Spores and more:
Updates in *Clostridioides difficile*

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Disclosure

The presenter does not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias this presentation

Objectives

At the completion of this activity, pharmacists will be able to:

1. Discuss current therapeutic options for *Clostridioides difficile* infection (CDI)
2. Review the medical evidence supporting therapeutic options for CDI
3. Analyze preventative strategies for reducing recurrent CDI

At the completion of this activity, pharmacy technicians will be able to:

1. Identify therapies used to treat *Clostridioides difficile* infection (CDI)
2. Review the medical evidence supporting therapeutic options for CDI
3. Analyze preventative strategies for reducing recurrent CDI

Background

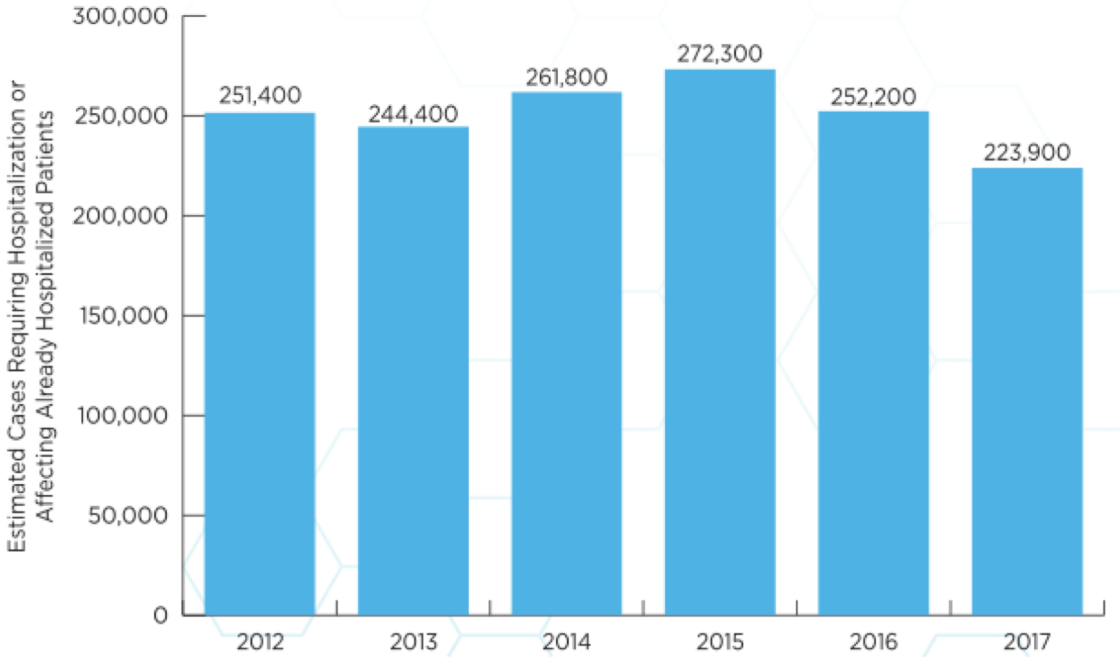
Clostridioides difficile is also known as *C. difficile, C. diff,* CDI (*Clostridioides difficile* infection), and CDAD (*Clostridioides difficile*-associated disease)

C. diff is a **Urgent Threat** to human health according to the Antibiotic Resistance Threats in the United States, 2019 report

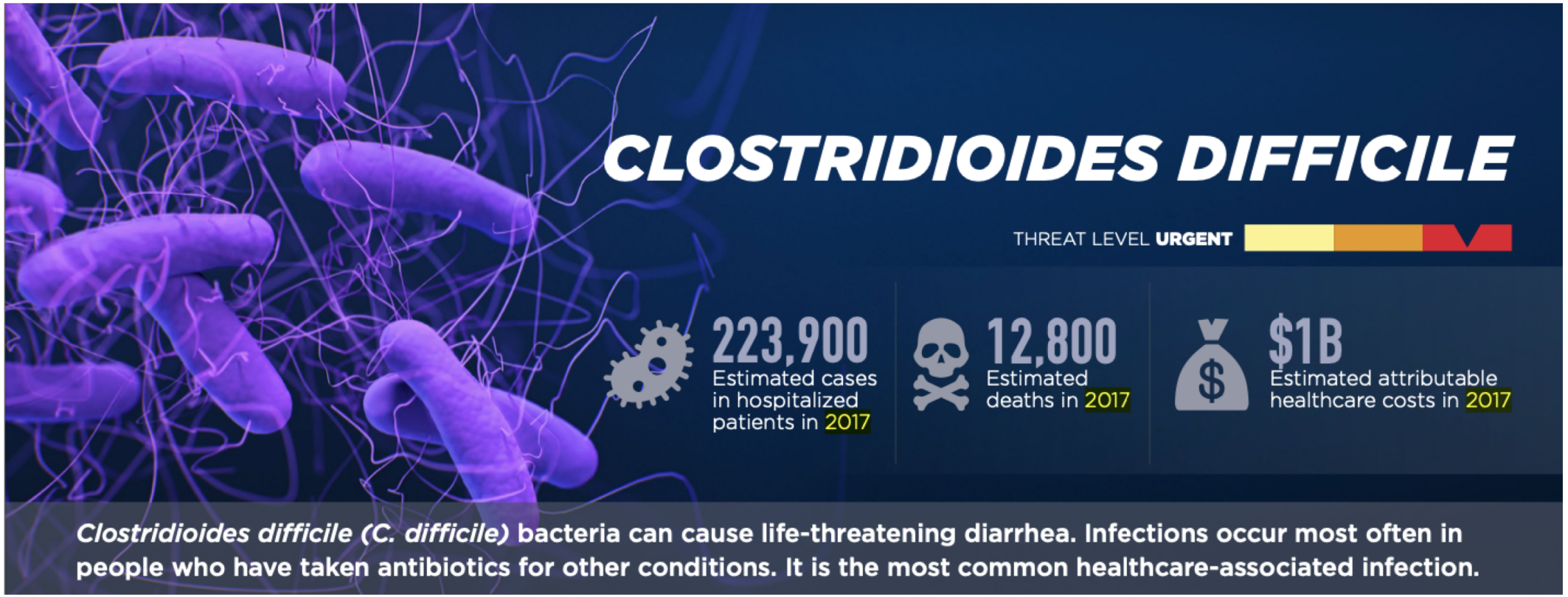
There were an estimated 223,900 cases of CDI in hospitalized patients and 12,800 deaths in the United States in 2017

CASES OVER TIME

Continued appropriate infection control, antibiotic use, and diagnostic testing are important to maintain decreases in *C. difficile* cases.



Antibiotic Resistance Threats in the United States, 2019



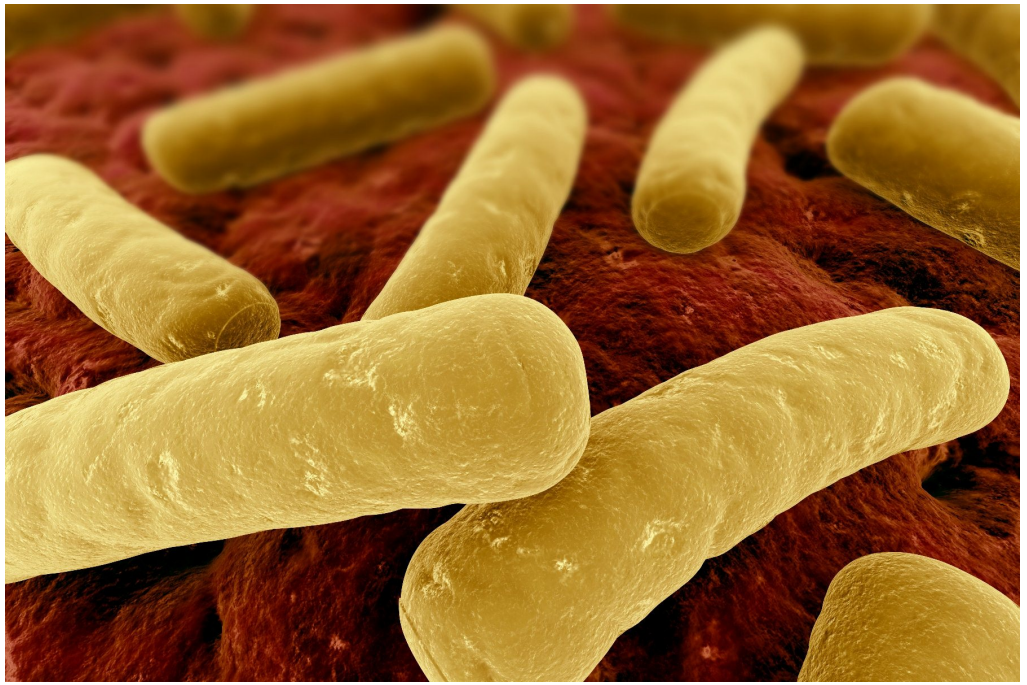
Etiology

Spore-forming, Gram-positive anaerobic bacillus

- Produces two exotoxins
  - Toxin A (TcdA)
  - Toxin B (TcdB2)
- Produces an enzyme called glutamate dehydrogenase (GDH)
  - Produced by both toxigenic and nontoxigenic strains of *C. difficile*

Hypervirulent strain

- NAP1/BI/027 strain AKA 027 ribotype



[Image]: http://www.bioquell.asia/interface/assets/images/content/NAP1_027_Clostridium_difficile_27143602_1.jpg
Cohen SH, et al. Infect Control Hosp Epidemiol. 2010 May;31(5):431-55.
Kelly CR, et aL. *Am J Gastroenterol* 2021;116:1124–1147.

