MANAGING THE COST OF C. DIFFICILE INFECTION

Are You Spending More Than You Know?

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MEDICAL EDUCATION RESOURCES

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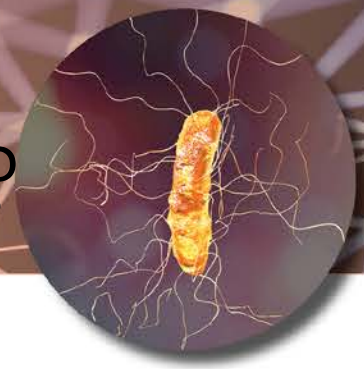
Live Webcast

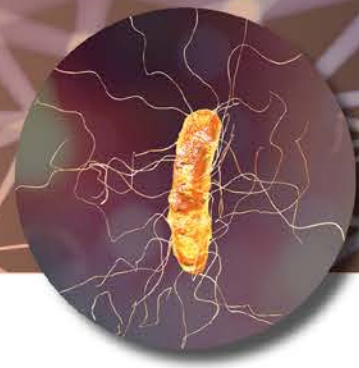
Friday, July 31, 2020

12:00 PM – 1:30 PM ET

Which of the following best describes your area of greatest educational need with regards to this webcast?



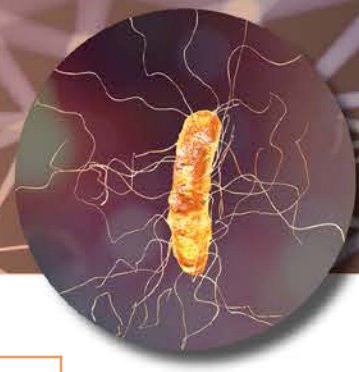
1. The epidemiology and prevalence of CDI
2. Evaluating novel treatment options for primary and recurrent CDI
3. Applying guideline-based management strategies for CDI
4. Illustrating avoidable costs related to CDI treatment management that can impact benefit design and coverage decision-making



Welcome

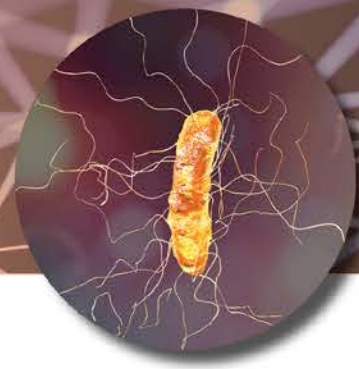
Vanita Pindolia, PharmD, MBA
Vice President
Ambulatory Clinical Pharmacy Programs_PCM
Henry Ford Health System (HFHS)
Health Alliance Plans (HAP)

Agenda

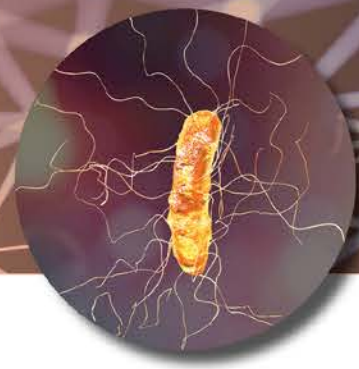


Pre-Activity Learning Assessment and Opening Comments/Overview **Vanita Pindolia, PharmD, MBA**
CDI Clinical Update – Why the Increase? **A. Krishna Rao, MD, MS**
Care Management Strategies to Address the Rising Costs of CDI **Edmund Pezalla, MD, MPH**
CDI Case Scenarios and Best Practice Recommendations **Vanita Pindolia, PharmD, MBA**
Audience Q&A Session Key Takeaways and Closing Comments; Post-Activity Assessment and Evaluation
Adjournment

Learning Objectives



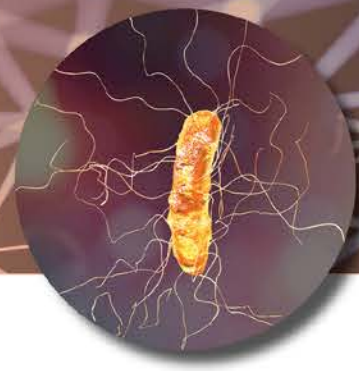
- Review the epidemiology and prevalence of CDI
- Evaluate novel treatment options for primary and recurrent CDI
- Apply guideline-based management strategies for CDI
- Illustrate avoidable costs related to CDI treatment management that can impact benefit design and coverage decision-making



CDI Clinical Update – Why the Increase?

A. Krishna Rao, MD, MS
Assistant Professor
Division of Infectious Diseases
Department of Internal Medicine
University of Michigan Medical School

Side Note: Nomenclature Change



Volume 3, Issue 1 Winter 2018

Updated CLSI AST Documents Are Here!

So what's new?

Nomenclature changes:

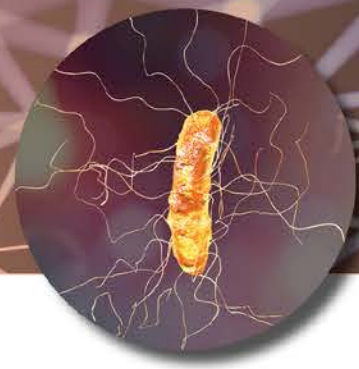
Propionibacterium acnes to *Cutibacterium acnes*

Clostridium difficile to *Clostridioides difficile*

Enterobacter aerogenes to *Klebsiella aerogenes*

Updated CLSI AST Documents Are Here! CLSI AST News Update. 2018; 3(1):2. https://clsi.org/media/1974/ast_news_update_jan18.pdf Accessed July 2020.

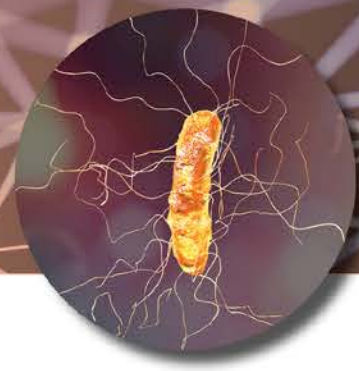
Clostridioides difficile Infection (CDI): Impact



- CDI is responsible for close to half a million illnesses each year
- It affects people of all ages (though very unlikely in infants)
- 1 in 5 patients will get at least one more CDI infection
- One in 11 people over 65 who are diagnosed with a healthcare-associated CDI infection die within a month

Lessa FC, Mu Y, Bamberg WM, et al. *N Engl J Med*. 2015;372(9):825-34.

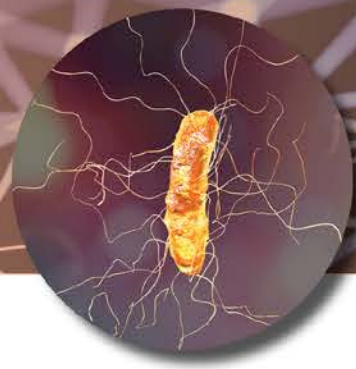
CDI: Risk



- People on antibiotics are 7 to 10 times more likely to get CDI, either while on the antibiotic or one-month after[1]
- Extended stays in healthcare settings such as hospitals and nursing homes, also increase risk of infection[2]
- Greater than 80% of CDI deaths occur in people 65 and older[3]

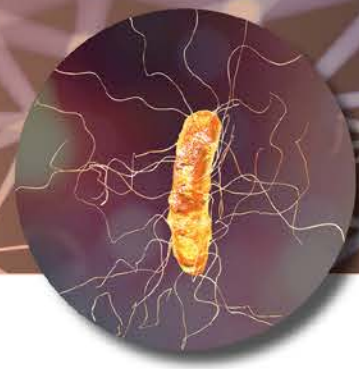
1 Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. *J Antimicrob Chemother*. 2012;67(3):742-8. 2. C Diff Factsheet. Centers for Disease Control and Prevention website https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-P.pdf. Accessed July 2020. 3. Asempa TE, Nicolau DP. *Clin Interv Aging*. 2017;12:1799-1809.

Risk Factors



- Current or recent antibiotic use (highest risk within 3 months of exposure)
- Advanced age (65 or older)
- Gastric acid suppression
- Severe comorbid diseases (Especially IBD and immunosuppression such as BMT)
- Prior history of CDI
- Hospitalization within 30 days

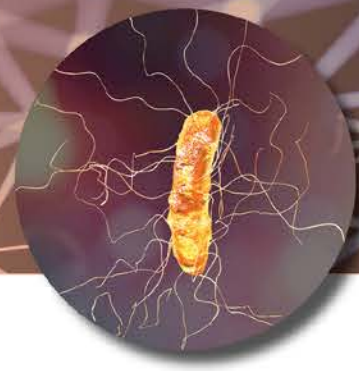
CDI: Spread

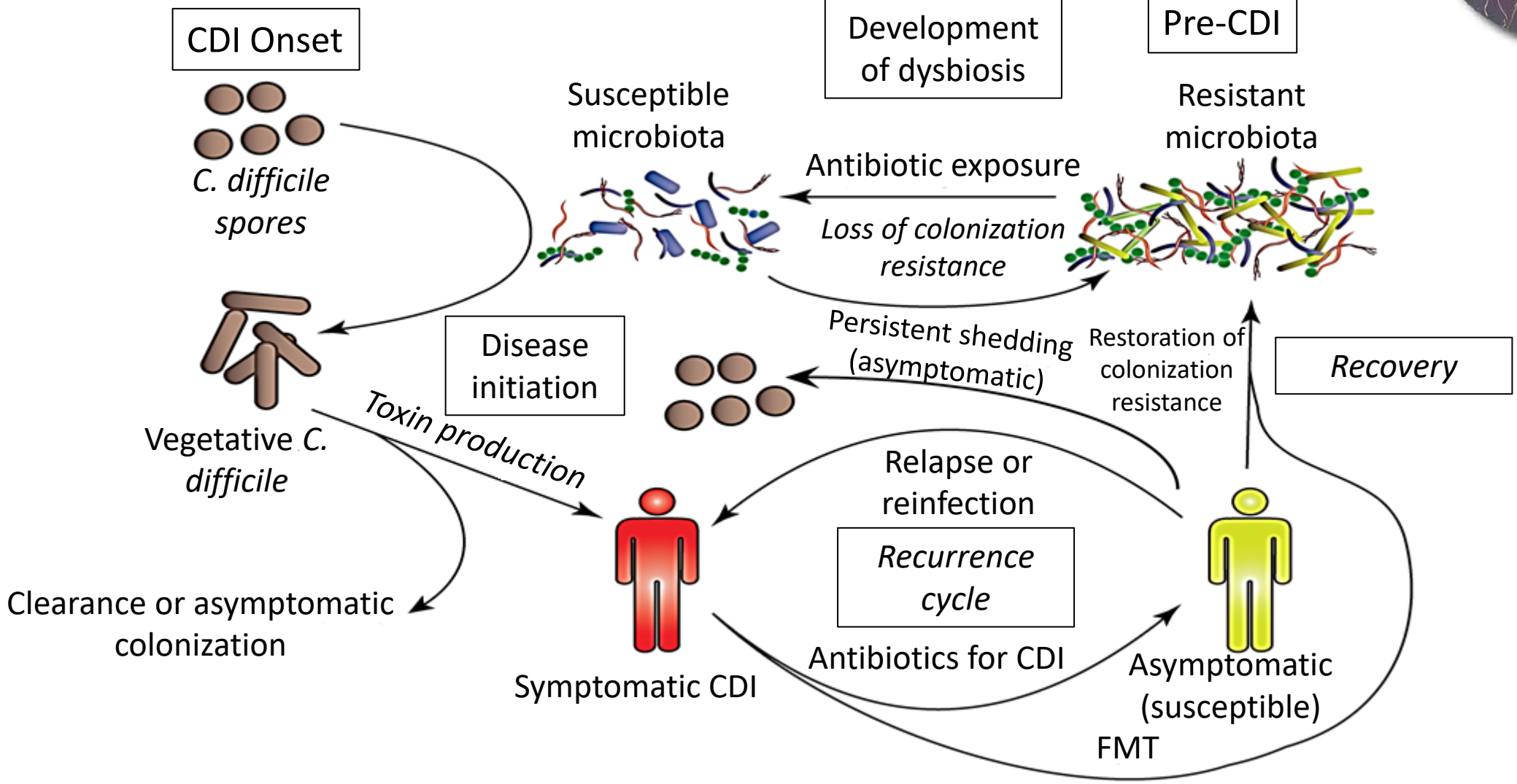


- Touching surfaces that are contaminated with stool from an infected person
- Not washing hands with soap and water
- A health care facility fails to notify another when transferring a patient with CDI

C Diff Factsheet. Centers for Disease Control and Prevention website https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-P.pdf. Accessed July 2020.

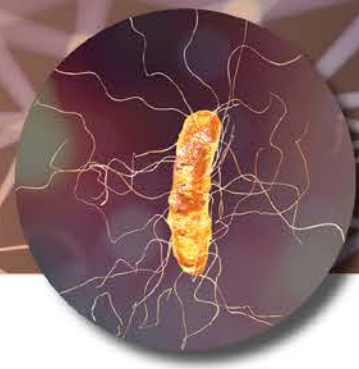
Pathogenesis of CDI

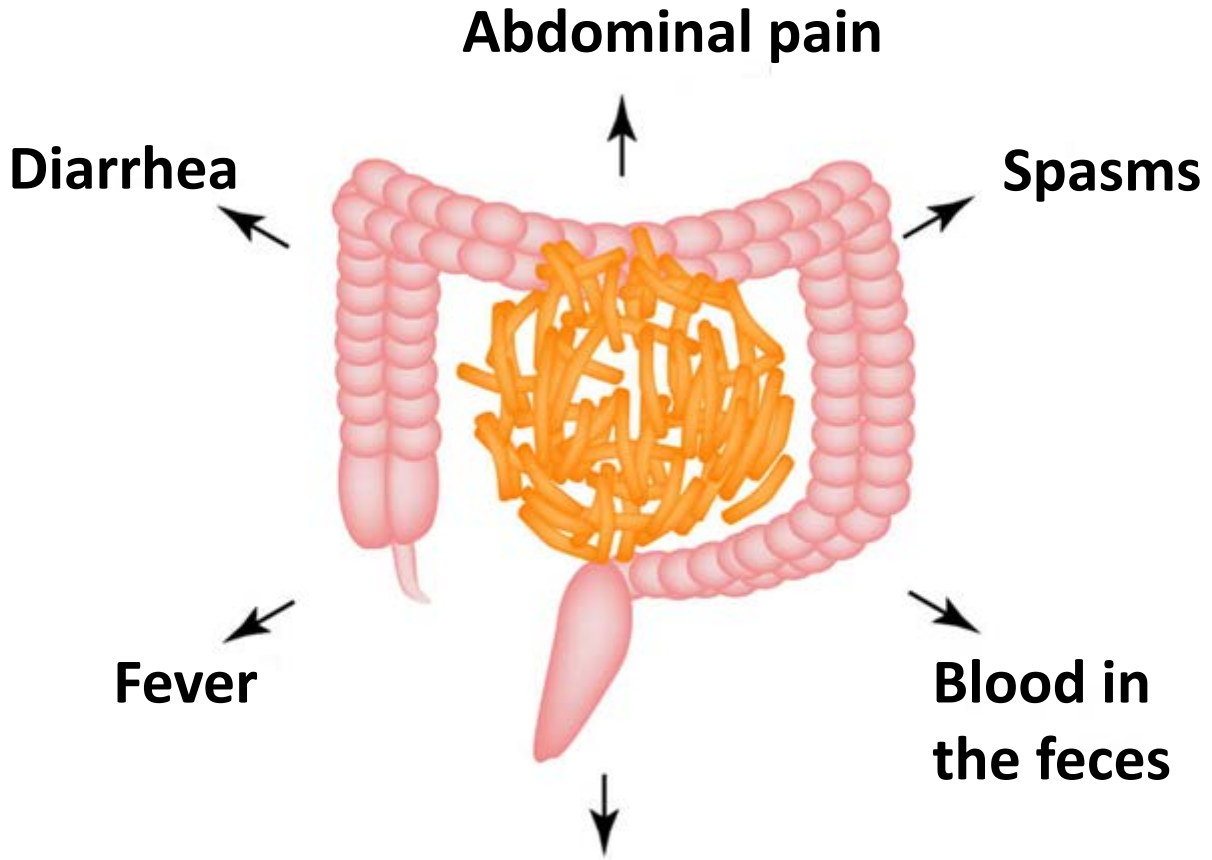




Rao K, Higgins PD. *Inflamm Bowel Dis*. 2016;22(7):1744-54.

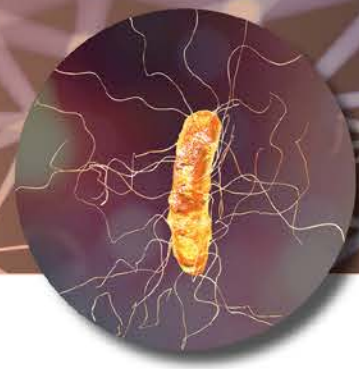
Symptoms of CDI

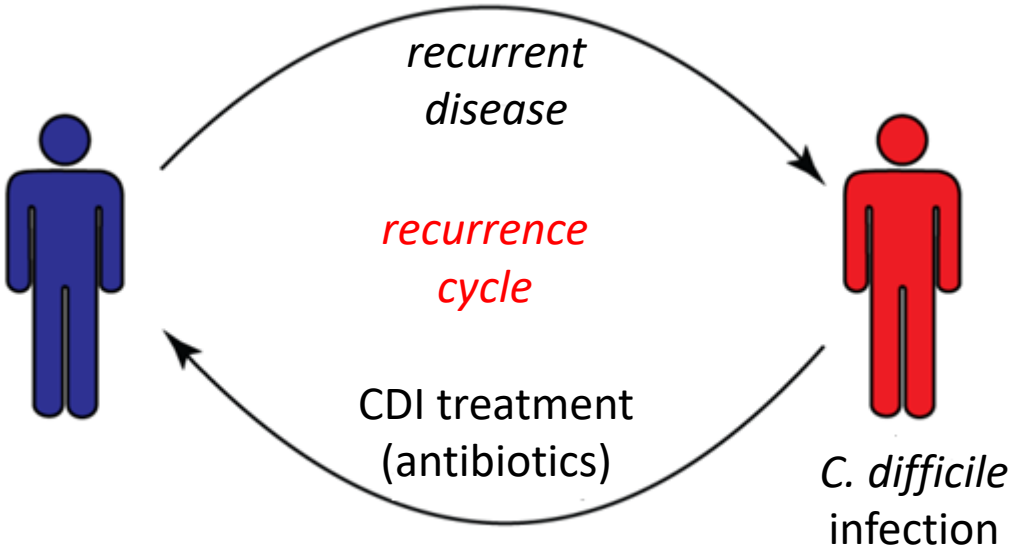




Alex D. British Biotech Receives €52M Boost to Beat Antimicrobial Resistance with New Antibiotic. Available at: https://www.labiotech.eu/medical/antibiotic-clostridium-difficile-barda/. Published December 9, 2017. Accessed January 2020.

Recurrent Disease

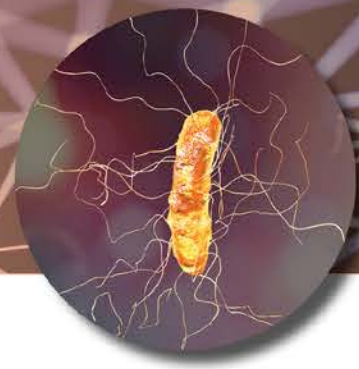


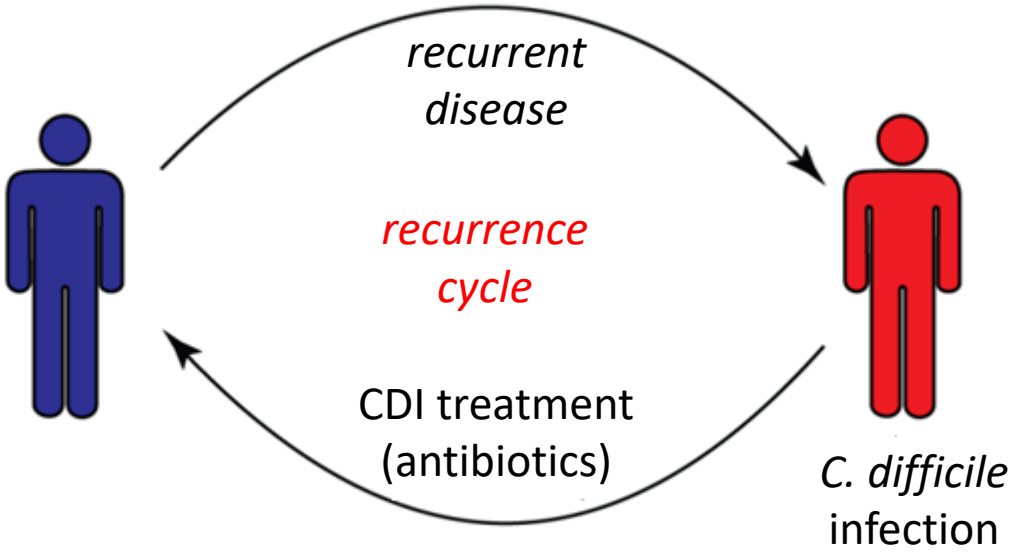


- Definition: initial resolution of symptoms followed by clinical re-emergence with positive testing >2 weeks but <8 weeks from the index episode[1]
- Happens in up to 25%![2]

1. Mcdonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis*. 2018;66(7):e1-e48. 2. Abou Chakra CN, et al. *PLoS One*. 2014;9(8):e107420. Published 2014 Aug 28. doi:10.1371/journal.pone.0107420.

