Tools for Loose Stools: Updates on the Management of *Clostridioides difficile* Colitis Infection

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Disclosures

- None to declare

Notable Definitions

Abbreviation	Definition
C.difficile or *C.diff*	*Clostridioides* (formerly *Clostridium*) *difficile*
CDI	*Clostridioides difficile* infection
CDAD	*Clostridioides difficile* associated diarrhea
VAN	Vancomycin
MTZ	Metronidazole
FDX	Fidaxomicin
BEZ	Bezlotoxumab
ACT	Actoxumab

Objectives

General Objectives

- Distinguish between initial occurrence, first recurrence, and second or subsequent recurrence *C.difficile* colitis infection
- Identify patients who may benefit from treatment with bezlotoxumab

Pharmacist

- Design a therapeutic regimen for the treatment of *C.difficile* colitis infection based on patient specific factors

Pharmacy Technician

- List medications that may worsen or contribute to *C.difficile* colitis infection

History of *C.difficile*

- First described in feces in newborn infants in 1935
- Dormant spores → fecal-oral → germination → vegetative state
  - Co-exist as non-toxigenic and toxigenic strains
- Toxin production results in colitis
- Genus re-classification from *Clostridium* to *Clostridioides* in 2016

Hall IC et al. *Am J Dis Child* 1935;49:390-402.
Gerding DN. *Int J Antimicrob Agents* 2009;33:2-8.
Dubberke ER at al. *Clin Infect Dis* 2012;55:88-92.
Peery AF et al. *Gastroenterology* 2012;143:1171-1173.

Burden of Disease

- Responsible for:
  - Up to 500,000 infections, approximately 29,000 deaths in 2011
  - Up to 500,000 infections, approximately 15,000 deaths in 2015
- Accounts for > $1 billion in health care expenditures annually
- In 2013, CDC categorized CDI threat level as 'urgent'

Centers for Disease Control and Prevention. Nearly half a million Americans suffered from Clostridium difficile infections in a single year. Available at: https://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html. Accessed March 26, 2019.

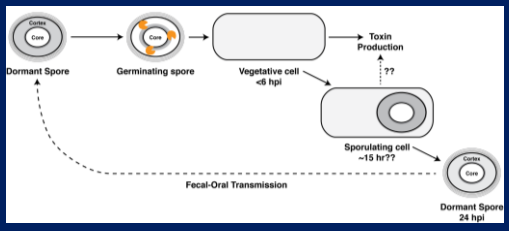
Morbidity Associated with CDI

- Colectomy
  - Pre-2000, colectomy rates associated with CDI : 0.48-1.3%
  - Early 2000s
    - Rising rates, 1.6-3.2% between 1989 to 1999
    - In 2000-2001, rate of emergency colectomy was 6.2%
- Recurrences (10-30%)
- CDI patients with ↑ rates of discharges to LTCFs*

*Long term care facility

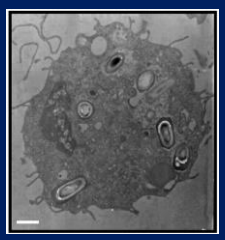
Muto CA et al. *Infect Control Hosp Epidemiol* 2005;26:273-280.
Garey KW et al. *J Hosp Infect* 2008;70:298-304.
Micek ST et al. *Crit Care Med* 2013;41:1968-1975.
Dubberke ER et al. *Emerg Infect Dis* 2008;14:1031-1038.

From Spore to Vegetation



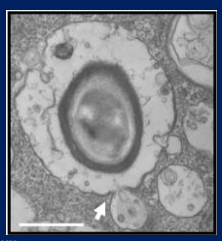
Shen A. *PLoS Pathog* 2015;11:e1005157.

Macrophage uptake of *C.difficile* spore



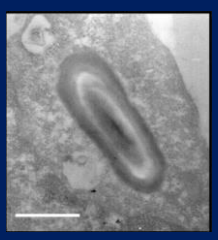
Parades-Sabia D et al. *PLoS One* 2012;7:e43635.

Lysosome fusion with macrophage

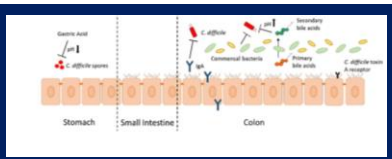


Parades-Sabia D et al. *PLoS One* 2012;7:e43635.

Survival of *C.difficile* spore after 24 hours



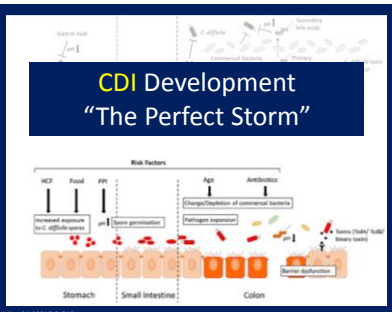
Parades-Sabia D et al. *PLoS One* 2012;7:e43635.



Colonization without CDI

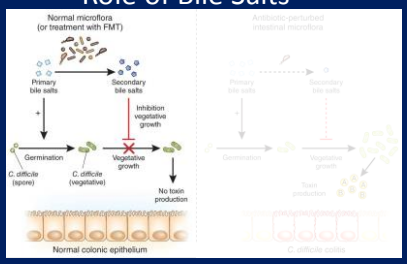
Schaffler H et al. *Front Microbiol* 2018;9:646.

CDI Development "The Perfect Storm"



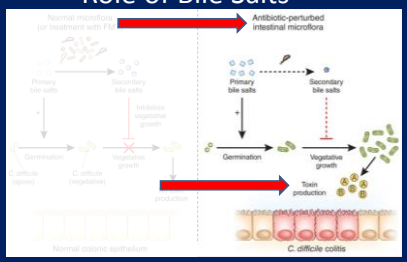
Schaffler H et al. *Front Microbiol* 2018;9:646.

Role of Bile Salts



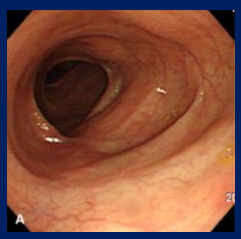
Taur Y et al. *Nat Med* 2014;20:246-247.

Role of Bile Salts



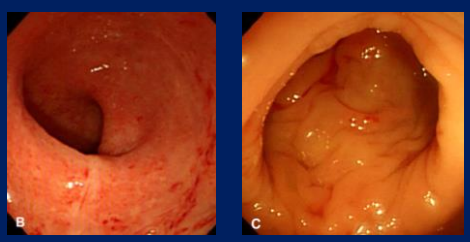
Taur Y et al. *Nat Med* 2014;20:246-247.