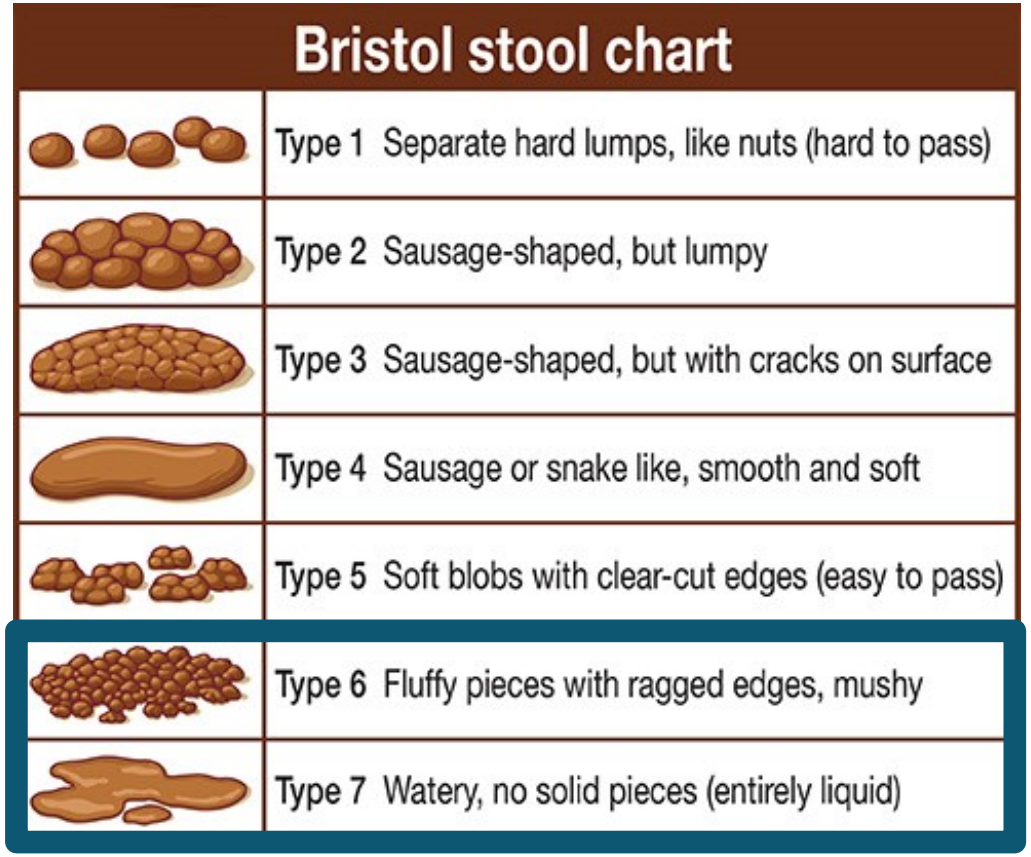
Signs and Symptoms

Definition of CDI: ≥3 unexplained and new-onset unformed stools in <24 consecutive hours plus

- Stool test positive for *C. difficile* toxins
- Toxigenic *C. difficile*
- Colonoscopic or histopathologic findings revealing pseudomembranous colitis

Symptoms caused by exotoxins: Toxin A and Toxin B

- NAP1/BI/027 strain over expresses these toxins



COHEN SH, ET AL. INFECT CONTROL HOSP EPIDEMIOL. 2010 MAY;31(5):431-55.
IMAGE [INTERNET] HTTPS://WWW.WEBMD.BOOTS.COM/DIGESTIVE-DISORDERS/POO-CHART-BRISTOL-STOOL-SCALE

IDSA/SHEA 2017 Severity Classification		
Non-severe	**Severe**	**Fulminant**
WBC ≤15,000 cells/mL	WBC ≥15,000 cells/mL	WBC ≥15,000 cells/mL
SCr <1.5 mg/dL	SCr ≥1.5 mg/dL	SCr >1.5 mg/dL
		Hypotension or shock
		Ileus
		Megacolon

Additional signs and symptoms		
Non-severe	**Severe**	**Fulminant**
	Abdominal tenderness	ICU admission
	Albumin <3g/dL	Fever ≥38.5°C
		Abdominal distension
		Altered mental status
		WBC ≥35,000 cells/mm3 or ≤2,000 cells/mm3
		Lactate >2.2mmol/L
		End organ failure

CLIFFORD MCDONALD L, ET AL. CID 2018:66 1 APRIL 2018
COHEN SH, ET AL. INFECT CONTROL HOSP EPIDEMIOL. 2010 MAY;31(5):431-55.

CDI Testing Options

Test	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Distinguishes colonization from active infection
Toxigenic culture	94	99	-	-	No
Cell cytotoxicity neutralization assay (CCNA)	93	98	-	-	Yes
Glutamate dehydrogenase (GDH)	94-96	90-96	34-38	100	No
Nucleic acid amplification testing (NAAT) e.g.: polymerase chain reaction (PCR) or loop-mediated isothermal amplification assay (LAMP)	95-96	94-98	46	100	No
Enzyme immunoassay (EIA) for toxins A and B	57-83	99	69-81	99	Yes

KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.

Question 1) Polling

What testing does your institution use for CDI?

A) Nucleic acid amplification testing (NAAT)/Polymerase chain reaction (PCR)

B) Glutamate dehydrogenase (GDH)

C) Enzyme immunoassay (EIA) for toxins A and B

D) A combination of the above

E) Don’t know/not sure

What testing does your institution use for CDI?

Nucleic acid amplification testing (NAAT)/Polymerase chain reaction (PCR)

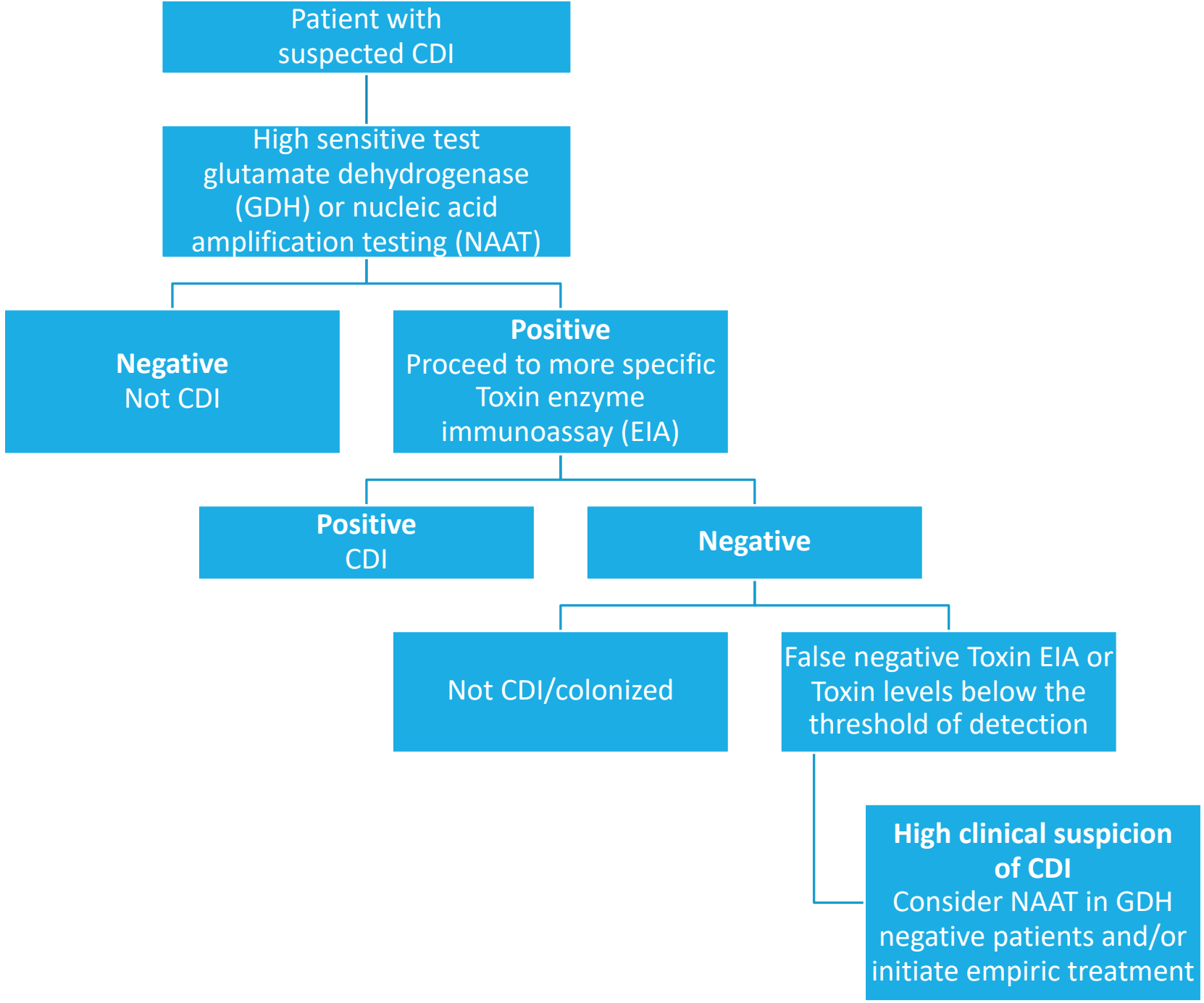
Glutamate dehydrogenase (GDH)

Enzyme immunoassay (EIA) for toxins A and B

A combination of the above

Don’t know/not sure

Testing



KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.

Question 2) Assessment

MJ is a 72 year old white female with a PMH of HTN and GERD on pantoprazole presenting to urgent care for an abscess on her thigh. Patient has a reported penicillin allergy of hives. The abscess was drained and the patient was prescribed clindamycin 300 mg PO TID x 7 days. Patient began having diarrhea on day 5 of clindamycin, which did not resolve after therapy was completed. She presents to the ED with complaints of 5 loose, watery, foul smelling bowel movements in the last 24 hours. The CDI **PCR returned positive for the detection of *C. difficile*, EIA was positive for Toxin B**.

Home meds include:

- Lisinopril 10 mg PO daily
- Pantoprazole 40 mg PO daily

Question 2) Assessment

What risk factors, if any, does MJ have for experiencing recurrent CDI?

I. Age

II. Pantoprazole use

III. Gender

IV. None

A. I, II and III

B. I and II only

C. II and III only

D. IV only

What risk factors, if any, does MJ have for experiencing recurrent CDI?

Age, pantoprazole use and gender

Age and pantoprazole use

Pantoprazole use and gender

None

Question 2) Assessment

What risk factors, if any, does MJ have for experiencing recurrent CDI?

