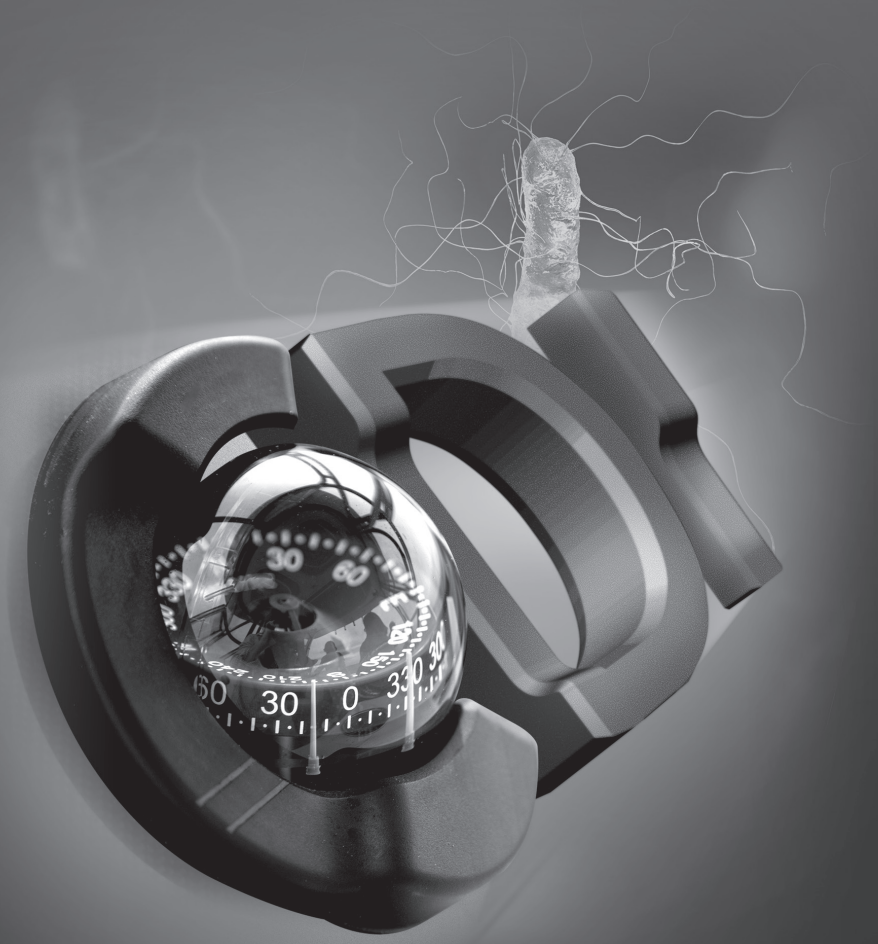


Identifying and Transitioning Patients with CDI: Roles and Responsibilities of the Hospitalist

William Ford, MD, SFHM
Regional Director Hospital Medicine
Clinical Associate Professor of Medicine
Abington Jefferson Health
Abington, PA

Audience Question

What is the size of your hospital?

1. <100 beds
2. 100 to 249 beds
3. >250 beds
4. Not applicable

Audience Question

How many cases of *C. difficile* infection do you encounter per week?

1. 0
2. 1–2
3. 3–5
4. >5
5. Not applicable

Audience Question

What percentage of your CDI cases are re-admissions?

1. <10%
2. 10–25%
3. 25–50%
4. >50%
5. Unsure
6. Not applicable

Audience Question

How often do you partner with your antimicrobial stewardship team (AST)?

1. Frequently (daily or weekly)
2. Occasionally (monthly or less)
3. Never
4. I am unaware of an AST at my hospital
5. Not applicable

C. difficile is an "Urgent Threat"

- Most common cause of healthcare-associated infections in US
- Over 450,000 incident cases per year[1]
  - Over 29,000 associated deaths
  - 83,000 people with at least one recurrence

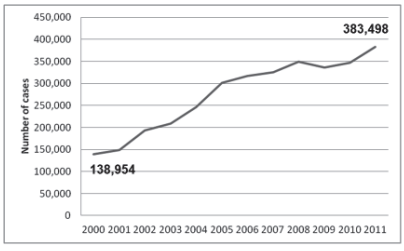
Point-prevalence survey of healthcare-associated infections, 2015[2]

Pathogen	All Healthcare-associated infections n (%)	Rank
C. difficile	66 (15)	1
S. aureus	48 (11)	2
E. coli	44 (10)	3
Candida spp.	26 (6)	4
Enterococcus spp.	23 (5)	5
Enterobacter spp.	22 (5)	6
P. aeruginosa	22 (5)	6
Klebsiella spp.	21 (5)	8
Streptococcus spp.	21 (5)	8

1. Lessa FC, et al. *N Engl J Med.* 2015;372:825-34.
2. Magill SS, et al. *N Engl J Med.* 2018;379:1732-44.

*C. difficile I*nfection (CDI): Rising Incidence and Fatalities

Total CDI Cases in U.S. Hospitals Nationwide Inpatient Sample (NIS)



Source: AHRQ HCUP data. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf.

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

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]

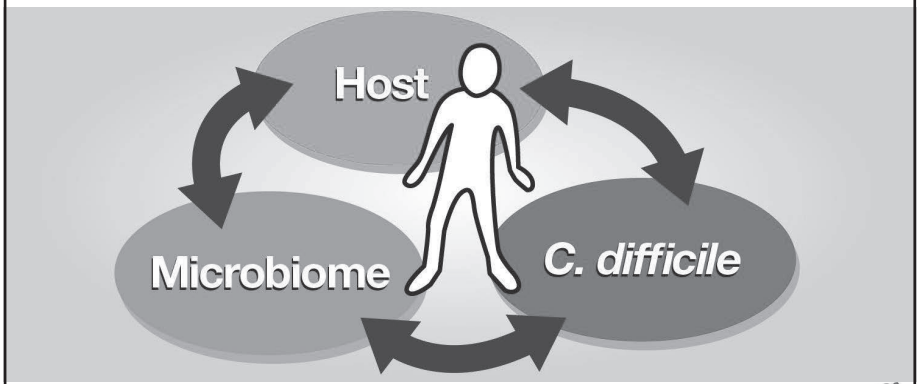
CDC. Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

Costs of CDI

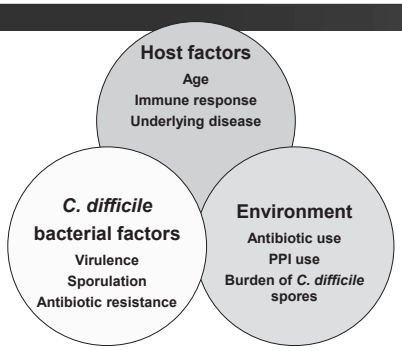
- Annual economic burden of CDI approached $5.4 billion in 2014, primarily driven by prolonged LOS[1]
- In 2014, US National Inpatient Sample data revealed mean hospital charges for CDI at $35,898, and LOS of 5.8 days[2]
- Attributable inpatients costs of initial CDI (2012 USD)[3]
  - $3,327 to $9,960 per episode (limited to studies with more robust methodology)
- Other costs not easily quantified
  - CDI outside of the hospital
  - Increase in transfers to skilled nursing at hospital discharge
  - Lost time from work (patient and/or caregiver)

1. Desai K, et al. *BMC Infect Dis.* 2016;16:303.
2. Shrestha MP, et al. *Am J Med.* 2018;131:90-96.
3. Kwon JH, et al. *Infect Dis Clin North Am.* 2015;29:123-34.

CDI Risk: Three Key Factors



CDI Risk Factors



CDI is a very common nosocomial infection

High:

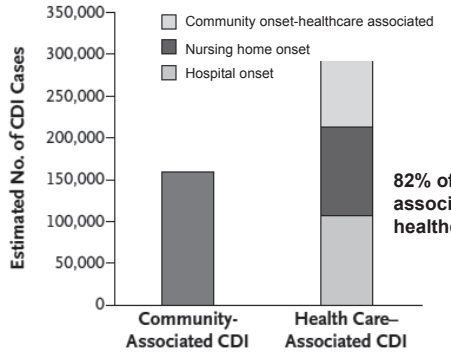
- **Incidence**
- **Morbidity**
- **Mortality**
- **Economic cost**
  - **Longer hospital stay**
  - **Discharge to nursing home/ healthcare institution more likely**
  - **Recurrence – often leading to re-admission**

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932–40.
Lessa FC, et al. *Clin Infect Dis.* 2012;55(Suppl 2):S65-S70.
McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-e48.

