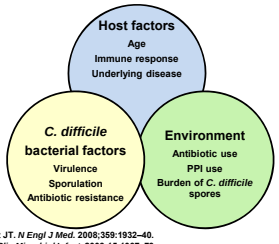
>500,000 cases annually
~2/3 are nosocomial
29,000 CDI-related deaths
~100 deaths per million annually

"Urgent Hazard" [highest threat level]

Age adjusted; US (CDC) mortality statistics.
Lessa FC, et al. *N Engl J Med.* 2015;372(9):825-34.

CDC. Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

CDI: Factors Contributing to Increased Incidence & Severity

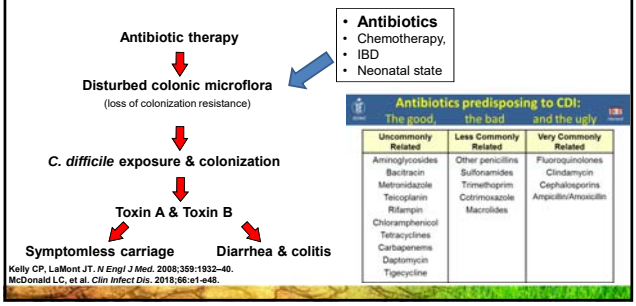


CDI is a very common nosocomial infection

High:
- Incidence
- Morbidity
- Mortality
- Economic cost
  - Longer hospital stay
  - Discharge to nursing home/ healthcare institution more likely
  - Recurrence – often leading to re-admission

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932–40.
Bauer MP, et al. *Clin Microbiol Infect.* 2009;15:1067–79.
Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431–55.

Pathogenesis of *C. difficile* Infection (CDI)



- **Antibiotics**
- Chemotherapy,
- IBD
- Neonatal state

Antibiotics predisposing to CDI: The good, the bad and the ugly

Uncommonly Related	Less Commonly Related	Very Commonly Related
Aminoglycosides	Other penicillins	Fluoroquinolones
Bacitracin	Sulfonamides	Clindamycin
Metronidazole	Trimethoprim	Cephalosporins
Teicoplanin	Cotrimoxazole	Ampicillin/Amoxicillin
Rifampin	Macrolides	
Chloramphenicol		
Tetracyclines		
Carbapenems		
Daptomycin		
Tigecycline		

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932–40.
McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-e48.

Recurrent *Clostridium difficile* Infection

- Common: ~25% of patients treated with metronidazole or vancomycin suffer a recurrence
- Mechanisms of recurrence:
  - NOT primarily due to **antimicrobial resistance**
  - Instead, antimicrobial therapy perpetuates **dysbiosis**
- Same strain as initial episode (**relapse**) or a new strain (**re-infection**)
- Several patient risk factors for CDI recurrence have been identified

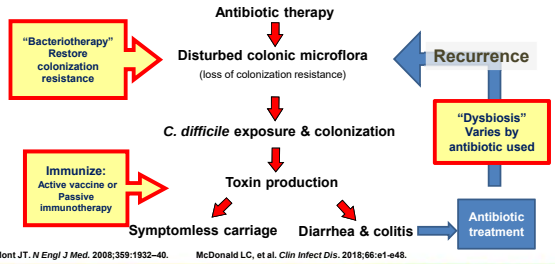
Cohen MB. *J Ped Gastroenterol Nutr.* 2009;48(Suppl. 2):S63–5.
Hu MY, et al. *Gastroenterology.* 2009;136:1206–14.
Bauer MP, et al. *Clin Microbiol Infect.* 2011;17(Suppl. 4):A1–4.
Bauer MP, et al. *Lancet.* 2011;377:63–73.
McFarland LV, et al. *Am J Gastroenterol.* 2002;97:1769–75.
Pépin J, et al. *Clin Infect Dis.* 2005;40:1591–7.

Risk Factors for Recurrent CDI

- Previous episode of recurrent CDI
- Age 65 years or over
- Additional antibiotic use (perpetuates dysbiosis)
- Impaired immune response to *C. difficile* toxins
- Prolonged hospitalization
- Severe underlying disease
  - ICU admission
  - Immunocompromised
  - Renal impairment
- Acid anti-secretory medication?

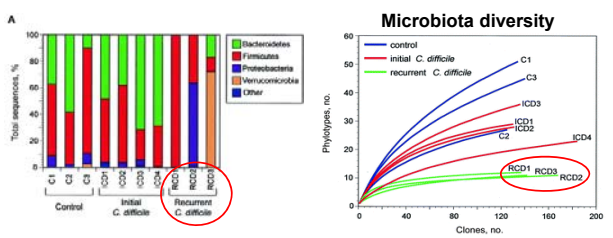
Cohen MB. *J Ped Gastroenterol Nutr.* 2009;48(Suppl. 2):S63–5.
Bauer MP, et al. *Lancet.* 2011;377:63–73.
Do AN, et al. *Clin Infect Dis.* 1998;26:954–9.
Pépin J, et al. *Clin Infect Dis.* 2005;40:1591–7.
Kyne L, et al. *Lancet.* 2001;357:189–93.
Hu MY, et al. *Gastroenterology.* 2009;136:1206–14.
Bauer MP, et al. *Clin Microbiol Infect.* 2011;17(Suppl. 4):A1–4.

Approaches to Breaking the Cycle of Recurrent *C. difficile* Infection



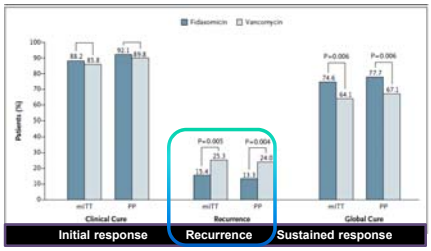
Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932–40.
McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-e48.

Decreased Diversity of Fecal Microbiome in Recurrent CDI



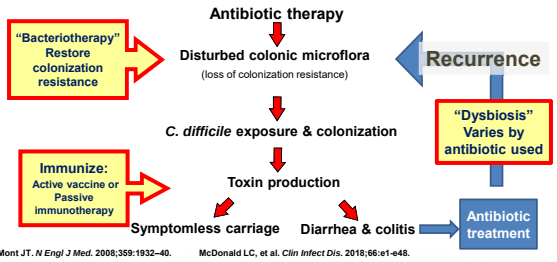
Chang JY, et al. *J Infect Dis.* 2008;197:435-8.

Fidaxomicin vs. Vancomycin for *C. difficile* Infection



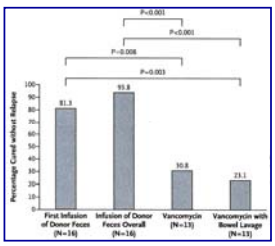
Louie TJ, et al. *N Engl J Med*. 2011;364:422-31.

Non-antibiotic Approaches to Break the Cycle of Recurrent *C. difficile* Infection

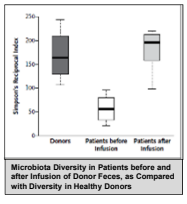


Kelly CP, LaMont JT. *N Engl J Med*. 2008;359:1932–40. McDonald LC, et al. *Clin Infect Dis*. 2018;66:e1-e48.

Fecal Microbiome Transplantation for Recurrent *C. difficile* Infection



Microbiota diversity



Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors

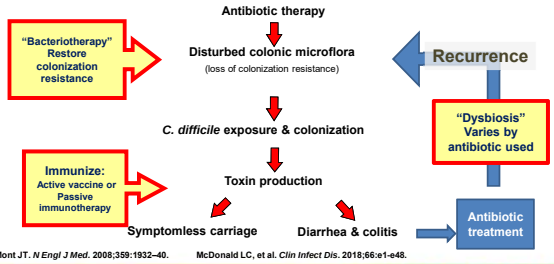
van Nood E, et al. *N. Engl J Med*. 2013;368:407-15.

Bacteriotherapy for Recurrent CDI: FMT and Beyond

- **Typical routes of administration:**
  - **Naso-enteric infusion**
  - **Luminal instillation at colonoscopy**
  - **Enema**
- **Oral options:**
  - **Encapsulated fecal preparations** (frozen or lyophylized)
  - **Defined bacterial cultures**
  - **Fecal spore preparations**
  - **Non-toxigenic *C. difficile* spores**

van Nood E, et al. *N. Engl J Med.* 2013;368:407-15.
Youngster I, et al. *JAMA.* 2014;312:1772-8.
Gerding DN, et al. *JAMA.* 2015;313:1719-27.

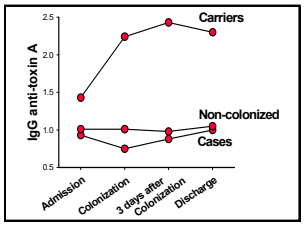
Non-antibiotic Approaches to Break the Cycle of Recurrent *C. difficile* Infection



Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932–40.
McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-e48.