Normal Healthy Colon



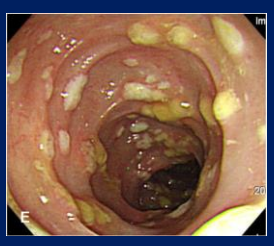
Song HJ et al. *Korean J Intern Med* 2008;23:9-15.

Non-specific Colitis



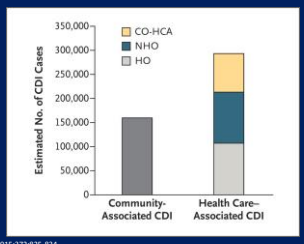
Song HJ et al. *Korean J Intern Med* 2008;23:9-15.

Pseudomembranous Colitis



Song HJ et al. *Korean J Intern Med* 2008;23:9-15.

CDI: A Widespread Problem



Lessa FC et al. *New Engl J Med* 2015;372:825-834.

Adjusted U.S. National Estimates of Burden and Incidence of CDI, 2011

Demographic Characteristic	Community-Associated CDI*		Health Care–Associated CDI†		All CDI	
	Estimated No. of Cases	Incidence per 100,000 Persons	Estimated No. of Cases	Incidence per 100,000 Persons	Estimated No. of Cases	Incidence per 100,000 Persons
All cases	159,700 (132,900–186,000)	51.9 (43.2–60.5)	293,300 (264,200–322,500)	95.3 (85.9–104.8)	453,000 (397,100–508,500)	147.2 (129.1–165.3)
Sex						
Male	64,300 (52,800–75,300)	42.5 (34.8–49.8)	132,700 (118,700–146,700)	87.7 (78.5–97.0)	197,000 (171,500–222,000)	130.2 (113.3–146.8)
Female	95,400 (80,100–110,700)	61.0 (51.2–70.8)	160,600 (145,500–175,800)	102.7 (93.1–112.5)	256,000 (225,600–286,500)	163.8 (144.3–183.3)

Lessa FC et al. *New Engl J Med* 2015;372:825-834.

Adjusted U.S. National Estimates of Burden and Incidence of CDI, 2011

Demographic Characteristic	Community-Associated CDI*		Health Care–Associated CDI†		All CDI	
	Estimated No. of Cases	Incidence per 100,000 Persons	Estimated No. of Cases	Incidence per 100,000 Persons	Estimated No. of Cases	Incidence per 100,000 Persons
Age group						
1–17 yr	12,500 (10,000–15,000)	17.9 (14.1–21.4)	4400 (3200–5800)	6.3 (4.6–8.3)	16,900 (13,200–20,800)	24.2 (18.7–29.7)
18–44 yr	35,600 (26,000–39,200)	28.7 (22.9–34.5)	20,800 (16,700–24,800)	18.3 (14.7–21.9)	53,400 (42,700–64,000)	47.0 (37.6–56.4)
45–64 yr	54,100 (45,600–62,600)	65.4 (55.1–75.6)	68,800 (61,000–76,600)	83.1 (73.7–92.5)	122,900 (106,600–139,200)	148.5 (128.8–168.1)
≥65 yr	60,500 (51,300–69,200)	146.2 (124.0–167.2)	193,300 (183,300–215,300)	481.5 (442.8–520.1)	259,800 (234,600–284,500)	627.7 (566.8–687.3)

Lessa FC et al. *New Engl J Med* 2015;372:825-834.

Defining the CDI Episode

- First episode
  - Patient has never experienced CDI
- First recurrence (second episode)
  - Patient must have responded to first episode treatment
  - Return of diarrhea 2 weeks to 2 months after successful treatment of first episode
- Second recurrence (third episode) and beyond
  - Any subsequent episodes

Defining Severity of CDI

	Mild-to-Moderate	Severe	Fulminant
WBC, cells/mm^3	≤ 15,000	> 15,000	n/a
SCr, mg/dL	< 1.5	> 1.5	n/a
No. of stools (in 24 hours)	≥ 3	≥ 3	≥ 3
Clinical presentation		Abdominal pain	Hypotension/shock, ileus, toxic megacolon

McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

Risk Factors for Severe CDI

- Leukocytosis (↑ WBC)
- Acute renal injury (↑ SCr)
- Fever (> 38.3° C)
- Hypotension
- Hypoalbuminemia
- Age > 60 years
- Toxic megacolon
- ICU
- Stool count

Zar FA et al. *Clin Infect Dis* 2007;45:302-7.
Rubin MS et al. *C. Dis Colon Rectum* 1995;38:350-4.
Fekety R et al. *Clin Infect Dis* 1997;24:324-33.
Fernandez A et al. *J Clin Gastroenterol* 2004;38:414-8.
Walk ST et al. *Clin Infect Dis* 2012;55:1661-8.
Dellinger RP et al. *Crit Care Med* 2013;41:580-637.

Goals of CDAD/CDI Management

Treat Episode
- Regimen selection
- ? ± Probiotic Use
- Minimize antibiotic exposure
- Assess for potential disease exacerbating medications

Minimize complications

Prevention of Recurrences

Historical Treatment Options

- Teicoplanin
- Fusidic acid
- Bacitracin

- Metronidazole
- Vancomycin

Evolution of CDI Management

	Initial, non-severe	Initial, severe	Initial, fulminant	First recurrence	Second recurrence
1997	MTZ	VAN	Intra-colonic VAN	Same as initial	• Tapered MTZ • Tapered VAN
2010	MTZ	VAN	• VAN (high dose) + IV MTZ • Intra-colonic VAN	Same as initial	• Tapered VAN
2017	• VAN • FDX	• VAN • FDX	• VAN (high dose) + IV MTZ • Intra-colonic VAN	• VAN tapered • FDX	• Tapered VAN • VAN + RFX • FDX • FMT

Oral administration route unless specified RFX – rifaximin FMT – fecal microbiota transplant

Fekety R. *Am J Gastroenterol* 1997;92:739-50.
Cohen SH et al. *Infect Control Hosp Epidemiol* 2010;31;431-55.
McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

A Snapshot into 2010 Guidelines

- Recognized emergence of hypervirulent strain NAP1/BI/027
  - Lack of trial data
  - Hypervirulence ≠ resistance (↑ MIC)
- VAN may result in earlier time to diarrhea resolution
- Characteristics associated with increased MTZ failure:
  - Low albumin
  - Admission to ICU
  - Pseudomembranous colitis on endoscopic exam

Cohen SH et al. *Infect Control Hosp Epidemiol* 2010;31;431-55.
Zar FA et al. *Clin Infect Dis* 2007;45:302-307.
Louie T et al. In: Proceedings of the 47th Annual ICAAC; 2007; Chicago IL. Washington, DC: ASM Press; 2007. Abstract K-425a.

What we took away in 2010..