I. Age

II. Pantoprazole use

III. Gender

IV. None

A. I, II and III

B. I and II only

C. II and III only

D. IV only

Risk Factors

Initial CDI

- Age ≥ 65 years
- Female gender
- Duration of hospitalization
- Exposure to antimicrobial agents
- Chemotherapy
- Gastrointestinal surgery
- Manipulation of the GI tract

Community-acquired CDI

- Exposure to antimicrobial agents
- White race
- Cardiac disease
- Chronic kidney disease
- Inflammatory bowel disease

Recurrent CDI

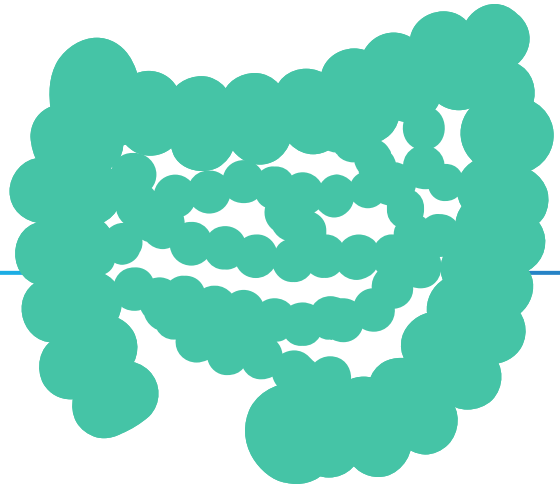
- Age ≥65 years
- Non–C. difficile antibiotics use
- Lower endogenous anti–toxin A and B antibody levels
- Prior CDI episodes
- CDI caused by a BI/NAP1/027 strain
- Healthcare-associated CDI
- Prior hospitalization in the last 3 months
- Proton pump inhibitors started during/after CDI diagnosis

COHEN SH, ET AL. INFECT CONTROL HOSP EPIDEMIOL. 2010 MAY;31(5):431-55.; YANG Z, ET AL. INFECT IMMUN. 2015 FEB;83(2):822-31.
GUPTA SB, ET AL. CLIN INFECT DIS. 2016 SEP 15;63(6):730-4. ; VAN PREHN J, ET AL. *CLIN MICROBIOL INFEC*T 2021;27:S1
KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.

Recurrence

Recurrence Rates

- 1 out of every 5 patients with a healthcare-associated CDI experienced a recurrence
- Up to 70% recurrence after 3rd episode



Mechanisms of Recurrence

- Persistence of *C. difficile* spores

- Diminished antibody response to *C. difficile toxins* A and B
- Persistent disturbance of intestinal flora

Yang Z, et al. Infect Immun. 2015 Feb;83(2):822-31.; van Nood E, et al. N Engl J Med. 2013 Jan 31;368(5):407-15.
Clostridium difficile Infection [Internet]. Atlanta, Georgia: Centers for Disease Control and Prevention; [updated 2016 Mar 1]
CDC Newsroom Releases [Internet]. Atlanta, Georgia: Centers for Disease Control and Prevention; [updated 2017 Mar 22]

Current Standard of Care for CDI

ORAL VANCOMYCIN (VAN)

- Mechanism of action
  - Inhibition of cell-wall biosynthesis
    - Bactericidal against the vegetative cell of *C. difficile*
- Commercially available as capsules, reconstituted oral solution, and powder for injection
- Tapered/pulsed vancomycin regimen example:
  - 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks
- Cost per day (Pricing from Lexicomp®)
  - 125 mg capsule: ~$415.00
  - Firvanq® oral solution (25 mg/mL): ~$18.00

FIDAXOMICIN (FDX)

- Trade name: Dificid®
- Mechanism of action
  - Inhibits RNA synthesis by binding to RNA polymerases
    - Bactericidal against *C. difficile in vitro*
- Narrow spectrum agent with limited activity against the gut microbiome
- Commercially available as tablets and oral suspension
- Cost per day (Pricing from Lexicomp®)
  - 200 mg tablet: ~$540.00
  - Oral suspension (40 mg/mL): ~$400.00

FIRVANQ® (VANCOMYCIN HYDROCHLORIDE FOR ORAL SOLUTION) [PACKAGE INSERT]. WILMINGTON, MA, AZURITY PHARMACEUTICALS, 12/2020; VANCOMYCIN (LEXI-DRUGS). LEXICOMP. WOLTERS KLUWER HEALTH, INC. RIVERWOODS, IL.; DIFICID® (FIDAXOMICIN) [PACKAGE INSERT]. WHITEHOUSE STATION, NJ, MERCK & CO., INC. S, 2/2021; DIFICID® (FIDAXOMICIN) (LEXI-DRUGS). LEXICOMP. WOLTERS KLUWER HEALTH, INC. RIVERWOODS, IL. JOHNSON S, ET AL. CID CIAB549, 14 JUNE 2021

Question 3) Polling

MJ is a 72 year old white female with a PMH of HTN and GERD on pantoprazole presenting with a chief complaint of CDI. This is her initial episode of CDI.

Pertinent labs and vitals:
WBC: 8,000 cells/mL
Serum creatinine: 1.1 mg/dL (baseline is 0.9 mg/dL)
Temperature: 99.1°F
Blood pressure:135/90 mmHg

What treatment do you initiate MJ on?

A) Metronidazole 500 mg PO q8h for 14 days

B) Vancomycin 125 mg PO q6h for 10 days

C) Fidaxomicin 200 mg PO BID x 10 days

D) Tapered/pulsed vancomycin regimen x 28 days

What treatment do you initiate MJ on?

Metronidazole 500 mg PO q8h for 14 days

Vancomycin 125 mg PO q6h for 10 days

Fidaxomicin 200 mg PO BID x 10 days

Tapered/pulsed vancomycin regimen x 28 days

2021 CDI Guidelines

Initial Episode	IDSA/SHEA 2017	IDSA/SHEA 2021	ACG 2021

Non-severe	• VAN 125 mg PO QID x 10 days, OR
	• FDX 200 mg PO BID x 10 days
	• Alternative: metronidazole 500 mg PO TID x 10 days
		• FDX 200 mg PO BID x 10 days
		• **Alternative:**
		  • VAN 125 mg PO QID x 10 days
		  • Metronidazole 500 mg PO TID x 10-14 days
			• VAN 125 mg PO QID x 10 days, OR
			• FDX 200 mg PO BID x 10 days
			• May consider metronidazole 500 mg PO TID x 10 days in low risk patients

Severe • WBC ≥15,000 cells/mL, or • Serum creatinine level >1.5 mg/dL	• VAN 125 mg PO QID x 10 days, OR • FDX 200 mg PO BID x 10 days		• VAN 125 mg PO QID x 10 days, OR • FDX 200 mg PO BID x 10 days
Fulminant • Hypotension or shock • Ileus • Megacolon	• VAN 500 mg PO/NG QID + metronidazole 500 mg IV q8hr • If ileus, consider adding rectal instillation of VAN	• VAN 500 mg PO/NG QID + metronidazole 500 mg IV q8hr • If ileus, consider adding rectal instillation of VAN	• VAN 500 mg PO/NG QID + metronidazole 500 mg IV q8hr • If ileus, consider adding rectal instillation of VAN

IDSA: Infectious Diseases Society of America (IDSA)/SHEA: Society for Healthcare Epidemiology of America
ACG: American College of Gastroenterology

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JOHNSON S, ET AL. CID CIAB549, 14 JUNE 2021
KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.

2021 CDI Guidelines

Episode	IDSA/SHEA 2017	IDSA/SHEA 2021	ACG 2021

First recurrence	• VAN 125 mg PO QID x 10 days (initial course of metronidazole), OR
	• Tapered/pulsed VAN PO regimen, OR
	• FDX 200 mg PO BID x 10 days if VAN was used for the initial episode
		• FDX 200 mg PO BID x 10 days, OR BID x 5 days followed by once every other day x 20 days
		• Alternative:
		  • Tapered/pulsed VAN PO regimen
		  • VAN 125 mg PO QID x 10 days
			• Suggest tapered/pulsed VAN PO regimen (initial course of fidaxomicin, vancomycin, or metronidazole)
			• Recommend FDX (initial course of VAN or metronidazole)

Second or subsequent recurrence	• Tapered/pulsed VAN PO regimen, OR
	• VAN 125 mg PO QID x 10 days followed by rifaximin 400 mg PO TID x 20 days, OR
	• FDX 200 mg PO BID x 10 days, OR
	• Fecal microbiota transplantation (FMT)
		• Same as first recurrence
		• Additional alternatives:
		  • VAN 125 mg PO QID x 10 days followed by rifaximin 400 mg PO TID x 20 days
		  • FMT (third or later recurrence)
			• Fecal microbiota transplantation

Adjunctive Bezlotoxumab	–	• Patients with a recurrent CDI episode within the last 6 months	• Patients at high risk of recurrence

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JOHNSON S, ET AL. CID CIAB549, 14 JUNE 2021
KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.

Fidaxomicin vs Vancomycin for Initial CDI Episode

Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Guidelines

- "**Comment:** This recommendation places a high value in the beneficial effects and safety of **fidaxomicin, but its implementation depends upon available resources.** Vancomycin remains an acceptable alternative."
- Fidaxomicin implementation considerations: "cost may be prohibitive without adequate insurance coverage"

American College of Gastroenterology 2021 Guidelines

- "…we believe that all 3 agents [metronidazole, vancomycin and fidaxomicin] have a role in first-line treatment of initial nonsevere CDI. **Vancomycin or fidaxomicin are appropriate initial treatments for most patients.** Although vancomycin is less expensive, lower recurrence rates of fidaxomicin imply overall similar cost-effectiveness for both agents. For lower-risk patients (younger outpatients with minimal comorbidities), particularly in cost-sensitive environments, metronidazole is an appropriate alternative."

JOHNSON S, ET AL. CID CIAB549, 14 JUNE 2021
KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.