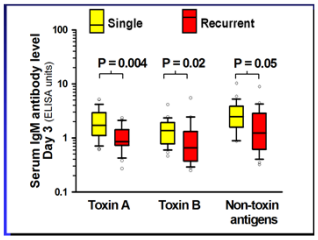
Asymptomatic Carriers of *C. difficile* Have High Serum IgG Anti-toxin

Natural protective immunity – memory immune response to *C. difficile* toxins



Kyne L, et al. *N Engl J Med.* 2000;342:390.

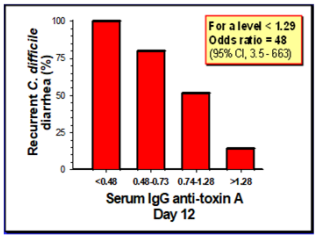
Day 3 Serum IgM Anti-*C. difficile* Antitoxin Levels are Low in Patients who Later Develop Recurrent CDI



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

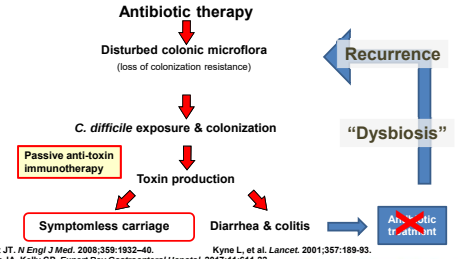
High Day 12 Serum IgG Antitoxin is Associated with a Lower Risk for Recurrent CDI

Acquired immune response to *C. difficile* toxins protects against recurrence



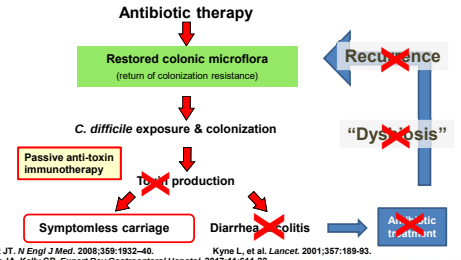
Kyne L, et al. *Lancet.* 2001;357:189-93.

Antitoxin Immunization to Break the Cycle of Dysbiosis in Recurrent *C. difficile* Infection



Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932–40.
Villafuerte Gálvez JA, Kelly CP. *Expert Rev Gastroenterol Hepatol.* 2017;11:611-22.
Kyne L, et al. *Lancet.* 2001;357:189-93.

Antitoxin Immunization to Break the Cycle of Dysbiosis in Recurrent *C. difficile* Infection



Kelly CP, LaMont JT. *N Engl J Med*. 2008;359:1932–40. Kyne L, et al. *Lancet*. 2001;357:189-93.
Villafuerte Gálvez JA, Kelly CP. *Expert Rev Gastroenterol Hepatol*. 2017;11:611-22.

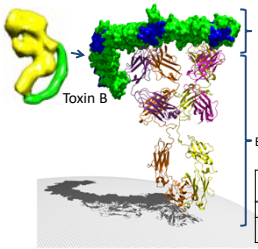
Bezlotoxumab Binds to the Putative Receptor Binding Domain (CROP) of Toxin B

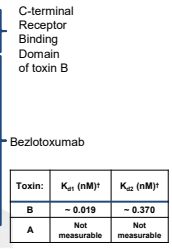
Bezlotoxumab

Human IgG1 monoclonal antibody (mol wgt ~148.2 kDa)

Binds to and neutralizes *C. difficile* toxin B

Binding site characterized: C-terminal putative receptor binding domain





Toxin:	K_{d1} (nM)†	K_{d2} (nM)†
B	~ 0.019	~ 0.370
A	Not measurable	Not measurable

Pruitt RN, et al. *Proc Natl Acad Sci USA*. 2010;107:13467-72.
Orth P, et al. *J Biol Chem*. 2014;289:18008-21.

†Data fit two binding site model best.

Bezlotoxumab Reduces CDI Recurrences

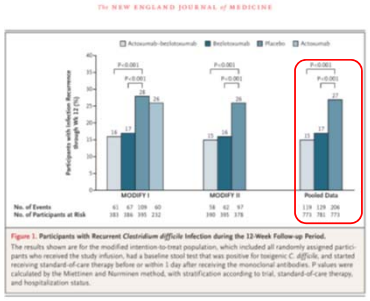
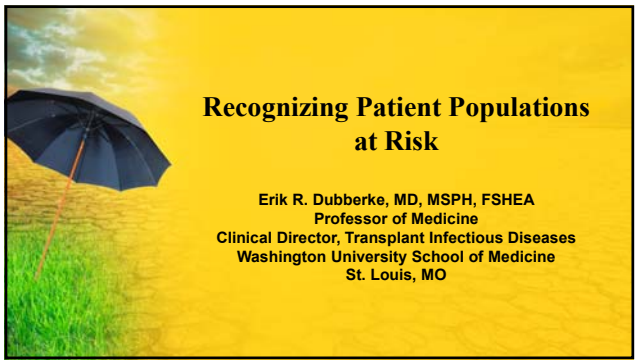


Figure 1. Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period.

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

Summary

- The incidence of CDI & recurrent CDI (rCDI) is high and both are associated with substantial morbidity, mortality and cost.
- Key factors in rCDI pathogenesis include:
  - Loss of colonization resistance (dysbiosis) perpetuated or worsened by CDI antibiotic therapy
  - Inadequate host anti-toxin immunity
- rCDI prevention approaches include:
  - Use of a CDI antimicrobial that has a less damaging effect on the colonic microbiome (e.g., fidaxomicin)
  - Restoring colonization resistance (e.g., by FMT)
  - Passive immunotherapy (using bezlotoxumab)

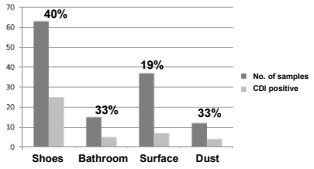


Recognizing Patient Populations at Risk

Erik R. Dubberke, MD, MSPH, FSHEA
Professor of Medicine
Clinical Director, Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO

C. difficile is an Ubiquitous Organism

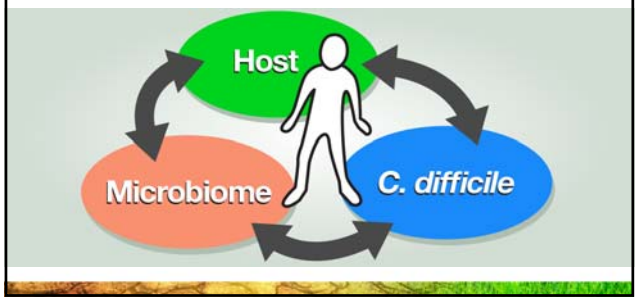
- Mammals
  - Near universal colonization in infancy
  - Prevalence decreases to <7% in adolescence/ adulthood
- Soil, water, food
- Recent study in homes:
  - 32% samples positive for toxigenic *C. difficile*
  - 83% of homes with at least one positive sample



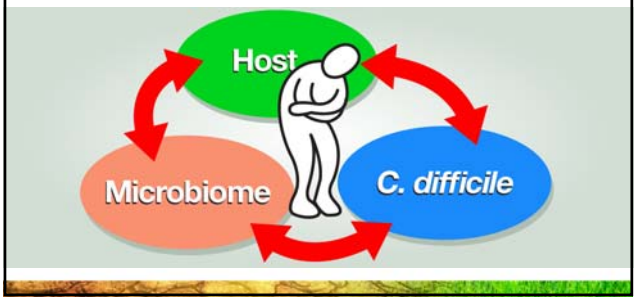
More common than in hospital rooms without CDI patients!

Alam MJ, et al. *Anaerobe*. 2014;27:31-3.

CDI Risk: Three Key Factors

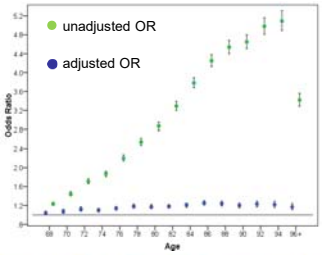


CDI Risk: Three Key Factors



Populations at Risk for CDI Simplified

- Healthcare exposures (especially unplanned hospitalizations)
  - Marker for severity of illness
  - Marker for antibiotic exposure
- Acute infections: antibiotics
  - Especially if hospitalized for treatment
- Impaired immune response
  - Severity of underlying illness
  - Physiological age vs. chronological age
  - Immunosuppression

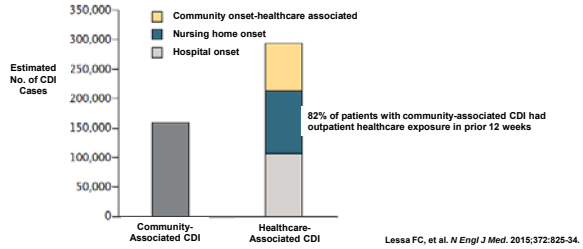


Olsen MA, et al. *Open Forum Infect Dis.* 2018;5:ofy160.