- Lack of sufficient evidence to deviate from metronidazole for uncomplicated CDI
- Disease with immune compromising component
  - Use of immunoglobulins
- Treatment cohorted to factors
  - High risk for failure (severity of CDI)
  - High risk for recurrence
- No role of probiotics

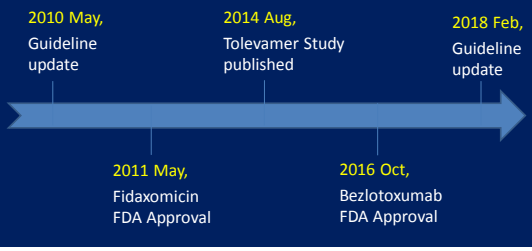
Cohen SH et al. *Infect Control Hosp Epidemiol* 2010;31;431-55.
Zar FA et al. *Clin Infect Dis* 2007;45:302-307.
Louie T et al. In: Proceedings of the 47th Annual ICAAC; 2007; Chicago IL. Washington, DC: ASM Press; 2007. Abstract K-425a.

Rationale for MTZ over VAN

- Concern for vancomycin-resistant Enterococci (VRE) development
- Metronidazole less costly
- No clear benefit in clinical trials (to date) suggesting clear benefit of VAN over MTZ

Teasley DG et al. *Lancet* 1983;2:1043-6.
Wenisch C et al. *Clin Infect Dis* 1996;22:813-8.
CDC. MMWR September 22, 1995. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/00039349.htm. Accessed March 26, 2019.

Through the Years



2017 Guidelines

- Zar FA et al. 2007
  - Cited as 1 of 2 studies pushing MTZ out of guideline recommendation
  - Where was it in 2010 iteration?
- Johnson S et al. 2014
  - Phase III study for polymer, tolevamer

Zar FA et al. *Clin Infect Dis* 2007;45:302-307. Johnson S et al. *Clin Infect Dis* 2014;59:345-54.

In '2010', Not Enough Muster..

Table 2. Rate of cure of *Clostridium difficile*–associated diarrhea by disease severity and treatment.

Disease severity	No. of patients cured/ no. of patients treated (%)			
	Mtz group	Vm group	Total	P^a
Mild	37/41 (90)	39/40 (98)	76/81 (94)	.36
Severe	29/38 (76)	30/31 (97)	59/69 (86)	.02
All	66/79 (84)	69/71 (97)	135/150 (90)	

NOTE. Mtz, metronidazole; Vm, vancomycin.
[a] *P* values were calculated using Fisher's exact test.

Zar FA et al. *Clin Infect Dis* 2007;45:302-307.

Combined clinical cure among RCTs

Outcomes	No. of Participants (No. of Studies)	Percentage Resolution	Relative Effect[a] (95% CI)	*P* Value	Quality of Evidence (GRADE)[b]	Reference, First Author
Direct comparisons of metronidazole and vancomycin						
Resolution of diarrhea at end of (10 days) treatment	RCTs prior to 2000: 156 (2)	95 (MTR) 98 (VAN)	RR, 0.97 (.91–1.03)	.4		Teasley [168] Wenisch [310]
	RCTs since 2000: 687[c] (3)	75 (MTR) 85 (VAN)	RR, 0.89 (.82–.96)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	78 (MTR) 87 (VAN)	RR, 0.89 (.85–.96)	.0008	⊕⊕⊕⊕ High	
Resolution of diarrhea at end of treatment without CDI recurrence –1 month after treatment	RCTs prior to 2000: 156 (2)	85 (MTR) 84 (VAN)	RR, 1.0 (.90–1.2)	1.0		Teasley [168] Wenisch [310]
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McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

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McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

Tolevamer in CDI

- Tolevamer
  - High molecular-weight polymer shown to bind/neutralize *C.difficile* toxins *in vitro*
  - Phase II dose-response study showed promising results
- Randomized, double-dummy, double-blinded, active-controlled, parallel-designed efficacy study
- Study sites:
  - United States, Canada, Europe, Australia

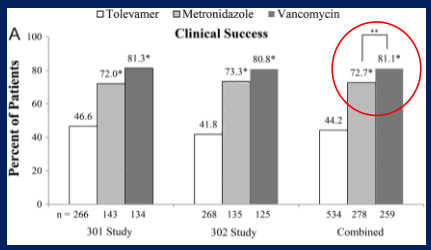
Johnson S et al. *Clin Infect Dis* 2014;59:345-54.

Study 301 vs. 302

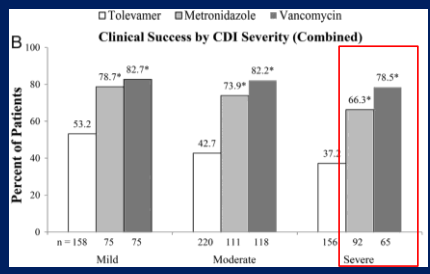
	Study 301 n=543	Study 302 n=528
Age, years		Slightly older population
mean ± SD	62 ± 17.7 (18-99)	68 ± 16.4 (18-97)
Body Weight, kg	Heavier patients	
mean ± SD	75 ± 24	68 ± 17
Inpatient, %		Majority inpatient population
	56%	91%

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

Metronidazole Inferior to Vancomycin



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



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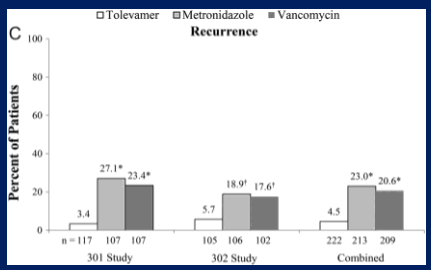

Johnson S et al. *Clin Infect Dis* 2014;59:345-54.

Disease Severity Matters

Recurrence rates tend to be lower with mild disease
- Vancomycin - 5%
- Metronidazole - 8%

	Classification	Tolevamer	Metronidazole	Vancomycin	P (M vs. V)
Recurrence* *in patients that met primary clinical cure definition	Mild	3/82 (3.7)	14/58 (24.1)	14/63 (22.2)	0.69
	Moderate	5/88 (5.7)	19/90 (21.1)	12/94 (12.8)	0.12
	Severe	2/52 (3.8)	16/65 (24.6)	17/52 (32.7)	0.41
	[p-value]	0.79	0.85	0.016	

Zar FA et al. *Clin Infect Dis* 2007;45:302-307. Johnson S et al. *Clin Infect Dis* 2014;59:345-54.

Recurrence Rates Across 2 Studies

	No. of patients who experienced relapse/no. of patients who were cured (%)			
	Zar FA et al		Johnson S et al	
	MTZ	VAN	MTZ	VAN
Mild	3/37 (8)	2/39 (5)	14/58 (24)	14/63 (22)
Severe	6/29 (21)	3/30 (10)	16/65 (25)	17/52 (33)

Zar FA et al. *Clin Infect Dis* 2007;45:302-307. Johnson S et al. *Clin Infect Dis* 2014;59:345-54.