Recurrent Disease

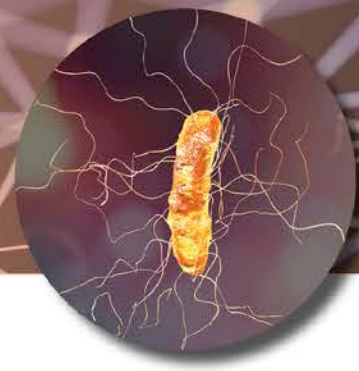


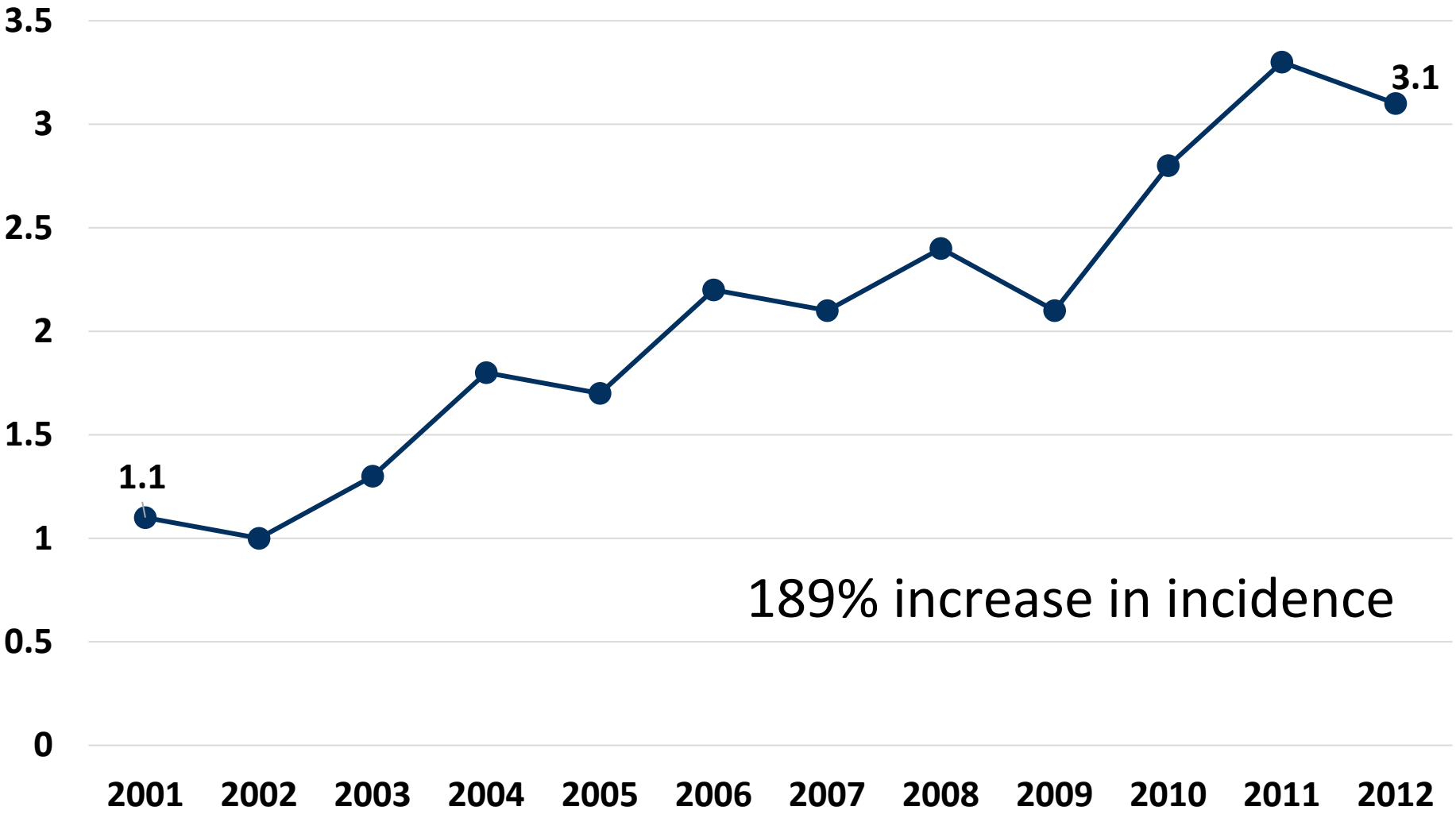


- 2nd Recurrence: 30-45% of 1st
- 3rd Recurrence: 45-60% of 2nd
- ≤5% of all patients → chronic, recurrent pattern
- No universal treatment algorithm

Gough E, Shaikh H, Manges AR. *Clin Infect Dis*. 2011;53(10):994-1002.
Leong C, Zelenitsky S. *Can J Hosp Pharm*. 2013;66(6):361-8.

Recurrent CDI Incidence 2001-2012

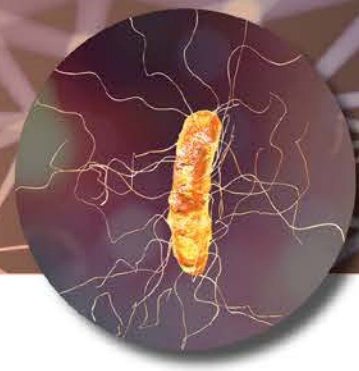




- Treated with at least three 14-day courses of CDI antibiotics
- Rate per 100,000 person-years

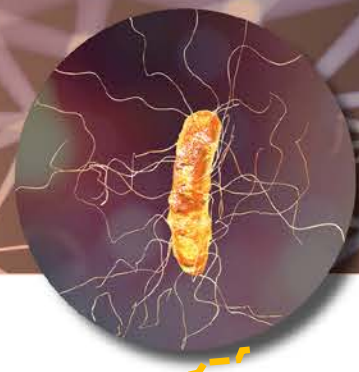
Ma GK, Brensinger CM, Wu Q, Lewis JD. *Ann Intern Med*. 2017;167(3):152-158.

What percent of patients with recurrent CDI require hospitalization?

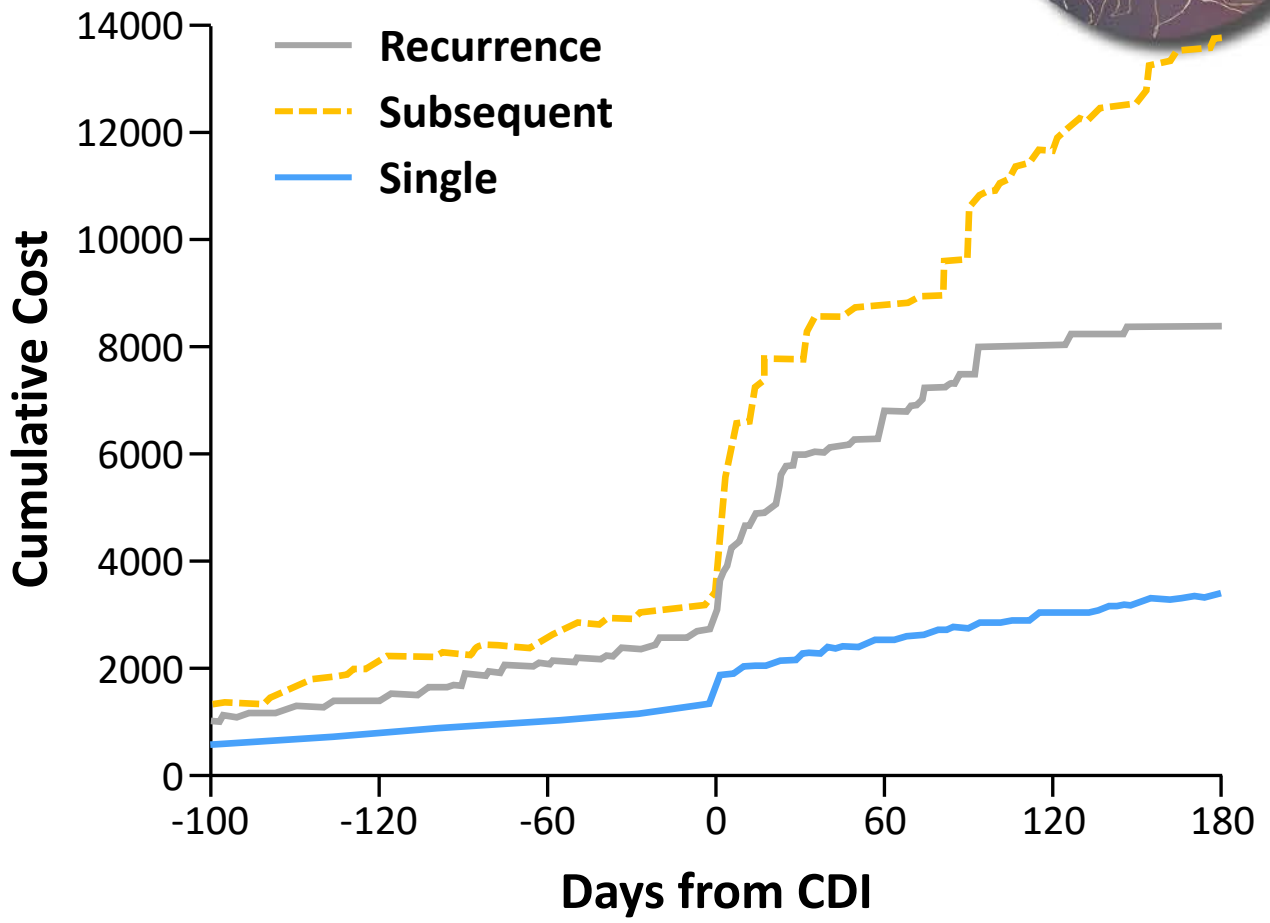


1. 38%
2. 55%
3. 64%
4. 84%

Recurrent CDI: Costs

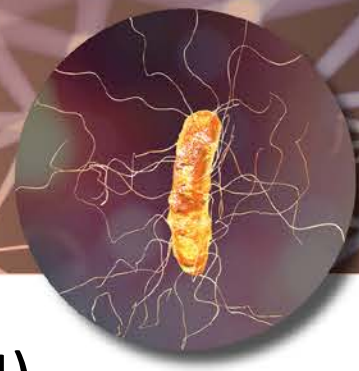


- Each recurrent CDI patient:
  - Average 4.4 stool tests for CD
  - 2.5 prescriptions for vancomycin
- 84% required hospitalization
- 6% required urgent colectomy
- Average cost per patient
  - $34,104
- 83,000 cases of recurrent CDI in the US per year
  - $5 billion annual costs



Rodrigues R, Barber GE, Ananthakrishnan AN. Infect Control Hosp Epidemiol. 2017;38(2):196-202.
Singh H, Nugent Z, Walkty A, et al. PLoS ONE. 2019;14(11):e0224609.
Zhang D, Prabhu VS, Marcella SW. *Clin Infect D*is. 2018;66(9):1326-1332.

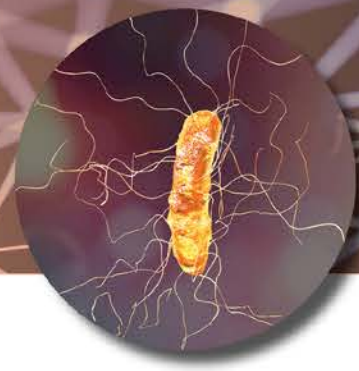
Shift to Community-onset CDI in the National Veterans Health Administration: 2003-2014

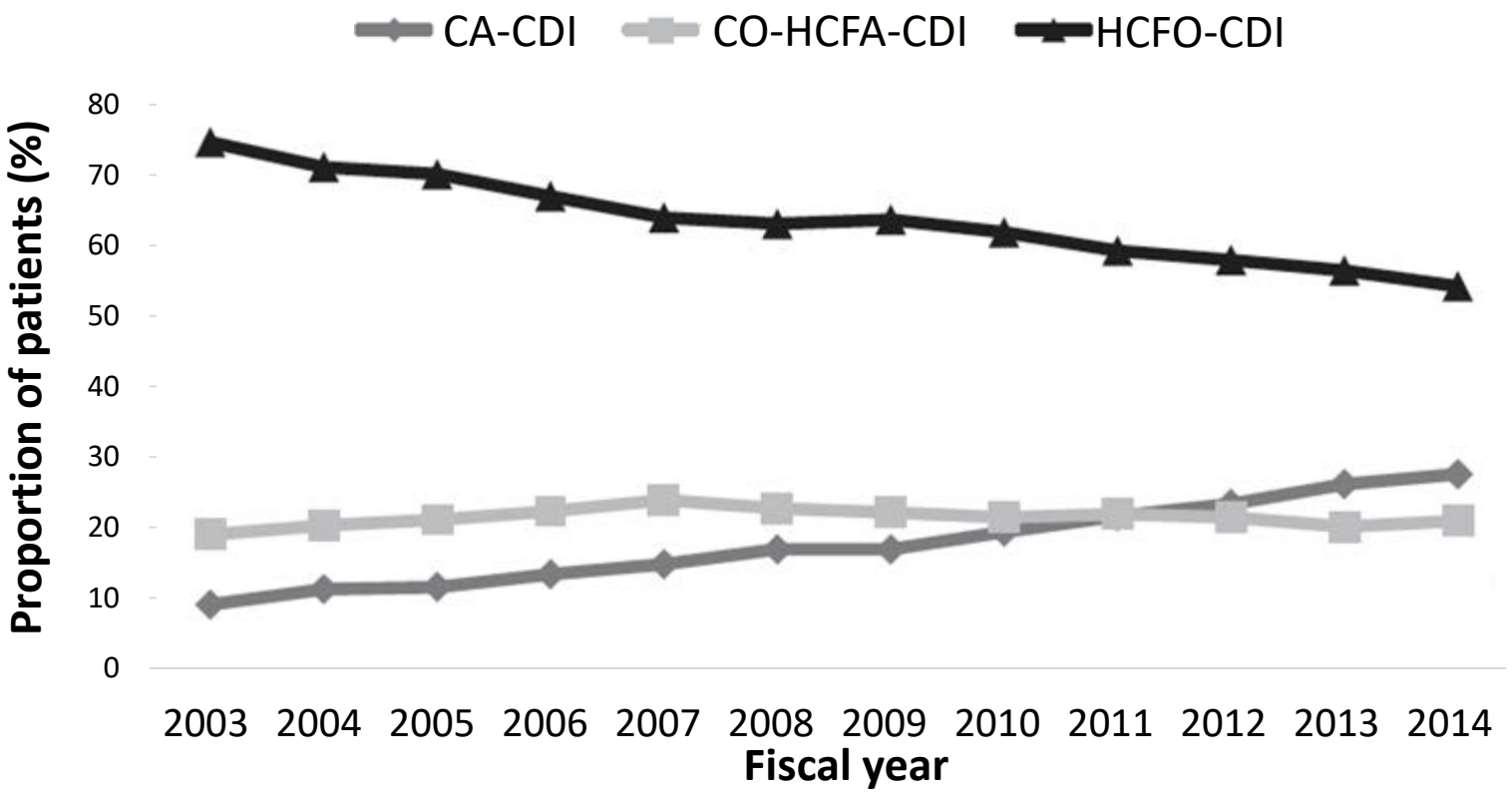


- The proportion of patients with community-associated CDI (CA-CDI) increased and health care facility-associated CDI (HCFO-CDI) decreased in recent years
- Patients with HCFO-CDI experienced higher rates of severe CDI and mortality

Reveles KR, Pugh MJV, Lawson KA, et al. *Am J Infect Control*. 2018;46(4):431-435.

Community Acquired CDI has Increased More than 2-fold

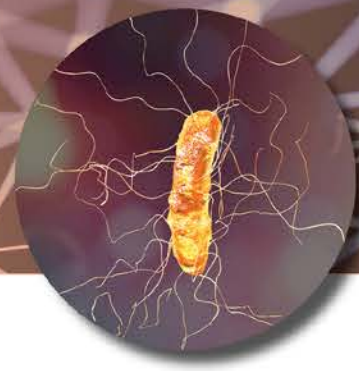


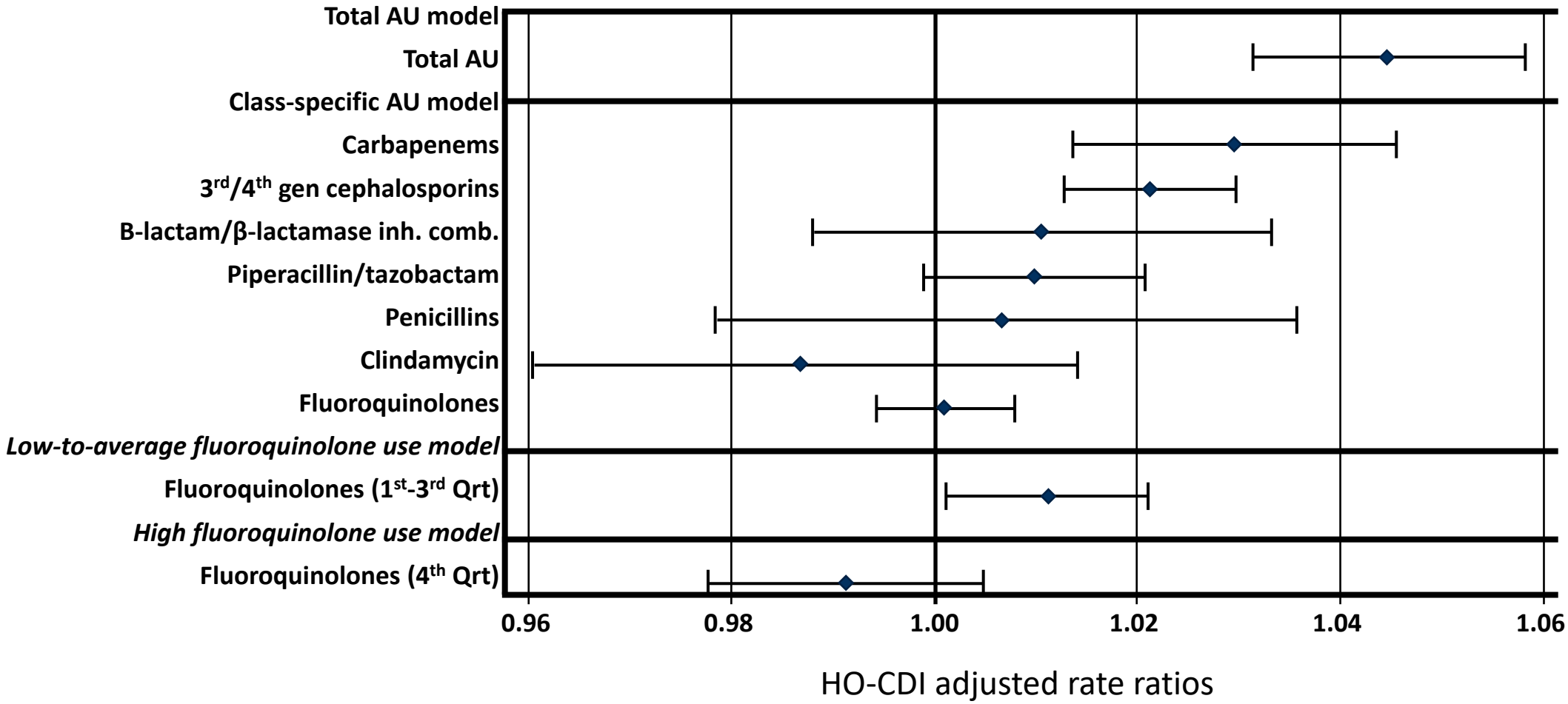


Proportion of patients with each CDI type from fiscal year 2003 to fiscal year 2014 (N = 30,326). CA-CDI, community-associated CDI; CO-HCFA-CDI, community-onset, health care facility-associated CDI; HCFO-CDI, health care facility-onset CDI.

Reveles KR, Pugh MJV, Lawson KA, et al. *Am J Infect Control*. 2018;46(4):431-435.

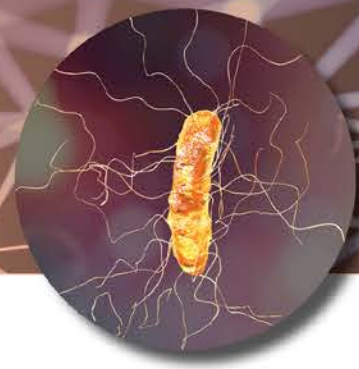
Adjusted Rate Ratios and 95% Confidence Intervals for the Association Between Hospital-onset CDI (HO-CDI) and Antibiotic Use





Kazakova SV, Baggs J, Mcdonald LC, et al. *Clin Infect Dis*. 2020;70(1):11-18.

We Are Now Able To Predict The Antibiotics Most Likely To Cause CDI!!