Special Populations at Risk in the Hospital

- Think:
  - Acuity of illness
  - Antimicrobial exposures (type, duration, number)
  - Impaired immune response
- Increased risk (examples)
  - Transplant
  - Oncology
  - ICU
  - Inflammatory bowel disease
  - Kidney dysfunction

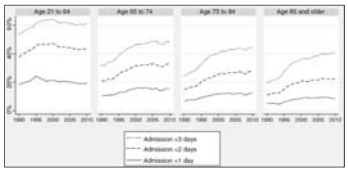
CDI in the Community



Lessa FC, et al. *N Engl J Med*. 2015;372:825-34.

Why CDI is More Common in the Community than Previously Recognized?

- Mirror trends seen in the hospital
  - Primary reservoir of *C. difficile* is community
- Improved surveillance
  - CDC Emerging Infection Program first population-based (versus hospital-based) surveillance in US
- Increased awareness
  - More likely to test
- Decreases in hospital length of stay (LOS)
  - Median LOS <3 days
  - "Sicker" patients in community than before



Lessa FC, et al. *N Engl J Med*. 2015;372:825-34.
Greenwald PW, et al. *Am J Emerg Med*. 2014;32:311-4.

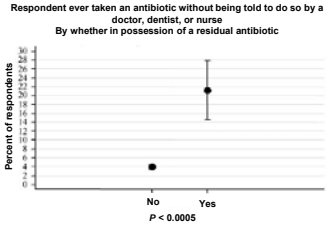
Risk Factors for Community-Associated CDI

- Most studies with <70% recent antimicrobial exposure, as low as 46%
  - Versus ≥90% for healthcare-onset CDI
  - But still the major risk factor
- Conflicting data on gastric acid suppression exposure
  - Correlation ≠ causation
- ? Exposure to infants
  - Wilcox: 14% vs 2% exposure in controls (p=0.02)

Dial S, et al. *JAMA*. 2005;294:2989-95.
Wilcox MH, et al. *J Antimicrob Chemother*. 2008;62:388-96.
CDC. *MMWR*. 2008;57(13):340-3.
Levy DG, et al. *Clin Ther*. 2000;22:91-102.
Hecker MT, et al. *Clin Infect Dis*. 2008;46:956-7.
Kuntz JL, et al. *BMC Infect Dis*. 2011;11:194.
Dial S, et al. *CMAJ*. 2008;179:767-72.
CDC. *MMWR*. 2005;54(47):1201-5.
Hirschhorn LR, et al. *J Infect Dis*. 1994;169:127-33.
Frost F, et al. *Emerg Infect Dis*. 1998;4:619-25.
Fellmeth G, et al. *J Infect Public Health*. 2010;3:118-23.

Potential Explanations for Fewer Antibiotic Exposures

- More people without antibiotic exposure than with antibiotic exposure
  - 30% to 40% with antibiotic exposure in last year
  - 10% to 15% with antibiotic exposure in last month
- Recall bias
- Taking "left over" antibiotics
  - 16% of people have kept "left over" antibiotics
  - 5% of people report taking antibiotics without advice from healthcare provider
  - 9% of people who take antibiotics use "left over" antibiotics



McNulty CA, et al. *J Antimicrob Chemother*. 2007;59:727-38.
Vanden Eng J, et al. *Emerg Infect Dis*. 2003;9:1128-35.

Conclusions

- Populations at highest risk for CDI have:
  - Healthcare exposures
  - Antibiotic exposures
  - Impaired immune response
- Within the hospital, the same but more extreme
- Within the community, the same but less extreme
  - In community, think CDI if persistent symptoms and other causes ruled-out, even if no obvious antibiotic exposure

Latest Approaches in CDI Diagnostics

Kevin W. Garey, PharmD, MS, FASHP
Chair, Department of Pharmacy Practice and Translational Research
Professor of Pharmacy Practice
College of Pharmacy
University of Houston
Houston, TX

Diagnostic Strategies for CDI

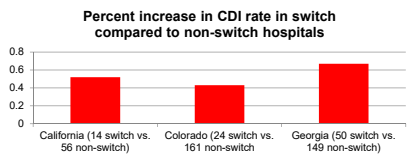
1. Only test unformed stool (or ileus)
2. Don't test asymptomatic patients (not applicable in our case)

1. Stool culture is the most sensitive diagnostic technique
2. Usually not clinically practical

Test for Toxins A and B
1. Cell cytotoxicity
2. Enzyme immunoassay (EIA)
3. Polymerase chain reaction (nucleic acid amplification test [NAAT])

PCR Diagnosis is Very Sensitive

May see an increase in rate with the switch from other diagnostics

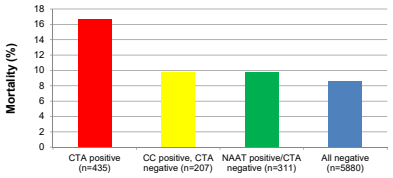


CDC: Increasing use of molecular-based diagnostics to diagnose CDI via presence of toxin genes: Increased rates vs. EIA!!

Gould CV, et al. *Clin Infect Dis*. 2013;57:1304-7.

PCR Diagnostic Strategies May Detect Patients Colonized with CDI but not Infected

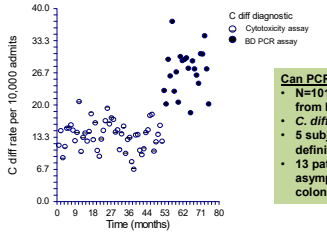
UK: prospective, multicenter study of suspected CDI patients tested by cytotoxicity assay (CTA), cytotoxigenic culture (CC), or nucleic acid amplification test (NAAT)



Mortality increased significantly in CTA-positive patients (OR 1.61; 95% CI, 1.12–2.31)

Planche TD, et al. *Lancet Infect Dis.* 2013;13:936-45.

We Observed the Same Phenomenon in Houston *C. difficile* Rates Before and After Use of the New PCR Diagnostic



Can PCR detect colonized patients?

- N=101 fecal specimens collected from hospitalized patients
- *C. difficile* in 18 subjects
- 5 subjects (28%) with either definite or probable CDI
- 13 patients (72%) with asymptomatic *C. difficile* colonization

Koo HL, et al. *Infect Control Hosp Epidemiol.* 2014;35:667-73.

CDI Laboratory Test Recommendations Based Upon Pre-agreed Institutional Criteria

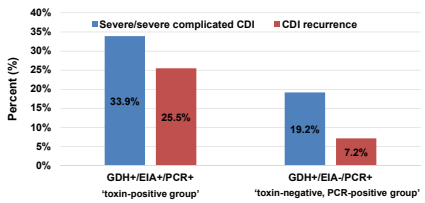
Clinicians and laboratory personnel agree at the institutional level to not submit stool samples on patients receiving laxatives and to submit stool specimens only from patients with unexplained and new-onset ≥3 unformed stools in 24 h for CDI testing

No	Yes
Stool toxin test as part of a multiple-step algorithm, usually GDH plus toxin test	**NAAT alone or stool EIA toxin test as part of a multiple-step algorithm**

McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-e48.

These Recommendations Have Already Spurred on New Research: Clinical Course of GDH+/EIA+ vs. GDH+/EIA-/PCR+

Retrospective cohort evaluation of 231 patients that tested positive for *C. difficile* with EIA vs. PCR



Origuen J, et al. *Clin Microbiol Infect.* 2018;24:414-21.

New Diagnostics are on the Way: Single Molecule Array Technology (SIMOA)

- Able to detect proteins (not genes) to a very low level
  - Limits of detection: toxin A: 0.6 and toxin B: 2.9 pg/mL
  - The optimal clinical thresholds for the toxin A and B: 22.1 and 18.8 pg/mL
  - Sensitivities: 84.8–95.5%
  - Comparator: a high-performing EIA toxin test had a sensitivity of 71.2%

Banz A, et al. *J Clin Microbiol.* 2018;56: pii:e00452-18.