Recurrence Rates Across 2 Studies

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	Zar FA et al		Johnson S et al	
		VAN		VAN
Mild		2/39 (5)		14/63 (22)
Severe		3/30 (10)		17/52 (33)

Zar FA et al. *Clin Infect Dis* 2007;45:302-307. Johnson S et al. *Clin Infect Dis* 2014;59:345-54.

Considerations for Recurrence Reduction

Of the patients who respond clinically:

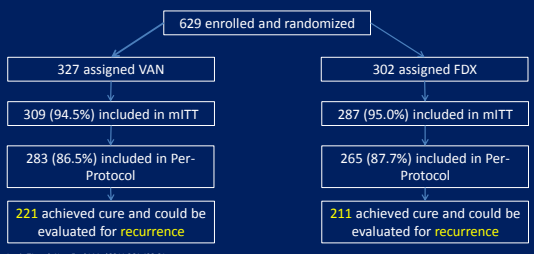
1. Do patients with severe CDI who receive vancomycin truly experience more recurrences?
2. If this is true, should we approach severe CDI patients differently?
   - Vancomycin + bezlotoxumab
   - Fidaxomicin
   - Fidaxomicin + bezlotoxumab
   - Rx + fecal microbiota transplant

REMEMBER: Goals should include considerations for recurrence

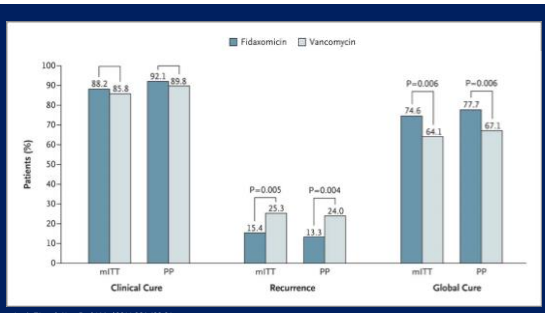
New Kid on the Block

- Fidaxomicin FDA approved May 27, 2011
- 2010 CDI management guidelines
  - Study abstract, 2007 ICAAC
  - Full manuscript, 2011 NEJM
- Incumbent on clinicians to self-evaluate clinical trial and apply to practice

FDX vs. VAN for CDI



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



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

Table 3. Rates of Recurrence of *C. difficile* Infection, According to Subgroups, in the Modified Intention-to-Treat and Per-Protocol Populations.

Subgroup	Modified Intention-to-Treat Population			Per-Protocol Population		
	Fidaxomicin	Vancomycin	P Value	Fidaxomicin	Vancomycin	P Value
	no./total no. (%)			*no./total no. (%)*		
Age						
<65 yr	19/150 (12.7)	27/134 (20.1)	0.09	12/126 (9.5)	22/118 (18.6)	0.04
≥65 yr	20/103 (19.4)	40/131 (30.5)	0.05	16/85 (18.8)	31/103 (30.1)	0.08
Hospital status						
Inpatient	24/136 (17.6)	40/146 (27.4)	0.05	19/106 (17.9)	29/111 (26.1)	0.15
Outpatient	15/117 (12.8)	27/119 (22.7)	0.05	9/105 (8.6)	24/110 (21.8)	0.007
Previous episode of *C. difficile* infection						
No	30/211 (14.2)	52/217 (24.0)	0.01	22/175 (12.6)	41/183 (22.4)	0.02
Yes	9/42 (21.4)	15/48 (31.2)	0.30	6/36 (16.7)	12/38 (31.6)	0.14

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

Table 3. Rates of Recurrence of *C. difficile* Infection, According to Subgroups, in the Modified Intention-to-Treat and Per-Protocol Populations.

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	Fidaxomicin	Vancomycin	P Value	Fidaxomicin	Vancomycin	P Value
	no./total no. (%)			*no./total no. (%)*		
Severity of disease at baseline						
Mild	7/59 (11.9)	20/68 (29.4)	0.02	4/44 (9.1)	13/55 (23.6)	0.06
Moderate	20/102 (19.6)	18/88 (20.5)	0.89	15/90 (16.7)	18/71 (25.4)	0.18
Severe	12/92 (13.0)	29/109 (26.6)	0.02	9/77 (11.7)	22/95 (23.2)	0.05
Strain type						
NAP1/BI/027	16/59 (27.1)	14/67 (20.9)	0.42	11/45 (24.4)	13/55 (23.6)	0.93
Non–NAP1/BI/027	12/117 (10.3)	34/121 (28.1)	<0.001	8/103 (7.8)	27/106 (25.5)	<0.001
Concomitant systemic antimicrobial therapy						
Yes	14/81 (17.3)	25/90 (27.8)	0.10	8/56 (14.3)	20/65 (30.8)	0.03
No	25/172 (14.5)	42/175 (24.0)	0.03	20/155 (12.9)	33/156 (21.2)	0.05

Lower recurrence rates among patients who received FDX driven by non-hypervirulent strain of *C.difficile*

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

In '2017', Not Enough Muster..

XXIX. What are the best treatments of an initial CDI episode to ensure resolution of symptoms and sustained resolution 1 month after treatment?

Recommendations

1. Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI.

McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

Thoughts on bezlotoxumab..

Lack of guidance in 2017 updates

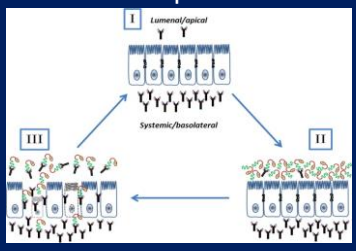
Since completion of this guideline, a new therapeutic agent and a molecular diagnostic test platform have become available for CDI. Bezlotoxumab, a monoclonal antibody directed against toxin B produced by *C. difficile*, has been approved as adjunctive therapy for patients who are receiving antibiotic treatment for CDI and who are at high risk for recurrence [10]. Multiplex polymerase chain reaction (PCR) platforms that detect *C. difficile* as part of a panel of >20 different enteric pathogens have also become available [11]. These most recent innovations and other innovations that may become available in the near future will be covered in subsequent guideline updates.

McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

Concept of Immunotherapy

If patients lacking innate anti-toxin immunoglobulins are prone to disease development, would immunoglobulin therapy directed against toxins aid in the management of CDAD?

Bezlotoxumab: Proposed Mechanism



Yang Z et al. *Infect Immun* 2015;83:822-31.
Orth P et al. *J Biol Chem* 2014;289:18008-21.

Zang Z et al. *Infect Immun* 2015;83:405-416.