Diagnostic Testing for CDI: 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

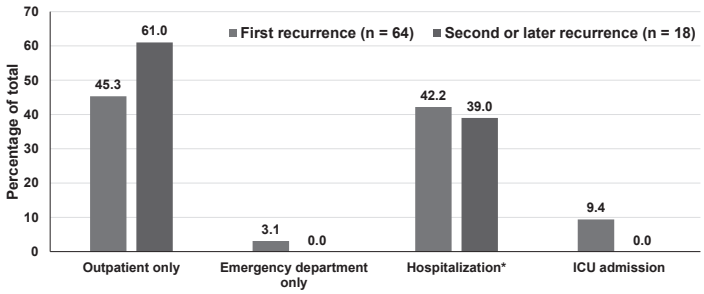
CDI in the Community



82% of patients with community-associated CDI had outpatient healthcare exposure in prior 12 weeks

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

Recurrent CDI is Costly: Healthcare Utilization for Recurrent CDI

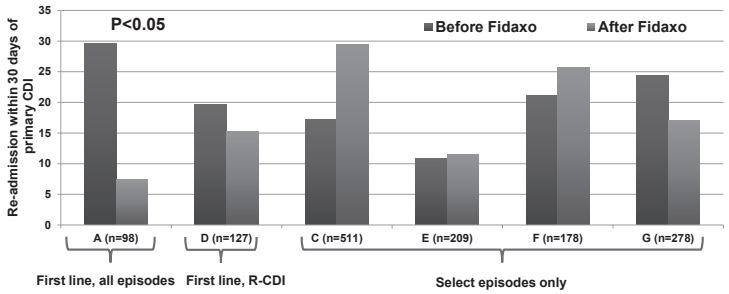


*Of disease-attributable readmission, 85% returned to the initial hospital for care

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

Real-world Evidence on Fidaxomicin Use and Re-admissions

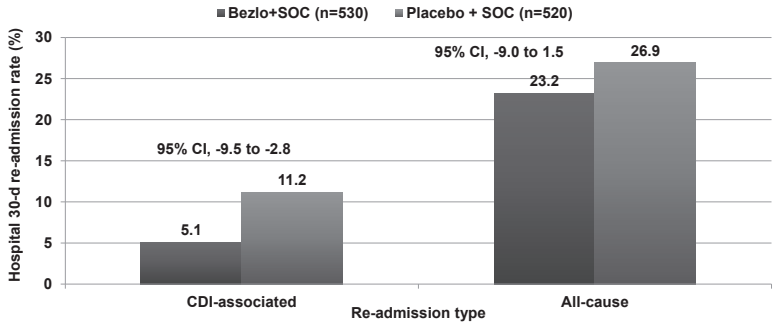
UK, 2012–13 : Seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% to 3.1% in hospital A (p<0.05)



Note: Hospital B did not provide re-admissions data

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

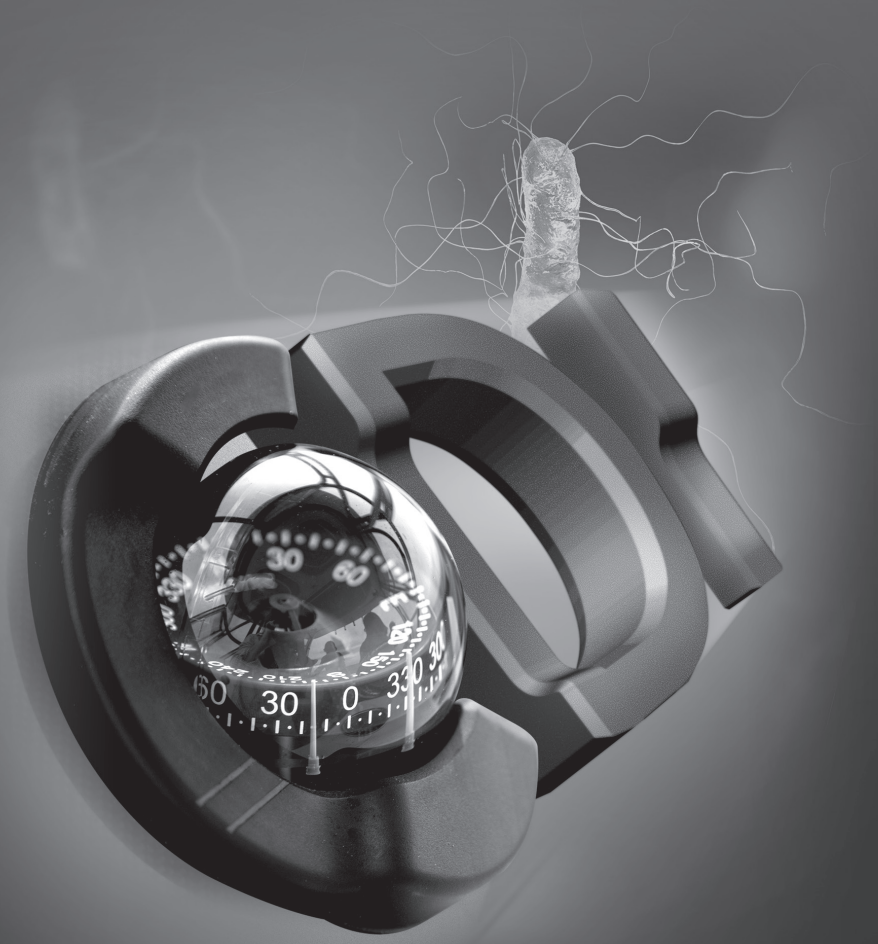
Bezlotoxumab and Hospital Re-admissions (MODIFY I/II Trials)



Prabhu VS, et al. *Clin Infect Dis*. 2017;65:1218-21.

The Role of the Hospitalist

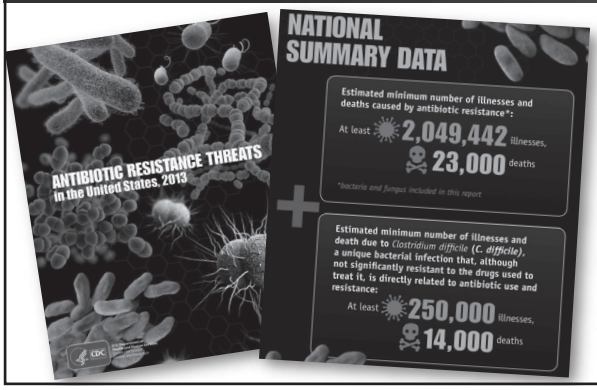
- Prevention
  - Adherence to infection control, patient isolation, etc.
- Diagnostics
  - Who should be tested?
  - How to interpret test results?
- Treatment
  - Selecting treatment based on patient factors
  - What can be done to limit LOS, re-admissions?
- Post-discharge
  - Transitioning the patient to home vs. skilled nursing facility
    - Communication with primary care provider and steps on prevention



Treatment of Initial and First Recurrence of CDI

Jason C. Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS
Clinical Professor
Clinical Specialist, Infectious Diseases
Director, PGY2 Residency in Infectious Diseases Pharmacy
Temple University
Philadelphia, PA

C. difficile Infection is Deadly



CDC report in 2015 estimated 29,300 US deaths from CDI in 2011

Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.
Lessa FC, et al. *New Engl J Med.* 2015;372:825-34.

Patient Case

Debbie is a 62-year-old woman with type 2 diabetes, obesity, and recurrent UTIs

- Following her last course of ciprofloxacin for UTI, she developed a mild case of diarrhea but it resolved without event
- One week later, she is admitted to the general ward with high-grade fever, nausea/vomiting, and flank pain. She is given levofloxacin plus a dose of ceftriaxone for suspected pyelonephritis.
- After 3 days of treatment, she develops severe diarrhea with abdominal cramping. Stool testing confirms *C. difficile* infection. Her WBC is 12,000/mm^3 and serum creatinine is 1.4 mg/dL

Audience Question

IDSA/SHEA guidelines recommend which of the following as first-line therapy for Debbie?