Conclusions

- A two-step approach will likely be needed for accurate diagnosis of CDI
- Current research is best defining the optimal two-step approach
- Future research ongoing to improve level of detection of functional toxins

Treatment of Initial and First Recurrent CDI Episode

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Chair, Department of Pharmacy Practice and Translational Research
Professor of Pharmacy Practice
College of Pharmacy
University of Houston
Houston, TX

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

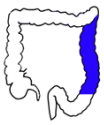
Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

Kevin W. Garey,[1] Dale N. Gerding,[2] Stuart Johnson,[3,4] Johan S. Bakken,[5] Karen C. Carroll,[6] Susan E. Coffin,[7] Erik R. Dubberke,[8] Sharon V. Gould,[9] Ciaran Kelly,[10] Vivian Loo,[11] Julia Shaklee Sammons,[12] Thomas J. Sandora,[13] and Mark H. Wilcox[14]

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

There Has Been an Explosion in Treatment Possibilities for CDI



Current:	Probiotics FMT Use narrow-spectrum antibiotics	Metronidazole Vancomycin Fidaxomicin	IVIG Monoclonal antibodies vs. *C. difficile* toxins
Future:	2nd-generation FMT Non-tox *C. difficile* M3 Ecobiotics	Ridinilazole	Toxoid vaccines

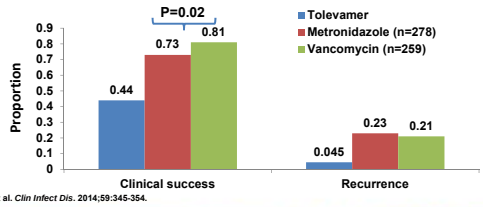
IDSA CDI Guidelines 2010

Episode	Clinical Signs	Severity	Recommended agent	Dosing Regimen	Strength of Recommendation
Initial	WBC <15,000 and SrCr <1.5 × premorbid level	Mild or moderate	Metronidazole	500 mg PO three times daily 10–14 days	A-I
Initial	WBC ≥15,000 or SrCr ≥1.5 × premorbid level	Severe	Vancomycin	125 mg PO four times daily 10–14 days	B-I
Initial	Hypotension, shock, ileus, megacolon	Severe, complicated	Vancomycin + metronidazole IV	Vancomycin: 500 mg PO or NG 4× daily + Metronidazole: 500 mg IV q8h. For ileus, consider adding rectal instillation of vancomycin	C-III
Second (1st recurrence)	----------	----------	Same as initial	Same as initial	A-II
Third (2nd recurrence)	----------	----------	Vancomycin	PO tapered and/or pulsed	B-III

Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31:431-55.

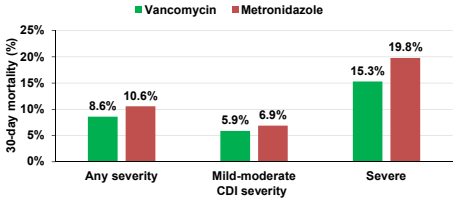
Metronidazole versus Vancomycin (Tolevamer Phase III RCT)

More recently, metronidazole has been shown to be globally inferior to vancomycin.



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

Increased Failure Rate of Metronidazole also Associated with Increased 30-day Mortality



VA dataset (vancomycin: n=2,068; metronidazole: n=8,069 propensity matched). Patients given vancomycin had a significantly lower risk of 30-day mortality (RR: 0.86, 95% CI: 0.74-0.98). No difference in CDI recurrence regardless of disease severity or choice of antibiotic (16.3–22.8%).

Stevens VW, et al. *JAMA Intern Med*. 2017;177:546-53.

Summary of Metronidazole vs. Vancomycin Clinical Studies

Study	Year	Location	n	Single center	Blinded	Randomized	Metro dose	Vanco dose	Clinical failure		Recurrence	
									metro	vanco	metro	vanco
Teasley, 1983	82-83	MN	101	yes	no	yes	250 mg QID	500 mg qid	2 of 37 (5.4%)	0 of 45 (0%)	2 of 37 (5.4%)	6 of 45 (13%)
Wenisch, 1996	93-95	Austria	62	yes	no	yes	500 mg TID	500 mg tid	2 of 31 (6%)	2 of 31 (6%)	5 of 31 (16%)	5 of 31 (16%)
Musher, 2006	02-04	USA (Houston)	34	no	yes	yes	250 mg QID	125 mg qid	6 of 34 (17%)	N/A	9 of 28 (32%)	N/A
Zar, 2007	94-02	Chicago	150	Yes	yes	yes	250 mg QID	125 mg qid	13 of 79 (16%)	2 of 71 (3%)	9 of 66 (14%)	5 of 69 (7%)
Johnson, 2013	05-07	World	552	no	yes	yes	375 mg QID	125 mg qid	76 of 278 (27%)	49 of 259 (19%)	48 of 202 (23%)	43 of 210 (21%)

There May Have Been MIC Creep With Metronidazole Over the Decades

Author	Location	Time period	Isolates	Metronidazole		
				MIC_{50}	MIC_{90}	Range
All strains						
Hecht et al	Various	1983–2004	110	0.125	0.25	0.025–0.5
Edlund et al	Sweden	1998	50	0.125	0.25	0.125–0.25
Betriu et al	Spain	2001	55	0.5	1	≤0.06–1
Citron et al	USA	2003	18	0.5	1	0.25–1
Finegold et al	USA (CA)	2003	72	0.5	1	0.25–2
Karlowsky et al	Canada (Manitoba)	2007	208	0.5	1	0.25–4
Debast et al	Europe	2008	398	0.25	0.5	<0.06-2
Reigadas et al	Spain	2013	100	0.25	0.5	0.06-1
Snydman et al	USA	2011-12	925	1	2	<0.06-4
BI/027/NAP1 strains						
Citron et al	USA	2004–2005		NR	2	0.5–2
Debast et al	Europe	2008		0.5	1	0.5-1
Snydman et al	USA	2011-12		2	2	<0.06-4

Shah D, et al. *Expert Rev Anti Infect Ther*. 2010;8:555-64.

Bottom Line: This May Simply be a PK/PD Problem

- Mean concentrations of metronidazole in stool: <0.25–9.5 μg/g
- MIC_{50}: 1 μg/mL MIC_{90}: 2 μg/mL
  - May be higher
- A poor response rate to metronidazole should be expected given these numbers!

Bolton RP, Culshaw MA. *Gut*. 1986;27:1169-72.

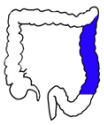
Recommendation for Initial Treatment of CDI in Adults

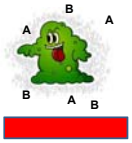
Clinical definition	Supportive clinical data	Recommended treatment
Initial episode, non-severe	WBC <15,000 cells/mL and serum creatinine <1.5 mg/dL	VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days Alternative if above agents are not available: metronidazole 500 mg three times daily by mouth for 10 days
Initial episode, severe	WBC ≥15,000 cells/mL or a serum creatinine >1.5 mg/dL	VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	VAN 500 mg given four times daily by mouth or nasogastric tube. If ileus, consider adding rectal instillation of VAN. Add intravenous metronidazole 500 mg every 8 hrs if ileus present

VAN, vancomycin; FDX, fidaxomicin; SD, standard dose

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

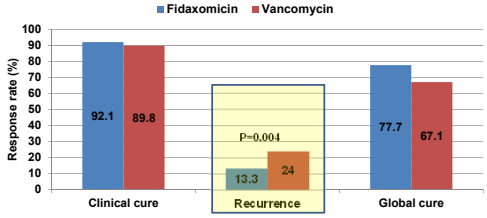
Explosion in Treatment Possibilities for CDI Minus 1





Current:	Probiotics FMT Use narrow-spectrum antibiotics	**Vancomycin** **Fidaxomicin**	IVIG Monoclonal antibodies vs. *C. difficile* toxins
Future:	2nd-generation FMT Non-tox *C. difficile* M3 Ecobiotics	Ridinilazole	Toxoid vaccines

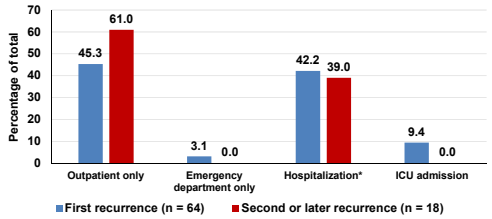
Fidaxomicin: Equal Efficacy as Vancomycin to Cure Patients and Lessens the Risk of Recurrence



The second phase III study showed similar results*

Louie T, et al. *N Eng J Med*. 2011;364:422.-310.
*Cornely OA, et al. *Lancet Infect Dis*. 2012;12:281-9.

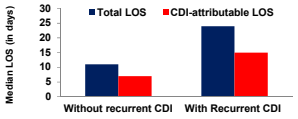
Recurrent CDI is Costly: Healthcare Utilization for Recurrent CDI



*Of disease-attributable readmission, 85% returned to the initial hospital for care

Aitken SL, et al. *PLoS One.* 2014;9(7):e102848.

Increased Healthcare Utilization = Increased Healthcare Costs



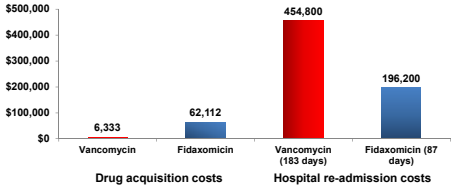
Cost in US dollars, median (IQR)	Without recurrent CDI	With recurrent CDI
CDI pharmacologic treatment	$60 (23 – 200)	$140 (30 – 260)
CDI-attributable hospitalization	$13,168 (7,525 – 24,455)	$28,218 (15,049 – 47,030)
Total hospitalization	$20,693 (11,287 – 41,386)	$45,148 (20, 693 – 82,772)

Shah DN, et al. ICAAC 2014 Poster #K-356, Sat., Sept 6, 2014.

Any Evidence That Fidaxomicin May Reduce These Costs?

Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for select patients.