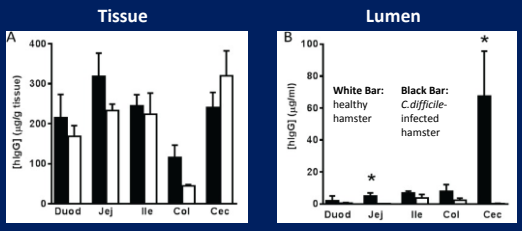
Release of antibodies into lumen

S – submucosa
E – epithelium
L – lumen
LP – lamina propria

Yang Z et al. *Infect Immun* 2015;83:822-31.
Orth P et al. *J Biol Chem* 2014;289:18008-21.

Zang Z et al. *Infect Immun* 2015;83:405-416.

Tissue vs. Lumen Concentrations



Zang Z et al. *Infect Immun* 2015;83:405-416.

Standard of Care (SoC) Regimens

Characteristic	Actoxumab plus Bezlotoxumab (N = 773)	Bezlotoxumab (N = 781)	Actoxumab (N = 232)	Placebo (N = 773)	All Participants (N = 2559)
	number of participants (percent)				
Standard-of-care antibiotic					
Metronidazole	366 (47.3)	365 (46.7)	112 (48.3)	353 (45.7)	1196 (46.7)
Vancomycin	366 (47.3)	370 (47.4)	113 (48.7)	372 (48.1)	1221 (47.7)
Fidaxomicin	25 (3.2)	30 (3.8)	7 (3.0)	30 (3.9)	92 (3.6)
Inpatient	523 (67.7)	530 (67.9)	158 (68.1)	520 (67.3)	1731 (67.6)
Female sex	423 (54.7)	442 (56.6)	130 (56.0)	449 (58.1)	1444 (56.4)
Age ≥65 years	441 (57.1)	390 (49.9)	122 (52.6)	405 (52.4)	1358 (53.1)
≥1 Episodes of *C. difficile* infection in previous 6 mo	200 (25.9)	216 (27.7)	69 (29.7)	219 (28.3)	704 (27.5)
≥2 Previous *C. difficile* infection episodes ever	103 (13.3)	100 (12.8)	34 (14.7)	126 (16.3)	363 (14.2)

Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Antibiotic Exposure after CDI Treatment

Characteristic	Actoxumab plus Bezlotoxumab (N = 773)	Bezlotoxumab (N = 781)	Actoxumab (N = 232)	Placebo (N = 773)	All Participants (N = 2559)
	number of participants (percent)				
Severe *C. difficile* infection*	142 (18.4)	122 (15.6)	31 (13.4)	125 (16.2)	420 (16.4)
Immunocompromised†	163 (21.1)	178 (22.8)	55 (23.7)	153 (19.8)	549 (21.5)
Other antibiotic use during standard-of-care therapy‡	333 (43.1)	292 (37.4)	86 (37.1)	317 (41.0)	1028 (40.2)
Other antibiotic use after standard-of-care therapy‡	274 (35.4)	273 (35.0)	83 (35.8)	275 (35.6)	908 (35.5)
PCR ribotype					
Participants with positive culture	477 (61.7)	490 (62.7)	144 (62.1)	486 (62.9)	1597 (62.4)
Most common strains**††	222 (46.5)	210 (42.9)	57 (39.6)	233 (47.9)	722 (45.2)
027, 078, or 244 strain††	90 (18.9)	102 (20.8)	30 (20.8)	115 (23.7)	337 (21.1)
027 strain††	76 (15.9)	89 (18.2)	24 (16.7)	100 (20.6)	289 (18.1)

Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Role of Bezlotoxumab

Did bezlotoxumab impact initial cure rates of infection?

- "Initial Cure": no diarrhea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for ≤ 16 days

	MODIFY I			MODIFY II		
	BEZ (n=386)	Placebo (n=395)	95% CI	BEZ (n=395)	Placebo (n=378)	95% CI
Initial Cure, n (%)	299 (77)	327 (83)	[-10.9,0.3]	326 (83)	294 (78)	[-0.9, 10.4]

BEZ: bezlotoxumab
CI : confidence interval

Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Impact of bezlotoxumab on initial cure

	MODIFY I			MODIFY II		
	ACT+BEZ (n=383)	Placebo (n=395)	95% CI	ACT+BEZ (n=390)	Placebo (n=378)	95% CI
Initial Cure, n (%)	286 (75)	327 (83)	[-13.9,-2.4]	282 (72)	294 (78)	[-11.6, 0.6]

BEZ: bezlotoxumab
ACT: actoxumab
CI : confidence interval

Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Pooled MODIFY I & II Cure Rates

	Pooled Dataset			
		Treatment vs. Placebo		
Treatment	Clinical Cure % (n/N)	Difference	Adjusted Difference [95% CI]	p-Value
ACT + BEZ	73.5 (568/773)	-6.9	-6.8 [-11.0, -2.6]	0.0014
BEZ	80 (625/781)	-0.3	-0.3 [-4.3, 3.7]	0.8832
Placebo	80.3 (621/773)	---	---	---

Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Signal towards ACT affecting clinical cure

	Pooled Dataset			
		Treatment vs. Placebo		
Treatment	Clinical Cure % (n/N)	Difference	Adjusted Difference [95% CI]	p-Value
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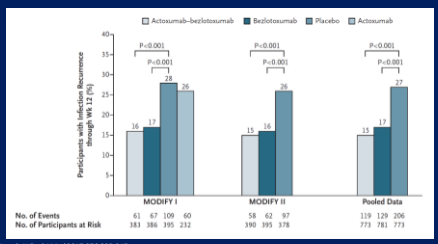
BEZ	80 (625/781)	-0.3	-0.3 [-4.3, 3.7]	0.8832
Placebo	80.3 (621/773)	---	---	---

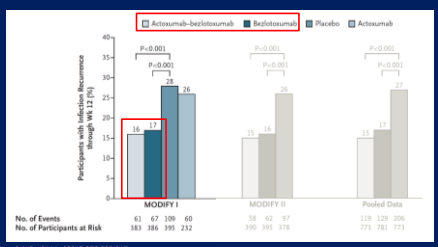
Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Overall Recurrence Rates



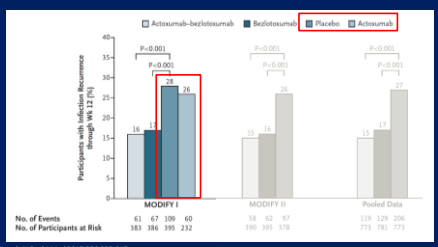
Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