IDSA/SHEA 2021: Favoring Fidaxomicin

Figure s1a. Forest plot, PICO 1: **Sustained response** of CDI (follow-up 4 weeks)

Study or Subgroup	Fidaxomicin Events	Fidaxomicin Total	Vancomycin Events	Vancomycin Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Louie	214	287	198	309	37.5%	1.16 [1.05, 1.30]	2011
Cornely	193	252	163	257	32.6%	1.21 [1.08, 1.36]	2012
Guery	124	177	106	179	18.0%	1.18 [1.01, 1.38]	2018
Mikamo	70	104	71	108	11.9%	1.02 [0.85, 1.24]	2018
Total (95% CI)		**820**		**853**	**100.0%**	**1.16 [1.09, 1.24]**	
Total events	601		538				

Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.54); I² = 0%

Test for overall effect: Z = 4.51 (P < 0.00001)

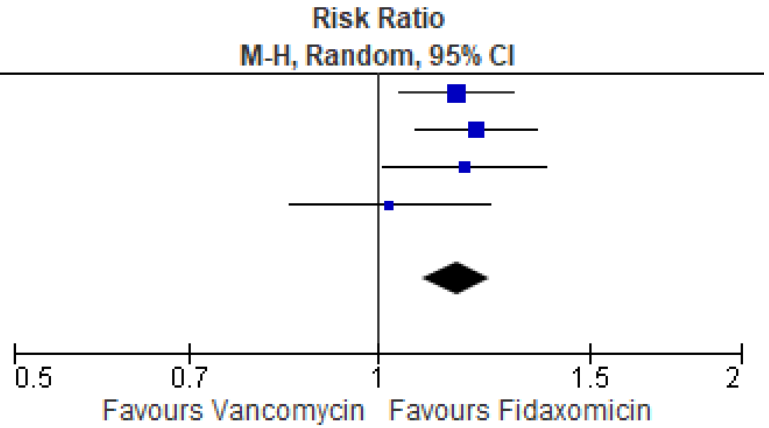
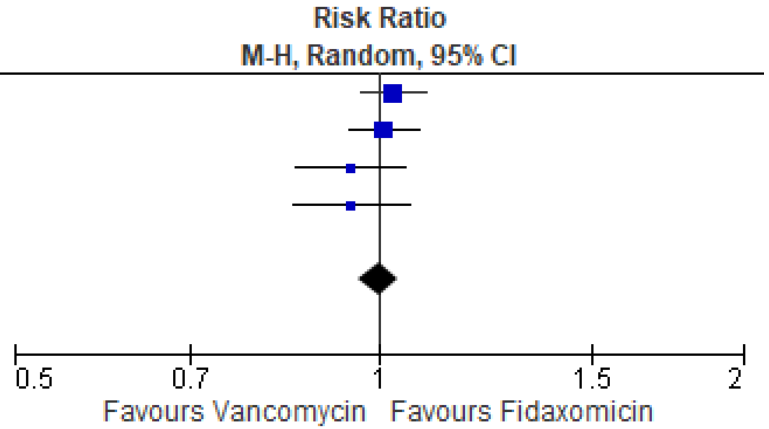


Figure s2. Forest plot, PICO 1: CDI initial clinical cure (after completion of SOC antibiotics)

Study or Subgroup	Fidaxomicin Events	Fidaxomicin Total	Vancomycin Events	Vancomycin Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Louie	253	287	265	309	39.2%	1.03 [0.97, 1.09]	2011
Cornely	221	252	223	257	34.3%	1.01 [0.95, 1.08]	2012
Guery	138	177	147	179	14.0%	0.95 [0.86, 1.05]	2018
Mikamo	87	104	95	108	12.5%	0.95 [0.85, 1.06]	2018
Total (95% CI)		**820**		**853**	**100.0%**	**1.00 [0.96, 1.04]**	
Total events	699		730				

Heterogeneity: Tau² = 0.00; Chi² = 2.66, df = 3 (P = 0.45); I² = 0%

Test for overall effect: Z = 0.04 (P = 0.97)



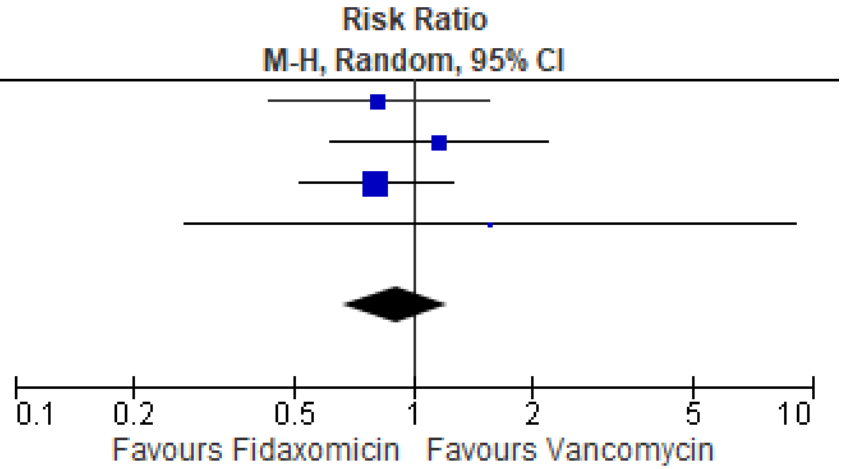
IDSA/SHEA 2021 Pooled Analysis

Figure s4. Forest plot, PICO 1: All-cause mortality (follow-up: 4 to 12 weeks)

Study or Subgroup	Fidaxomicin Events	Fidaxomicin Total	Vancomycin Events	Vancomycin Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Louie	16	300	21	323	23.9%	0.82 [0.44, 1.54]	2011
Cornely	20	264	17	260	24.5%	1.16 [0.62, 2.16]	2012
Guery	29	181	36	181	48.5%	0.81 [0.52, 1.26]	2018
Mikamo	3	104	2	108	3.0%	1.56 [0.27, 9.13]	2018
Total (95% CI)		**849**		**872**	**100.0%**	**0.90 [0.66, 1.23]**	
Total events	68		76				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.33$, df = 3 (P = 0.72); $I^2 = 0\%$

Test for overall effect: Z = 0.65 (P = 0.51)



ACG 2021

VANCOMYCIN OR FIDAXOMICIN

Mikamo H, *et al*. (2018)

Design

- Phase III, vancomycin-controlled, double-blind, parallel-group study of Japanese adults hospitalized with CDI
  - Non-inferiority margin of 10%

Objective

- Global cure rate of CDI (proportion of patients cured at end of treatment with no recurrence during 28-day follow-up)

Intervention

- Fidaxomicin 200 mg PO BID for 10 days
- Vancomycin 125 mg PO QID for 10 days

Mikamo H, *et al*. (2018) – Results

Severity			Prior CDI ≤ 3 months before screening, n (%)		
	Fidaxomicin (n = 104)	Vancomycin (n = 108)		Fidaxomicin (n = 104)	Vancomycin (n = 108)
Mild/Moderate (%)	79 (76.0)	86 (79.6)	**No (%)**	92 (88.5)	96 (88.9)
Severe (%)	25 (24.0)	22 (20.4)	**Yes (%)**	12 (11.5)	12 (11.1)

	Fidaxomicin (n = 104)	Vancomycin (n = 108)	Difference
Global cure rate of CDI	67.3% (70/104) [95% CI 58.3-76.3]	65.7% (71/108) [95% CI 56.8-74.7]	1.2% [95% CI -11.3-13.7]

	Fidaxomicin (n = 87)	Vancomycin (n = 95)	Difference
Recurrence at end of follow up	19.5% (17/87)	25.3% (24/95)	-4.9% [95% CI -16.7-7.0]

Gentry CA, *et al*. (2019)

Design

- Retrospective, multicenter, propensity score-matched analysis of patients ≥18 years of age treated for severe CDI from any US Veterans Affairs Medical Center between 1 June 2011 and 30 June 2017

Objective

- To compare clinical outcomes of fidaxomicin versus oral vancomycin in the management of **severe CDI**
  - Baseline white blood cell count of ≥15,000 cells/mL, or
  - Serum creatinine of 1.5 times baseline levels

Gentry CA, *et al*. (2019) – Results

Variable/outcome	Fidaxomicin (n = 213)	Vancomycin (n = 639)	P value
Episode type Initial episode Recurrence Subsequent episode	 42 (19.7) 155 (72.8) 16 (7.51)	 128 (20.0) 469 (73.4) 42 (6.57)	0.90
Age >65 years	141 (66.2)	423 (66.2)	1.0
Primary end point clinical failure and/or CDI recurrence	68 (31.9)	163 (25.5)	0.071
Secondary outcomes			
Failure By conversion/addition of vancomycin or fidaxomicin	20 (9.39) 19 (8.92)	9 (1.41) 6 (.939)	<0.001 <0.001
Recurrence within 90 days	52 (24.4)	156 (24.4)	1.0
Death within 90 days	48 (22.5)	140 (21.9)	0.85

Question 4) Polling

MJ is a 72 year old white female with a PMH of HTN and GERD on pantoprazole presenting with a chief complaint of CDI. This is her initial episode of CDI.

Pertinent labs and vitals:
WBC: 8,000 cells/mL
Serum creatinine: 1.1 mg/dL (baseline is 0.9 mg/dL)
Temperature: 99.1°F
Blood pressure:135/90 mmHg

Based on the 2021 guideline updates, what treatment do you initiate MJ on?