1. Fidaxomicin
2. Metronidazole
3. Vancomycin (oral)
4. Options 1 and 3
5. Options 1, 2 and 3

IDSA/SHEA CDI Guidelines 2010

Episode	Clinical Signs	Severity	Recommended agent	Dosing Regimen
Initial	WBC <15,000 and SrCr <1.5 × premorbid level	Mild or moderate	Metronidazole	500 mg PO three times daily 10–14 days
Initial	WBC ≥15,000 or SrCr ≥1.5 × premorbid level	Severe	Vancomycin	125 mg PO four times daily 10–14 days
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
Second (1st recurrence)	----------	----------	Same as initial	Same as initial
Third (2nd recurrence)	----------	----------	Vancomycin	PO tapered and/or pulsed

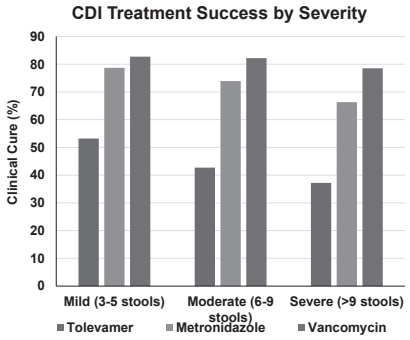
Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431-55.

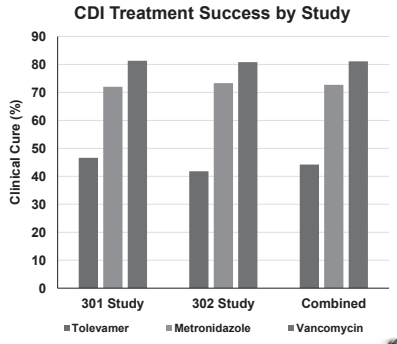
IDSA/SHEA Guidelines: 2017 Update

Episode/Clinical Signs	Recommendations
Initial episode, non-severe (WBC <15K and SCr <1.5 mg/dL)	• Vancomycin 125 mg PO q6h x 10d OR • Fidaxomicin 200 mg PO BID x 10d • *Alternate if those are not available:* metronidazole 500 mg PO TID x 10d
Initial episode, severe (WBC >15K OR SCr ≥1.5 mg/dL)	• Vancomycin 125 mg PO q6h x 10d OR • Fidaxomicin 200 mg PO BID x10d
Fulminant (Hypotension or shock, ileus, megacolon)	• Vancomycin 500 mg PO/NG q6h AND metronidazole 500 mg IV q8h
1st recurrence	• Vancomycin, if metronidazole used OR • Tapered and pulsed vancomycin OR • Fidaxomicin, if vancomycin used
2nd or greater recurrence	• As above, or fecal microbiota transplant

McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-48.

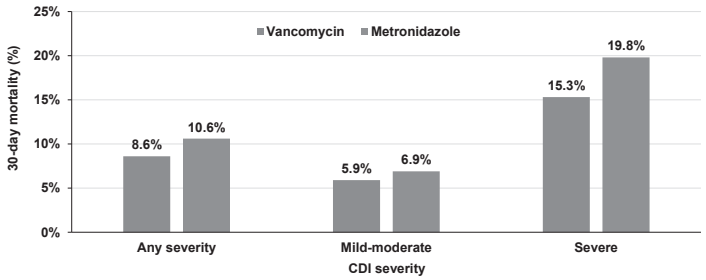
Oral Vancomycin is Superior to Metronidazole





Johnson S, et al. *Clin Infect Dis.* 2014;59:345-54.

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.

Vancomycin Oral Dosing Even the Lowest is High Enough

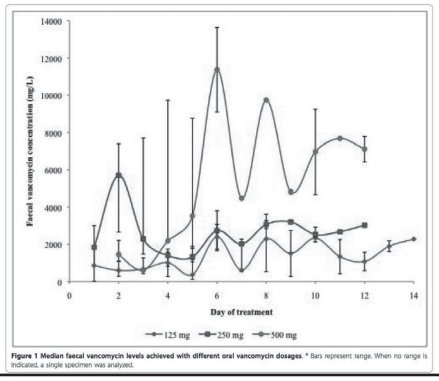
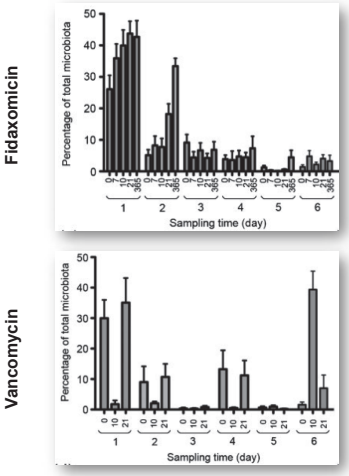


Figure 1 Median faecal vancomycin levels achieved with different oral vancomycin dosages. * Bars represent range. When no range is indicated, a single specimen was analyzed.

Gonzales M, et al. *BMC Infectious Diseases*. 2010;10:363.

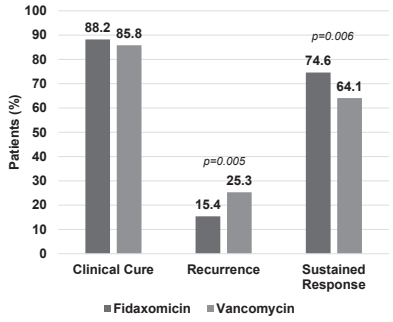
Fidaxomicin

- Non-absorbed macrolide antibiotic
- Highly selective for *C. difficile*
- Well-tolerated
- 200 mg q12h x 10 days

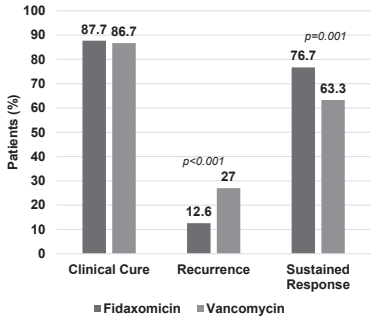


Tannock GW, et al. *Microbiology*. 2010;156:3354-9.

Fidaxomicin vs. Vancomycin for *C. difficile* Infection (mITT Population)

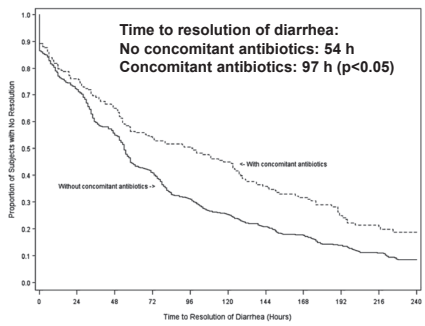


Louie TJ, et al. *N Engl J Med.* 2011;364:422-31.



Cornely OA, et al. *Lancet Infect Dis.* 2012;12:281-9.

Fidaxomicin may Have an Advantage for Patients Receiving Concomitant Antibiotics

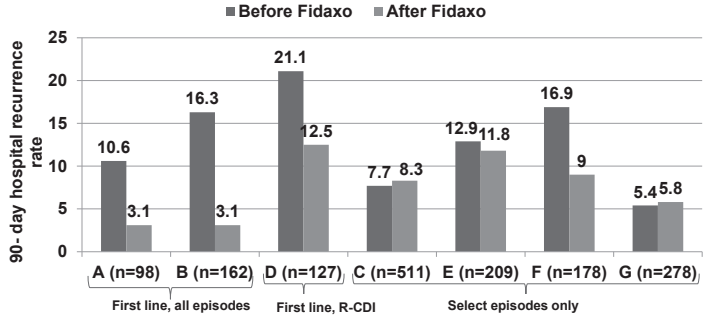


Mullane KM, et al. *Clin Infect Dis.* 2011;53:440-7.