MODIFY I: Effect of Bezlotoxumab



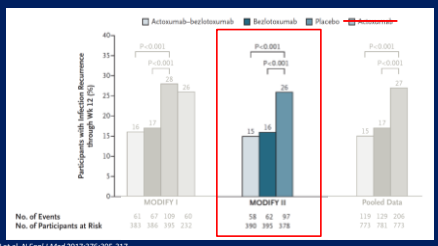
Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

MODIFY I: Effect of Actoxumab



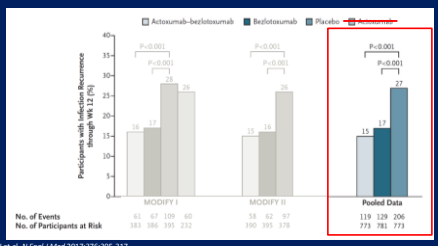
Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

MODIFY II: Bezlotoxumab, No Actoxumab



Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Pooled: MODIFY I & II



Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Safety analysis

- Overall adverse drug events (ADE) similar
  - Infusion related: 10% BEZ vs. 7.6% placebo
  - Drug related: 7.5% BEZ vs. 5.9% placebo
- History of congestive heart failure
  - Serious ADE due to heart failure: 12.7% BEZ vs. 4.8% placebo
  - Deaths due to cardiac ADE: 19.5% BEZ vs. 12.5% placebo
  - Death occurrence monitored and collected through 12-week follow-up period

Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Merck & Co, Inc. Zinplava (bezlotoxumab) [package insert]. Merck & Co, Inc: Whitehouse Station, NJ, 2016.

Lessons from Phase III Trial

- Actoxumab (anti-toxin A) did not impact clinical cure or recurrence
- Bezlotoxumab effective in reducing recurrences
  - NNT to prevent 1 recurrent CDI (all population) : 10
  - NNT to prevent 1 recurrent CDI (among ≥ 65 years) : 6
- Difficult to describe role of FDX + BEZ; FDX underrepresented
- Cautious use in patients with cardiac history

NNT : number needed to treat

Wilcox MH et al. *N Engl J Med* 2017;376:305-317.

Cost Considerations

		
Zinplava® (bezlotoxumab) $4,560 per vial Packaging: 25 mg/mL, 40mL	Dificid® (fidaxomicin) $4,639 per bottle Packaging: 200 mg tab, 20 tabs	Firvanq® (vancomycin oral sol) $150 - 50 mg/mL, 150 mL (125 mg 4x daily) $239 - 50 mg/mL, 300 mL (500 mg 4x daily)

Red Book Online Ann Arbor, Michigan: Truven Health Analytics. Accessed March 26, 2019.

Prices displayed as average wholesale prices.

PROBIOTICS

No guideline probiotic recommendation

XXVII. What is the role of probiotics in primary prevention of CDI?

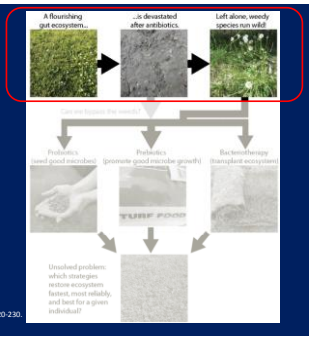
Recommendation

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

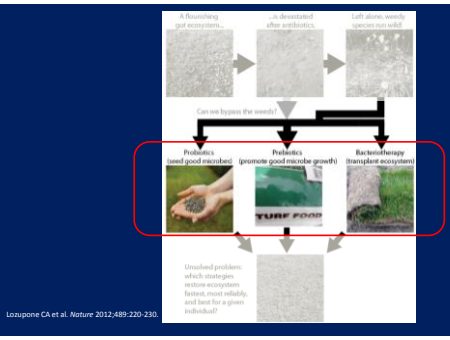
McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

Rationale for Probiotic Use in CDAD

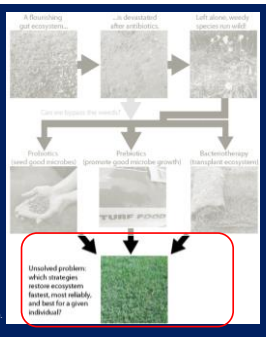
- Deliver bacteria, other microorganisms to gastrointestinal tract and restore equilibrium
- Decrease available area for pathogenic microorganisms to colonize and develop into disease downstream



Lozupone CA et al. *Nature* 2012;489:220-230.



Lozupone CA et al. *Nature* 2012;489:220-230.



Lozupone CA et al. *Nature* 2012;489:220-230.

Challenges of Probiotic Therapy in CDI

- Patient selection
- Efficacy
- 'Agent' selection
  - Diversity
  - Safety
- Timing

Saccharomyces boulardii

- Immunocompromised patients with certain underlying conditions at highest risk
  - Intravenous catheter
  - Previous receipt of antibiotic therapy
- Of 37 cases reviewed, 32 cases involved *S.boulardii*-containing probiotic use
- Despite overall low rates of *Saccharomyces* spp. infections, 40% of all reported cases identified probiotic as the source

Enache-Angoulvant A et al. *Clin Infect Dis* 2005;41:1559-1568.

Lactobacillus Complications

Reported cases of *Lactobacillus* spp. complications attributed to probiotic use

- Bacteremia
- Endocarditis
- Secondary gastrointestinal complications
- Catheter-associated infections

Crow JR et al. *Pharmacotherapy* 2015;35:1016-25.

Lactobacillus Complications

Reported cases [illegible] olications attributed to pr

- Bacteremia
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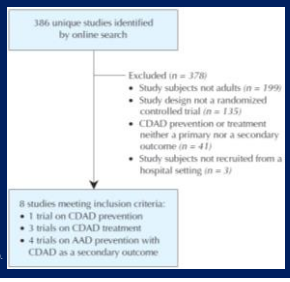
Crow JR et al. *Pharmacotherapy* 2015;35:1016-25.

Pre-2005 Stance on Probiotics



Dendukuri N et al. *CMAJ* 2005;173-167-170.

Trial	Probiotic and duration	Outcome measure (length of follow-up)	Comments
Primary outcome			
Plummer et al, 2004;[17] prevention	*Lactobacillus acidophilus* and *Bifidobacterium bifidum* for 20 d	Presence of *C. difficile* (20 d)	No difference in toxin positivity between treatment arms among patients with positive culture; lower incidence of diarrhea reported among culture- and toxin-positive subjects in probiotic group; short follow-up
McFarland et al, 1994;[16] treatment	*Saccharomyces boulardii* for 4 wk	Diarrhea and at least 1 positive assay for *C. difficile* by culture or toxin A or B (8 wk)	Concomitant use of different antibiotics for differing lengths of time; no difference in culture positivity between treatment arms, but significantly fewer toxin B positive cases in probiotic group
Surawicz et al, 2000;[15] treatment	*S. boulardii* for 28 d	Diarrhea and at least 1 positive assay for *C. difficile* by culture or toxin A or B (8 wk)	Concomitant antibiotic assigned to patients after randomization; no difference in culture or toxin positivity in subgroup taking high-dose vancomycin; results not reported for other groups
Wullt et al, 2003;[18] treatment	*L. plantarum* 299v for 38 d	Diarrhea (5–10 d) Positive assay for *C. difficile* toxins A or B (11–13 d)	Small sample; no difference in culture positivity after treatment among 20 patients who had no diarrhea after 5–10 d

Dendukuri N et al. *CMAJ* 2005;173-167-170

Since 2010 Guidelines..