A) Metronidazole 500 mg PO q8h for 14 days

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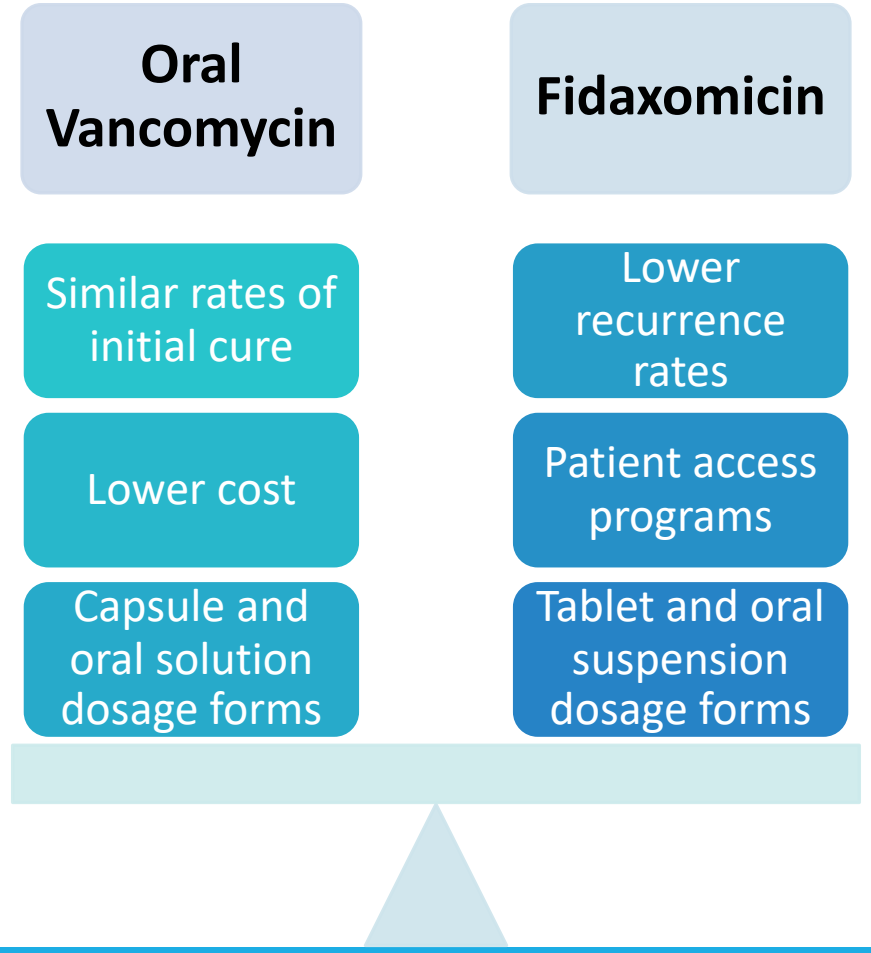
Pros and Cons



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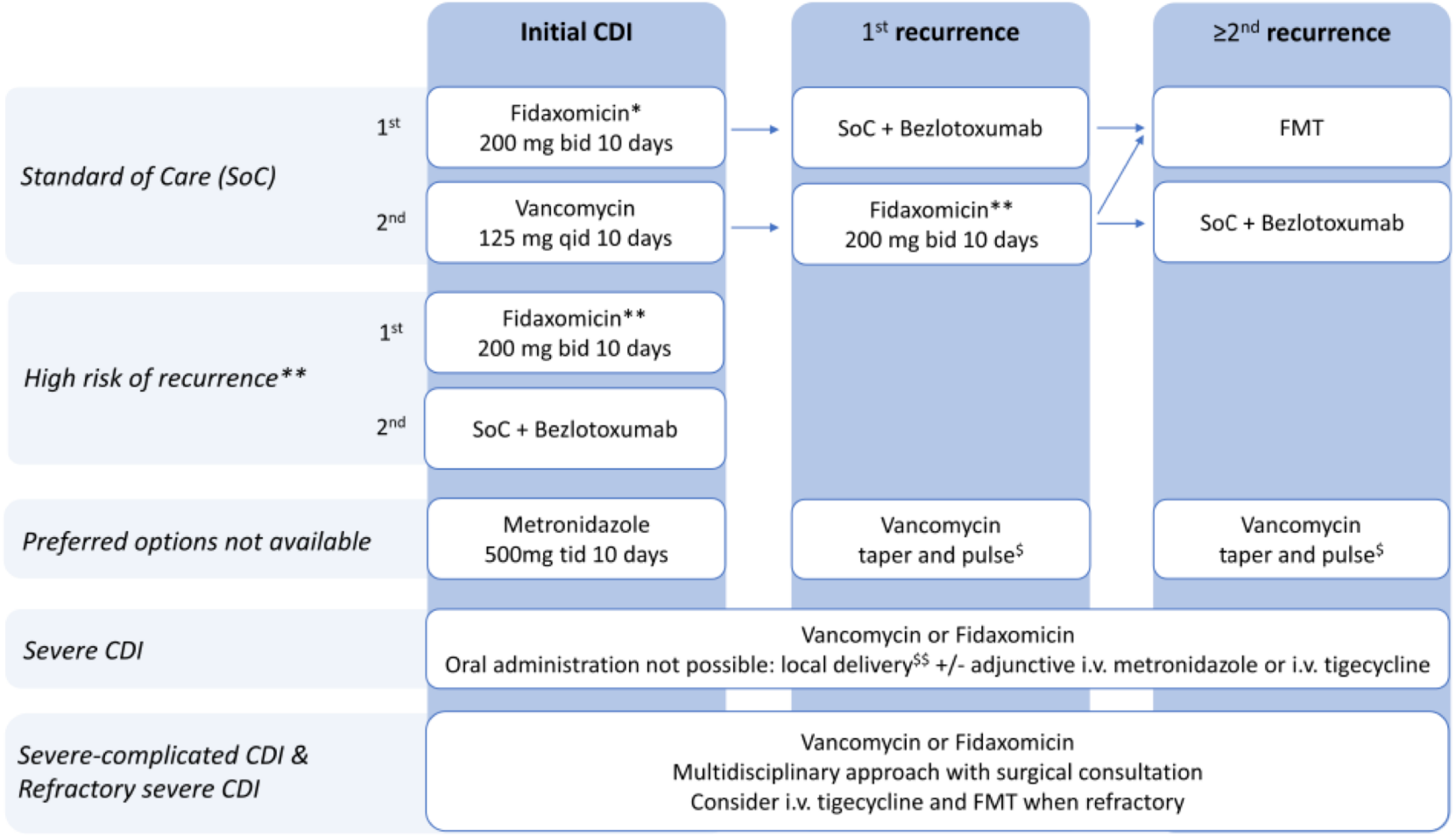
KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.

Tiebreaker?

European Society of Clinical Microbiology and Infectious Diseases (ESCMID)



VAN PREHN J, ET AL. CLIN MICROBIOL INFECT 2021;27:S1

CDI Prevention

Strategies to Reduce CDI Rates

Antibiotic stewardship program (good practice recommendation)

Use minimal, effective duration of antibiotic therapy

Use minimum number of antibiotic agents

Restriction of fluoroquinolones, clindamycin, and cephalosporins should be considered (strong recommendation, moderate quality of evidence)

Pear SM, *et al* (1994): Clindamycin restriction was associated with a decrease in CDI rates from 15.8 to 1.9 CDI cases per 1000 hospital discharges

Carling P, *et al* (2003): Prospective audit and feedback on third-generation cephalosporins and aztreonam was associated with a decrease in CDI rates from 2.2 to 0.3 CDI cases per 10000 patient-days

Diagnostic stewardship

Identifying appropriate patients to test

CLIFFORD MCDONALD L, ET AL. CID 2018:66 1 APRIL 2018. PEAR SM, ET AL. ANN INTERN MED 1994; 120:272–7.
CARLING P, INFECT CONTROL HOSP EPIDEMIOL 2003; 24:699–706. KELLY CR, ET AL. AM J GASTROENTEROL 2021;116:1124–1147.

Probiotics for Primary Prevention of CDI

ACG 2021:

- "We recommend **against** probiotics for the prevention of CDI in patients being treated with antibiotics (primary prevention)" (conditional recommendation, moderate quality of evidence)

IDSA/SHEA 2017:

- "There are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials" (no recommendation)

KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.
CLIFFORD MCDONALD L, ET AL. CID 2018:66 1 APRIL 2018

Vernaya M, *et al*. (2017)

Methods	Interventions	Inclusion Criteria	Exclusion criteria
Systematic review to answer if probiotics effective in decreasing the incidence of CDI in elderly hospitalized patients	Randomized controlled trials that evaluated the impact of taking a probiotic compared to placebo in elderly hospitalized patients	Aged ≥ 60 years Admitted to acute and post-acute care facilities Undergoing or planning for antibiotic treatment for the management of any infectious condition(s)	Studies including participants undergoing treatment for CDI

VERNAYA M, MCADAM J, HAMPTON MD. *JBI DATABASE SYSTEM REV IMPLEMENT REP*. 2017 JAN;15(1):140-164. DOI: 10.11124/JBISRIR-2016-003234. PMID: 28085732.

Studies Included

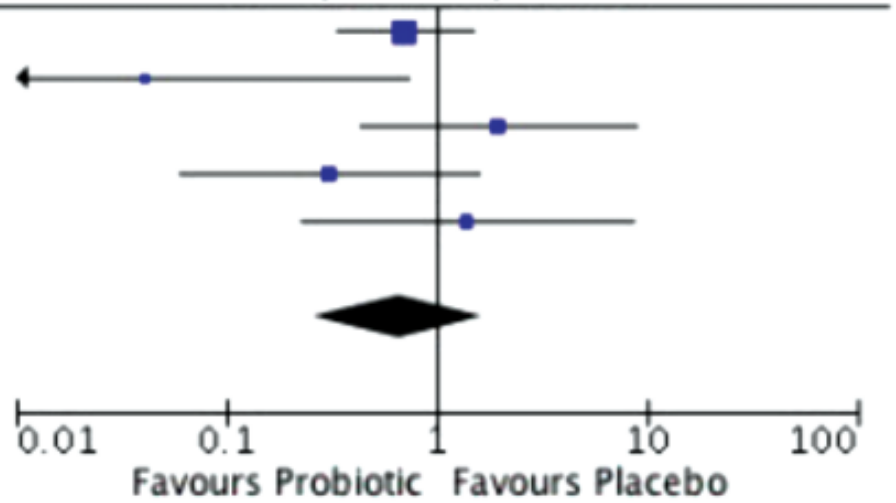
Reference	Probiotic type	Administration and duration of probiotics
Allen, *et al*. (2013)	Probiotic capsules: Two strains of *Lactobacillus acidophilus* and two strains of Bifidobacterium (*Bifidobacteriaum bifidum* and *B. lactis*)	- One capsule daily for 21 days with food between antibiotic doses
Hickson, *et al.* (2007)	Probiotic drink: *Lactobacillus casei*, *L. caseiimunitass*, *L. bulgaris* and *Streptococcus therophilus*	- Given within 48 h of starting antibiotic therapy, then continued for one week after the course was finished - Administered BID half an hour before or 1 to 2 h after meals
Lewis, *et al.* (1998)	Probiotic drink: *Saccharomyces boulardii*	- Given twice a day during antibiotics administration
Plummer, *et al.* (2004)	Probiotic capsules: *Lactobacillus and bifidobacteriaum*	- Administered for 20 days - Started within 36 h of antibiotic prescription
Pozzoni, *et al*. (2012)	Probiotic drink: *Saccharomyces boulardii*	- Started within 48 h after the start of antibiotic therapy - Continued for 7 days after antibiotic withdrawal - Given fasting – at least 2 h – after meals twice a day

Vernaya M, *et al*. (2017) - Results

Study or Subgroup	Probiotic Events	Probiotic Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Allen et al 2013	12	1470	17	1471	35.6%	0.70 [0.34, 1.48]
Hickson et al 2007	0	56	9	53	8.4%	0.04 [0.00, 0.73]
Lewis et al 1998	5	33	3	36	20.5%	1.96 [0.43, 8.96]
Plummer et al 2004	2	69	6	69	18.8%	0.31 [0.06, 1.61]
Pozzoni et al 2012	3	106	2	98	16.6%	1.40 [0.23, 8.55]
Total (95% CI)		**1734**		**1727**	**100.0%**	**0.66 [0.26, 1.66]**
Total events	22		37			

Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 7.37$, df = 4 (P = 0.12); $I^2 = 46\%$

Test for overall effect: Z = 0.89 (P = 0.38)



Author's conclusion

- Probiotics were not found to be more effective for the reduction of CDI incidence in elderly hospitalized patients compared to placebo
  - However, there were inconsistencies among the probiotics and as a result, it cannot be determined if probiotic treatment can effectively reduce CDI incidence in elderly hospitalized patients

VERNAYA M, MCADAM J, HAMPTON MD. *JBI DATABASE SYSTEM REV IMPLEMENT REP*. 2017 JAN;15(1):140-164. DOI: 10.11124/JBISRIR-2016-003234. PMID: 28085732.