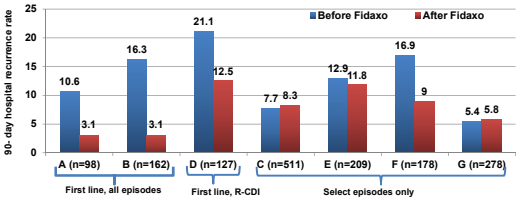
CDI-related re-admissions: fidaxomicin: 20.4%; vancomycin: 41.3%



Gallagher JC, et al. *Antimicrob Agents Chemother.* 2015;59:7007-10.

Real-world Evidence That Fidaxomicin May Reduce These Costs?

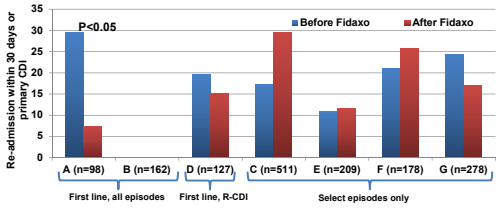
UK, 2012–13: Seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals



Goldenberg SD, et al. *Eur J Clin Microbiol Infect Dis*. 2016;35:251-9.

Real-world Evidence That Fidaxomicin May Reduce These Costs?

UK, 2012–13 : Seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively (p<0.05, each)



Goldenberg SD, et al. *Eur J Clin Microbiol Infect Dis*. 2016;35:251-9.

Recommendation for Recurrence of CDI in Adults

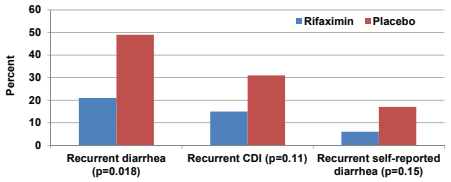
Clinical definition	Supportive clinical data	Recommended treatment
First recurrence		• VAN SD if metronidazole was used for the first episode, OR • Prolonged tapered and pulsed VAN if VAN SD was used for first regimen, OR • FDX SD if VAN was used for the initial episode
Second or subsequent recurrences		• VAN in a tapered or pulsed regimen, OR • VAN SD followed by rifaximin 400 mg three times daily for 20 days, OR • FDX SD, OR • Fecal microbiota transplantation

VAN, vancomycin; FDX, fidaxomicin; SD, standard dose

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Effect of Rifaximin to Prevent Recurrent Diarrhea

A Randomized Double-blind, Placebo-controlled Pilot Study to Assess the Effect of Rifaximin to Prevent Recurrent Diarrhea in 68 patients with *Clostridium difficile* Infection

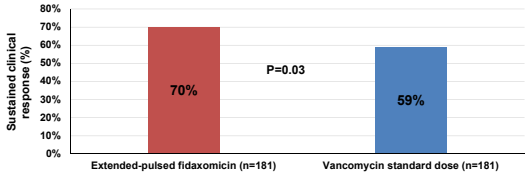


Patients were given a 20-day course of rifaximin or matching placebo after completing a 10–14-day course of metronidazole or vancomycin therapy.

Garey K, et al. *J Antimicrob Chemother*. 2011;66:2850-5.

What Do You Do If You Chose Fidaxomicin Standard Dose as First-Line Therapy and the Patient Now has CDI Recurrence?

Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomized, controlled, open-label, phase 3b/4 trial

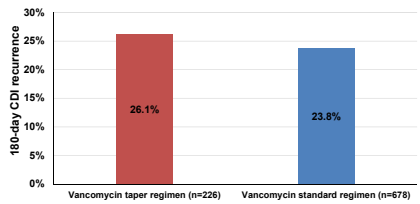


Extended-pulsed fidaxomicin: Fidaxomicin 200 mg twice daily days 1-5 then once daily on alternate days on days 7-25.

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

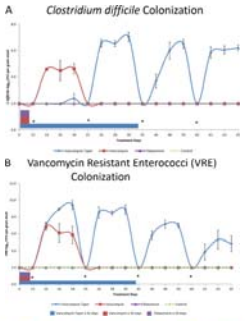
…And The Data Supporting Tapered Oral Vancomycin is Not Super Convincing

Propensity-matched analysis between standard and tapered oral vancomycin for adult patients treated for recurrent CDI, VHA dataset



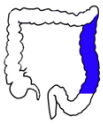
Gentry CA, et al. *Open Forum Infect Dis*. 2017;4(4):ofx235.

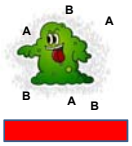
Vancomycin Extended Taper Regimen Continues to Disrupt the Microbiome and Allows for Overgrowth of *Clostridium difficile* (A) and Vancomycin-resistant Enterococci (VRE) (B)



Tomas ME, et al. *Antimicrob. Agents Chemother.* 2018;62:e02237-17.

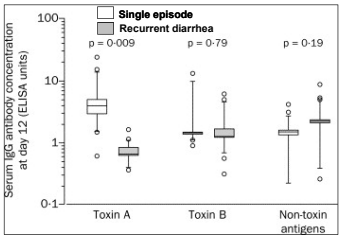
Explosion in Treatment Possibilities for CDI: Augment Immune Response!





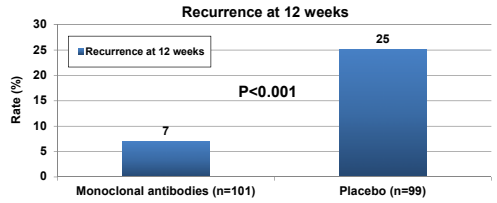
Current:	Probiotics FMT Use narrow-spectrum antibiotics	Vancomycin Fidaxomicin	IVIG **Monoclonal antibodies vs. *C. difficile* toxins**
Future:	2nd-generation FMT Non-tox *C. difficile* M3 Ecobiotics	Ridinilazole	Toxoid vaccines

Serum Concentrations of IgG Antibodies Against Toxin A, Toxin B, and Non-toxin Antigens



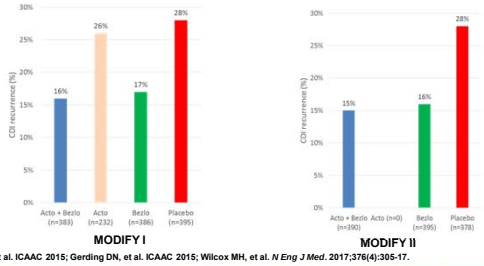
Kyne L, et al. *Lancet.* 2001;357:189-93.

Monoclonal Antibody: Phase II Study



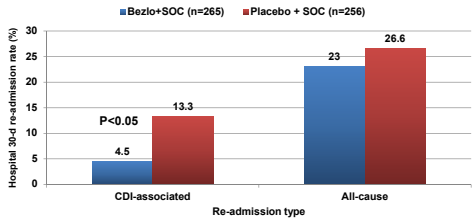
Lowy I, et al. *N Engl J Med*. 2010;362:197-205.

Phase III Studies of Actoxumab (Acto) and Bezlotoxumab (Bezlo): Overall



Wilcox MH, et al. ICAAC 2015; Gerding DN, et al. ICAAC 2015; Wilcox MH, et al. *N Eng J Med*. 2017;376(4):305-17.

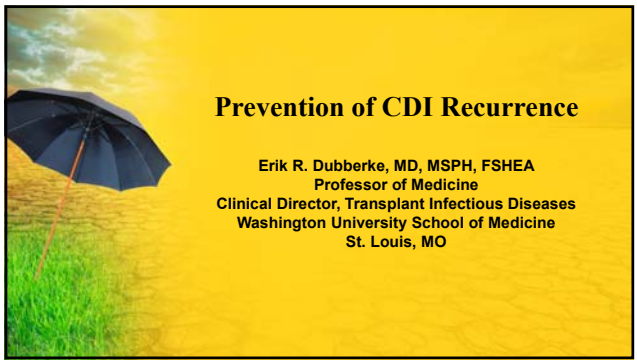
Bezlotoxumab Was Also Shown to Reduce Hospital Re-admissions (European Population)



Gerding DN, et al. Abstract 2000. Presented at: ECCMID; April 9-12, 2016; Amsterdam.
Wilcox MH, et al. Abstract 1996. Presented at: ECCMID; April 9-12, 2016; Amsterdam.

Final Conclusions

- Limit (eliminate) use of metronidazole
  - Pick a place for fidaxomicin
  - Be prepared for more competition in the narrow-spectrum anti-*C. difficile* world
- Immune response
  - Bezlotoxumab is here (and can be used in outpatient infusion centers)
- Complete the triad: Correct dysbiosis



Prevention of CDI Recurrence

Erik R. Dubberke, MD, MSPH, FSHEA
Professor of Medicine
Clinical Director, Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO

C. difficile is an "Urgent Threat"

- Most common cause of healthcare-associated infections in US
- Over 450,000 incident cases per year
  - Over 29,000 associated deaths
  - 83,000 people with at least one recurrence

Pathogen	All Health Care–Associated Infections (N = 504)†	
	no. (%)	rank
Clostridium difficile	61 (12.1)	1
Staphylococcus aureus	54 (10.7)	2
Klebsiella pneumoniae or K. oxytoca	50 (9.9)	3
Escherichia coli	47 (9.3)	4
Enterococcus species‡	44 (8.7)	5
Pseudomonas aeruginosa	36 (7.1)	6
Candida species§	32 (6.3)	7
Streptococcus species¶	25 (5.0)	8
Coagulase-negative staphylococcus species	24 (4.8)	9
Enterobacter species	16 (3.2)	10

Lessa FC, et al. *N Engl J Med*. 2015;372:825-34.
Magill SS, et al. *N Engl J Med*. 2014;370:1198-208.