Endpoint Study period	% (proportion) of subjects		Difference (95% CI)
	Fidaxomicin	Vancomycin	
No CA			
Clinical cure			
Treatment	92.33 (361/391)	92.79 (386/416)	-0.46 (-4.13 to 3.19)
Recurrence			
Treatment	12.23 (40/327)	23.42 (78/333)	-11.19 (-16.89 to -5.35)
Follow-up	11.52 (38/330)	23.88 (80/335)	-12.37 (-18.01 to -6.57)
At any time	11.92 (36/302)	23.13 (71/307)	-11.21 (-17.10 to -5.16)
Global cure			
At any time	80.80 (282/349)	69.07 (259/375)	11.74 (5.43-17.89)
Any CA			
Clinical cure			
Treatment	90.00 (81/90)	79.41 (81/102)	10.59 (0.23-20.34)
Recurrence			
Treatment	17.19 (11/64)	30.00 (21/70)	-12.81 (-26.41 to 1.66)
Follow-up	21.31 (13/61)	27.94 (19/68)	-6.63 (-20.98 to 8.29)
At any time	16.85 (15/89)	29.17 (28/96)	-12.31 (-23.90 to -0.12)
Global cure			
At any time	72.73 (96/132)	59.44 (85/143)	13.29 (2.11-24.05)

Real-world Evidence That Fidaxomicin may Reduce These Costs – Impact on Recurrence

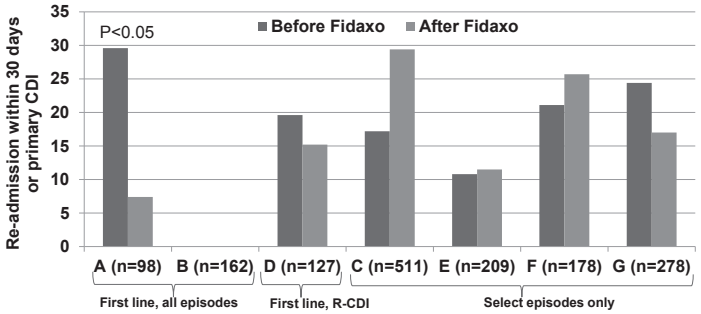
UK, 2012-13: seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals



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

Real-world Evidence That Fidaxomicin may Reduce These Costs – Impact on Re-admission

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)

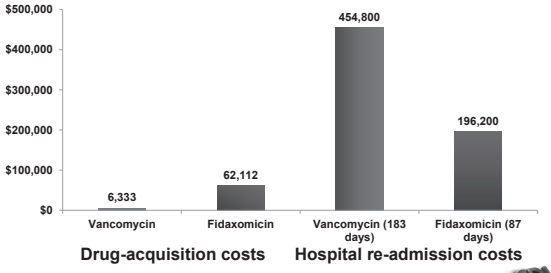


Goldenberg SD, et al. *Eur J Clin Microbiol Infect Dis*. 2016;35:251-9.

Does Fidaxomicin Reduce CDI 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.

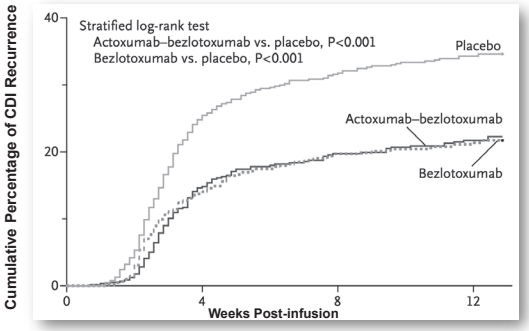
Characteristic	Vancomycin (n=46)	Fidaxomicin (n=49)
Age (years)	72.1 ± 10.1	73.2 + 11.8
ICU	9 (19.6)	13 (26.5)
Recurrent episode	22 (47.8)	38 (77.6)*
Concomitant antibiotics	14 (30.4)	24 (49)
Moderate or severe CDI	23 (50)	34 (69.4)
Creatinine >1.5x	9 (19.6)	18 (36.7)
90-d readmission with CDI	19 (41.3)	10 (20.4)*



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

Reducing the Risk of Recurrence: Bezlotoxumab

- Intravenous monoclonal antibody directed against toxin B
- Reduces recurrence without changing treatment success
- Dose: 10 mg/kg x1
- Dose given at any point in therapy



Sustained cure:
64% (496/781) bezlotoxumab
54% (415/773) placebo
NNT = 10

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

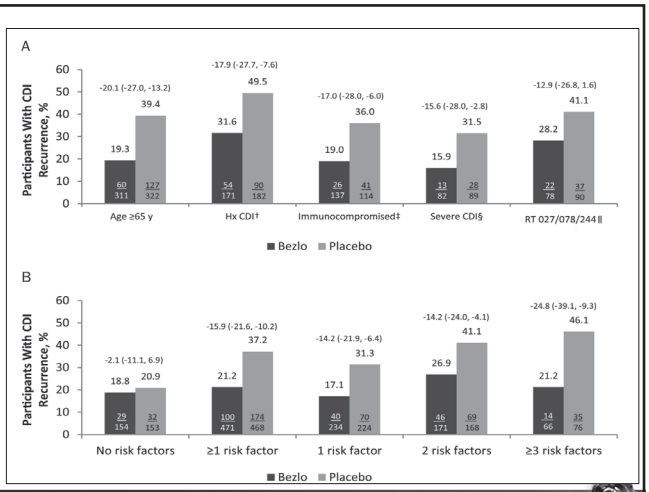
Who Is At Greatest Risk of Recurrence?

Reference	Predictors of Recurrence
Hu 2009	Age > 65 Horn index: severe or fulminant disease Additional antibiotics after CDI therapy Antitoxin A IgG <1.29 ELISA units
Miller 2009	Age <60 / 60-79 / ≥80 (years) Temperature ≤37.5 / 37.6-38.5 / ≥38.6 (°C) Leukocytosis <16 / 16-25 / >25 (x 10^9/L) Albumin >3.5 / 2.6-3.5 / ≤2.5 (g/dL) Systemic concomitant antibiotics

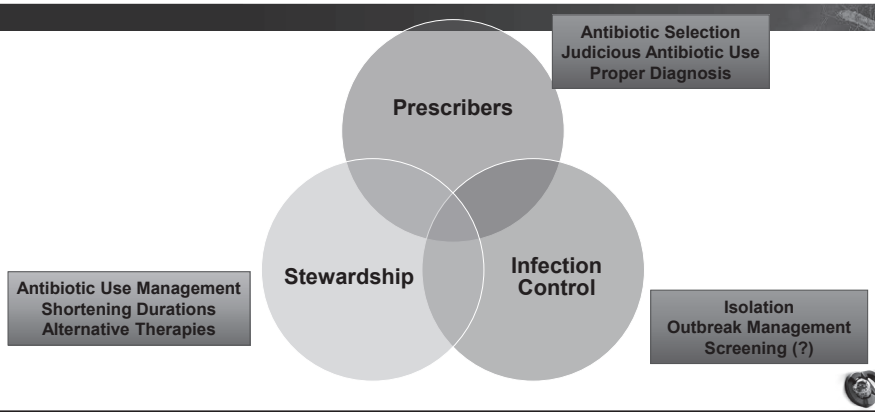
Abou Chakra CN et al. *PLoS ONE* 2012;*7(1):* e30258. doi:10.1371/journal.pone.0030258.
Miller et al. IDSA Annual Meeting, 2009.
Hu MY, et al. *Gastroenterol*. 2009;136:1206-14.