Bezlotoxumab

Tradename: Zinplava™

Mechanism of action: human monoclonal antibody that binds to *C. difficile* toxin B and neutralizes its effects

Dosing: 10 mg/kg actual body weight IV once (in addition to standard of care CDI treatment)

Warnings: heart failure

- In patients with a history of CHF:
  - 12.7% (15/118) of bezlotoxumab-treated patients vs 4.8% (5/104) of placebo patients had the serious adverse reaction of heart failure
  - More deaths were reported in the bezlotoxumab 19.5% (23/118) vs placebo 12.5% (13/104) group

Cost (Pricing from Lexicomp®): 1000 mg/40 mL - $4,560/vial

ZINPLAVATM (BEZLOTOXUMAB) [PACKAGE INSERT]. WHITEHOUSE STATION, NJ, MERCK & CO., INC. S, 10/2016
ZINPLAVATM (BEZLOTOXUMAB) (LEXI-DRUGS). LEXICOMP. WOLTERS KLUWER HEALTH, INC. RIVERWOODS, IL.
[IMAGE] HTTPS://IMGCDN.MCKESSON.COM/CUMULUSWEB/IMAGES/HIGH_RES/1069979_PPKGLEFT.JPG

Benefits of *C. difficile* Monoclonal Antibodies

Shown to have reduced the rate of recurrent CDI

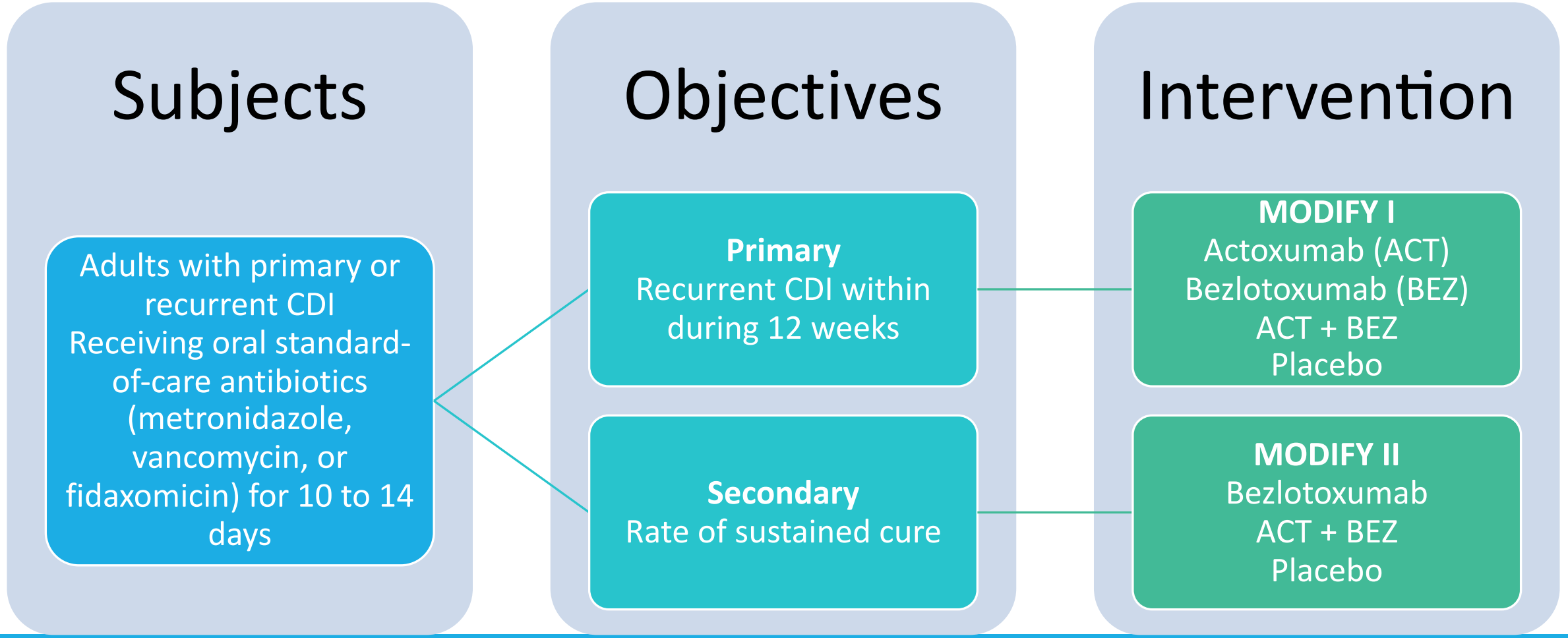
- In addition to treatment with standard of care (SOC) antibiotics
  - Vancomycin or fidaxomicin

Increased rates of global cure

- Associated with reduced recurrence rates in patients with risk factors for recurrent CDI
  - ≥65 years
  - History of CDI in the past 6 months
  - 027 ribotype
  - Severe CDI

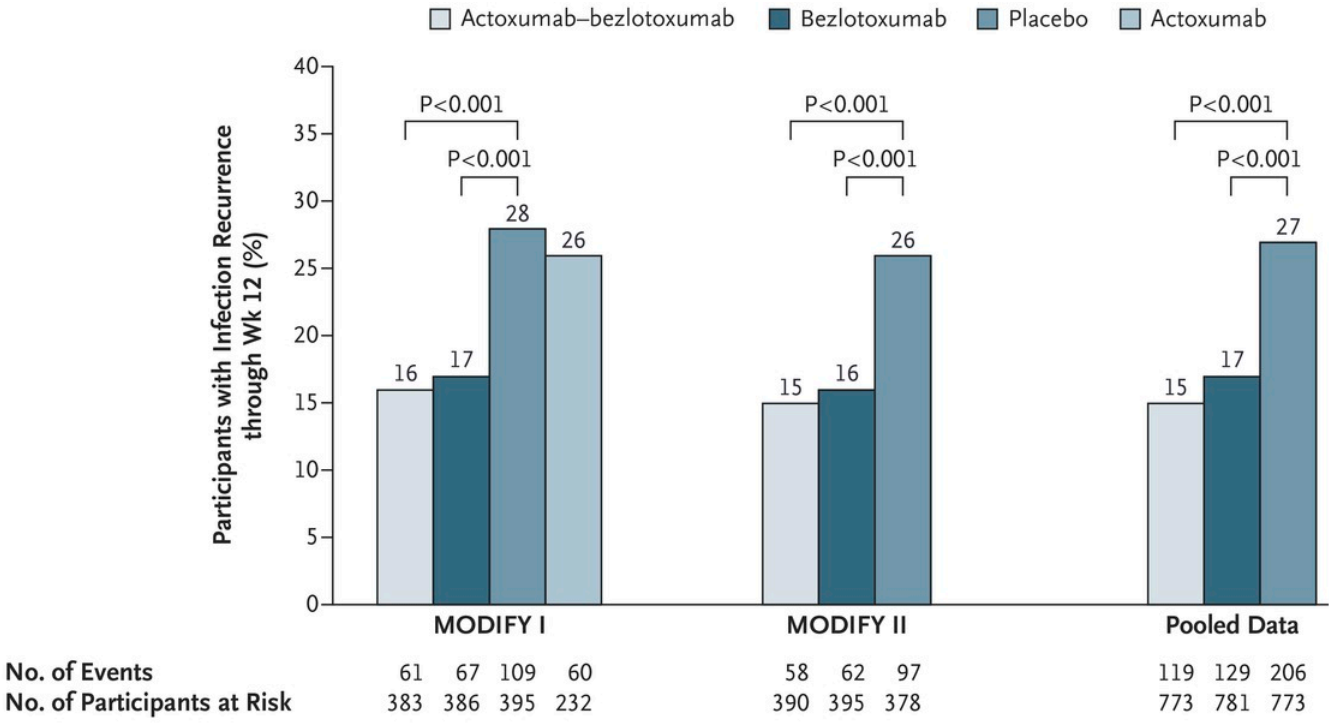
Lowy I, et al. N Engl J Med. 2010 Jan 21;362(3):197-205.
Wilcox M, et al. Open Forum Infect Dis. 2015;2(suppl 1):S1.