Incidence of Recurrent CDI

- ~10% to ~30% of patients with an incident episode will have at least one recurrence
- In general:
  - Retrospective hospital-based studies: lower end
  - Prospective observation studies: middle
  - Clinical trials: higher end

Zilberberg MD, et al. *J Hosp Med*. 2014;9:418-23.
Garey KW, et al. *J Hosp Infect*. 2008;70:298-304.
McDonald LC, et al. *Clin Infect Dis*. 2018;66:e1-e48.

Multiply Recurrent CDI

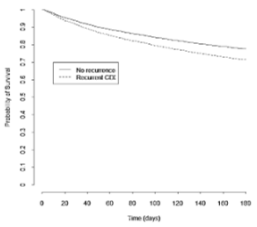
- Historically: risk increased with each subsequent recurrence to >65% once ≥2 prior episodes
- More recent data: ~30% to ~50%
  - Lower if attempts to prevent recurrence

Study	Design	# prior CDI episodes, recurrence incidence		
		0	1	≥2
Sheitoyan-Pesant	Observational	25%	38%	29%
Wilcox	Bezlotoxumab trial, placebo arm	21%	41%	42%
Dubberke	RBX2660 trial, placebo arm	NA	NA	55%

Sheitoyan-Pesant C, et al. *Clin Infect Dis*. 2016;62:574-580.
Wilcox M, et al. *N Engl J Med*. 2017;376:1594-6.
Dubberke ER, et al. *Clin Infect Dis*. 2016; doi: 10.1093/cid/ciy259 [Epub ahead of print].

Recurrent CDI Outcomes

- Associated with worse outcomes
  - Readmissions (RR = 2.5; 95% CI, 2.2–2.9)
  - Costs ($11,631; 95% CI $8,937–$14,588)
  - Mortality (HR 1.3; 95% CI 1.1–1.6)
- Devastating to the patient
  - Embarrassment
  - Inability to leave house
  - Physical toll



Olsen MA, et al. *Am J Infect Control*. 2015;43:318-22.
Olsen MA, et al. *Clin Microbiol Infect*. 2015;21:164-70.
Dubberke ER, et al. *Infect Control Hosp Epidemiol*. 2014;35:1400-7.

Risk Factors for Recurrent CDI

- Age
- Exposure to non-CDI treatment antibiotics
- Gastric acid suppression
- Lack of anti-toxin antibody response

Variable	Univariate [Odds ratio (p=value)]	Multivariable [Odds ratio (p=value)]
Age ≥65	3.93 (.009)	3.76 (0.24)
Female	1.02 (.971)	
Horn index >1	4.20 (.077)	
Concomitant antibiotics	2.20 (.095)	2.06 (.19)
Gastric acid suppression	0.92 (.870)	
Prior CDI	2.70 (.041)	2.58 (.09)
Anti-toxin A	0.40 (.401)	
Anti-toxin B	**0.12 (.045)**	**0.11 (.05)**

Garey KW, et al. *J Hosp Infect*. 2008;70:142-7.
Gupta SB, et al. *Clin Infect Dis*. 2016;63:730-4.

C. difficile Strain and Recurrent CDI

			Recurrence		
Variable	Test	Reference	OR	95% CI	*P* Value
REA group	BI group	Non-BI group	1.57	1.01 – 2.45	.046
	No isolate	Non-BI group	0.91	.57 – 1.47	.70
Age	≥ 65	< 65	1.36	.93 – 1.98	.11
CDI history	One prior episode	No prior episode	1.82	1.15 – 2.87	.01
Region	Canada	United States	1.37	.91 – 2.07	.13
	Europe	United States	0.78	.43 – 1.39	.14
Antibiotic history prior to CDI treatment	Yes	No	NA	NA	NA
CA during treatment period	Yes	No	…	…	…
CA during treatment or follow-up period	Yes	No	1.57	1.03 – 2.39	.04
Comorbidity	Yes	No	NA	NA	NA
Treatment	Fidaxomicin	Vancomycin	0.45	.31 - .65	<.0001

Petrella LA, et al. *Clin Infect Dis*. 2012;55:351-7.

Difficult to Predict Recurrent CDI

- Risk factors for recurrence are same as risk factors for incident episode
  - Most patients have multiple risk factors
- Risk for recurrence is already high
- Risk may be influenced by local epidemiology/practices
- No commercially-available assays to measure anti-*C. difficile* antibody levels
  - Markers: age, immunosuppressed, acuity of illness

Prediction of *C. difficile* Recurrence

TABLE 2 Factors found to predict rCDI in the logistic regression model

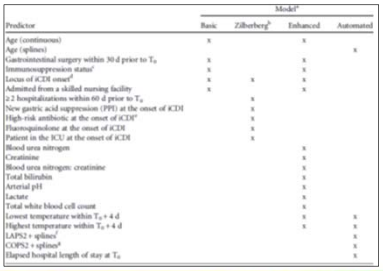
Factor	*Odds ratio*	*95% CI*
Age (per 1 year)	1.21	1.04 - 1.40
CO-HCFA CDI (ref: HO-CDI)	1.71	1.32 - 2.22
2+ hospitalization in prior 60 days (ref: 0 hospitalizations)	1.49	1.08 - 2.06
New gastric acid suppression at the onset of iCDI	1.59	1.13 - 2.23
High-risk antibiotic at the onset of iCDIa	1.25	1.01 - 1.55
Fluoroquinolone at the onset of iCDI	1.31	1.04 - 1.65
ICU at the onset of iCDI	0.49	0.34 - 0.72

*High risk antibiotics included all cephalosporins, clindamycin, and penicillins.

The validated model had a C statistic of 0.63.

Zilberberg MD, et al. *J Hosp Med*. 2014;9:418-23.

Comparison of Multiple Recurrent CDI Prediction Models: Variables Included



Predictor	Model[a]			
	Basic	Zilberberg[b]	Enhanced	Automated
Age (continuous)	x		x	
Age (splines)				x
Gastrointestinal surgery within 30 d prior to T_0	x		x	
Immunosuppression status[c]	x		x	
Locus of iCDI onset[d]	x	x	x	
Admitted from a skilled nursing facility	x		x	
≥ 2 hospitalizations within 60 d prior to T_0		x		
New gastric acid suppression (PPI) at the onset of iCDI		x		
High-risk antibiotic at the onset of iCDI[e]		x		
Fluoroquinolone at the onset of iCDI		x		
Patient in the ICU at the onset of iCDI		x		
Blood urea nitrogen			x	
Creatinine			x	
Blood urea nitrogen: creatinine			x	
Total bilirubin			x	
Arterial pH			x	
Lactate			x	
Total white blood cell count			x	
Lowest temperature within T_0 + 4 d			x	x
Highest temperature within T_0 + 4 d			x	x
LAPS2 + splines[f]				x
COPS2 + splines[g]				x
Elapsed hospital length of stay at T_0				x

Escobar GJ, et al. *Infect Control Hosp Epidemiol.* 2017;38:1196-203.

Comparison of Multiple Recurrent CDI Prediction Models: Results

Model	Statistic	Sensitivity	Specificity	PPV	NPV	NNE
Age ≥ 65 years	0.546	67.36	41.86	11.04	92.30	9.06
Basic model	0.591	75.69	41.19	12.11	94.06	8.26
Zilberberg model	0.591	74.31	39.03	11.54	93.42	8.66
Enhanced model	0.587	69.44	43.64	11.66	93.03	8.58
Automates model	0.605	79.17	32.04	11.09	93.49	9.02

PPV, positive predictive value; NPV, negative predictive value; NNE, number of incident cases to evaluate for 1 recurrence

Age alone worked nearly as well as models!

Escobar GJ, et al. *Infect Control Hosp Epidemiol.* 2017;38:1196-203.

Recurrent CDI Prediction: KISS Approach

"Keep It Simple, Stupid"

- Handful of risk factors associated with recurrent CDI
- If any present, then increased risk for recurrence

IDSA/SHEA Guidelines: Treatment of an Initial Episode

Clinical Definition	Supportive Clinical Data	Recommended Treatment (Strength of Recommendation/Quality of Evidence)
Initial episode, non-severe	WBC ≤15,000 cells/ml, serum Cr <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days (Strong/High), OR • 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	WBC >15,000 cells/ml, serum Cr >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days (Strong/High), OR • 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 (Strong/Moderate). If ileus, consider adding rectal instillation of VAN. IV metronidazole (500 mg every 8 hours) (Strong/Moderate) should be administered together with oral or rectal VAN (Weak/Low), particularly if ileus is present.