Bezlotoxumab Finding a Role

The magnitude of benefit of bezlotoxumab increases with the degree of risk for recurrences



CDI Management Requires Multiple Disciplines



Prescribers
Antibiotic Choice, Dose, and Duration Affect CDI Risk

Class-any during hospitalization	Adjusted hazard ration (95% CI)
Aminoglycosides	0.9 (.3, 3.0)
Cephalosporins	
First- and second-generation	2.4 (1.4, 4.1)
Third- and fourth-generation	3.1 (1.9, 5.2)
Clindamycin	1.9 (.8, 4.4)
Macrolides	1.5 (.7, 3.1)
Metronidazole	0.3 (.1, 0.9)
Penicillins	1.9 (.9, 4.0)
β-Lactamase inhibitor combinations	2.3 (1.5, 3.5)
Quinolones	4.0 (2.7, 5.9)
Sulfas	1.9 (1.1, 3.4)
Vancomycin	2.6 (1.7, 4.0)
Miscellaneous	1.3 (.7, 2.6)

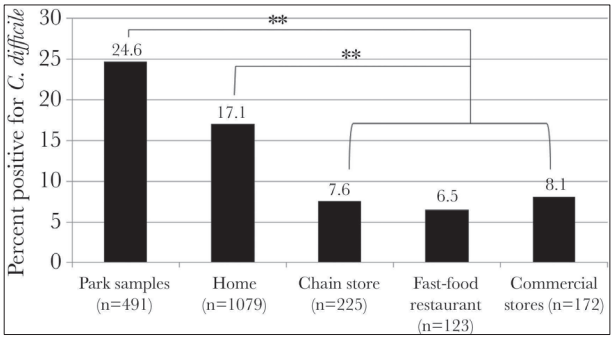
Stevens V, et al. *Clin Infect Dis.* 2011;53:42-8.

Prescribers
Antibiotic Choice, Dose, and Duration Affect CDI Risk

Characteristics	Adjusted hazard ration (95% CI)
Defined daily dose, median (IQR)	
<3.0	REFERENCE
3.0 to 7.79	1.2 (.7, 2.1)
7.80 to 21.0	2.8 (1.7, 4.6)
>21.0	5.3 (3.1, 9.0)
Antibiotic days, median (IQR)	
<4	REFERENCE
4 to 7	1.4 (.8, 2.4)
8 to 18	3.0 (1.9, 5.0)
>18	7.8 (4.6, 13.4)
Number of antibiotics, median (IQR)	
1	REFERENCE
2	2.5 (1.6, 4.0)
3 or 4	3.3 (2.2, 5.2)
5 or more	9.6 (6.1, 15.1)

Stevens V, et al. *Clin Infect Dis.* 2011;53:42-8.

Infection Control
This Bug is Everywhere!



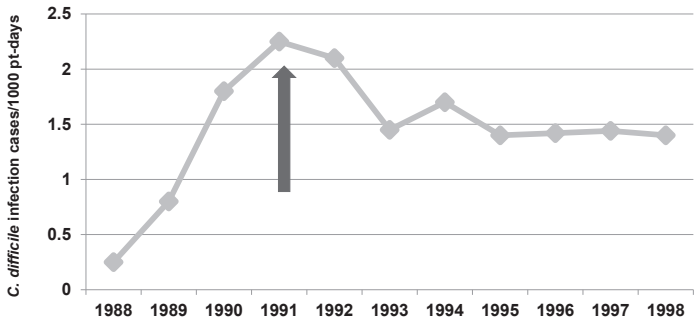
**p<0.001
Alam MJ, et al. *Open Forum Infect Dis.* 2017;4(1):ofx018.

Antimicrobial Stewardship
Shortened Antibiotic Courses - Same Efficacy, Lower Exposure

Infection	Duration (Agent)
Community-Acquired Pneumonia	5 days (multiple) 3 days (azithromycin)
Skin/skin structure	6 days (tedizolid) 5 days (levofloxacin)
Cystitis	3 days (FQs, TMP/SMX) 5 days (nitrofurantoin)
Pyelonephritis	5 days (levofloxacin) 7 days (ciprofloxacin)
Hospital-Acquired Pneumonia	8 days (multiple)
Intra-abdominal infections	3 days (ertapenem) 4 days (multiple)

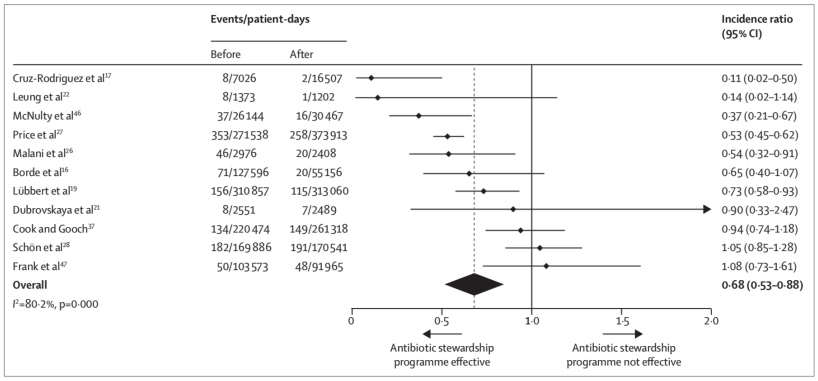
Hanretty AM, Gallagher JC. *Pharmacother.* 2018;38:674-87.

Antibiotic Stewardship
Impact on *C. difficile* Infections



Adapted from: Carling P, et al. *Infect Control Hosp Epidemiol.* 2003;24:699-706.

Antimicrobial Stewardship and CDI

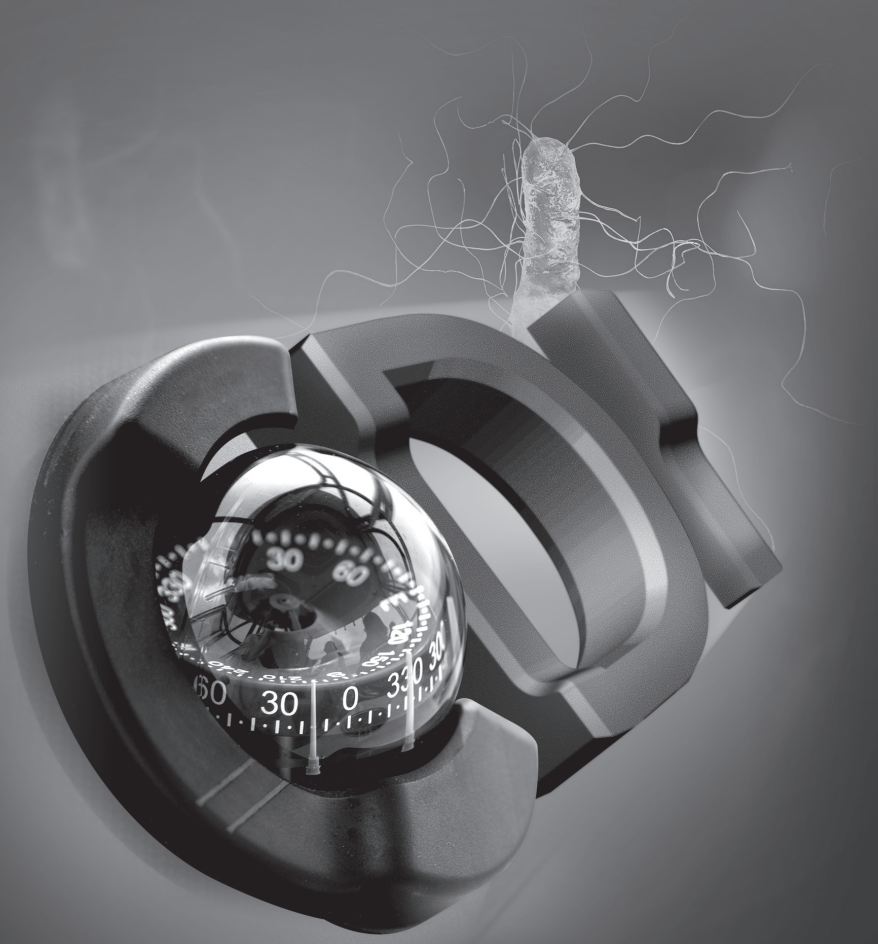


Bauer D, et al. *Lancet Infect Dis.* 2017;17:990-1001.