- Increasing case-reports, retrospective observational analysis associating probiotic use as source of invasive infections
- Subject to bias
- Mainly in 'at risk' population
  - Immunocompromised
  - Certain age cohort (> 60 years)

Box MJ et al. *Open Forum Infect Dis* 2018;5:ofy192.
Costa RL et al. *BMC Complement Altern Med* 2018;18:329.
Boyle RJ et al. *Am J Clin Nutr* 2006;83:1256-64.
Leedahl DD et al. *Pharmacotherapy* 2019;39:399-407.

PROTON PUMP INHIBITORS (PPIS)

No guidance on PPI use

XXVI. What is the role of proton pump inhibitor restriction in controlling CDI rates?

Recommendation

1. Although there is an epidemiologic association between proton pump inhibitor (PPI) use and CDI, and unnecessary PPIs should always be discontinued, there is insufficient evidence for discontinuation of PPIs as a measure for preventing CDI *(no recommendation)*.

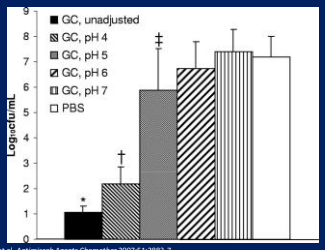
McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

Effect of High pH Environment

- Gastric acid does not kill *C.difficile* spores
- Proposed mechanism for PPI contributions to CDI
  - Vegetative form of *C.difficile* killed by acid
  - Survival of vegetative form of *C.difficile* as ↑ pH
  - Presence of bile salts ↑ pH

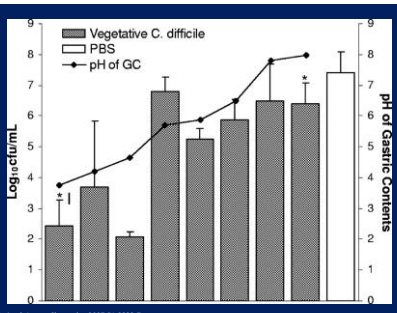
Rao A et al. *Antimicrob Agents Chemother* 2006;50:3901-3904. Jump RLP et al. *Antimicrob Agents Chemother* 2007;51:2883-7.

Growth of Vegetative *C.difficile*



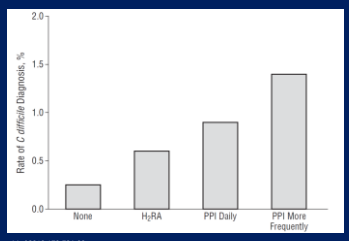
GC : gastric contents
PBS : Phosphate-buffered saline

Jump RLP et al. *Antimicrob Agents Chemother* 2007;51:2883-7.



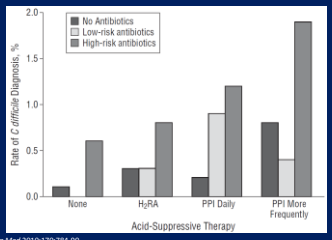
Jump RLP et al. *Antimicrob Agents Chemother* 2007;51:2883-7.

Association of CDI & acid suppression



Howell MD et al. *Arch Intern Med* 2010;170:784-90.

Antibiotic use compounds risk of CDI



Howell MD et al. *Arch Intern Med* 2010;170:784-90.

Impact of PPI on Nosocomial CDI

Factor	Odds Ratio (95% CI)	*P*-value
No acid suppression therapy	1 [reference]	
H_2RA only	1.53 (1.12-2.10)	0.008
Daily PPI	1.74 (1.39-2.18)	<0.001
PPI more frequent than daily	2.36 (1.79-3.11)	<0.001
Low-risk antibiotics	1.82 (1.17-2.82)	0.008
High-risk antibiotics	3.37 (2.64-4.31)	<0.001

Howell MD et al. *Arch Intern Med* 2010;170:784-90.

Recent reviews of PPIs association with CDI

Cao F et al.
- Time period up to Dec 2016
- Analysis of 50 studies
- PPI users vs. non-users
  - OR 1.26
  - [CI: 1.12-1.39], p <0.001
- I^2 : 40.8%

Cao F et al. *J Hosp Infect* 2018;98:4-13.

Trifan A et al. *World J Gasteroenterol* 2017;32:6500-6515.

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Trifan et al.
- Time period up to Mar 2017
- Analysis of 56 studies
- PPI users vs. non-users
  - OR 1.99
  - [CI: 1.73-2.30], p <0.001
- I^2 : 85.4%

Cao F et al. *J Hosp Infect* 2018;98:4-13.

Trifan A et al. *World J Gasteroenterol* 2017;32:6500-6515.

No Rigor, No Consensus

- Conflicting clinical trial data
- Development of CDI[1,2]
  - Patients in ICU on PPIs were twice is likely to develop CDI than those not on PPIs
  - Estimated 65% increase in CDI among PPI users
- Recurrence of CDI[3,4]
  - Continuous use of PPIs 1.5 times risk of CDI recurrence
  - No association among 894 inpatients; unadjusted for antibiotic exposure

1. Barletta JF et al. *Critical Care* 2014;18:714.
2. Janarthanan S et al. *Am J Gastroenterol* 2012;107:1001-10.
3. McDonald EG et al. *JAMA Intern Med* 2015;175:784-791.
4. Freedberg DE et al. *Am J Gastroenterol* 2013;108:1794-1801.

CONCLUDING THOUGHTS

Goals of CDAD/CDI Management

Treat Episode
- Regimen selection
- ? ± Probiotic Use
- Minimize antibiotic exposure
- Assess for potential disease exacerbating medications

Minimize complications

Prevention of Recurrences

Tackling Challenge of Recurrence

XXIX. What are the best treatments of an initial CDI episode to ensure resolution of symptoms and sustained resolution 1 month after treatment?

Recommendations

1. Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI.

McDonald LC et al. *Clin Infect Dis* 2018;66:987-994.