Any antibiotic that kills firmicutes and/or *Bacteroidetes* will almost immediately increase CDI risk

Thus: the most common antibiotic used with these properties will be the most likely to be associated with CDI

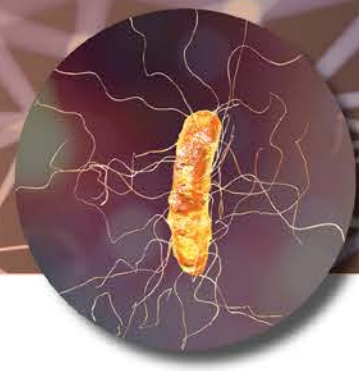
Seekatz AM, Theriot CM, Molloy CT, Wozniak KL, Bergin IL, Young VB. *Infect Immun*. 2015;83(10):3838-46.
Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, Mcdonald LC. *Clin Infect Dis*. 2018;66(7):1004-1012.

Antibiotics that Increase CDI Risk

Drug	Kills Firmicutes	Kills Bacteroidetes	Commonly Used
Ampicillin-sulbactam	Yes	Yes	Medium
Cefepime	Yes	No	Yes
Ceftriaxone	Yes	No	Yes
Carbapenems	Yes	Yes	Yes and increasing
Piperacillin-tazobactam	Yes	Yes	Yes
Clindamycin	Yes	Yes	No
Fluoroquinolones	Yes	Yes	Not as much

Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, Mcdonald LC. *Clin Infect Dis*. 2018;66(7):1004-1012.

Older Adults and CDI: An Unhappy Relationship



- ↑Primary infection, severe disease, and recurrence
- 92% of CDI-related deaths
- 18th leading cause of death
- Hospitalization rate for age ≥85 *more than all other age groups combined*
- ↑Treatment failures

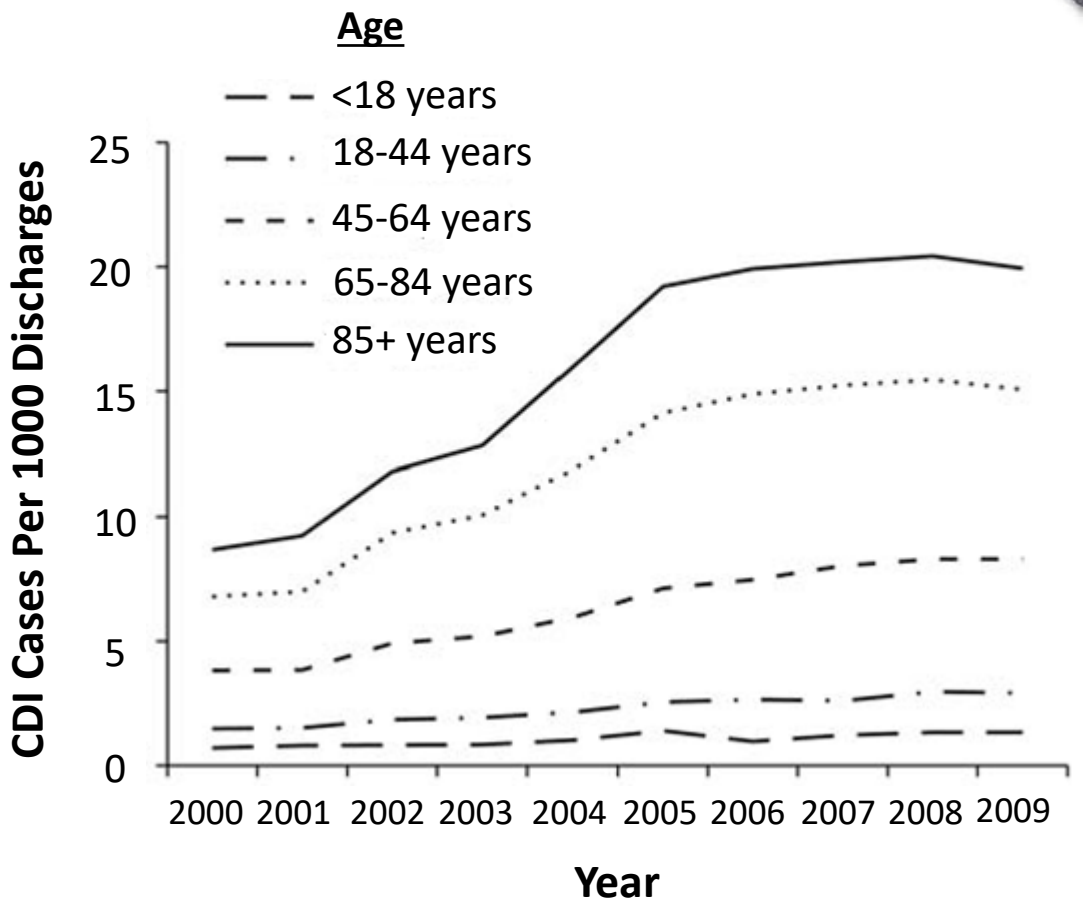
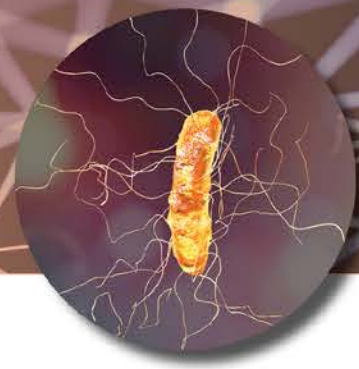


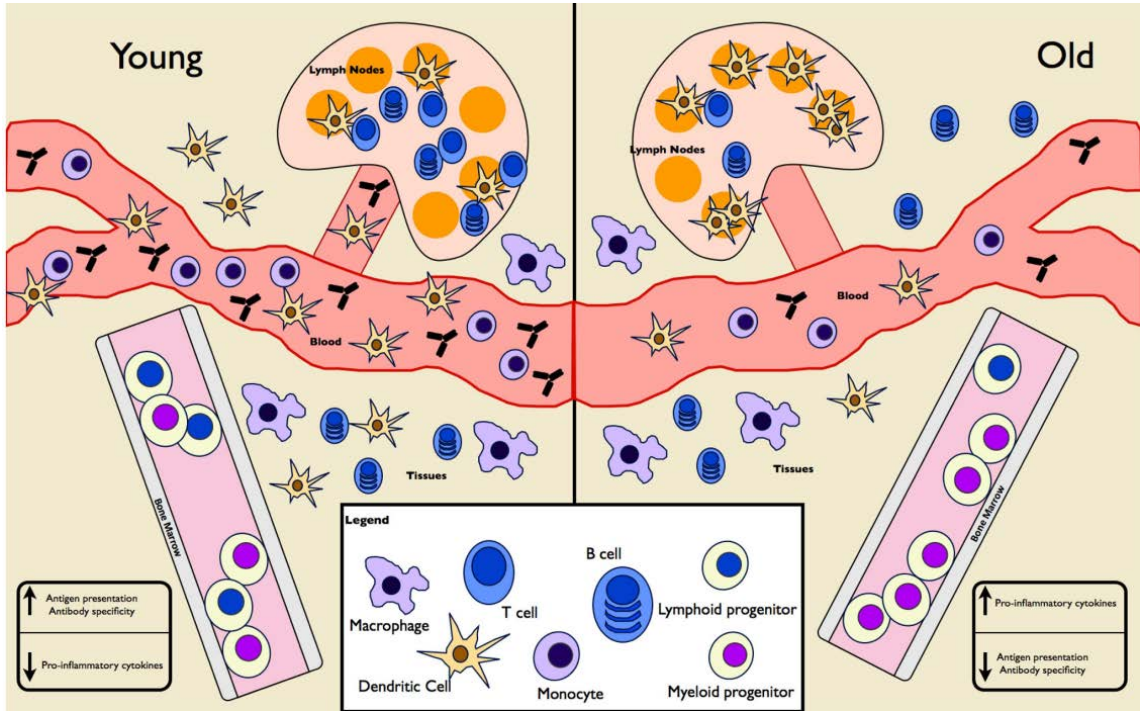
Figure 1. Discharge rate for *Clostridium difficile* infection from US short-stay hospitals by age. CDI = *Clostridium difficile* infection

Lessa FC, Gould CV, McDonald LC. *Clin Infect Dis.* 2012;55 Suppl 2:S65-70.

Immunosenescence in Aging

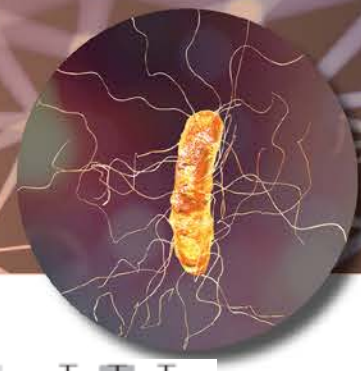


- Thymic involution
- Endogenous viruses tie up resources (EBV, CMV)
- Chronic pro-inflammatory state
- ↓Immunoresponsive, virgin B and T-cells
- Less responsive to neoantigens

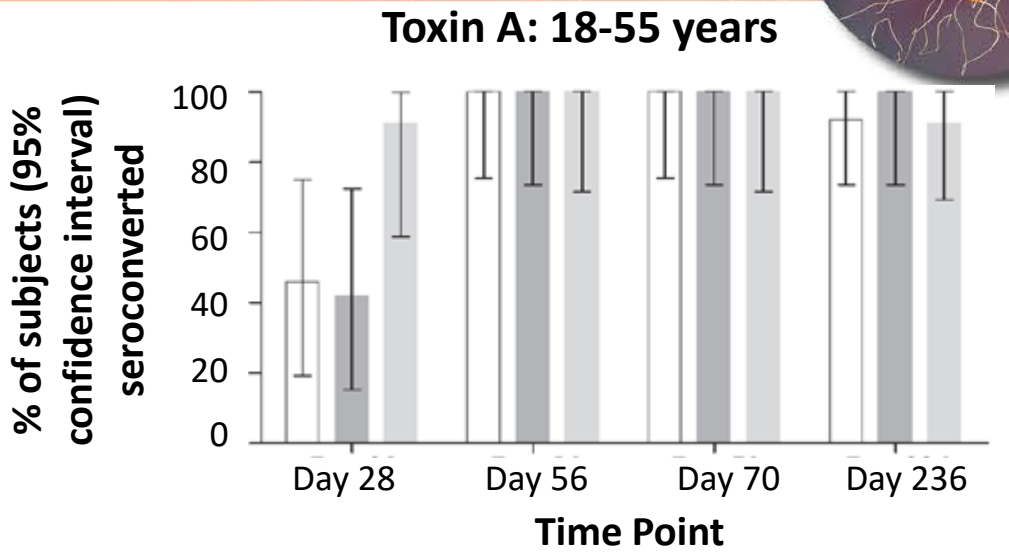


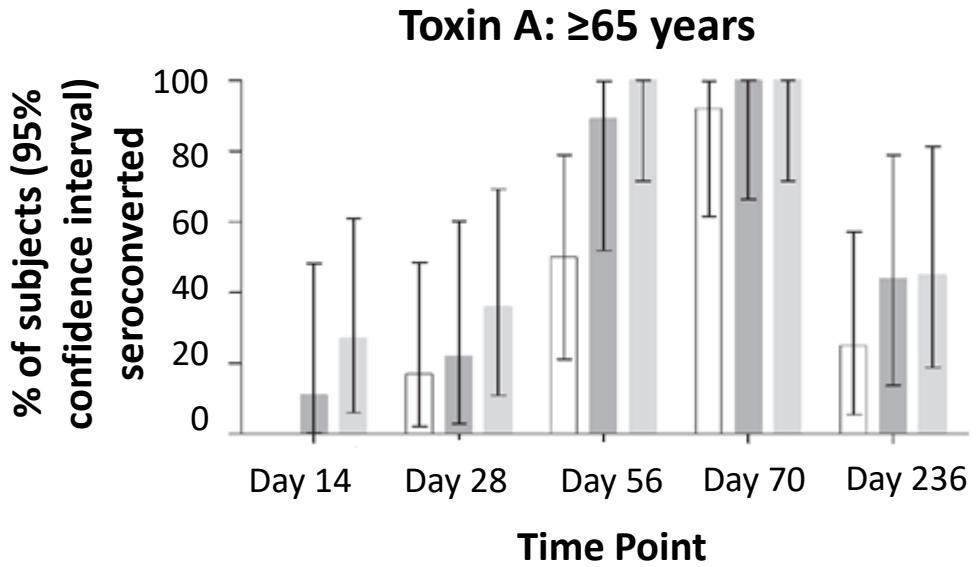
Dorrington MG, Bowdish DM. *Front Immunol.* 2013;4:171.

Immune Response to CDI in Older Adults



- Less likely to seroconvert
- Seroconversion transient
- Initial exposure has minimal effect



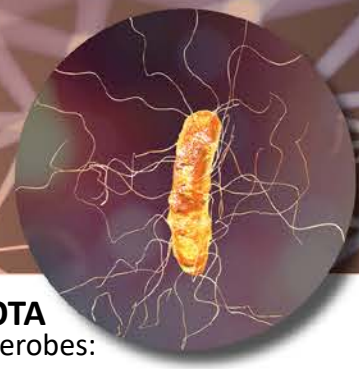


C. difficile toxoid vaccine group

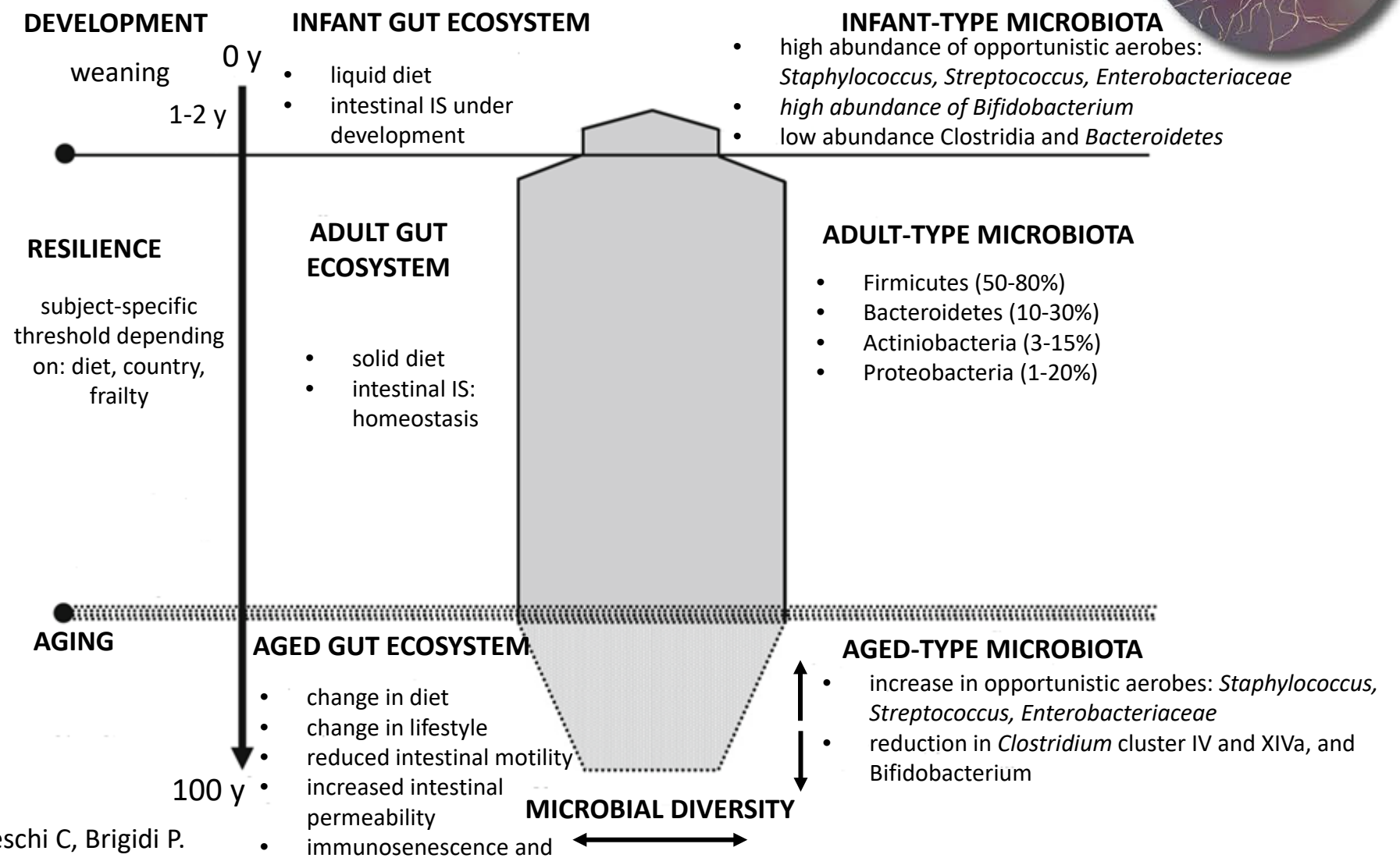
- 2ug
- 10ug
- 50ug

Greenberg RN, Marbury TC, Foglia G, Warny M. *Vaccine*. 2012;30(13):2245-9.

Aging, Primary CDI, and the Microbiome

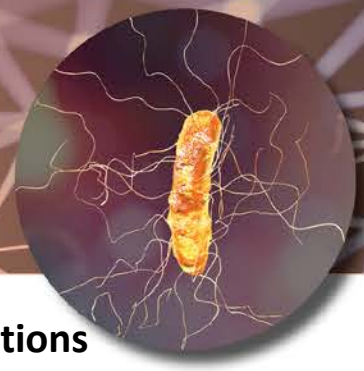


- Colonization resistance decreases
- Fewer competing anaerobes (*Bacteroides, Bifidobacterium*)
- Less diversity



Biagi E, Candela M, Fairweather-tait S, Franceschi C, Brigidi P. *Age (Dordr)*. 2012;34(1):247-67.

Primary CDI in Older Adults: Increased Exposure to *C. difficile* Risk Factors



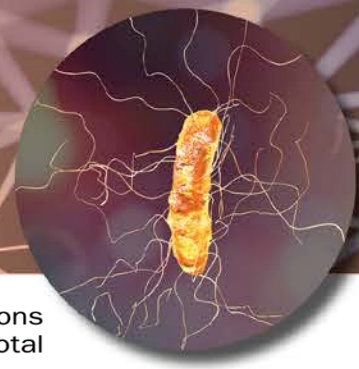
- Health care facilities: colonization in 25-55%
- PPI use and low innate gastrointestinal acidity
- Comorbid disease
- More infections: ↑cumulative antimicrobial exposure
  - Number and duration impact risk

Comparison of Cumulative Antibiotic Exposures for Case and Noncase Hospitalizations

Characteristic	CDI positive n (%)	CDI negative n (%)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Defined daily doses, median (IQR)	14.8 (21.2)	7.2 (12.3)	-	-
<3.0	18 (7)	1502 (15)	Ref	Ref
3.0 to 7.79	49 (20)	3702 (37)	1.1 (.7, 2.1)	1.2 (.7, 2.1)
7.80 to 21.0	89 (37)	2952 (30)	2.9 (1.8, 4.8)	2.8 (1.7, 4.6)
>21.0	85 (35)	1757 (18)	5.3 (3.2, 8.8)	→ 5.3 (3.1, 9.0)
Antibiotic days, median (IQR)	14.0 (23.0)	7.0 (9.0)	-	-
<4	22 (9)	2208 (22)	Ref	Ref
4 to 7	41 (17)	3071 (31)	1.5 (.9, 2.4)	1.4 (.8, 2.4)
8 to 18	87 (36)	3097 (31)	3.4 (2.1, 5.4)	3.0 (1.9, 5.0)
>18	91 (38)	1537 (16)	9.8 (6.0, 16.0)	→ 7.8 (4.6, 13.4)
Number of antibiotics, median (IQR)	3.0 (4.0)	2.0 (2.0	-	-
1	31 (13)	3744 (38)	Ref	Ref
2	54 (22)	2507 (25)	2.7 (1.8, 4.3)	2.5 (1.6, 4.0)
3 or 4	70 (29)	2505 (25)	3.7 (2.4, 5.7)	3.3 (2.2, 5.2)
5 or more	86 (36)	1157 (12)	11.6 (7.7, 17.4)	→ 9.6 (6.1, 15.1)

Stevens V, Dumyati G, Fine LS, Fisher SG, Van wijngaarden E. *Clin Infect Dis*. 2011;53(1):42-8.