Summary

- CDI management has changed, and keeps changing
- Fidaxomicin and bezlotoxumab prevent CDI recurrence, and can be cost effective
- We cause and exacerbate CDI and need to realize this

NOTES

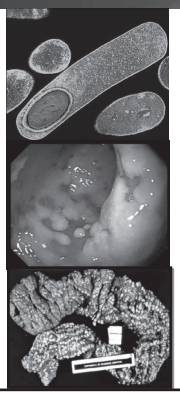


Addressing the Burden of CDI Recurrence

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

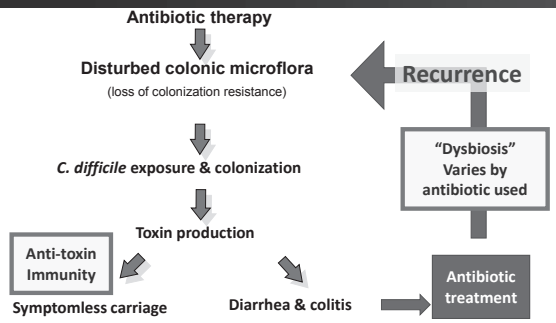
Recurrent *C. difficile* Infection (rCDI): Outline

- Mechanisms of recurrence
- Risk factors for recurrence
- Treatment of multiply recurrent CDI
- Restoring colonization resistance
- Enhancing anti-toxin immunity



Aslam S et al. *Lancet Infect Dis.* 2005;5:549-557.

Recurrent *C. difficile* Infection A Self-perpetuating Cycle



Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.
Kyne L, et al. *Lancet.* 2001;357:189-93.

Antimicrobials Predisposing to CDI

Rarely	Occasionally	Frequently
Aminoglycosides	Other penicillins	Clindamycin
Bacitracin	Cephalosporins	Ampicillin
Metronidazole	(1st generation)	Amoxicillin
Teicoplanin	Sulfonamides	Cephalosporins
Rifampin	Trimethoprim	(2nd and 3rd generation)
Chloramphenicol	Cotrimoxazole	Fluoroquinolones
Tetracyclines	Macrolides	Carbapenems
Daptomycin		
Tigecycline		

The Good The Bad & The Ugly

Commonly Used Stool Tests for CDI

Test	*Accuracy*	*Cost*	*Comments*
Toxin EIA Enzyme Immuno-assay	Specific but not highly sensitive	Low	Rapid (2-4 hours) Sensitivity moderate (~85%) *- frequent false negative results*
GDH EIA EIA for Glutamate Dehydrogenase *"C. difficile* antigen"	Sensitive but not specific	Low	Rapid Used as a "triage" step *- frequent false positive results* *- positive result must be confirmed by a different assay*
NAAT - Nucleic acid amplification (e.g., PCR)	Highly sensitive	High but falling	Rapid Increasingly used (in place of EIA) *- may detect bacteria or spores in the absence of toxin or disease*

Other stool tests for CDI include anaerobic bacterial culture, and tissue culture cytotoxicity

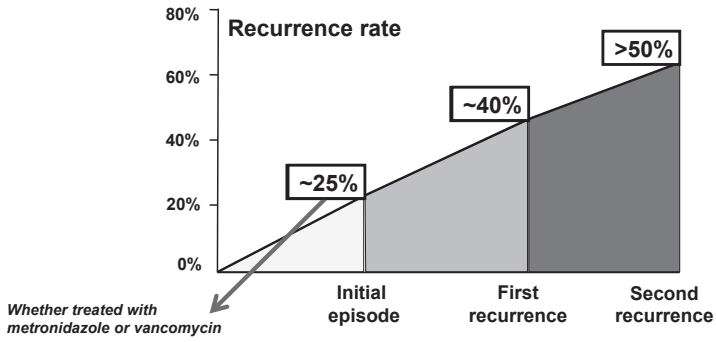
Kelly CP et al. *N Engl J Med.* 2008;359:1932-40. Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-55; Debast SB, et al. *Clin Microbiol Infect.* 2014;20 Suppl 2:1-26; Surawicz CM, et al. *Am J Gastroenterol.* 2013;108(4):478-98.

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. *J Ped Gastroenterol Nutr* 2009;48(Suppl. 2):S63–5; Kyne et al. *Lancet* 2001;357:189–93; Bauer et al. *Clin Microbiol Infect* 2009;15:1067–79; Bauer et al. *Lancet* 2011;377:63–73; Hu et al. *Gastroenterology* 2009;136:1206–14; McFarland et al. *Am J Gastroenterol* 2002;97:1769–75; Do et al. *Clin Infect Dis* 1998;26: 954–9; Bauer et al. *Clin Microbiol Infect* 2011;17(Suppl. 4):A1–4; Pépin et al. *Clin Infect Dis* 2005;40:1591–7.

Prior CDI Recurrence & Recurrence Risk



McFarland LV, et al. *JAMA* 1994;271:1913–8; Pépin J, et al. *Clin Infect Dis.* 2005;40:1591–7; McFarland LV, et al. *Am J Gastroenterol* 2002;97:1769–75.

Risk Factors for Recurrent CDI

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

Cohen. *J Ped Gastroenterol Nutr* 2009;48(Suppl. 2):S63–5; Kyne et al. *Lancet* 2001;357:189–93; Bauer et al. *Clin Microbiol Infect* 2009;15:1067–79; Bauer et al. *Lancet* 2011;377:63–73; Hu et al. *Gastroenterology* 2009;136:1206–14; McFarland et al. *Am J Gastroenterol* 2002;97:1769–75; Do et al. *Clin Infect Dis* 1998;26: 954–9; Bauer et al. *Clin Microbiol Infect* 2011;17(Suppl. 4):A1–4; Pépin et al. *Clin Infect Dis* 2005;40:1591–7.

GASTROENTEROLOGY 2009;136:1206–1214

Prospective Derivation and Validation of a Clinical Prediction Rule for Recurrent *Clostridium difficile* Infection

MARY Y. HU,* KIANOOSH KATCHAR,* LORRAINE KYNE,‡ SEEMA MAROO,* SANJEEV TUMMALA,* VALLEY DREISBACH,* HUA XU,* DANIEL A. LEFFLER,* and CIARÁN P. KELLY*

Predictors of recurrence:
1 for **Age > 65 y**
1 for **Severe underlying disease** (Horn's index)
1 for **Additional antibiotic** use

Score	Recurrence rate (validation cohort)
0	0%
1	17%
2	31%
3	67%

Predictive accuracy (in validation cohort)	**72%**
Score of 0 or 1 versus 2 or 3	[95% CI:59.2 to 82.4%]

Patient Case, continued

- Debbie is given oral vancomycin 125 mg QID for 10 days for her initial episode of CDI. Her CDI symptoms resolve by the end of treatment.
  - Her levofloxacin treatment for pyelonephritis was continued until completion at 10 days
- 9 days after successfully completing the vancomycin regimen, she returns to the hospital again with diarrhea and abdominal cramping
- Stool NAAT testing for toxigenic *C. difficile* is positive

Audience Question

What would you recommend now?

1. Repeat vancomycin treatment followed by taper/pulse
2. Vancomycin 125 mg QID × 10 d followed by rifaximin 400 mg BID × 14 d
3. Vancomycin 125 mg QID × 10 d plus bezlotoxumab
4. Fidaxomicin 200 mg BID × 10 d
5. Fecal microbiota transplant

Treatment of Recurrent CDI*:* 2017 Guidelines

Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

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)

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

[1]Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Edward Hines Jr Veterans Administration Hospital, Hines, and [3]Loyola University Medical Center, Maywood, Illinois; [4]St Luke's Hospital, Duluth, Minnesota; [5]Johns Hopkins University School of Medicine, Baltimore, Maryland; [6]Children's Hospital of Philadelphia, Pennsylvania; [7]Washington University School of Medicine, St Louis, Missouri; [8]University of Houston College of Pharmacy, Texas; [9]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [10]McGill University Health Centre, McGill University, Montréal, Québec, Canada; [11]Boston Children's Hospital, Massachusetts; and [12]Leeds Teaching Hospitals NHS Trust, United Kingdom

McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-48.