MODIFY I and MODIFY II (2017)

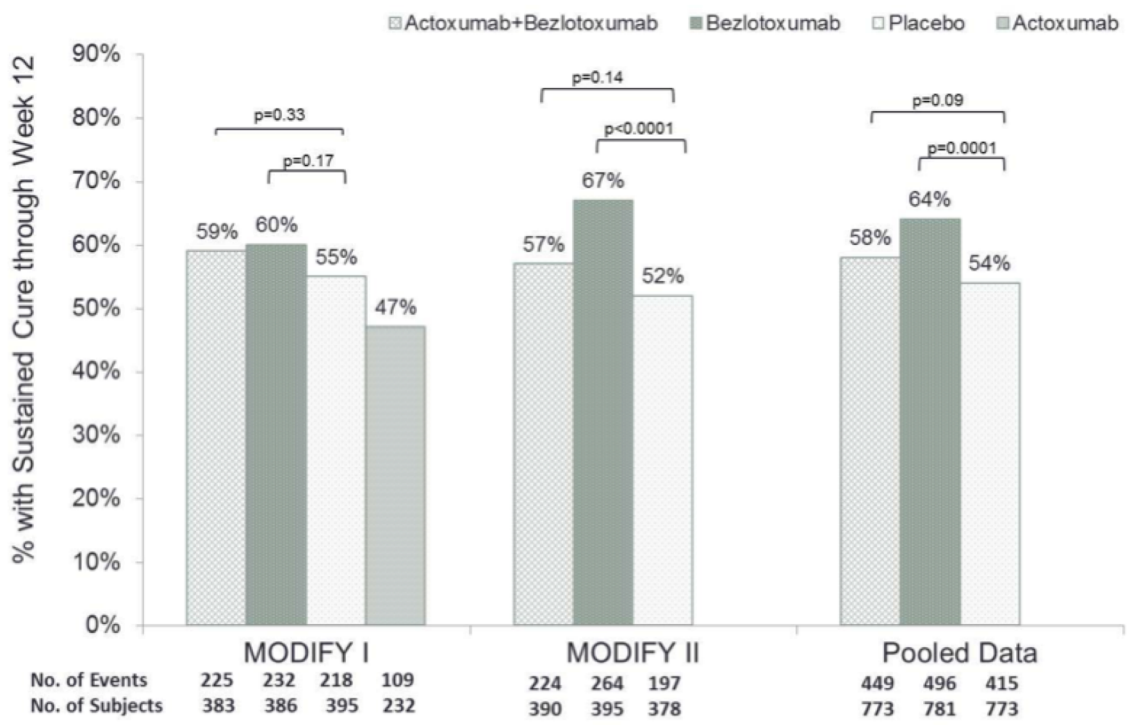


MODIFY I and MODIFY II (2017) - Results

PRIMARY ENDPOINT



SECONDARY ENDPOINT



2021 Guideline Updates on Bezlotoxumab

IDSA/SHEA 2021

"For patients with **a recurrent CDI episode within the last 6 months**, we suggest using bezlotoxumab as a co-intervention along with standard-of-care (SOC) antibiotics rather than SOC antibiotics alone (conditional recommendation, very low certainty of evidence **Comment:** This recommendation places a high value on potential clinical benefits, but implementation is often limited by feasibility considerations. **In settings where logistics is not an issue, patients with a primary CDI episode and other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host, and severe CDI on presentation) may particularly benefit from receiving bezlotoxumab."**

ACG 2021

"We suggest bezlotoxumab (BEZ) be considered for prevention of CDI recurrence in patients who are **at high risk of recurrence"** (conditional recommendation, moderate quality of evidence).

Risk Factors for recurrence:

- Aged ≥65 years PLUS ≥1 of the following:
  - Second episode of CDI within the past 6 months
  - Immunocompromised
  - Severe CDI

JOHNSON S, ET AL. CID CIAB549, 14 JUNE 2021
KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.

Fecal Microbiota Transplantation (FMT)

Restoration of the gut microbiome

Shown in clinical trials to be more effective than vancomycin for the treatment of recurrent CDI

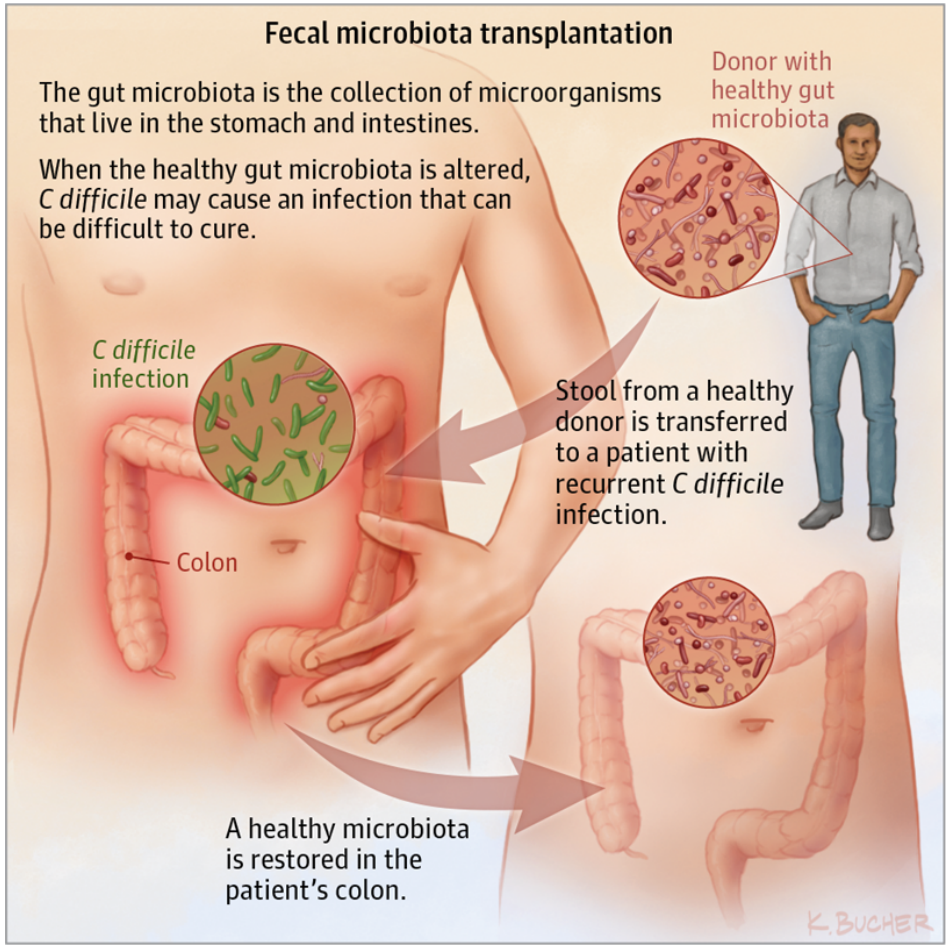
- van Nood, *et al*: Statistically superior to vancomycin + bowel lavage for the outcome of cure without relapse within 10 weeks after the initiation of therapy
  - 13/16 (81%) patients achieved resolution of CDI after 1 infusion, P<0.01
    - Overall cure 15/16 (94%), P<0.001
    - Compared to 31% vancomycin and 23% vancomycin + bowel lavage
- Lower rates of recurrence at 5 weeks compared to vancomycin
  - 6% vs 62% vs 54%, respectively

FDA Safety Alerts – Transmission of Infection via FMT

- 2020 – infections caused by enteropathogenic *Escherichia coli* (EPEC) and Shigatoxin-producing *Escherichia coli* (STEC) that have occurred following investigational use of FMT
- 2020 – potential risk of transmission of SARS-CoV-2 virus by the use of FMT

van Nood E, et al. N Engl J Med. 2013 Jan 31;368(5):407-15.; Johnson S, et al. CID ciab549, 14 June 2021; Gupta A, et al. *World J Gastroenterol*. 2020 Feb 28; 26(8): 777–788.
US Food and Drug Administration. 2020. www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections.
US Food and Drug Administration. 2020. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections

FMT



Routes of administration:

- Lower delivery: colonoscopy, enema, or sigmoidoscopy
- Upper delivery: nasogastric tube or capsule

Donor stool:

- Stool banks, healthy volunteers, a family member, or friend

Donors are tested for:

- Human immunodeficiency virus and hepatitis A, B, and C viruses; and stool tests for bacterial, viral, and parasitic infections.

Considered an investigational treatment by the FDA

- An investigational new drug (IND) permit is not required
- Requires patient consent

GUPTA A, KHANNA S. FECAL MICROBIOTA TRANSPLANTATION. *JAMA.* 2017;318(1):102.
IDSA. EMERGING CLINICAL ISSUES FECAL MICROBIOTA TRANSPLANTATION. **INVESTIGATIONAL NEW DRUG PROTOCOL** AVAILABLE FROM: HTTPS://WWW.IDSOCIETY.ORG/PUBLIC-HEALTH/EMERGING-CLINICAL-ISSUES/EMERGING-CLINICAL-ISSUES/FECAL-MICROBIOTA-TRANSPLANTATION/
US FOOD AND DRUG ADMINISTRATION 29 JAN 2020 HTTPS://WWW.FDA.GOV/REGULATORY-INFORMATION/SEARCH-FDA-GUIDANCE-DOCUMENTS/ENFORCEMENT-POLICY-REGARDING-INVESTIGATIONAL-NEW-DRUG-REQUIREMENTS-USE-FECAL-MICROBIOTA-0

Suppressive and Prophylactic Vancomycin

American College of Gastroenterology 2021 Guidelines

- "For patients with recurrent CDI who are not candidates for FMT, who relapsed after FMT, or who require ongoing or frequent courses of antibiotics, **long-term suppressive oral vancomycin may be used to prevent further recurrences**"(conditional recommendation, very low quality of evidence)

- "Oral vancomycin prophylaxis (OVP) **may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence** to prevent further recurrence" (conditional recommendation, low quality of evidence)

Oral Vancomycin-Fecal Concentrations

Vancomycin PO for *C. difficile* epidemiological cutoff value (ECV): ≤2 mcg/mL

Vancomycin PO Dose	Approximate Stool Concentration	Stool Concentration:ECV
125 mg PO QID	500-1000 mcg/mL	250-500x
250 mg PO QID	2000 mcg/mL	1000x
500 mg PO QID	4000 mcg/mL	1000x

Prophylaxis dosing is typically ¼-½ treatment dose

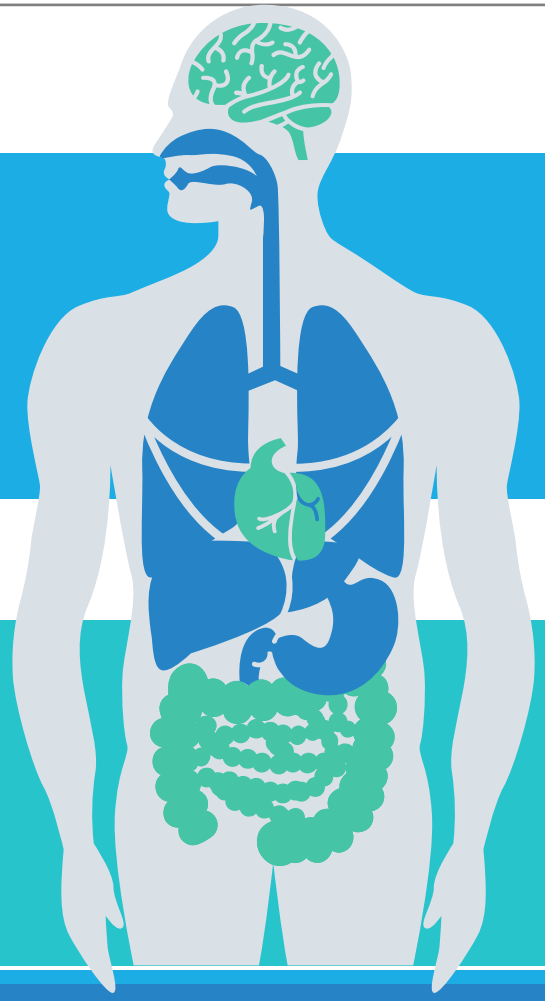
- Vancomycin 125 mg PO daily approximate stool concentration: 125-250 mcg/mL

CLSI M100-ED32:2022 PERFORMANCE STANDARDS FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING, 32ND EDITION
GONZALES M, ET AL. BMC INFECT DIS. 2010 DEC 30;10:363.