Tackling Challenge of Recurrence

- Consider initial cure first
  - Gauge severity of illness
  - Compile risk factors for failing to achieve initial cure
- Evaluate risk for recurrence

Age ≥ 75 years	**Unformed bowel movements ≥ 10 in 24H**
SCr ≥ 1.2 mg/dL	**Previous CDI episode(s)**

- Modifiable risk factors and/or behaviors
  - Correctable reason for receiving frequent antibiotics
  - Medication review (PPIs, probiotics, GI motility agents)

D'Agostino RB et al. *Clin Infect Dis* 2014;58:1386-93.

No. of Risk Factors	Points for Each Risk Factor: Age ≥75 y	UBM ≥10/d	Cr ≥1.2 mg/dL	Predicted Risk of Recurrence: FDX	VAN
(A) Score sheet for people with no prior episode					
No risk factors	0	0	0	10%	18%
1 Risk factor					
Age	1	0	0	13%	24%
UBM	0	1	0	13%	24%
Cr	0	0	2	17%	29%
2 Risk factors					
Age and UBM	1	1	0	17%	29%
Age and Cr	1	0	2	21%	35%
UBM and Cr	0	1	2	21%	35%
3 Risk factors					
Age, UBM, and Cr	1	1	2	28%	44%

D'Agostino RB et al. *Clin Infect Dis* 2014;58:1386-93.

No. of Risk Factors	Points for Each Risk Factor: Age ≥75 y	UBM ≥10/d	Cr ≥1.2 mg/dL	Predicted Risk of Recurrence: FDX	VAN
(B) Score sheet for people with prior episode					
No risk factors	0	0	0	14%	25%
1 Risk factor					
Age	1	0	0	19%	32%
UBM	0	1	0	19%	32%
Cr	0	0	2	24%	39%
2 Risk factors					
Age and UBM	1	1	0	24%	39%
Age and Cr	1	0	2	29%	45%
UBM and Cr	0	1	2	29%	45%
3 Risk factors					
Age, UBM, and Cr	1	1	2	37%	54%

D'Agostino RB et al. *Clin Infect Dis* 2014;58:1386-93.

Interpretation Example

I have a patient who I have identified would benefit more from FDX than VAN.

- The patient has experienced CDI in the past
- Patient has 'recurrence' risk factors including:
  - Age 78
  - Unformed bowel movements of 14 in past 24 hours

No. of Risk Factors	Points for Each Risk Factor: Age ≥75 y	UBM ≥10/d	Cr ≥1.2 mg/dL	Predicted Risk of Recurrence: FDX	VAN
(B) Score sheet for people with prior episode					
No risk factors	0	0	0	14%	25%
1 Risk factor					
Age	1	0	0	19%	32%
UBM	0	1	0	19%	32%
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Age and Cr	1	0	2	29%	45%
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D'Agostino RB et al. *Clin Infect Dis* 2014;58:1386-93.

By selecting FDX, you have inherently reduced the risk of recurrence from 39% to 24%. Is 24% predicted risk of recurrence acceptable?

Prophylaxis in HSCT Population

- Mean duration of therapy
  - Fidaxomicin: 22 ± 8.61 days
  - Placebo: 22.7 ± 8.99 days
- Approximately 64% of each cohort completed follow-up
- Additional antibiotic exposure in 75% of study participants

Mullane KM et al. *Clin Infect Dis* 2019;68:196-203.

Safety analysis of FDX vs. Placebo

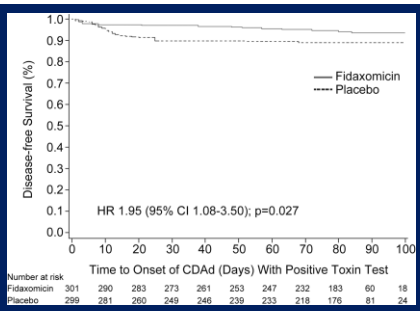
- Reported ADEs similar between fidaxomicin and placebo
  - Diarrhea 71% FDX vs. 73% placebo
  - Nausea 62% FDX vs. 67% placebo
  - Febrile neutropenia 48% FDX vs. 37% placebo
  - Vomiting 41% FDX vs. 41% placebo
- Median time to neutrophil engraftment 9 days in both cohorts

Mullane KM et al. *Clin Infect Dis* 2019;68:196-203.

Confirmed CDAD at Pre-defined Endpoints

	Fidaxomicin n=301	Placebo n=299	95% CI	*P*-value
30 days after end of treatment, n (%)	13 (4.3)	32 (10.7)	[2.2, 10.6]	0.0014
60 days after end of treatment, n (%)	17 (5.6)	32 (10.7)	[0.7, 9.4]	0.0117
70 days after end of treatment, n (%)	14 (4.7)	32 (10.7)	[1.8, 10.3]	0.0026

Mullane KM et al. *Clin Infect Dis* 2019;68:196-203.



Mullane KM et al. Clin Infect Dis 2019;68:196-203.

Recurrence: understudied, undervalued

- ICU population[1]
  - PPI, stress ulcer prophylaxis
  - Broad spectrum antibiotic exposure
- Rx prophylaxis in antibiotic-necessary scenarios
  - MTZ
  - VAN[2]
  - FDX[3]

1. Leedahl DD et al. *Pharmacotherapy* 2019;39:399-407.
2. Van Hise NW et al. *Clin Infect Dis* 2016;63:651-3.
3. Mullane KM et al. *Clin Infect Dis* 2019;68:196-203.

4 Do's for the 'Diff'

- Reserve oral metronidazole for scenarios where vancomycin or fidaxomicin is unavailable
- Fidaxomicin or vancomycin?
  - Not a slam dunk
  - Consider cost: benefit profile
  - Insurances may shift towards covering fidaxomicin
- Help manage disease by reviewing all medications patients may be taking
  - Probiotics
  - Unnecessary proton pump inhibitors
  - GI motility agents (stimulant laxatives, osmotic laxatives)
  - Stool softeners
  - Ask about over-the-counters!
- Recurrence considerations
  - Risk factor assessment
  - Bezlotoxumab may have a role in ↓ risk of CDI recurrences in select populations
  - Rx prophylaxis (think about residual damage, ADEs)
  - Initial agent selection

Parting Thoughts

- *C.difficile* colitis is a disease that presents as a spectrum
  - Mild or mild-to-moderate
  - Moderate-to-severe
  - Fulminant or toxic megacolon
- Risk factors for failure, mortality, recurrences are important to consider when selecting and reviewing pharmacotherapy
- Be comfortable with the data and consider all options
  - Fidaxomicin vs. oral vancomycin
  - Fecal microbiota transplantation
  - Bezlotoxumab

Unanswered Areas of CDI Management

- Would tolevamer have been better studied as add-on to SoC for reducing recurrence?
- If BEZ does not impact initial cure of CDI, does it need to be given at the same time as treatment?
  - Outpatient
- What role do probiotics (in any form) play down the road after patients achieve initial clinical cure?