Severe CDI and Older Adults



- More severe disease and adverse outcomes
- Risk factors for severity common
  - comorbid disease[1]
  - decreased functional status[2]
- Cannot stop concurrent antibiotics
- Decreased immune response
- NAP1 infection more likely

Table 2. Demographics, Comorbidities, and Conditions Present at Admission in Patients Who Underwent Total Colectomy for *Clostridium difficile*

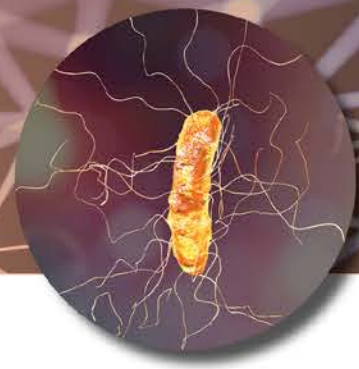
Characteristic	Survivors	Nonsurvivors
n	**13,425**	**5,949**
Age, y (range)	65 (56–78)	73 (66–82)
Comorbidities		
Deficiency anemia	21.2	16.4
Blood loss anemia	4.2	1.9
Hypertension	37.3	40.1
Diabetes-uncomplicated	14.0	12.4
Diabetes-complicated	3.4	3.0
Obesity	4.8	3.3
Weight loss	34.6	25.4
Hypothyroidism	7.9	6.2
Congestive heart failure	18.2	28.4
Chronic lung disease	25.4	33.4
Chronic liver disease	2.3	3.4
Chronic kidney disease	14.2	21.2
Peripheral vascular disease	6.6	12.4
Neurologic disorder	6.5	5.6
Depression	8.0	4.5

Table 3. Multiple Logistic Regression for Severity Score

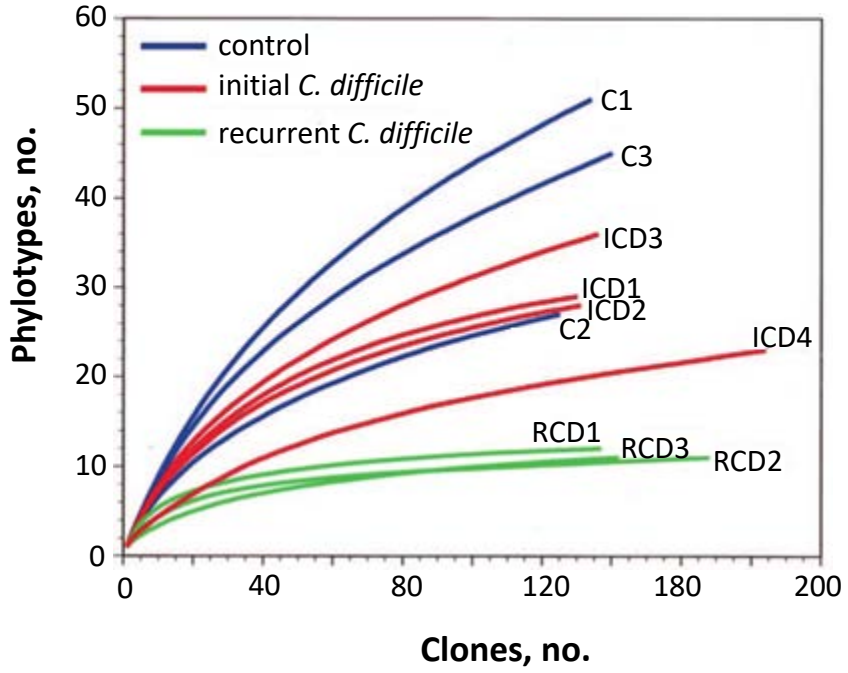
Variable	Odds Ratio (95% Confidence Interval) *P*-Value
Age	1.07 (1.01–1.13) .03
ADL class	
Some assistance[a]	4.54 (0.56–37.07) .16
Full assistance[b]	8.10 (1.24–52.95) .03

1. Halabi WJ, Nguyen VQ, Carmichael JC, Pigazzi A, Stamos MJ, Mills S. *J Am Coll Surg*. 2013;217(5):802-12.
2. Rao K, Micic D, Chenoweth E, et al. *J Am Geriatr Soc*. 2013;61(10):1738-42.

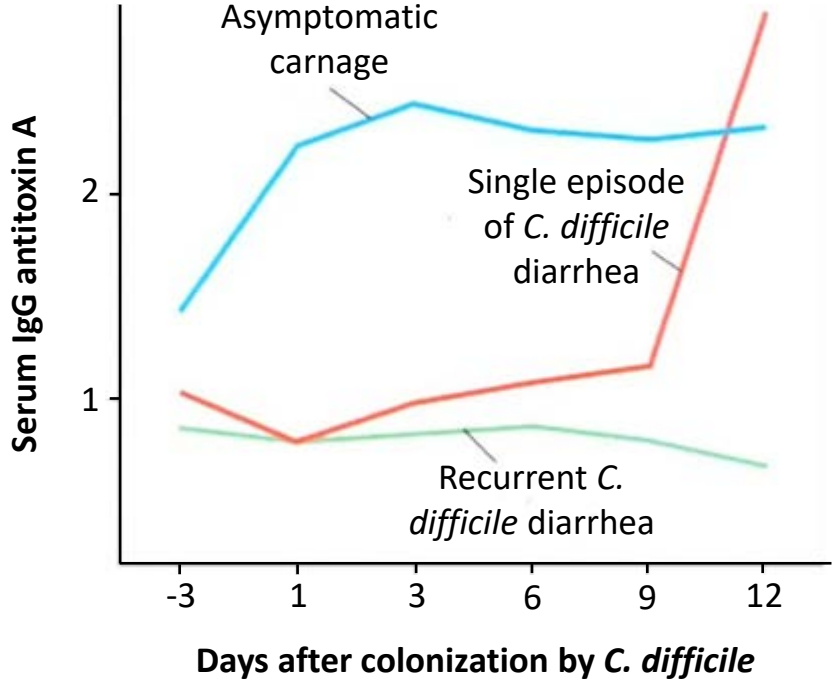
Recurrent CDI and Older Adults



Poor microbiome recovery[1]



Lower immune response[1, 2]



1. Chang JY, Antonopoulos DA, Kalra A, et al. *J Infect Dis*. 2008;197(3):435-8.
2. Kyne L, Warny M, Qamar A, Kelly CP. *N Engl J Med*. 2000;342(6):390-7.

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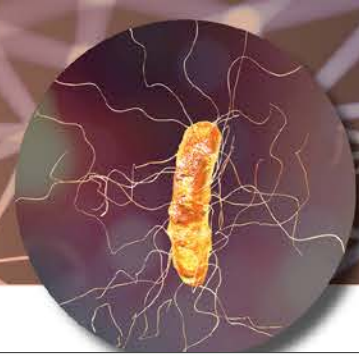

2017 IDSA/SHEA Clinical Practice Guidelines for C. difficile Infection in Adults and Children

What is the best-performing method (ie, in use positive and negative predictive value) for detecting patients at increased risk for clinically significant C. difficile infections in **commonly submitted stool specimens**?

Recommendation:

Use stool toxin test as part of a multistep algorithm (ie, GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a NAAT alone for all specimens received in the clinical laboratory where there are no pre-agreed institutional criteria for patient stool submission.

Clinical Infectious Diseases

IDSA GUIDELINE

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)

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A panel of experts was convened by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) to update the 2010 clinical practice guideline on *Clostridium difficile* infection (CDI) in adults. The update, which has incorporated recommendations for children (following the adult recommendations for epidemiology, diagnosis, and treatment), includes significant changes in the management of this infection and reflects the evolving controversy over best methods for diagnosis. *Clostridium difficile* remains the most important cause of healthcare-associated diarrhea and has become the most commonly identified cause of healthcare-associated infection in adults in the United States. Moreover, *C. difficile* has established itself as an important community pathogen. Although the prevalence of the epidemic and virulent ribotype 027 strain has declined markedly along with overall CDI rates in parts of Europe, it remains one of the most commonly identified strains in the United States where it causes a sizable minority of CDIs, especially healthcare-associated CDIs. This guideline updates recommendations regarding epidemiology, diagnosis, treatment, infection prevention, and environmental management.

Keywords. *Clostridium difficile*; *Clostridioides difficile*; Guidelines; CDI; CDAD.

EXECUTIVE SUMMARY

Summarized below are recommendations intended to improve the diagnosis and management of *Clostridium difficile* infection (CDI) in adults and children. CDI is defined by the presence of symptoms (usually diarrhea) and either a stool test positive for *C. difficile* toxins or detection of toxigenic *C. difficile*, or colonoscopic or histopathologic findings revealing pseudomembranous colitis. In addition to diagnosis and management, recommended methods of infection control and environmental management of the pathogen are presented. The panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system (Figure 1). A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guidelines. The extent to which these guidelines can be implemented is impacted by the size of the institution and the resources, both financial and laboratory, available in the particular clinical setting.

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Clinical Infectious Diseases® 2018;66(7):987–94

DOI: 10.1093/cid/ciy149

GUIDELINE RECOMMENDATIONS FOR *CLOSTRIDIUM DIFFICILE* INFECTION

EPIDEMIOLOGY

1. How are CDI cases best defined?

Recommendation

1. To increase comparability between clinical settings, use available standardized case definitions for surveillance of (1) healthcare facility-onset (HO) CDI; (2) community-onset, healthcare facility–associated (CO-HCFA) CDI; and (3) community-associated (CA) CDI (*good practice recommendation*).

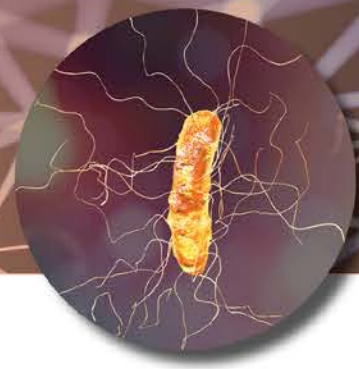
Mcdonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis*. 2018;66(7):987-994.

Laboratory Diagnosis of CDI

Assay	Targets	Advantages	Disadvantages
Toxin enzyme immunoassay (EIA)	Toxin A and B	Rapid (2-6 h); easy to perform	Low sensitivity (50-75%)
Cell cytotoxicity neutralization assay (on stool filtrate)	Primarily toxin B but also toxin A to some extent	High sensitivity (94-100%) and specificity (97%)	Long TAT (up to 48 hrs); requires cell culture facility; labor-intensive
Toxigenic stool culture (culture for *C. difficile* then perform an assay to detect toxin)	Toxigenic *C. difficile*	Most sensitive test	Long TAT (48-96 hrs); labor-intensive
Nucleic acid amplification	*C. difficile* toxin genes	High sensitivity	Concern for detection of colonization state
Glutamate dehydrogenase EIA	Highly conserved enzyme present in all *C. difficile*	High sensitivity	Poor specificity (toxigenic & non-toxigenic strains) so only a screening step

Adapted from Schuetz AN. *Clinical Laboratory News*. www.aacc.org/publications/cln/articles/2018/november/diagnosis-of-c,-d-,-difficile. November 1, 2018. Accessed January 2020. TAT=turnaround time.

Diagnosis Summary



- Lab testing alone will not make the diagnosis
- Must integrate results with clinical picture
- Test only symptomatic patients
- Don’t “test for cure” and be aware of post-infectious IBS
- Repeat testing usually not indicated
- Endoscopy with biopsy for a histologic diagnosis may be helpful when uncertainty exists or with ileus

IDSA/SHEA CDI Guidelines 2018: Initial Episode

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

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a] All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances. [b] The criteria proposed for defining severe or fulminant Clostridium difficile infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

Mcdonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

IDSA/SHEA CDI Guidelines 2018: Recurrent CDI

Clinical Definition	Recommended Treatment [a]	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, OR • Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR • FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Low Weak/Low Weak/Moderate
Second or subsequent recurrence	• VAN in a tapered and pulsed regimen, OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR • FDX 200 mg given twice daily for 10 days, OR • Fecal microbiota transplantation[a] (Not FDA-approved)	Weak/Low Weak/Low Weak/Low Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a] The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

Mcdonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Comparative Treatment Efficacy in CDI

Outcomes	No. of Participants	Resolution, %	*P* Value	Quality of Evidence
Direct comparisons of metronidazole and vancomycin				
Resolution at end (10 days) of treatment	843 (5 studies)	**87 (VAN)** 78 (MTR)	0.0008	High
Resolution of diarrhea at end of treatment without recurrence*	843 (5 studies)	**73 (VAN)** 63 (MTR)	0.003	High
Direct comparisons of fidaxomicin and vancomycin				
Resolution at end (10 days) of treatment	1105 (2 studies)	88 (FDX) 86 (VAN)	0.36	High
Resolution of diarrhea at end of treatment without recurrence**	1105 (2 studies)	**71 (FDX)** 57 (VAN)	<0.0001	High

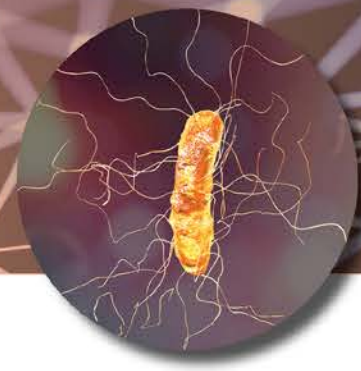
*1 month after treatment; **56 days after treatment

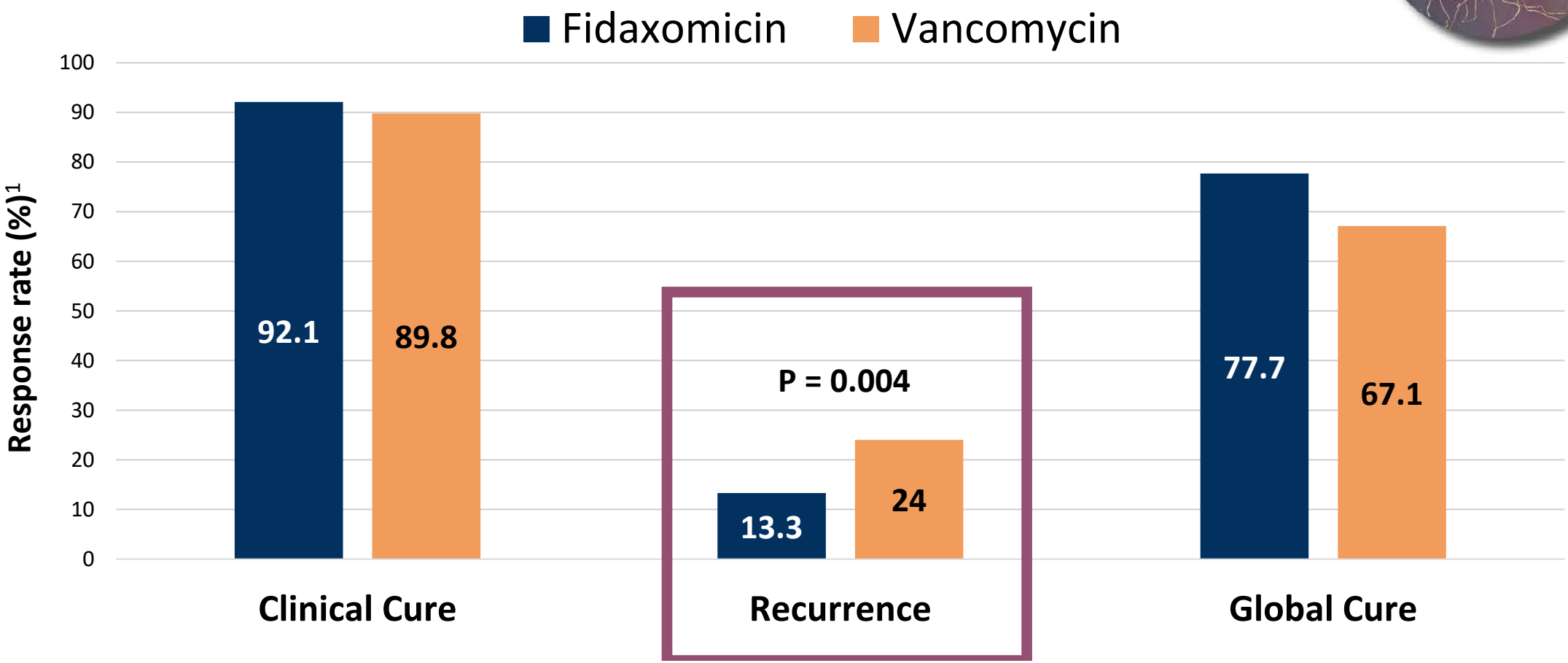
VAN = vancomycin, MTR = metronidazole, FDX = fidaxomicin

Mcdonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis*. 2018;66(7):987-994.

Fidaxomicin/Vancomycin: Equal Efficacy for Primary Episode

Note: Vancomycin Has a Higher Reoccurrence Rate

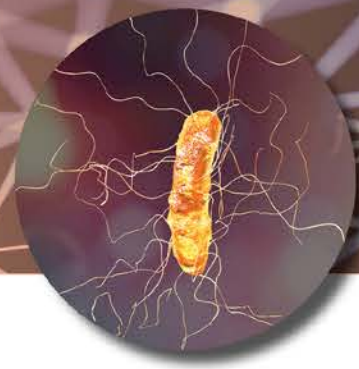




The second phase III study showed similar results [2]

1. Louie TJ, Miller MA, Mullane KM, et al. *N Engl J Med*. 2011;364(5):422-31. 2. Cornely OA, Crook DW, Esposito R, et al. *Lancet Infect Dis.* 2012;12(4):281-289.

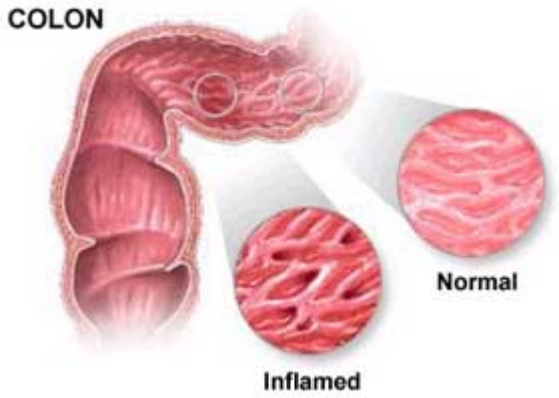
CDI and Inflammatory Bowel Disease (IBD)



CDI in patients that have IBD is associated with: [1]

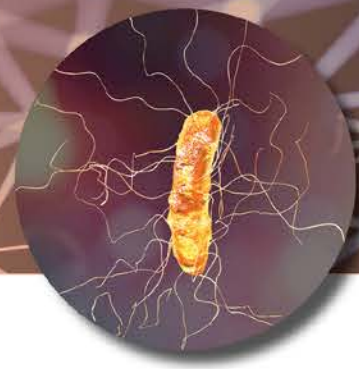
- Increased morbidity
- Subsequent escalation in IBD medical therapy
- Urgent colectomy
- Increased hospitalization
- Excess mortality

- Asymptomatic carriage is common (20-50%)[2]
- CDI can mimic a flare
- CDI can trigger a flare
- Do you treat CDI, flare, or both?
  - Gastroenterologists divided evenly[3]
  - Combination therapy with worse outcomes[4]



1. D'aoust J, Battat R, Bessissow T. *World J Gastroenterol*. 2017;23(27):4986-5003. 2. Berg AM, Kelly CP, Farraye FA. *Inflamm Bowel Dis*. 2013;19(1):194-204. 3. Yanai H, Nguyen GC, Yun L, et al. *Inflamm Bowel Dis*. 2011;17(7):1540-6. 4. Ben-horin S, Margalit M, Bossuyt P, et al. *Clin Gastroenterol Hepatol*. 2009;7(9):981-7.

Bezlotoxumab for Prevention of Recurrent CDI

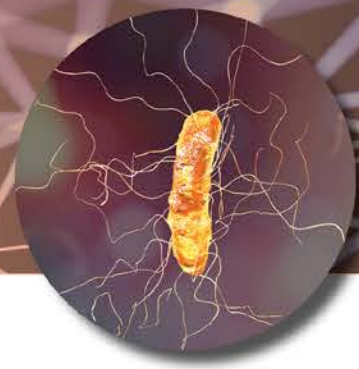


Methods

- Double-blind, randomized, placebo-controlled, phase 3 trials, MODIFY I (NCT01241552) and MODIFY II (NCT01513239)
- 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection
- Participants received an infusion of bezlotoxumab (10 mg per kilogram of body weight), actoxumab plus bezlotoxumab (10 mg per kilogram each), or placebo; actoxumab alone (10 mg per kilogram) was given in MODIFY I but discontinued after a planned interim analysis
- Primary end point was recurrent infection (new episode after initial clinical cure) within 12 weeks after infusion in the modified intention-to-treat population

Wilcox MH, Gerding DN, Poxton IR, et al. *N Engl J Med*. 2017;376(4):305-317.

Bezlotoxumab for Prevention of Recurrent CDI, cont.