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

IDSA/SHEA Guidelines: Treatment of an Initial Episode

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Initial episode, severe		• VAN, 125 mg 4 times per day by mouth for 10 days (Strong/High), OR • 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 (Strong/Moderate). If ileus, consider adding rectal instillation of VAN. IV metronidazole (500 mg every 8 hours) (Strong/Moderate) should be administered together with oral or rectal VAN (Weak/Low), particularly if ileus is present.

Fidaxomicin now first-line agent

Major change: metronidazole is no longer first-line agent for non-severe CDI in settings where access to VAN/FDX is not limited

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Should Treatment of Initial CDI Focus on Recurrence Risk?

- If metronidazole is no longer a first-line agent for CDI, no need to select treatment based on CDI severity
- Major differentiator in currently-available recommended treatments
  - Recurrence

Fidaxomicin vs. Vancomycin Clinical Outcomes in mITT Populations

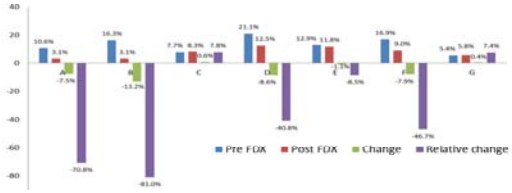
- Novel macrocyclic antimicrobial
- Narrow spectrum
- No activity against Gram-negative bacteria
- Sparing of *Bacteroides* spp., *Bifidobacterium*, clostridial clusters IV and XIV

Clinical Outcomes	Fidaxomicin, n (%)	Vancomycin, n (%)	Treatment Difference	*P* Value
Clinical cure				
Louie[a]	253/287 (88.2)	265/309 (85.8)	-3.1*	
Cornely[b]	221/252 (87.8)	223/257 (86.7)	-4.9*	
Recurrence†				
Louie[a]	39/253 (15.4)	67/265 (25.3)	-9.9 (-16.6 to -2.9)	*P* =.0005
Cornely[b]	28/221 (12.7)	60/223 (26.9)	-14.2 (-21 to -6.8)	*P* =.0002
Sustained clinical response‡				
Louie[a]	214/287 (74.6)	198/309 (64.1)	10.5 (3.1 to 17.7)	*P* =.006
Cornely[b]	193/252 (76.6)	163/257 (63.4)	13.2 (5.3 to 21)	*P* =.001

*Lower boundary 97.5% CI.
†95% CI.

[a] Louie TJ, et al. *N Engl J Med*. 2011;364:422-31
[b] Cornely OA, et al. *Lancet Infect Dis*. 2012;12:281-9.

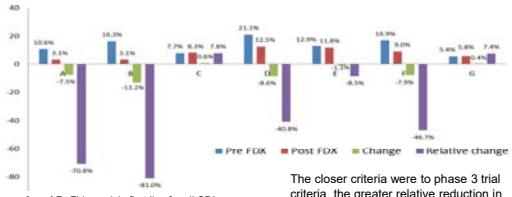
Fidaxomicin Experience in England



A and B: Fidaxomicin first-line for all CDI
C: Recurrences only or with ID consult
D: Recurrence only
E and G: Select patients
F: First-line all >75 years old, or if comorbidities/concomitant antibiotics

Goldenberg SD, et al. *Eur J Clin Microbiol Infect Dis*. 2016;35:251-9.

Fidaxomicin Experience in England



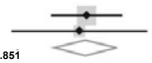
The closer criteria were to phase 3 trial criteria, the greater relative reduction in CDI recurrence

A and B: Fidaxomicin first-line for all CDI
C: Recurrences only or with ID consult
D: Recurrence only
E and G: Select patients
F: First-line all >75 years old, or if comorbidities/concomitant antibiotics

Goldenberg SD, et al. *Eur J Clin Microbiol Infect Dis*. 2016;35:251-9.

When Should Fidaxomicin be Used?

- First episode
  - "Risk of" first recurrence
    - Or risk of complications
  - Age
  - Immune status
  - High severity of underlying illness
  - Concomitant antibiotics
- First recurrence
  - Absolutely



Prior CDI				
No Prior Episodes	0.61 (0.48, 0.76)	88/479	151/499	<.0001
Single Prior Episodes	0.58 (0.37, 0.90)	22/93	38/93	.012
Subtotal (I-squared = 0.0%, *P* = .851	0.60 (0.49, 0.74)	110/572	189/592	<.0001

Crook DW, et al. *Clin Infect Dis*. 2012;55(Suppl 2):S93-103.

IDSA/SHEA Guidelines: Treatment of Recurrent CDI

Clinical Definition	Recommended Treatment (Strength of Recommendation/Quality of Evidence)
First recurrence	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode (Weak/Low), OR • Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (Weak/Low), OR • 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 (Weak/Low), OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days (Weak/Low), OR • FDX 200 mg given twice daily for 10 days (Weak/Low), OR • Fecal microbiota transplantation (FMT)(Strong/Moderate) (appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation)

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

IDSA/SHEA Guidelines: Treatment of Recurrent CDI

Clinical Definition	Recommended Treatment (Strength of Recommendation/Quality of Evidence)
First recurrence	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode (Weak/Low), OR • Use a prolonged tapered and pulsed VAN regimen was used for the initial episode (Weak/Low), OR • FDX 200 mg given twice daily for 10 days if VAN was used for the initial Episode (Weak/Moderate)
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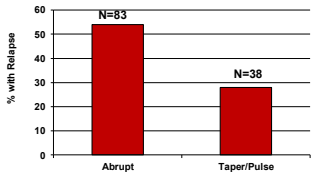
Do not give same regimen a second time

More options provided for second or subsequent recurrence

McDonald LC, et al. *Clin Infect Dis*

Abrupt Stop vs. Taper or Pulse of Vancomycin

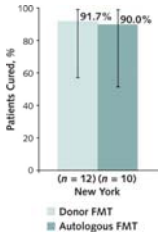


- Mean number of CDI episodes 3 ± 2.1 (range 1–14)
- Relative Risk of Relapse = 0.51 (95% CI: 0.29–0.90)

McFarland LV, et al. *Am J Gastroenterol*. 2002;97:1769-75.

Microbiota Replacement Therapy / FMT

- Still with challenges
  - Not available everywhere
  - Optimal dosing and route of administration not defined
- Misleading data on efficacy
  - Allowing repeat dosing after failure but still counted as success
  - Meta-analyses with multiple studies that include same patients
  - Proponents with efficacy same as control arm

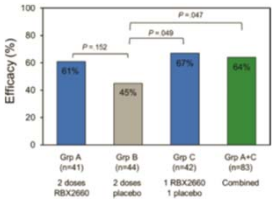


Kelly CR, et al. *Ann Intern Med*. 2016;165:609-16.

Microbiota Replacement Therapy "True" Efficacy

Study	Single dose	Second dose
Youngster (n=20)	70%	90%
Hirsch (n=19)	68%	89%
Orenstein (n=35)	60%	88%
Youngster (n=14)	70%	90%
Van Nood (n=16)	81%	94%
Lee (PP n=178, mITT n=219)	62% / 51%	84% / 73%
Khanna (n=30)*	87%	97%
Press release (n=59)*	56%	NA
Combined (n=371)	**65% / 60%**	

*same product

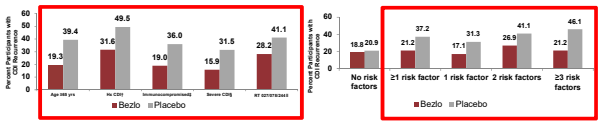


Youngster I, et al. *Clin Infect Dis*. 2014;58:1515-22.
Orenstein R, et al. *Clin Infect Dis*. 2016;62:596-602.
van Nood E, et al. *N Engl J Med*. 2013;368:407-15.
Khanna S, et al. *J Infect Dis*. 2016;214:173-81.
Seres Therapeutics. http://ir.serestherapeutics.com/phoenix.zhtml?c=254006&p=irol-newsArticle&ID=2190006.
Hirsch BE, et al. *BMC Infect Dis*. 2015;15:191.
Youngster I, et al. *JAMA*. 2014;312:1772-8.
Lee CH, et al. *JAMA*. 2016;315:142-9.
Dubberke ER, et al. *Clin Infect Dis*. 2018; doi:10.1093/cid/ciy259.

Bezlotoxumab: Approved too Late to be Included in Guidelines

- Monoclonal antibody against *C. difficile* toxin B
  - Administered as single IV infusion in addition to standard of care CDI treatment antibiotics
  - Indication: prevention of recurrent CDI

KISS



Gerding DN, et al. *Clin Infect Dis*. 2018; doi:10.1093/cid/ciy171 [Epub ahead of print].