PO Vancomycin Secondary Prophylaxis Zhang K, *et al*. (2019)

Design

Retrospective case-series of 20 consecutive cases of long-term vancomycin for CDI prophylaxis amongst patients with multiple episodes who failed FMT, or were not candidates for FMT



Intervention

Patients with ≥3 CDI episodes who were prescribed at least 8 weeks of oral vancomycin 125 mg once daily to prevent CDI relapse, and who were not taking concomitant antibiotics for other infections

PO Vancomycin Secondary Prophylaxis Zhang K, *et al*. (2019)

Demographics

Demographics
- Age, median (min, max): 80 years (53,91)
- Male: 7 (35%)
- CDI Episodes, median (min, max): 4 (2,11)

Previous CDI Treatment

- Vancomycin: 20 (100%)
  - Courses of vancomycin, median (min, max): 3 (1, 12)
- Fidaxomicin: 4 (20%)
- Fecal Microbiota Transplantation (FMT): 15 (75%)
  - Number of FMTs, median (min, max): 3 (1, 12)

Zhang K, *et al*. (2019) Results

- 1 breakthrough infection
- 4/13 (31%) relapses were observed within 8 weeks of discontinuation
- 1 delayed episode of CDI was observed
  - Likely reinfection
- 5 patients died during follow-up,
  - None of the deaths were ascribed to CDI
- Author's conclusion
  - "Prolonged vancomycin prophylaxis at a dose of 125 mg orally daily is an effective and well-tolerated option for secondary prevention of relapsing *C. difficile* infection, and may be considered in those without access to FMT, or who relapse or fail FMT."

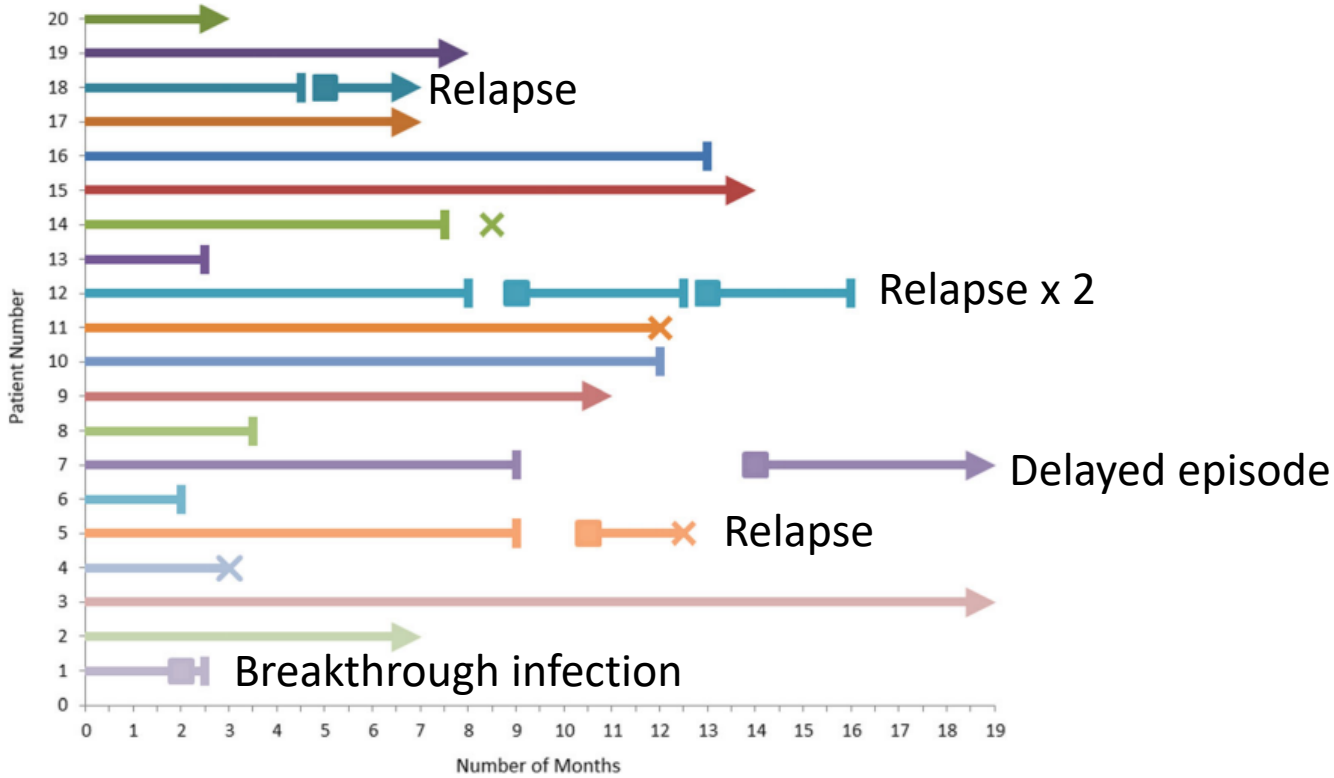


Fig. 1 Effect of prolonged vancomycin 125 mg daily as secondary prophylaxis of relapsing *Clostridium difficile* infection. Legend: ■ *C. difficile* episode; ✕ Death; ⊣ Completed Vancomycin Prophylaxis; → Ongoing Vancomycin Prophylaxis

ZHANG K, ET AL. BMC INFECT DIS. 2019 JAN 14;19(1):51. DOI: 10.1186/S12879-019-3676-1.

Oral Vancomycin Prophylaxis Van Hise, *et al.* (2016)

Purpose

To compare rates of recurrent CDI in patients receiving oral vancomycin prophylaxis (OVP) with systemic antimicrobial therapy compared to patients who didn't

Outcome

Recurrent CDI within 4 weeks after the completion of systemic antibiotics

Design & Intervention

Retrospective cohort

3 arms:

- Vancomycin PO 125 mg PO BID
- Vancomycin PO 250 mg PO BID
- No OVP

Patients receiving antimicrobial therapy

- Fluoroquinolones
- Cephalosporins
- Aminopenicillins
- Aztreonam
- Combination: vancomycin, levofloxacin and pip/tazo

Van Hise, *et al.* (2016) – Results

Subjects
N = 203 patients enrolled
- n = 71: 125 mg BID
- n = 42: 250 mg BID
- n = 132: control

Outcomes
3 patients who received OVP developed CDI vs. **35** patients in the control group (P <0.001)
- 2 received 250 mg BID
- 1 received 125 mg BID

Conclusion
OVP may be effective in reducing the risk of recurrent CDI in patients requiring antibiotics

CDI in Special Populations

Hematopoietic Cell Transplant (HCT) Recipients

Risk Factors for CDI

- Antibiotic treatment
  - Including prophylaxis
- Disruption to the bacterial microbiota and mucosa secondary to chemotherapy/conditioning regimens
- Immunocompromised

American Society for Transplantation and Cellular Therapy (ASTCT)

Treatment Recommendations

INITIAL EPISODE

First-line treatment is oral fidaxomicin

- Fidaxomicin may cause less disruption to the gut microbiome

Alternative:

- Vancomycin standard dose if fidaxomicin is not available

Can consider adding bezlotoxumab for patients at risk for recurrent CDI

Fulminant CDI – same recommendations as IDSA/SHEA 2021 and ACG 2021

FIRST RECURENCE

First-line treatment is oral fidaxomicin

Alternative:

- Vancomycin taper/pulsed dose

Belzotoxumab

Inflammatory Bowel Disease

ACG 2021

- "suggest vancomycin 125 mg PO 4 times a day for a **minimum** of 14 days in patients with IBD and CDI (strong recommendation, very low quality of evidence)."
  - Longer duration of vancomycin therapy (21–42 days) compared with shorter duration (10-14 days) had a lower incidence of CDI recurrence of 1.8% vs 11.7%, respectively (OR 0.13, P = 0.043) in a single-center retrospective study by Lei, *et al*
  - Limited data on the use of fidaxomicin in this population

KELLY CR, ET AL. *AM J GASTROENTEROL* 2021;116:1124–1147.
LEI DK, ET AL. *AM J GASTROENTEROL* 2019;114: 1904–8

Conclusion

Two guideline updates on CDI in 2021

- IDSA/SHEA 2021: suggests using fidaxomicin rather than a standard course of vancomycin (conditional recommendation, moderate certainty of evidence)
- ACG 2021: recommends vancomycin (strong recommendation, low quality of evidence) or fidaxomicin (conditional recommendation, very low quality of evidence) as initial therapy for severe CDI

Strategies for reducing recurrent CDI

- Bezlotoxumab can be considered for prevention of CDI recurrence in patients who are at high risk of recurrence
- FMT can be used to restore of the gut microbiome in patients with recurrent CDI
- Oral vancomycin prophylaxis may be considered in patients with a history of CDI who are at high risk of recurrence who are receiving systemic antibiotics

Questions?

Thank you for attending!

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