Results

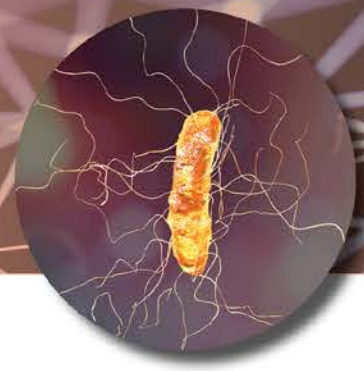
- In both trials, the rate of recurrent CDI was significantly lower with bezlotoxumab alone than with placebo
- In prespecified subgroup analyses (combined data set), rates of recurrent infection were lower in both groups that received bezlotoxumab than in the placebo group in subpopulations at high risk for recurrent infection or for an adverse outcome
- The rates of initial clinical cure were:
  - 80% with bezlotoxumab alone
  - 73% with actoxumab plus bezlotoxumab
  - 80% with placebo
- The rates of sustained cure (initial clinical cure without recurrent infection in 12 weeks) were 64%, 58%, and 54%, respectively. The rates of adverse events were similar among these groups; the most common events were diarrhea and nausea

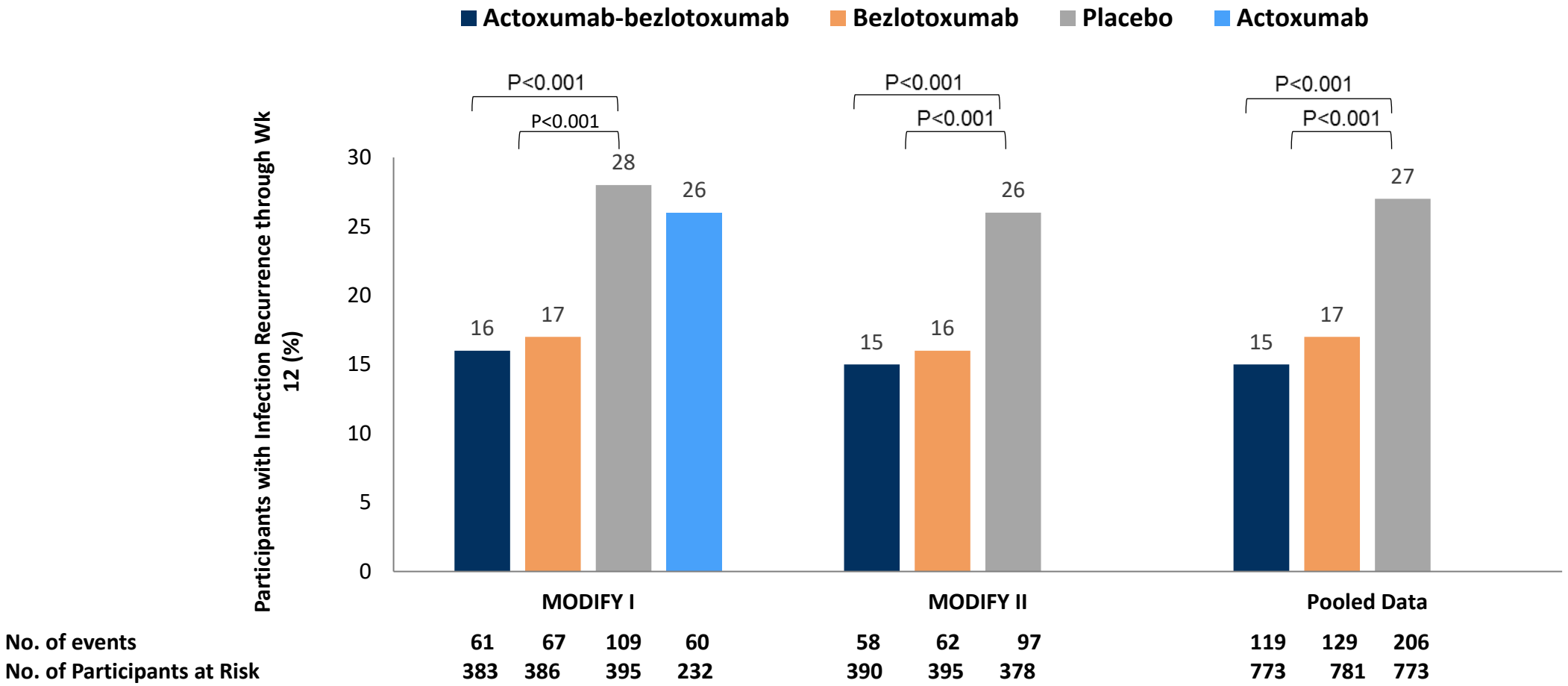
Conclusion

- Among participants receiving antibiotic treatment for primary or recurrent CDI, bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo and had a safety profile similar to that of placebo
  - The addition of actoxumab did not improve efficacy

Wilcox MH, Gerding DN, Poxton IR, et al. *N Engl J Med*. 2017;376(4):305-317.

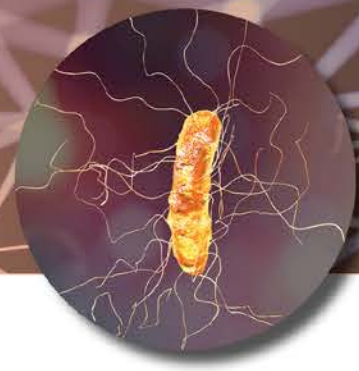
Bezlotoxumab is Associated with a Substantially Lower Rate of Recurrent Infection





Wilcox MH, Gerding DN, Poxton IR, et al. *N Engl J Med*. 2017;376(4):305-317.

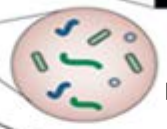
FMT for Patients with Recalcitrant CDI



Healthy colon

Healthy individual

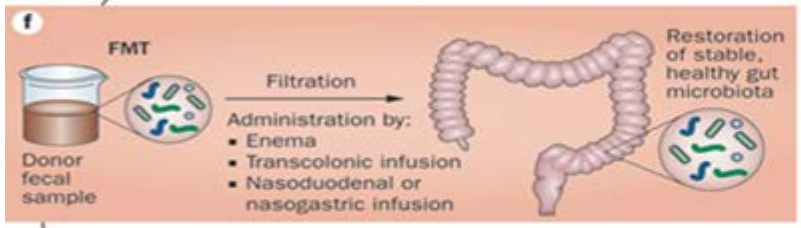
Resolution of symptoms

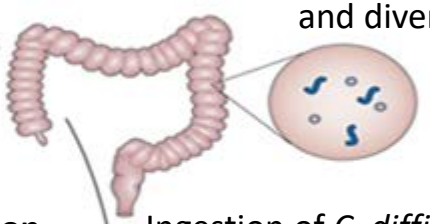


'Healthy' microbiota

Antibiotics

Reduced gut microbial species and diversity

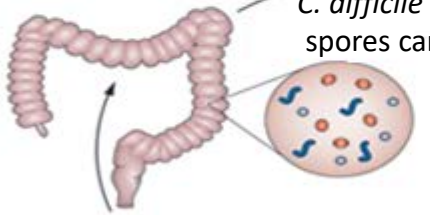




Ingestion of *C. difficile* spores from the environment

Recurrent infection

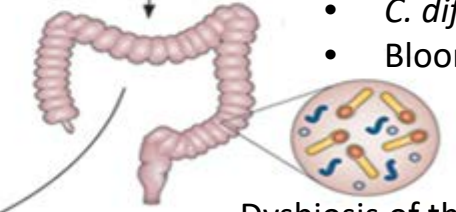
C. difficile killed but spores can remain



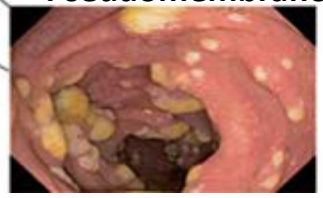
- *C. difficile* spores germinate
- Bloom of *C. difficile*

Antibiotics

Pseudomembranous colitis



Dysbiosis of the gut microbiota

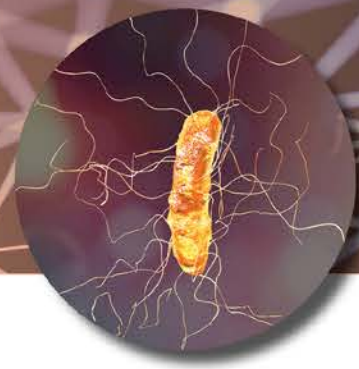


Development of CDI

- Severe diarrhea, abdominal pain, nausea and fever
- C. difficile toxins induce inflammation and cell death
- CDI can cause pseudomembranous colitis

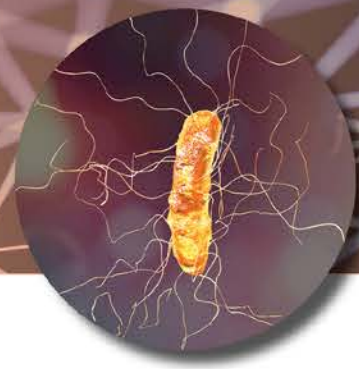
Borody TJ, Khoruts A. *Nat Rev Gastroenterol Hepatol*. 2011;9(2):88-96.

FMT: Fecal Microbiota Transplantation

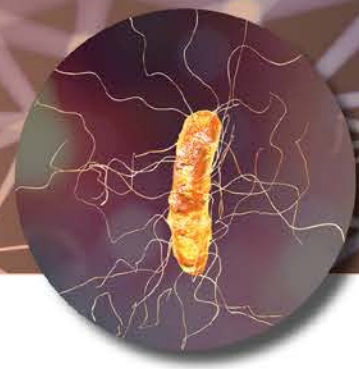


- Not FDA-approved
- A consideration for recurrent CDI refractory to medical therapy
  - Only FDA-approved indication
- Not proven in severe CDI or primary CDI
- Mechanism of action poorly understood
- Appears to be safe and effective

Summary



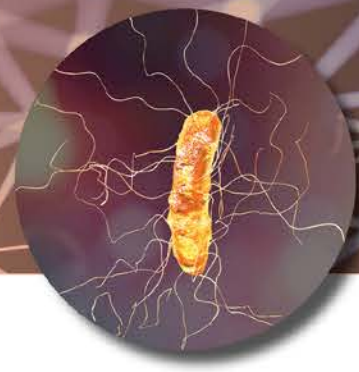
- Recurrent CDI is a major reason for increased costs
- Community acquired CDI has also increased
- We can now predict antibiotics that most likely cause CDI
- Laboratory testing alone is not sufficient to make a CDI diagnosis
- Antimicrobial stewardship strategies have been shown to be effective to decrease CDI rates
- New IDSA/SHEA guidelines de-emphasize use of metronidazole and increased use of vancomycin and fidaxomicin
- FMT, novel uses of indicated agents (fidaxomicin), and new treatment modalities (bezlotoxumab) may help decrease the burden of recurrent CDI



Care Management Strategies to Address the Rising Costs of CDI

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Health Care Costs Attributable to Primary CDI, Overall and by Age, Sex, and Immunocompromising Status

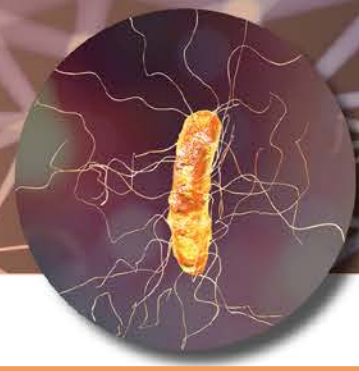


Characteristic	Healthcare Costs in $CDI_{Primary1}$ Cohort, $ (n = 41767)	Healthcare Costs in Non-CDI Cohort, $ (n = 41767)	Healthcare Costs Attributable to Primary CDI, $
Overall	43718 (43001-44572)	19513 (19053-20046)	24205 (23436-25013)
Age <65 y	44704 (43585-45861)	18041 (17423-18652)	26663 (25551-27846)
Age ≥65 y	42497 (41513-43549)	21337 (20646-22042)	21160 (20016-22335)
Male	53450 (51931-55105)	22378 (21569-23351)	31073 (29542-32700)
Female	37463 (36668-38369)	17672 (17161-18196)	19791 (18944-20736)
Not immunocompromised	33213 (32571-33900)	12998 (12650-13334)	20215 (19556-20913)
Immunocompromised	77801 (75468-80618)	40653 (39028-42320)	37148 (34561-40070)

- Data are presented as mean (95% confidence interval)
- $CDI_{PRIMARY1}$, cohort with primary CDI only matched to those without CDI

Zhang D, Prabhu VS, Marcella SW. *Clin Infect Dis*. 2018;66(9):1326-1332.

Burden of CDI in the Elderly in the Different Databases, Including all Episodes of CDI



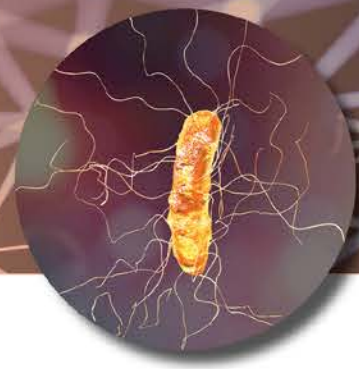
Adults < 65 Years	Lab/Rx	SID	PHD	NIS
Rate of CDI/100,000 person-year	66.0	37.5[a]	N/A	N/A
Rate of hospital onset CDI/10,000 pt. days	1.1	5.7	5.4	6.9
Prevalence of CDI at admission/1,000 hospitalizations	N/A	1.5	1.9	2.0
Rate of health care facility-associated CDI/10,000 pt. days	2.1	N/A	N/A	N/A
Elderly	**Medicare**	**SID**	**PHD**	**NIS**
Rate of CDI/100,000 person-years	677	383[b]	N/A	N/A
Rate of hospital onset CDI/10,000 pt. days	9.8	15.9	11.6	15.5
Prevalence of CDI at admission/1,000 hospitalizations	5.4	4.7	6.3	6.2
Rate of health care facility-associated CDI/10,000 pt. days	12.5	N/A	N/A	N/A

[a]rate/100,000 persons in 7 states aged 18-64 years
[b]rate/100,000 persons in 7 states aged ≥ 65 years

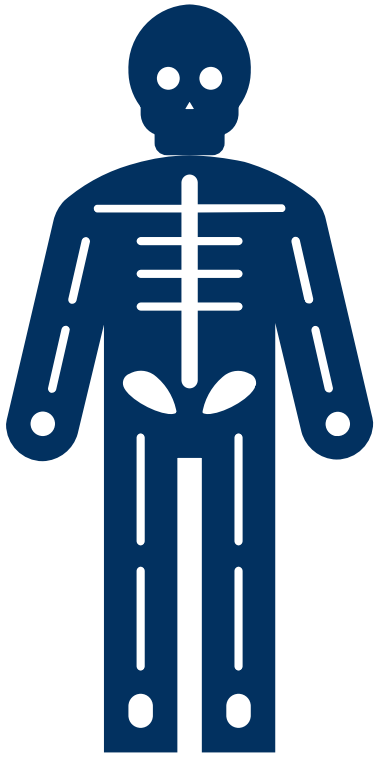
SID = State Inpatient Database
PHD = Premier Health care Database
NIS = National Inpatient Sample Database

Olsen MA, Young-xu Y, Stwalley D, et al. *BMC Infect D*is. 2016;16:177.

Incidence of Nosocomial CDI

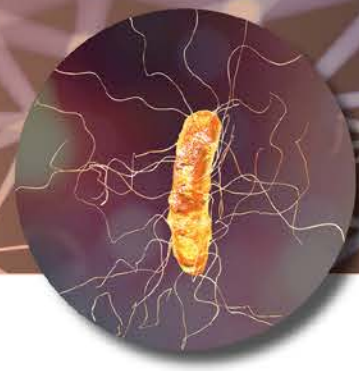


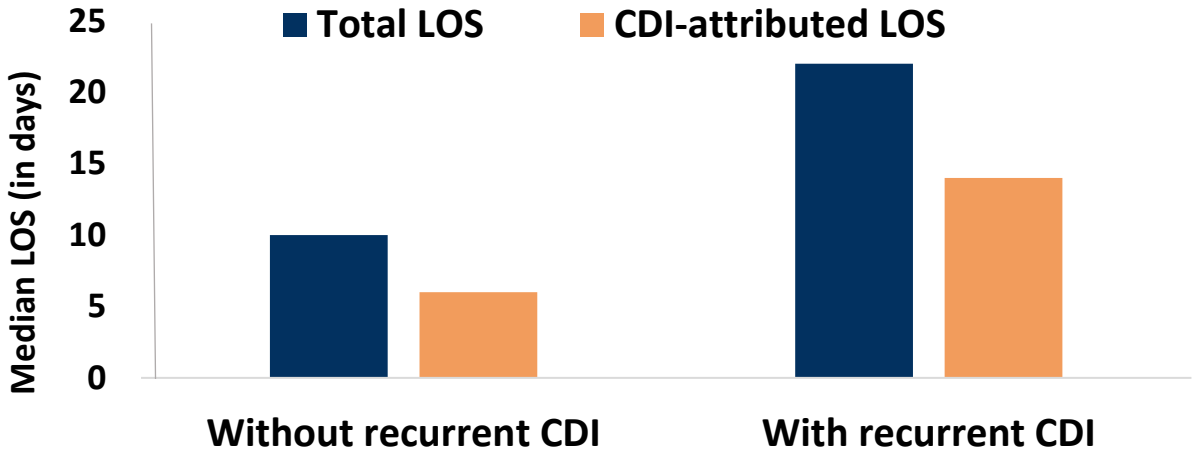
- The incidence of *C. difficile* infection among hospitalized patients has been increasing[1]
- Almost 15 cases per 1000 hospital discharges[1]
- Approximately 20 cases per 100,000 person-years in the community[1]
- Study by Olsen et al[2] found that the incidence of CDI was 35% higher in the Medicare data
  - The incidence of CDI was 10-fold lower and the proportion of community-onset CDI was much higher in the privately insured younger LabRx population compared to the elderly Medicare population



1. Leffler DA, Lamont JT. *N Engl J Med*. 2015;372(16):1539-48. 2. Olsen MA, Young-xu Y, Stwalley D, et al. *BMC Infect D*is. 2016;16:177.

Health Care Costs Associated with Recurrent CDI

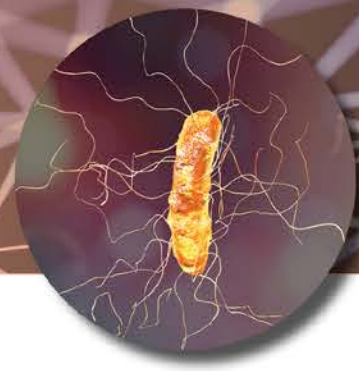


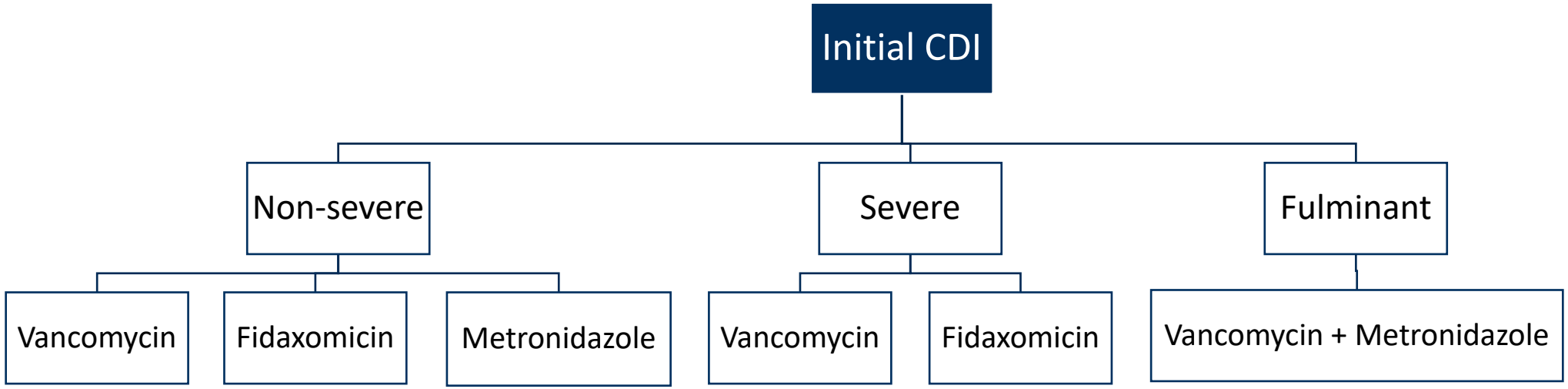


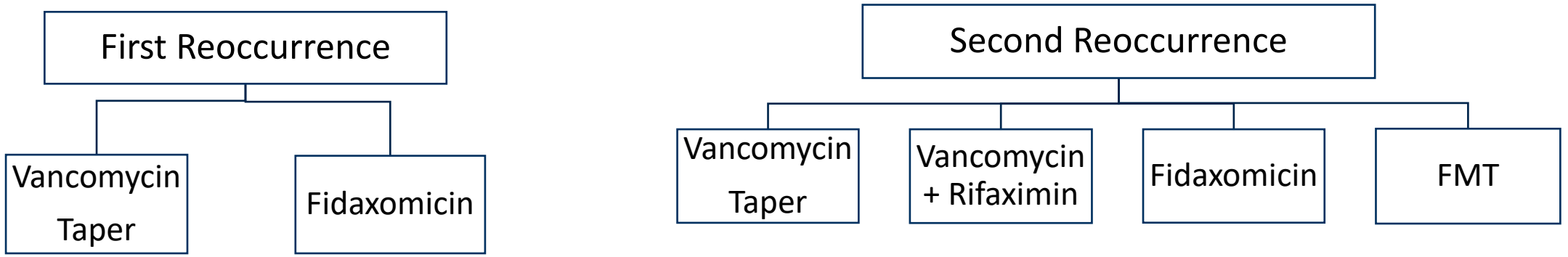
Cost in US dollars; Median (IQR)	Without Recurrent CDI	With Recurrent CDI
CDI pharmacologic treatment	$60 (23 - 200)	$140 (30 - 260)
CDI attributable hospitalization	$13,168 (7,525 - 24,456)	$28,218 (15,050 - 47,030)
Total hospitalization	$20,693 (11,287 - 41,386)	$45,148 (20,693 - 82,772)

Shah DN, Aitken SL, Barragan LF, et al. *J Hosp Infect*. 2016;93(3):286-9.

Available Treatment Options for CDI (IDSA/SHEA Guidelines)







Rajasingham R, Enns EA, Khoruts A, Vaughn BP. *Clin Infect Dis*. 2020;70(5):754-762.