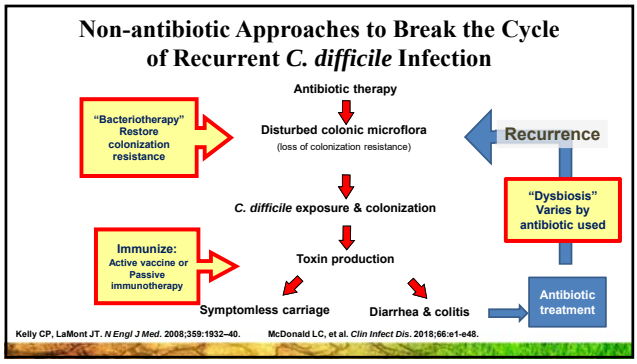
When I Administer Bezlotoxumab

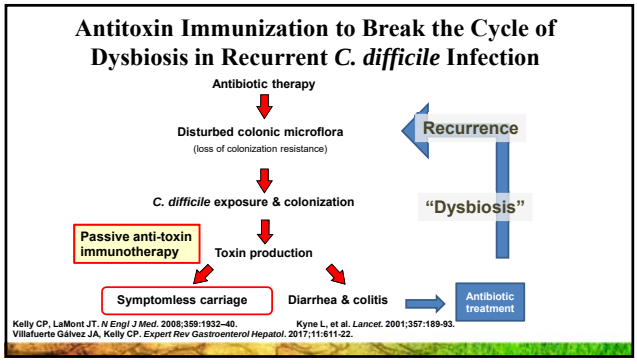
- Any KISS criteria present
- No benefit for clinical cure
  - No urgency to administer
- Maximize durability: end of CDI treatment
  - Different from trials (median time to administration 7 days)
  - Antibodies protect against recurrent CDI while microbiome is recovering
  - CDI will not recur while still on treatment
  - Half-life ~19 days

Conclusions

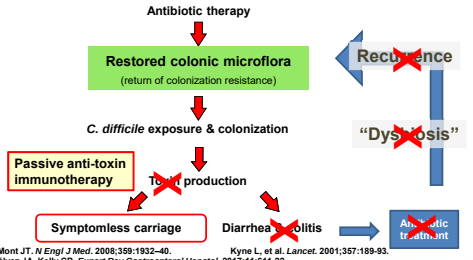
- Recurrent CDI is a significant problem
- Keep it simple when identifying patients at risk for recurrence
  - ≥65 years old
  - Concomitant antibiotics
  - Past history of CDI
  - Immunocompromised
  - High severity of underlying illness (CDI or otherwise)
  - 027 / BI / NAP1 strain
- Effective treatments for decreasing recurrent CDI


Place of Immunotherapy in CDI Management
Ciarán P. Kelly, MD
Professor of Medicine
Harvard Medical School
Director Gastroenterology Fellowship Training
Director Celiac Center
Beth Israel Deaconess Medical Center
Boston, MA


Non-antibiotic Approaches to Break the Cycle of Recurrent C. difficile Infection
Antibiotic therapy
"Bacteriotherapy" Restore colonization resistance
Disturbed colonic microflora
(loss of colonization resistance)
Recurrence
"Dysbiosis" Varies by antibiotic used
C. difficile exposure & colonization
Immunize: Active vaccine or Passive immunotherapy
Toxin production
Symptomless carriage
Diarrhea & colitis
Antibiotic treatment
Kelly CP, LaMont JT. N Engl J Med. 2008;359:1932–40.
McDonald LC, et al. Clin Infect Dis. 2018;66:e1-e48.


Antitoxin Immunization to Break the Cycle of Dysbiosis in Recurrent C. difficile Infection
Antibiotic therapy
Disturbed colonic microflora
(loss of colonization resistance)
Recurrence
C. difficile exposure & colonization
"Dysbiosis"
Passive anti-toxin immunotherapy
Toxin production
Symptomless carriage
Diarrhea & colitis
Antibiotic treatment
Kelly CP, LaMont JT. N Engl J Med. 2008;359:1932–40.
Villafuerte Gálvez JA, Kelly CP. Expert Rev Gastroenterol Hepatol. 2017;11:611-22.
Kyne L, et al. Lancet. 2001;357:189-93.

Antitoxin Immunization to Break the Cycle of Dysbiosis in Recurrent *C. difficile* Infection



Kelly CP, LaMont JT. *N Engl J Med*. 2008;359:1932–40.
Villafuerte Gálvez JA, Kelly CP. *Expert Rev Gastroenterol Hepatol*. 2017;11:611-22.
Kyne L, et al. *Lancet*. 2001;357:189-93.

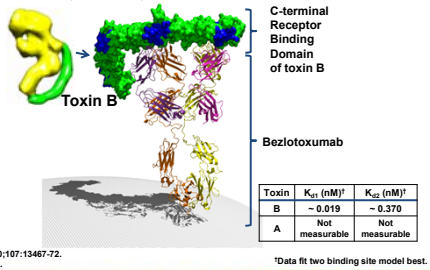
Bezlotoxumab Binds to the Putative Receptor Binding Domain (CROP) of Toxin B

Bezlotoxumab

Human IgG1 monoclonal antibody (mol wgt ~148.2 kDa)

Binds to and neutralizes *C. difficile* toxin B

Binding site characterized: C-terminal putative receptor binding domain

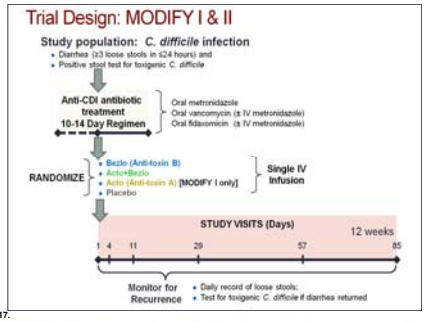


Toxin	K_{d1} (nM)†	K_{d2} (nM)†
B	~ 0.019	~ 0.370
A	Not measurable	Not measurable

†Data fit two binding site model best.

Pruitt RN, et al. *Proc Natl Acad Sci USA*. 2010;107:13467-72.
Orth P, et al. *J Biol Chem*. 2014;289:18008-21.

Bezlotoxumab



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

Bezlotoxumab Reduces CDI Recurrences

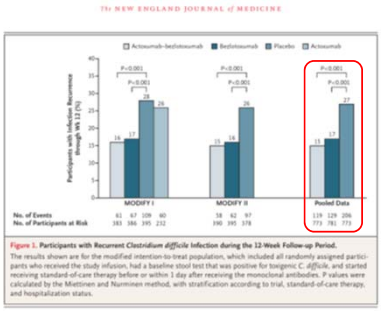
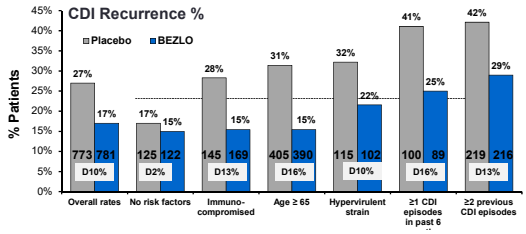


Figure 1. Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period.
The results shown are for the modified intention-to-treat population, which included all randomly assigned participants who received the study infusion, had a baseline stool test that was positive for toxigenic *C. difficile*, and started receiving standard-of-care therapy before or within 1 day after receiving the monoclonal antibodies. P values were calculated by the Miettinen and Nurminen method, with stratification according to trial, standard-of-care therapy, and hospitalization status.

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

Bezlotoxumab Efficacy in Reducing CDI Recurrence in Patients with Baseline Risk Factors, MODIFY I + II



Gerding DN, et al. *Clin Infect Dis*. 2018; doi: 10.1093/cid/ciy171 [Epub ahead of print].

Bezlotoxumab

Indicated to reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older:

- **Who are at a high risk for CDI recurrence**

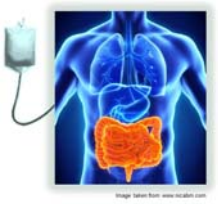
Single dose of 10 mg/kg IV over 60 min

- **While receiving antibacterial drug treatment for CDI**

T½ 19 days in CDI patients

Cleared via protein catabolism (similar to endogenous Abs)

- **No known metabolic drug-drug interactions**
- **No dose modifications needed for renal or hepatic impairment or age**



Villafuerte Gálvez JA, Kelly CP. *Expert Rev Gastroenterol Hepatol*. 2017;11:611-22.

Summary: Immunotherapy for *C. difficile* Infection

Bezlotoxumab

- Administer by IV infusion during antimicrobial therapy for CDI
  - Can be performed at outpatient infusion centers
- Neutralizes toxin B and prevents recurrent diarrhea and colitis
- Indicated for CDI patients at high risk for recurrence
  - Immunocompromised
  - Age >65 years
  - Infected by highly-virulent CDI strain (e.g., ribotypes 027 or 078)
  - History of recurrent CDI