CDI: 2017 Guidelines
Treatment of a First Recurrence of CDI

Recurrence episode	Treatment
First: If initial therapy with metronidazole	**Vancomycin** 125 mg, 4 times daily, PO for 10 days
OR	**Prolonged vancomycin** (standard course followed by taper and pulse dosing)
OR - If initial therapy with vancomycin	**Fidaxomicin** 200 mg, 2 times daily, PO for 10 days

Metronidazole not recommended

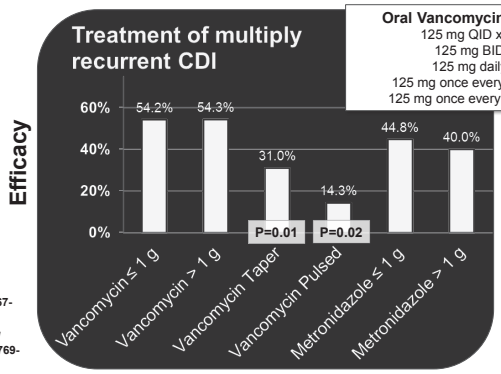
McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-48.

CDI: 2017 Guidelines
Treatment of Multiply Recurrent CDI

Recurrence episode	Treatment
Second or subsequent:	**Prolonged vancomycin** (standard course followed by taper and pulse dosing)
OR	**Vancomycin** 125 mg, 4 times daily, PO x 10d followed by "chaser" of **Rifaximin** 400 mg 3 times daily for 20 days
OR	**Fidaxomicin** 200 mg, 2 times daily, PO for 10 days
OR	**Fecal microbial transplant (FMT)**

McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-48.

Oral Vancomycin for Recurrent CDI:
Taper and Pulsed dosing

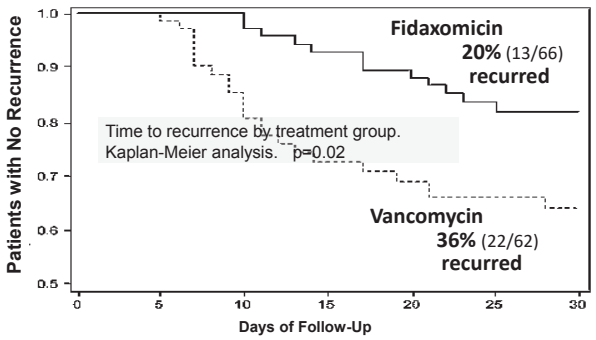


Oral Vancomycin Taper & Pulse
125 mg QID x 10-14 days
125 mg BID x 7 days
125 mg daily x 7 days
125 mg once every 2 days x 8 days
125 mg once every 3 days x 15 days

Tedesco F, et al. *Am J Gastroenterol.* 1985;80:867-868.

McFarland LV, et al. *Am J Gastroenterol.* 2002;97:1769-1775.

Fidaxomicin versus Vancomycin for a First CDI Recurrence



Cornely OA, et al. *Clin Infect Dis.* 2012:55 (Suppl 2);154-61.

Extended-pulsed Fidaxomicin versus Vancomycin for CDI in Patients 60 Years and Older (EXTEND)

Randomized, Controlled, Open-label, Phase 3b/4 Trial

- Treatment Comparison:
  - Extended-pulsed fidaxomicin (200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7-25), or
  - Vancomycin (125 mg oral capsules, four times daily on days 1–10)
- Primary endpoint:
  - Sustained clinical cure 30 days after end of treatment (day 55 for extended-pulsed fidaxomicin and day 40 for vancomycin)
- Results (sustained clinical cure):
  - Extended-pulsed fidaxomicin: 70% (124 of 177)
  - Vancomycin: 59% (106 of 179)
    - Difference 11% [95% CI, 1.0–20.7]; p=0.030
    - Odds ratio 1.62 [95% CI, 1.04–2.54])

Guery B, et al. *Lancet infect Dis*. 2018;18(3):296-307.

Patient Case, continued

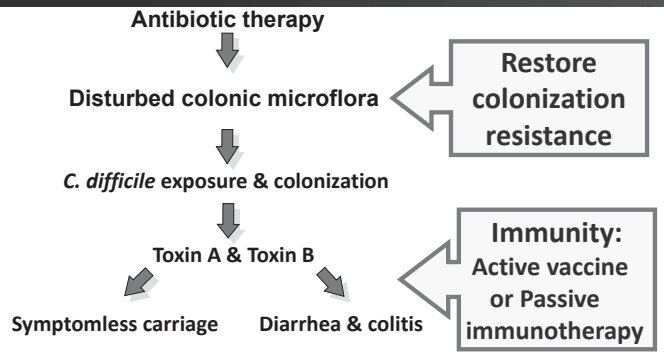
- Debbie is given another regimen of vancomycin 125 mg QID for 10 days followed by taper and pulse dosing.
- After 6 days of treatment, she is ready for discharge.

Audience Question

What would you consider to reduce the risk of CDI recurrence for Debbie?

1. Encourage the daily use of probiotics
2. Administer one dose of FMT (oral encapsulated pill)
3. Order a dose of bezlotoxumab
4. Nothing, the vancomycin with taper and pulse dosing should be effective

Turning to Nature's Cures for CDI: Non-antibiotic Approaches



Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

FECAL ENEMA AS AN ADJUNCT IN THE TREATMENT OF PSEUDOMEMBRANOUS ENTEROCOLITIS

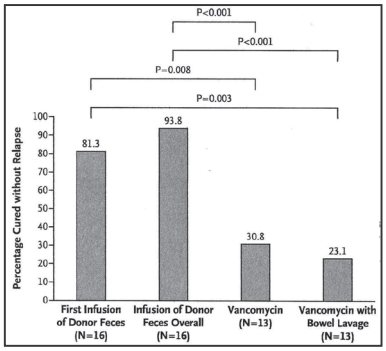
B. Eiseman, M.D., W. Silen, M.D., G. S. Bascom, M.D., and A. J. Kauvar, M.D., Denver, Colo.

(From the Departments of Surgery and Medicine, University of Colorado School of Medicine and the Veterans Administration Hospital)

- Fecal transplantation by enema for four patients with fulminant, life-threatening, pseudomembranous enterocolitis.
- Empiric therapy to "re-establish the balance of nature" within the intestinal flora to correct the disruption caused by antibiotic treatment.
- They reported "immediate and dramatic" responses and concluded that "this simple yet rational therapeutic method should be given more extensive clinical evaluation".

Eiseman B, et al. *Surgery.* 1958;44:854-9.

Duodenal Infusion of Donor Feces for Recurrent *C. difficile* infection



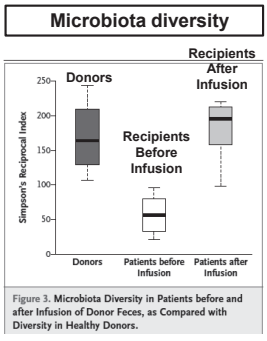
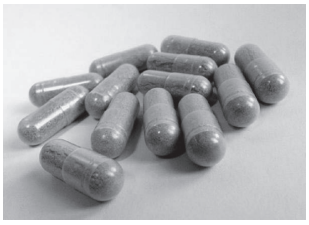


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

van Nood E, et al. *N Engl J Med.* 2013;368:407-15.; Kelly CP. *N Engl J Med.* 2013;368:474-5.

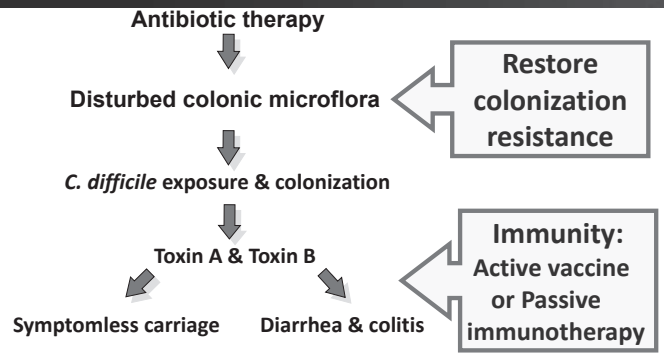
FMT & Beyond *(None are FDA approved)*

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



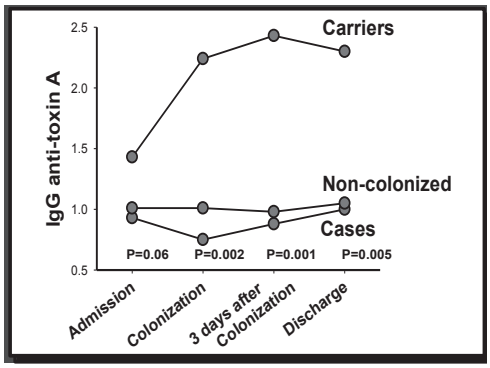
Youngster I, et al. *JAMA*. 2014;312:1772-8

Turning to Nature's Cures for CDI: Non-antibiotic Approaches



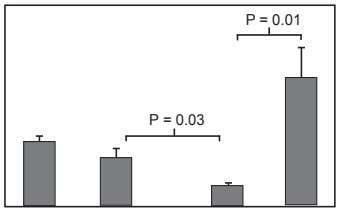
Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

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



Kyne L, et al. *N Engl J Med.* 2000;342:390-397.