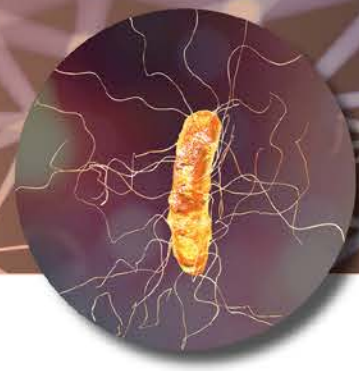
Medication Costs

Medication	Unit, mg	Estimated Purchasing Price for 1 Unit	Course Duration, d	Total Price for Course (0.4 of AWP)	Range (0.2–0.6 of AWP)
Vancomycin	125	$0.35	10	$14.08	$7.04–$21.12
Metronidazole	500	$0.29	10	$8.76	$4.38–$13.14
Rifaximin	1000	$3.68	20	$88.32	$44.16–$132.48
Fidaxomicin	200	$88.36	10	$1,767.20	$883.60–$2,650.80
Metronidazole (IV)	500	$0.94	14	$39.12	$19.56–$58.68

- All costs are given as US dollars.
- Abbreviations: AWP, average wholesale price; IV, intravenous

Rajasingham R, Enns EA, Khoruts A, Vaughn BP. *Clin Infect Dis*. 2020;70(5):754-762.

Fidaxomicin: An Overview

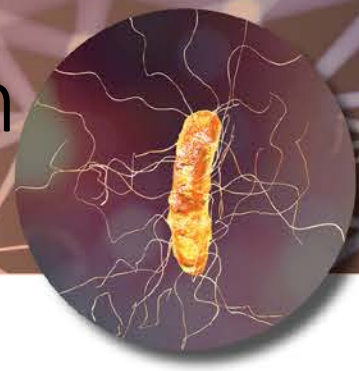


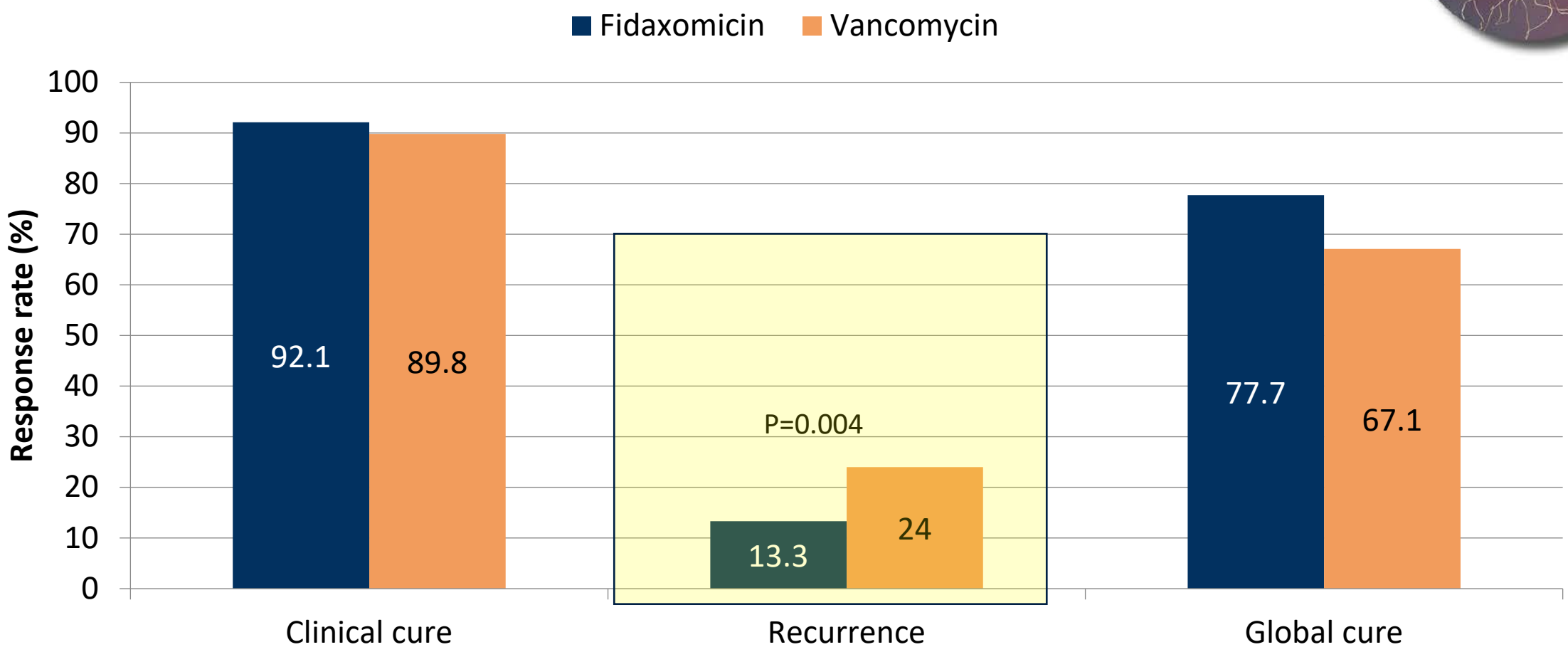
- Narrow spectrum, non-absorbable antibiotic
- Studied for 1st or 2nd episode
- Noninferior to vancomycin for cure[1]
- 50% reduction in recurrent CDI[1]
- Possible role at the end of a taper (chaser) in place of rifaximin[2]

1. Crook DW, Walker AS, Kean Y, et al. *Clin Infect Dis*. 2012;55 Suppl 2:S93-103. 2. Johnson AP, Wilcox MH. *J Antimicrob Chemother*. 2012;67(12):2788-92.

Fidaxomicin: Equal Efficacy Compared to Vancomycin

(Note: Vancomycin Reduces the Risk for Reoccurrence)

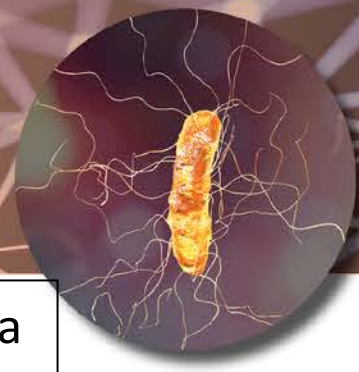




The second phase III study showed similar results (Crook et al. Lancet ID)

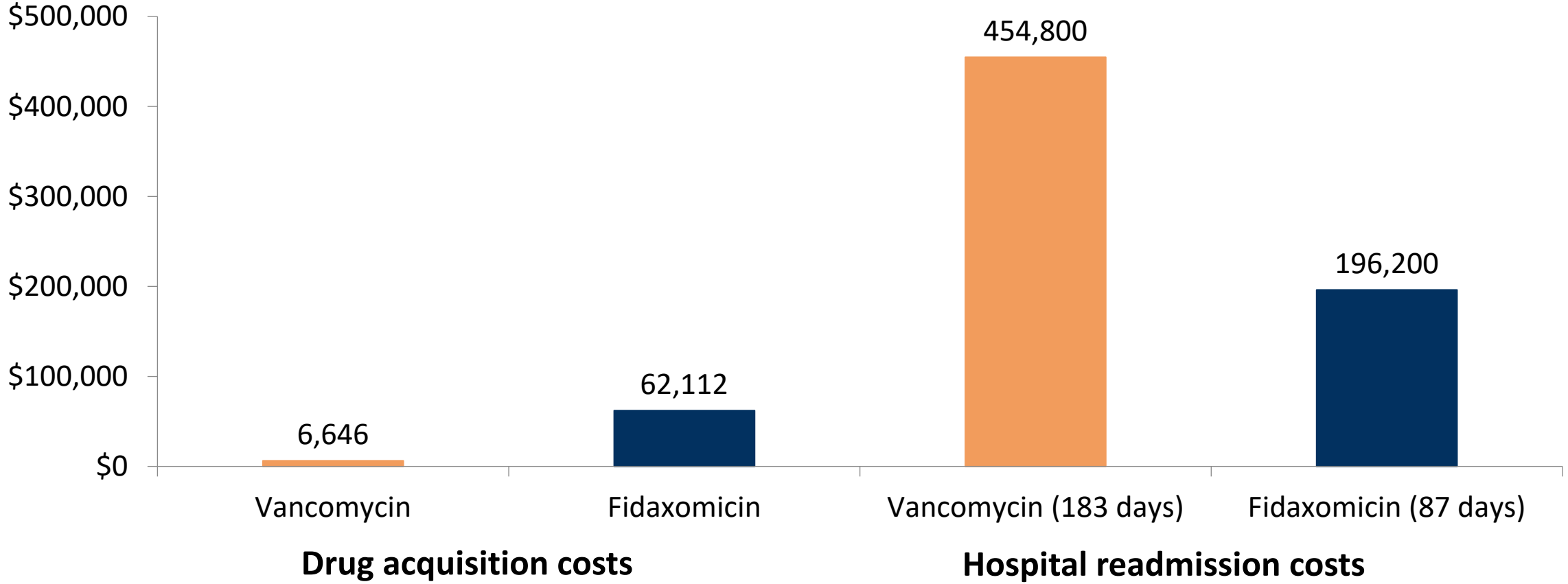
Louie TJ, Miller MA, Mullane KM, et al. *N Engl J Med*. 2011;364(5):422-31.

Fidaxomicin May Reduce Costs from Reduced Readmissions



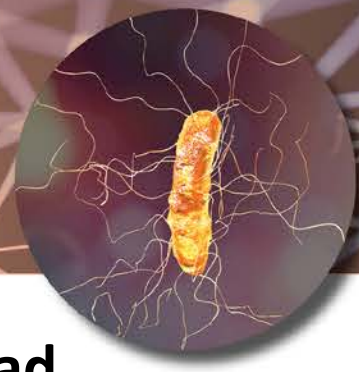
Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for selected patients.

CDI-related readmissions: Fidaxo: 20.4% Vanco: 41.3%



Gallagher JC, Reilly JP, Navalkele B, Downham G, Haynes K, Trivedi M. *Antimicrob Agents Chemother*. 2015;59(11):7007-10.

Fidaxomicin: Cost-effectiveness

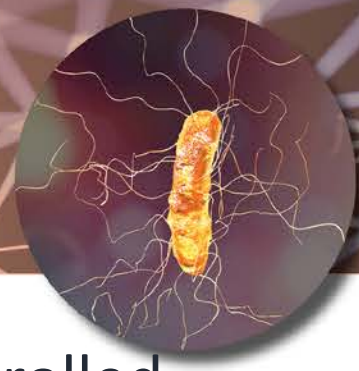


Cost savings with fidaxomicin are largely due to lower recurrence rates that lead to fewer re-hospitalizations

- Bartsch et al. 2013[1]
  - Incremental cost-effectiveness ratio (ICER) >$43.7 million per quality-adjusted life year (QALY)
  - Assuming 50% NAP1/BI/027 strain, not cost-effective until ≤$150 per course
  - For those with a non-NAP1/BI/027 strain between $160 and $400 to be cost-effective
- Stranges et al. 2013[2]
  - ICER $67,576 per QALY
  - Simulation: 80% chance of being cost-effective at $100K threshold
- Nathwani et al. 2014[3]
  - ICER ~$ 20,522 (£16, 529) per QALY for severe CDI
  - Dominant (more effective & less costly) for 1st recurrence
  - Simulation: 60% probability of cost-effectiveness for severe CDI and 68% for first recurrence at ~$37,248 (£30 000) threshold

1. Bartsch SM, Umscheid CA, Fishman N, Lee BY. *Clin Infect Dis*. 2013;57(4):555-61 2. Stranges PM, Hutton DW, Collins CD. *Value Health*. 2013;16(2):297-304. 3. Nathwani D, Cornely OA, Van engen AK, Odufowora-sita O, Retsa P, Odeyemi IA. *J Antimicrob Chemother*. 2014;69(11):2901-12.

Fidaxomicin vs Vancomycin for Treatment of First Episode CDI: A Meta-analysis and Systematic Review



- Four observational studies with a total of 2,303 patient with CDI were enrolled
  - Recurrence Rate: Compared with vancomycin, fidaxomicin use was associated with a significantly lower recurrence with a pooled OR of 0.47 (95% CI, 0.37 - 0.60, I2 = 0)
  - Cure Rate: There was no significant association of fidaxomicin use with CDI cure rate compared to vancomycin with a pooled OR of 1.22 (95% CI, 0.93 - 1.60, I2 = 0)
- Fidaxomicin has a more sustained clinical response with a statistically significant lower recurrence rate
- Fidaxomicin appears to be the better drug with statistical significance, its cost-effectiveness continues to be evaluated
- More randomized clinical trials are needed to shed light on this matter to assess if there is any clinical significance in fidaxomicin superiority

Al momani LA, Abughanimeh O, Boonpheng B, Gabriel JG, Young M. *Cureus*. 2018;10(6):e2778.

Vancomycin: An Overview

Has been used for CDI for three decades now

Non-inferior for cure compared with fidaxomicin

Many extreme cases have been tested

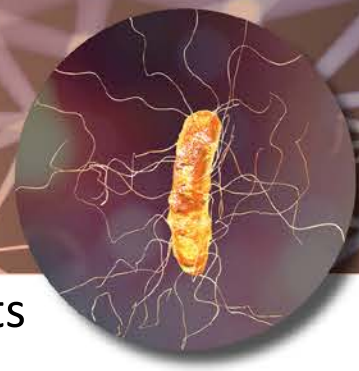
- Severe, complicated with multiple recurrences
- Immune compromised patients

Can be given as a taper for recurrence and may be even better than FMT?

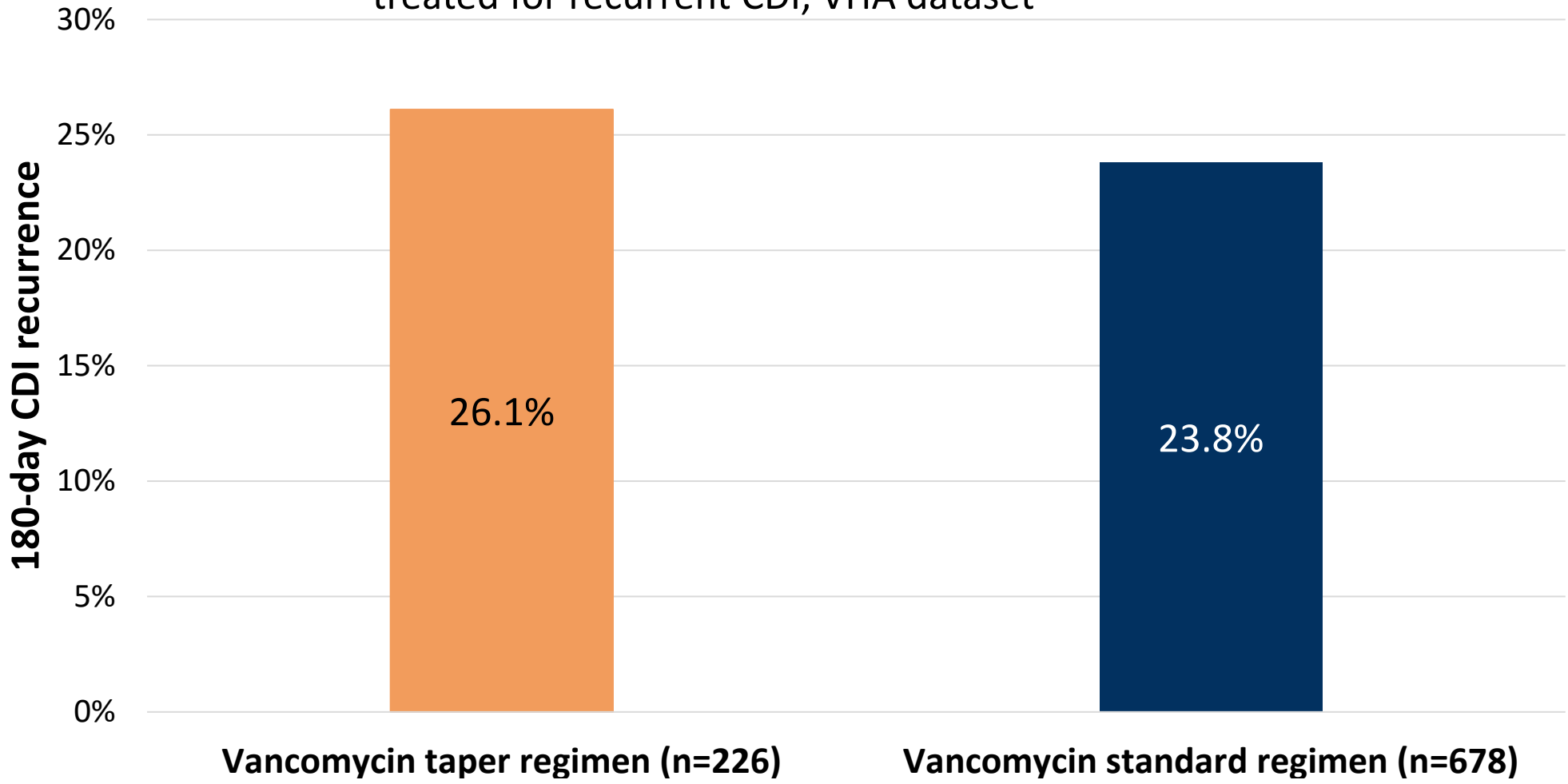
- FMT no better than vancomycin taper in recent RCT[1] of acute CDI patients, although enema only
- The authors on difference with prior RCTs not using a placebo control arm (emphasis mine):
  - "Without a control arm in either trial, it is not known what proportion of patients would have been symptom-free ***had their antibiotics been simply discontinued***."

1. Hota SS, Sales V, Tomlinson G, et al. *Clin Infect Dis*. 2017;64(3):265-271.

Paucity of Data to Support Pulse Taper Oral Vancomycin for CDI Recurrence Prevention

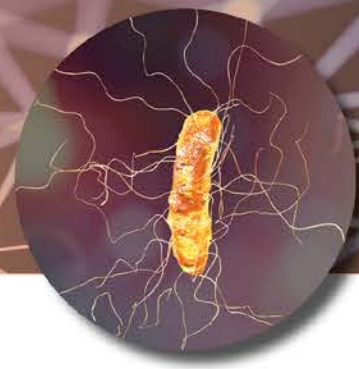


Propensity-matched analysis between standard and tapered oral vancomycin for adult patients treated for recurrent CDI, VHA dataset

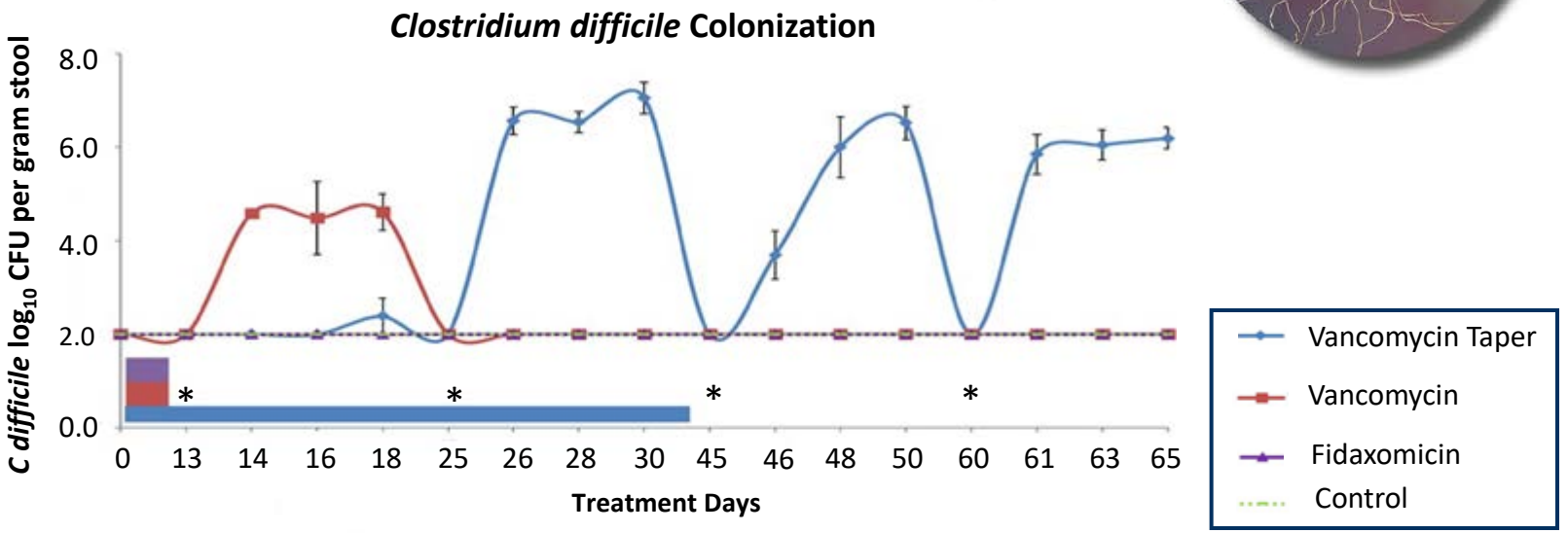


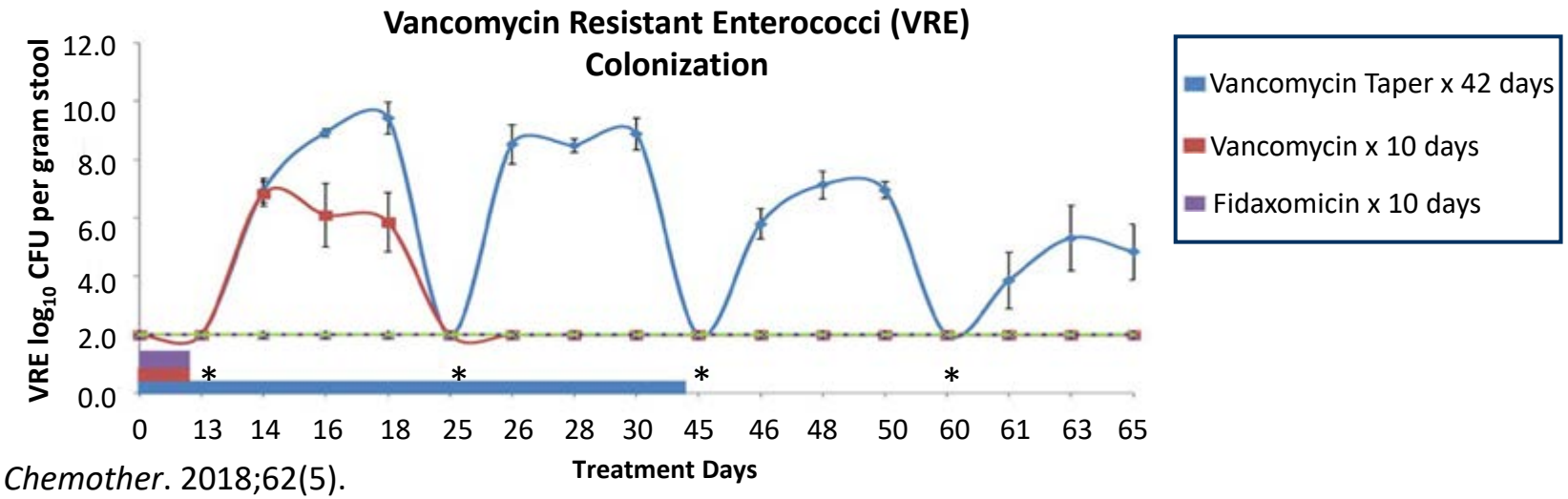
Gentry CA, Giancola SE, Thind S, Kurdgelashvili G, Skrepnek GH, Williams RJ. *Open Forum Infect Dis*. 2017;4(4):ofx235.