Passive Immunotherapy in Recurrent CDI
Intravenous Immunoglobulin (IVIG)



Also used in severe & refractory disease
Efficacy not proven – no controlled trial

Leung DY, et al. *J Pediatr.* 1991;118:633-637.

Introduction: Bezlotoxumab (Bezlo)

- Fully human IgG1 HumAb (human monoclonal antibody)
- Binds to and neutralizes *C. difficile* toxin B
- Single IV infusion during standard antibiotic therapy for CDI – systemic half life ~19 days
- Reduces CDI recurrences in high risk patients (from 27% down to 17% overall in Phase III trials).
- "High risk" includes: Age > 65 years, prior CDI recurrence(s), immunocompromised

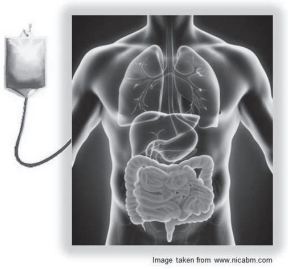


Image taken from www.nicabm.com

Wilcox MH, et al. *N Engl J Med.* 2017;376:305-17.
Babcock GJ, et al. *Infect Immun.* 2006;74:6339-47.
Villafuerte Gálvez JA, Kelly CP. *Expert Rev Gastroenterol Hepatol.* 2017;11:611-22.

Bezlotoxumab: A Non-Antibiotic Approach for Prevention of rCDI


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 26, 2017 VOL. 376 NO. 4

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

M.H. Wilcox, D.N. Gerding, I.R. Poxton, C. Kelly, R. Nathan, T. Birch, O.A. Cornely, G. Rahav, E. Bouza, C. Lee, G. Jenkin, W. Jensen, Y.-S. Kim, J. Yoshida, L. Gabryelski, A. Pedley, K. Eves, R. Tipping, D. Guris, N. Kartsonis, and M.-B. Dorr, for the MODIFY I and MODIFY II Investigators*

"Since completion of this guideline,
a new therapeutic agent … (has) become available for CDI.

Bezlotoxumab, a monoclonal antibody directed against toxin B produced by *C. difficile,* has been approved as adjunctive therapy for patients who are receiving antibiotic treatment for CDI and who are at high risk for recurrence."*

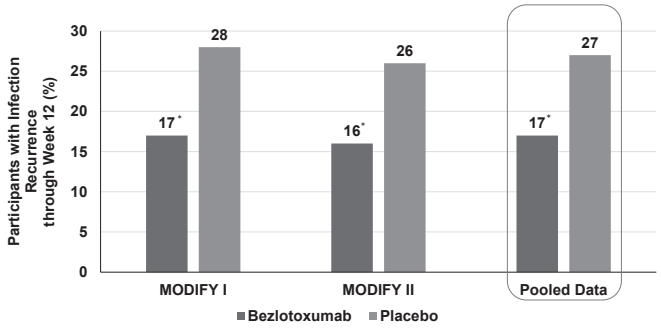
Wilcox MH, et al. *N Engl J Med.* 2017;376:305-17.
*McDonald LC, et al. *Clin Infect Dis.* 2018;66:e1-48.

World Society of Emergency Surgery (WSES) – 2019 Guideline Update

- Recommendations for >1 CDI Recurrence:
  - Antimicrobial therapy can include oral vancomycin therapy using a tapered or pulsed regimen (Recommendation 1C)
  - Fecal microbiota transplantation (FMT) may be an effective option for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments (Recommendation 2C)
  - **Coadjuvant treatment with monoclonal antibodies (bezlotoxumab) may prevent recurrences of CDI, particularly in patients with CDI due to the 027 epidemic strain, in immunocompromised patients, and in patients with severe CDI (Recommendation 1A)**

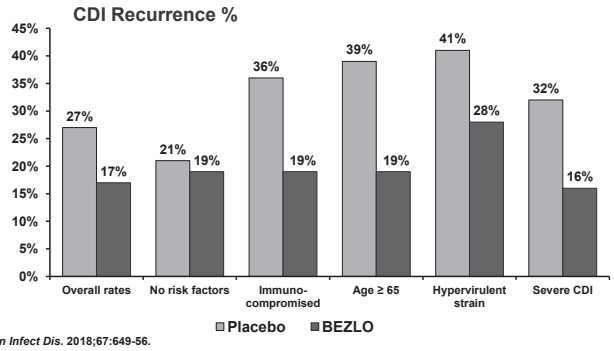
Sartelli M, et al. *World J Emerg Surg*. 2019;14:8.

Bezlotoxumab Reduces CDI Recurrence



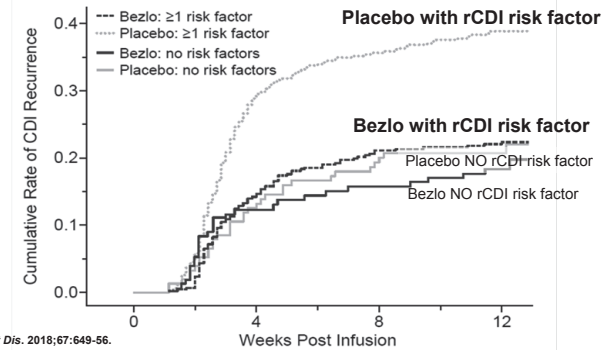
*p<0.001
Wilcox MH, et al. *N Engl J Med*. 2017;376:305-17.

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



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

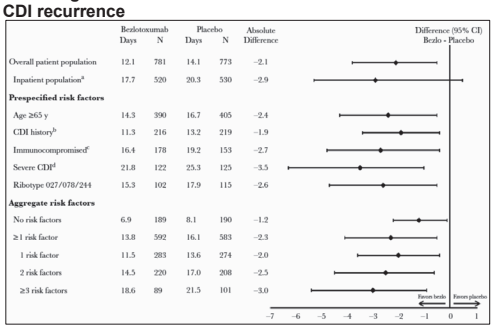
Bezlotoxumab - Reduces CDI Recurrences (rCDI)



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

MODIFY I/II Results – Bezlotoxumab Reduces Cumulative Hospitalized Days in the Overall and High-Risk Patient Populations

Patients treated with bezlotoxumab had lower mean cumulative hospitalized days compared with placebo in all subgroups assessed, including those with no risk factors for CDI recurrence and those with ≥1 risk factors associated with CDI recurrence



	Bezlotoxumab Days	N	Placebo Days	N	Absolute Difference
Overall patient population	12.1	781	14.1	773	−2.1
Inpatient population[a]	17.7	520	20.3	530	−2.9
Prespecified risk factors					
Age ≥65 y	14.3	390	16.7	405	−2.4
CDI history[b]	11.3	216	13.2	219	−1.9
Immunocompromised[c]	16.4	178	19.2	153	−2.7
Severe CDI[d]	21.8	122	25.3	125	−3.5
Ribotype 027/078/244	15.3	102	17.9	115	−2.6
Aggregate risk factors					
No risk factors	6.9	189	8.1	190	−1.2
≥1 risk factor	13.8	592	16.1	583	−2.3
1 risk factor	11.5	283	13.6	274	−2.0
2 risk factors	14.5	220	17.0	208	−2.5
≥3 risk factors	18.6	89	21.5	101	−3.0

Basu A, et al. *Open Forum Infect Dis*. 2018;5(11):ofy218.

Recurrent *C. difficile* Infection (rCDI): Summary

- The incidence of CDI & rCDI are 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 (i.e., using bezlotoxumab)