Vancomycin Extended Taper Regimen



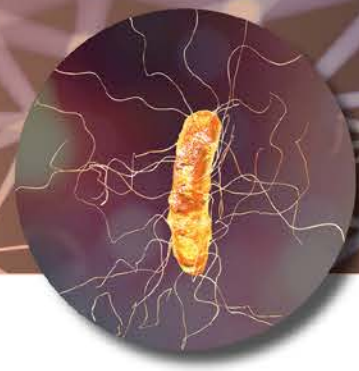
Continues to Disrupt the Microbiome and Allows for Overgrowth of Clostridium difficile (A) and Vancomycin-resistant Enterococci (VRE) (B)





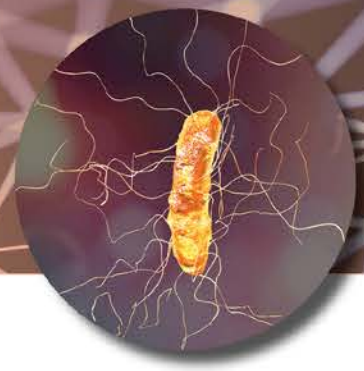
Tomas ME, Mana TSC, Wilson BM, et al. *Antimicrob Agents Chemother*. 2018;62(5).

Vancomycin has Versatility



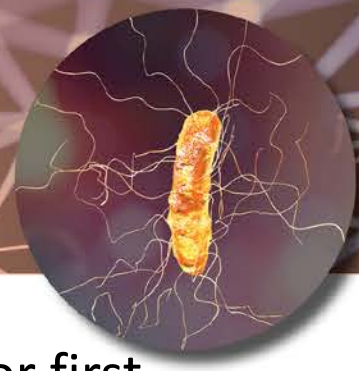
1. Capsules that can be opened
2. Liquid formulation upon compounding the IV form
3. Varying doses from 125-500 mg
4. Used orally and can be infused rectally for ileus
5. Useful in severe AND complicated CDI

The optimal, cost-effective CDI treatment strategy for severe CDI is:



1. Fidaxomicin
2. Metronidazole
3. Vancomycin
4. FMT
5. None of the above

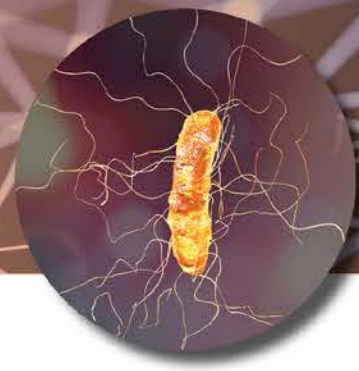
Cost-effectiveness of Treatment Regimens for CDI: An Evaluation of the 2018 IDSA Guidelines



- Use of fidaxomicin for non-severe initial CDI, vancomycin for severe CDI, fidaxomicin for first recurrence, and fecal microbiota transplantation (FMT) for subsequent recurrence (strategy 44) cost an additional $478 for 0.009 QALYs gained per CDI patient, resulting in an ICER of $31,751 per QALY, below the willingness-to-pay threshold of $100,000/QALY
- Metronidazole is suboptimal for non-severe CDI as it is less beneficial than alternative strategies
- The optimal, cost-effective CDI treatment strategy is:
  - Fidaxomicin for non-severe CDI
  - Vancomycin for severe CDI
  - Fidaxomicin for first recurrence
  - FMT for subsequent recurrence
- The most effective treatments, with highest cure rates, are also cost-effective due to averted mortality, utility loss, and costs of rehospitalization and/or further treatments for recurrent CDI

Rajasingham R, Enns EA, Khoruts A, Vaughn BP. *Clin Infect Dis*. 2020;70(5):754-762.

Diagnostic Stewardship



Ordering the correct diagnostic tests

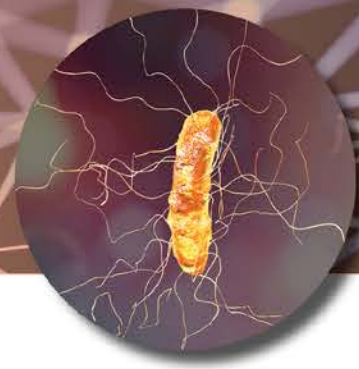
- Colonization occurs asymptomatically and should not be treated (no difference in subsequent risk of symptomatic disease and may increase shedding/spread)
- Testing, primarily via PCR, has gotten much more sensitive and will readily pick up asymptomatic colonization
- Thus, important only to test patients with appropriate symptoms

Reducing inappropriate testing

- EMR- or stewardship personnel-based approval of testing in patients that are on laxatives, received oral contrast for imaging studies, or just started tube feeds (diarrhea is expected in these settings)
- Laboratory-based rejection of formed specimens

Bagdasarian N, Rao K, Malani PN. *JAMA*. 2015;313(4):398-408.

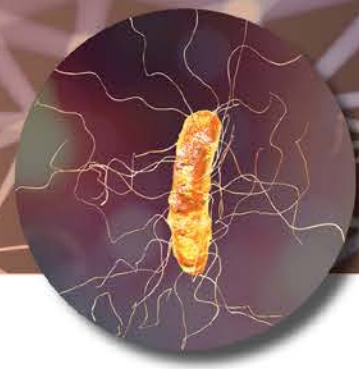
Who should be tested?
Symptomatic Patients



- Diarrhea
  - ≥ 3 loose BMs/24 hours
  - No alternate explanation
  - Ileus + leukocytosis
  - Colitis on imaging
  - Acute abdomen with bowel wall thickening
  - Toxic megacolon
  - Pseudomembranes on endoscopy
- Without diarrhea (but suspect CDI despite no stools / diarrhea)
  - testing via PCR from a rectal swab

Bagdasarian N, Rao K, Malani PN. *JAMA*. 2015;313(4):398-408.

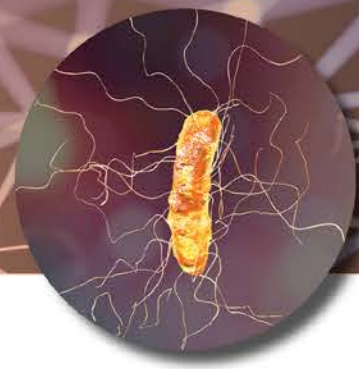
Who should not be tested?



- Asymptomatic Carriers
  - Asymptomatic carriage of CDI affects 10 to 52% of defined populations
  - Asymptomatic fecal shedding of CDI may be transient
- Colonization
  - 60-70% of infants
  - 3% of healthy adults
  - 20-50% of adults in long-term acute care (LTACs)
  - Treatment not recommended
    - Doesn't decrease risk of CDI
    - Doesn't affect epidemiology or spread

Bagdasarian N, Rao K, Malani PN. *JAMA*. 2015;313(4):398-408.

Who should not be tested?



- While on therapy
- Immediately following therapy (prolonged shedding)
  - Up to 56% of patients 6 weeks after completion of therapy
  - 10-20% become long-term carriers
  - Repeat testing for “cure” and retreatment not recommended during this period unless accompanied by symptoms

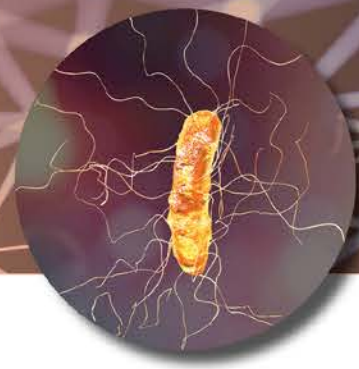
Bagdasarian N, Rao K, Malani PN. *JAMA*. 2015;313(4):398-408.

Who should not be tested?

- Post-infectious IBS
- Long-term asymptomatic colonization following CDI occurs
  - Following treatment and recovery, transient IBS symptoms in 35%
  - Rarely persists as post-infectious IBS
  - Difficult to distinguish from recurrent CDI

Bagdasarian N, Rao K, Malani PN. *JAMA*. 2015;313(4):398-408.

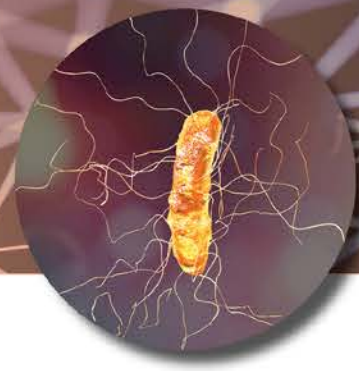
Antibiotics that Increase CDI risk



Drug	Kills Firmicutes	Kills Bacteroidetes	Commonly Used
Ampicillin-sulbactam	Yes	Yes	Medium
Cefepime	Yes	No	Yes
Ceftriaxone	Yes	No	Yes
Carbapenems	Yes	Yes	Yes and increasing
Piperacillin-tazobactam	Yes	Yes	Yes
Clindamycin	Yes	Yes	No
Fluoroquinolones	Yes	Yes	Not as much

Garey K, Rao KA. Live Webinar presented October 24, 2018. https://ashpadvantagemedia.com/cdiff/files/Cdiff%20-%20Pre-MCM%20Webinar%20Handout.pdf

Which antibiotics are risk factors?



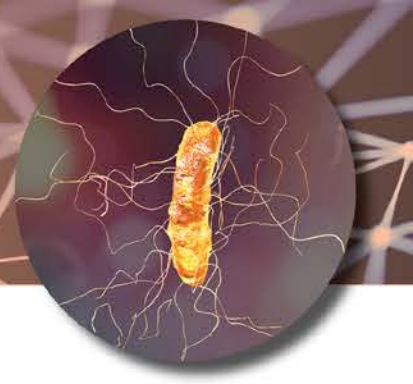
30-day risk of CDI among 97,130 hospitalized patients. 1,481 of whom developed CDI.

Individual Antibiotic	OR (ABX Received (Y/N))	*P*-Value	Antibiotic Use
Ampicillin/Sulbactam	1.640	0.012	1.7%
Cefepime	1.673	< 0.001	16.1%
Ceftriaxone	1.464	< 0.001	21.8%
Ertapenem	1.864	< 0.001	3.6%
Imipenem	2.077	< 0.001	3.2%
Meropenem	1.335	0.020	2.8%
Piperacillin/Tazobactam	1.655	< 0.001	16.6%
Age	1.009	< 0.001	N/A
Proton Pump Inhibitor (Y/N)	1.375	< 0.001	N/A
Charlson Comorbidity Index	1.208	< 0.001	N/A

OR – odds ratio; ABX - antibiotic

Davis ML, Sparrow HG, Ikwuagwu JO, Musick WL, Garey KW, Perez KK. *Clin Microbiol Infect*. 2018;24(11):1190-1194.

PPIs and High-risk Antibiotics



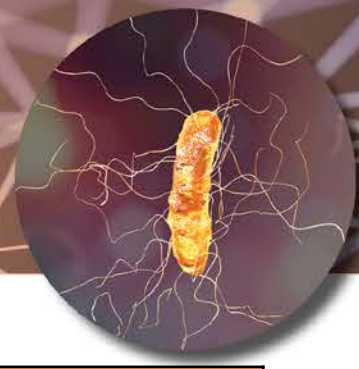
Risk of CDI increased from 0.14% to 6.21% in comorbid patients who received high risk antibiotics and a PPI

Received High-Risk Antibiotic?	**No**						**Yes**					
Charlson Comorbidity Index	0		1		≥2		0		1		≥2	
Received PPI?	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
CDI Incidence (%)	0.14	0.58	0.82	0.70	2.31	1.84	0.73	1.33	1.30	2.59	4.04	6.21

Independent of receipt of high-risk antibiotic, more severe Charlson comorbidity index increases CDI risk

Davis ML, Sparrow HG, Ikwuagwu JO, Musick WL, Garey KW, Perez KK. *Clin Microbiol Infect*. 2018;24(11):1190-1194.

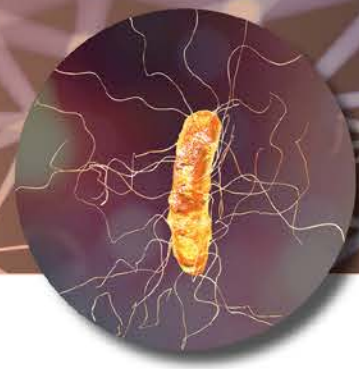
Antibiotic Stewardship Approaches to Protect the Microbiome



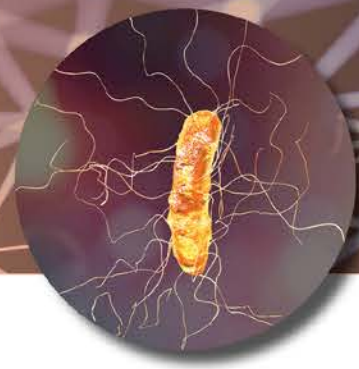
Stewardship Intervention	Will it work to decrease CDI rates?	Caveat
Antibiotic time-out	Yes	Get an initial microbiome hit that persists but perhaps faster restoration
Rapid diagnostics	Yes	Especially if get rid of early, broad-spectrum antibiotic use
IV to PO conversion	Maybe	Only if switch to oral that doesn't damage microbiome (aka, no cipro or amox-clav, please)
Formulary restriction	Yes	Most evidence supports this approach
Anything that slows down carbapenem use	Yes	No caveats here, this is always a good idea when you can do it!!

McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. *Clin Infect Dis*. 2018; 66:987-94.

Summary



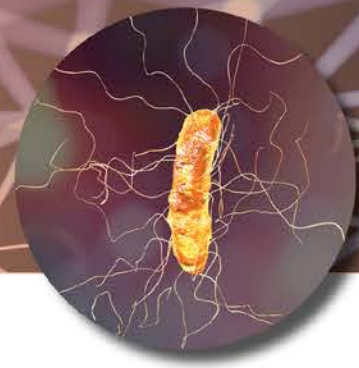
- Recurrent CDI is costly
- New IDSA/SHEA guidelines de-emphasize use of metronidazole and increased use of vancomycin and fidaxomicin
- Fidaxomicin has a higher cost than vancomycin but is associated with lower risks of recurrence
- Diagnostic stewardship is important to reduce inappropriate testing
- Antimicrobial stewardship strategies have been shown to be useful
- Despite our best stewardship efforts, patients are still going to get CDI and many will get recurrent CDI



CDI Case Scenarios and Best Practice Recommendations

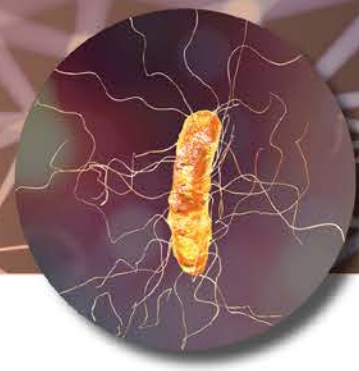
Vanita Pindolia, PharmD, MBA
Vice President
Ambulatory Clinical Pharmacy Programs_PCM
Henry Ford Health System (HFHS)
Health Alliance Plans (HAP)

Patient Case: CDI primary infection



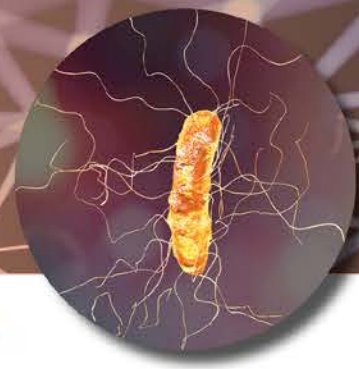
- 71-year-old female patient presents with diarrhea (watery stools) over the past 3 weeks at a frequency of 4-6 times a day. She is dehydrated.
- She has tried over-the-counter medications and the BRAT (bananas, rice, applesauce, and toast) diet. However, the diarrhea remains profuse.
- Three weeks ago, she took clindamycin as prophylaxis for a dental procedure.

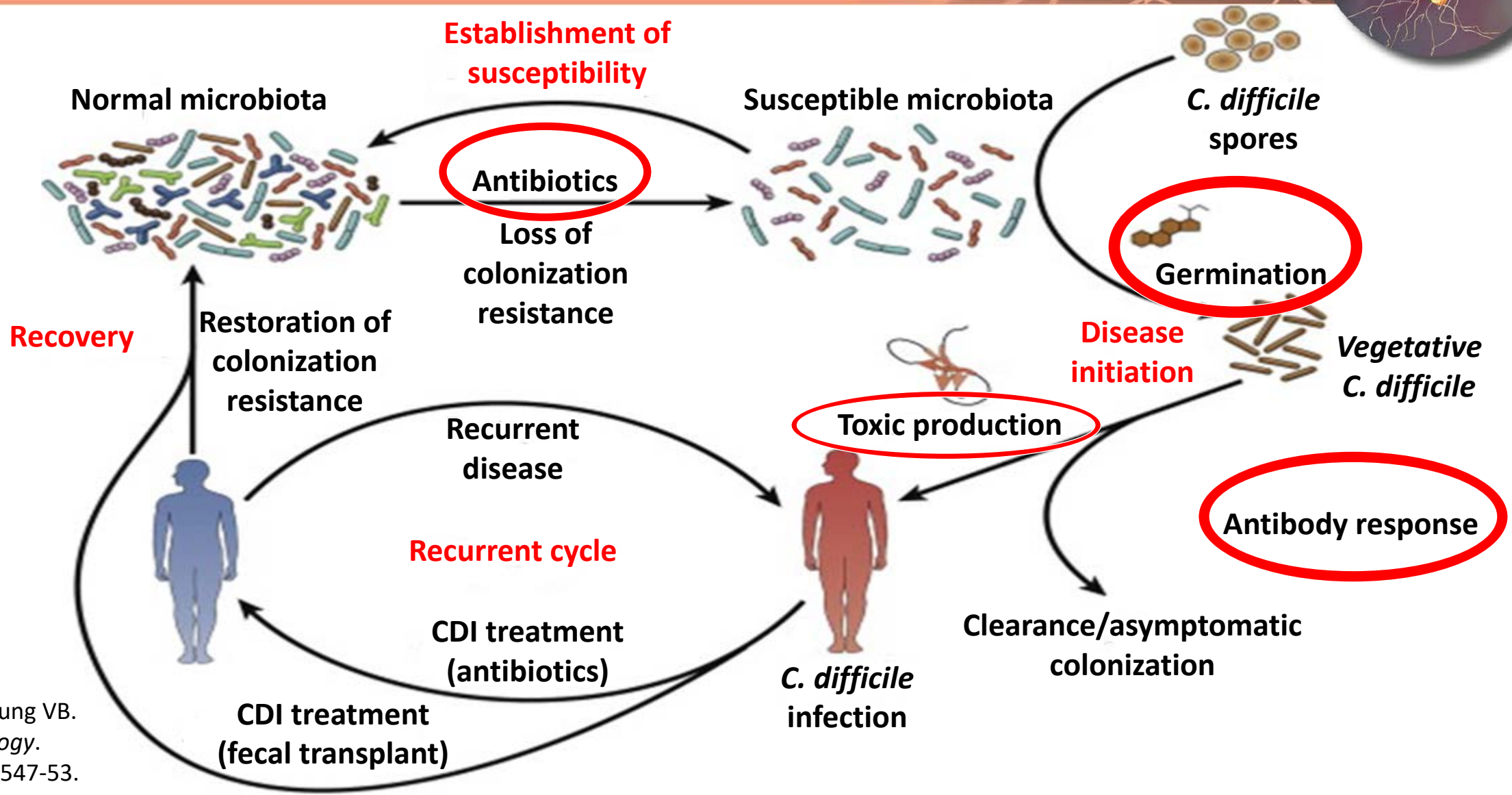
Risk Factors



- Current or recent antibiotic use (highest risk within 3 months of exposure)
- Advanced age (65 or older)
- Gastric acid suppression
- Severe comorbid diseases (Especially IBD and immunosuppression such as BMT)
- Prior history of CDI
- Hospitalization within 30 days

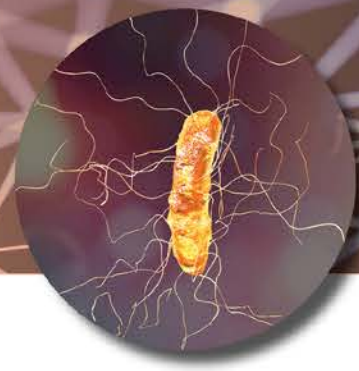
Cycle of CDI





Britton RA, Young VB. *Gastroenterology*. 2014;146(6):1547-53.

Antibiotics that Increase CDI Risk



Drug	Commonly used
Ampicillin-sulbactam	Medium
Cefepime	Yes
Ceftriaxone	Yes
Carbapenems	Yes and increasing
Piperacillin-tazobactam	Yes
Clindamycin	No
Fluoroquinolones	Not as much

Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, Mcdonald LC. *Clin Infect Dis*. 2018;66(7):1004-1012.

IDSA/SHEA CDI Guidelines 2018

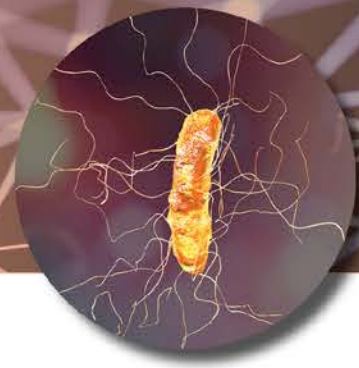
Clinical Definition	Supportive Clinical Data	Recommended Treatment [a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, • FDX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

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a] All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances. [b] The criteria proposed for defining severe or fulminant Clostridium difficile infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

Mcdonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Patient Case



Tests ordered?

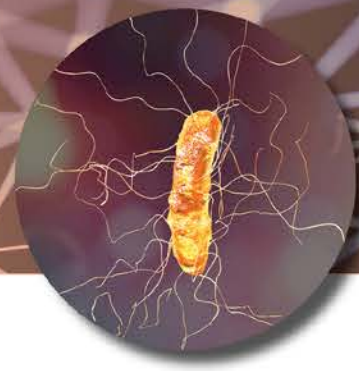
Treatment?

Follow up?

Patient Case 2: Recurrent CDI

- A 72-year-old man received a course of vancomycin after testing positive for *C. difficile*.
- Vancomycin dose: 125 mg 4 times a day for 10 days
- His clinical symptoms resolved 10 weeks ago, but he currently presents with 10-12 watery stools each day for the past 5 days.
- His Bristol score is 7
- His primary care physician referred him to an ID or GI specialist.

Recommendation for Recurrence of CDI in Adults

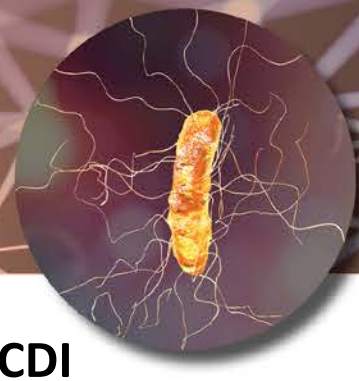


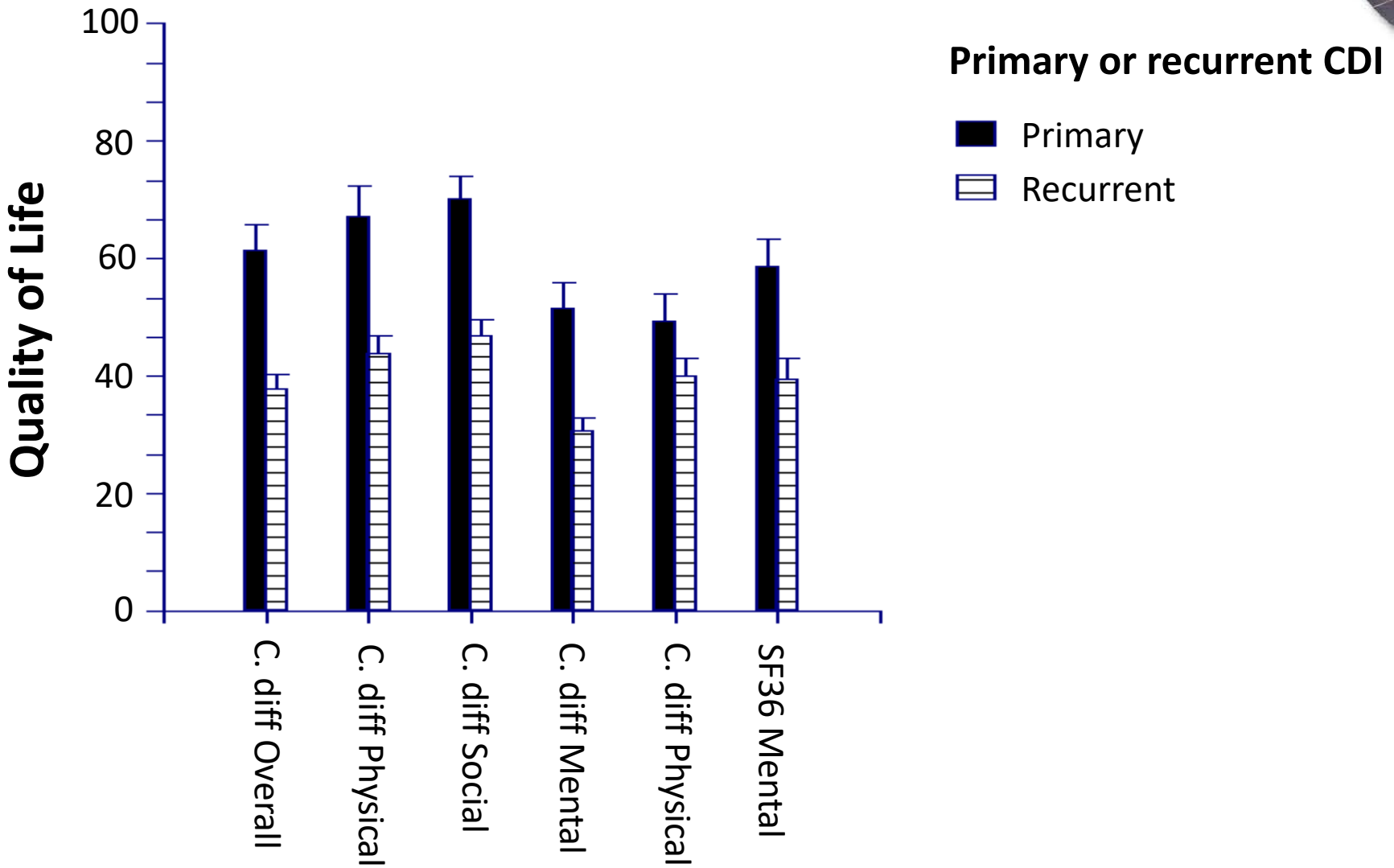
Clinical definition	Recommended treatment
First recurrence	• VAN SD if metronidazole was used for the first episode, OR • Prolonged tapered and pulsed VAN if VAN SD was used for first regimen, OR • FDX SD if VAN was used for the initial episode
Second or subsequent recurrences	• VAN in a tapered or pulsed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

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

McDonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis.* 2018; 66(7):987-94.

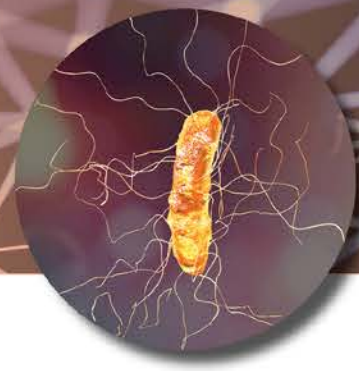
Quality of Life (QOL) Goes Down Considerably with Recurrent CDI





Garey KW, Aitken SL, Gschwind L, et al. *J Clin Gastroenterol*. 2016;50(8):631-7.

Impact of Recurrent CDI

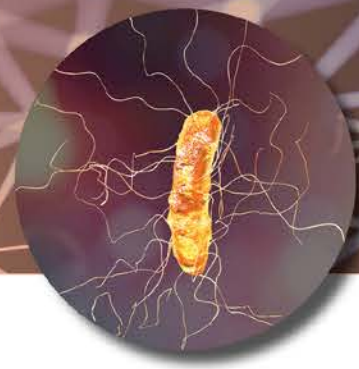


Amount of worry on 5-point scale; percent reporting 4 or 5

Worry	Amount of Worry
Unable to sleep	32%
Fear of leaving home	33%
Felt dirty	34%
Was unable/unwilling to eat	34%
Worry about being contagious	37%
Felt like a prisoner in my house	38%
Fear of getting sick again	56%

Weaver FM, Trick WE, Evans CT, et al. *Infect Control Hosp Epidemiol*. 2017;38(11):1351-1357.

First Word: FMT is Effective



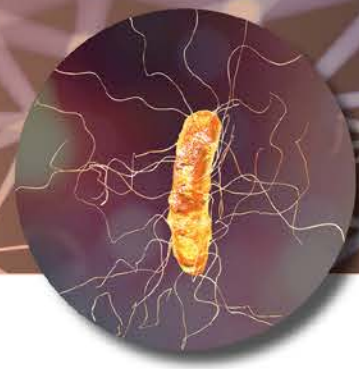
- 92% of patients had resolution, 89% after 1 treatment and 5% after retreatment
- 4% had a relapse; 87.5% had resolution with retreatment
- No serious adverse events

Not FDA-approved

A consideration for recurrent CDI refractory to medical therapy (Only FDA approved indication)

Gough E, Shaikh H, Manges AR. *Clin Infect Dis*. 2011;53(10):994-1002.

Does FMT Really Work That Well?



- Prior studies used non-standard comparators (2 weeks of vancomycin, chronic recurrence)
- No better than vancomycin taper in recent RCT on acute CDI patients, although enema only
- The authors on difference with prior RCTs not using a placebo control arm (emphasis mine)…

"Without a control arm in either trial, it is not known what proportion of patients would have been symptom-free had their antibiotics been simply discontinued."

Hota SS, Sales V, Tomlinson G, et al. *Clin Infect Dis*. 2017;64(3):265-271.

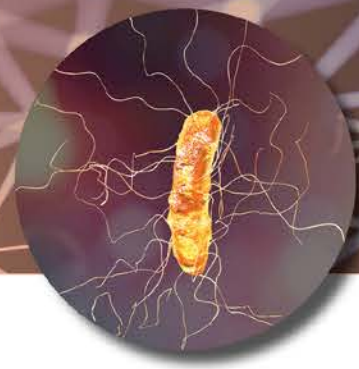
Recreated from: Gary K, Rao AK. Best practice update on Clostridium difficile Infection (CDI): Focus on Prevention, Treatment and Recurrence. Presented as live webinar October 24, 2018. https://ashpadvantagemedia.com/cdiff/files/Cdiff%20-%20Pre-MCM%20Webinar%20Handout.pdf

FMT

- Who benefits the most? Unknown
- Long term safety? Unknown – Microbiota associated with diabetes mellitus, obesity, cancer, atopic/autoimmune disorders
- Safe in immunocompromised? Possibly – Concern in patients with IBD raised
- Effective / safe for primary / severe CDI? – Yet to be established
- Optimal route, preparation, and stool characteristics unknown

Recreated from: Gary K, Rao AK. Best practice update on Clostridium difficile Infection (CDI): Focus on Prevention, Treatment and Recurrence. Presented as live webinar October 24, 2018. https://ashpadvantagemedia.com/cdiff/files/Cdiff%20-%20Pre-MCM%20Webinar%20Handout.pdf

Bezlotoxumab for Prevention of Recurrent CDI



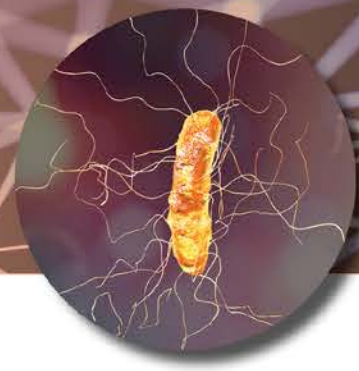
- Among participants receiving antibiotic treatment for primary or recurrent CDI, bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo and had a safety profile similar to that of placebo
- The addition of actoxumab did not improve efficacy

Bezlotoxumab (BEZ) anti-toxin B

- Monoclonal antibody
- IV infusion
- **FDA approved to prevent CDI reoccurrence**

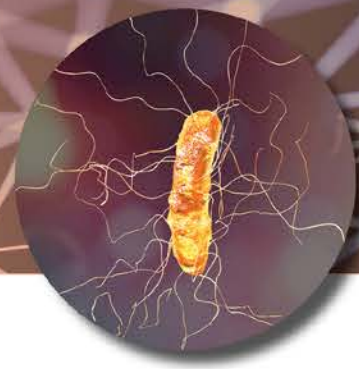
Wilcox MH, Gerding DN, Poxton IR, et al. *N Engl J Med*. 2017;376(4):305-317.

Patient Case: Tests and Treatment



- A 72-year-old man received a course of vancomycin after testing positive for CDI
- Vancomycin dose: 125 mg 4 times a day for 10 days
- His clinical symptoms resolved 10 weeks ago, but he currently presents with 10-12 watery stools each day for the past 5 days (Bristol score = 7)
- His primary care physician referred him to an ID or GI specialist
- How should he be treated?
- Is he eligible for FMT?
  - Why?
  - Why not? What are the alternative options?
- Tests ordered?
- Treatment?
- Follow up?

Patient Case 3: CDI or IBS?



- A 70-year-old woman presents with gaseous distension and diarrhea (watery stools) over the past 3 weeks at a frequency of 5-6 times a day.
- Prior to this, she was treated for CDI on 2 separate occasions in the prior 3 months.
- She has tried over-the-counter medications and the BRAT (bananas, rice, applesauce, and toast) diet. However, the diarrhea remains profuse.
- Her symptoms include cramping, spasm, bloating, nausea, fatigue, post-prandial nausea and bloating that suggest IBS.

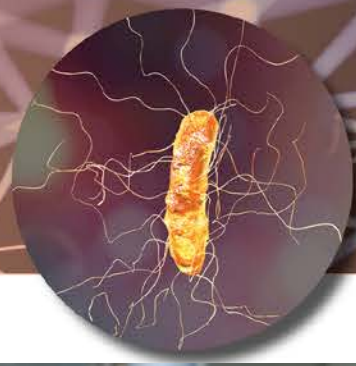
Patient Case

IBS possibility?

- Does this only happen when she eats?
- Does fasting help?
- What about at night?
- Is it only with certain foods?
- Did CDI treatment help during the prior episodes?

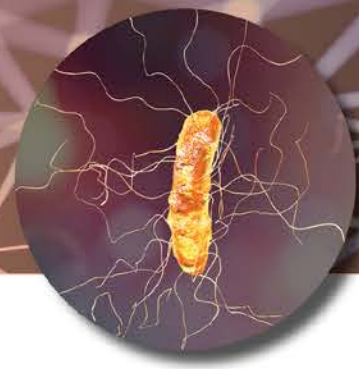
Only if these are addressed and still suggestive of CDI > IBS, and the testing is positive for CDI, should the provider move on to CDI specific treatment.

Differential Diagnosis



- **Antibiotic associated diarrhea**
- *Klebsiella oxytoca*
- **Post-infectious IBS**
- **IBD**
- Celiac
- **Ischemic colitis**
- Collagenous colitis
- CMV colitis
- Routine enteric pathogens
- Parasitic pathogens
  - Right risk factors or exposures (Giardia/ Cryptosporidium)
- Carcinoid syndrome / other hypermotility states

How to Test: Not all stools

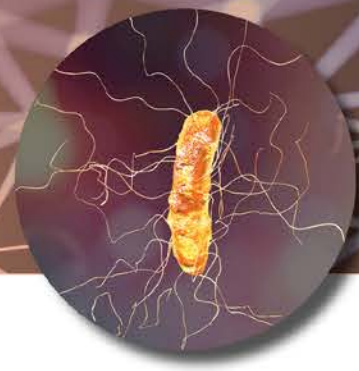


Some labs only test diarrheal stool

The Brecher Guidelines	
Observation	**Response**
Look at the stool specimen	If it ain't loose, it's of no use
Put a thin lab grade stick in the specimen	If the stick stands, the test is banned If the stick falls, test them all

Brecher SM, Novak-weekley SM, Nagy E. *Clin Infect Dis*. 2013;57(8):1175-81.

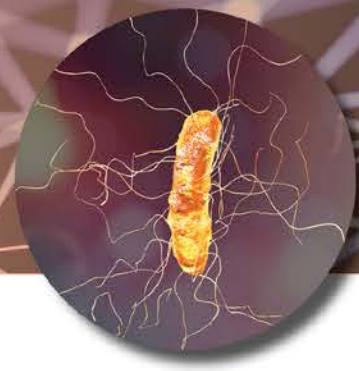
CDI and IBS/IBD: A Complicated Relationship



- CDI can be associated in patients that have IBD [1]
- CDI can mimic a flare
- CDI can trigger a flare
- Asymptomatic carriage is common (20-50%)[2]

1. D'aoust J, Battat R, Bessissow T. World J Gastroenterol. 2017;23(27):4986-5003.
2. Berg AM, Kelly CP, Farraye FA. *Inflamm Bowel Dis*. 2013;19(1):194-204.

Post Infection IBS (PI-IBS)



- New-onset IBS is common after CDI (PI-IBS) [1, 2]
- Patients with CDI have a high risk for developing post-infectious IBS, especially those patient that had a longer duration of CDI, anxiety and higher BMI[1]

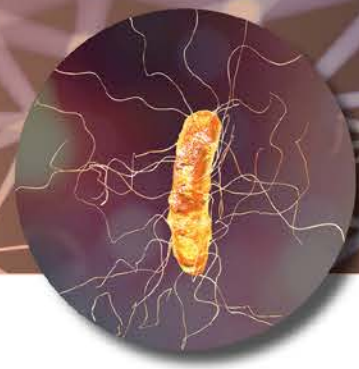
1. Wadhwa A, Al nahhas MF, Dierkhising RA, et al. *Aliment Pharmacol Ther*. 2016;44(6):576-82.
2. Dayananda P, Wilcox MH. *Curr Opin Gastroenterol.* 2019;35(1):1-5

Patient Case

Treatment (depends on prior therapy)

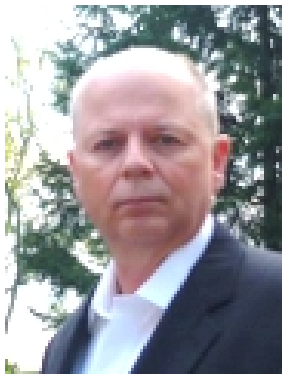
- FMT
- Vancomycin taper
- Fidaxomicin +/- Bezlotoxumab
- Only consider the more experimental treatments in truly refractory patients, which she is not.

Summary



- There are several risk factors that predispose patients to CDI
- Certain antibiotics increase the risk for CDI
- Recurrent CDI is a concern that contributes to increased health care costs
- Quality of life goes down considerably with recurrent CDI
- CDI and IBS can complicate diagnosis and treatment decisions
- Differential diagnosis is very important to an accurate diagnosis for CDI

Faculty Idea Exchange and Q&A Session



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Please go to www.impactedu.net/cpe
Enter code: **0731**

You will then need to log in or create an account ensuring your NABP and DOB information is entered and correct. Be sure to enter today's date, **July 31, 2020**, as the date of participation. You will be immediately notified if your submission has been accepted or if there are any issues. Once accepted, the record of your participation will appear in the CPE Monitor within 48 hours. **Credit must be uploaded to CPE Monitor within 30 days.**

Option 2: Print the 'Fax Evaluation Form' in the *Handouts* section and turn in the completed version via fax or email to the number or email address located at the top of the form. A certificate will be emailed to you within 3-4 weeks.
For Pharmacists: upon receipt of the completed evaluation form, you will receive an email within 3 weeks with a link and directions to submit your credit to the NABP CPE Monitor Service. **Pharmacists have up to 30 days to complete the evaluation and claim credit for participation so that information can be submitted to CPE Monitor as required.**