Nevada Antimicrobial Stewardship
HAI Caucus 2017

Updates on *C. difficile* Testing and Treatment

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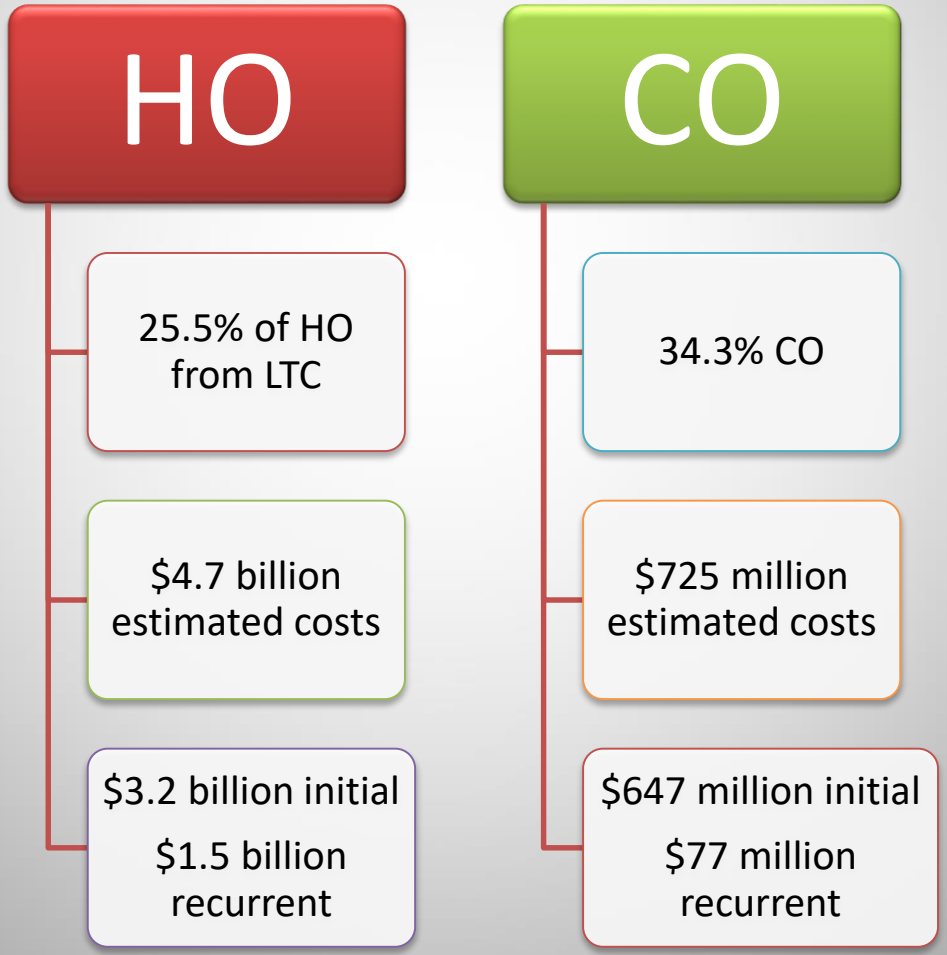
All Data is Transparent

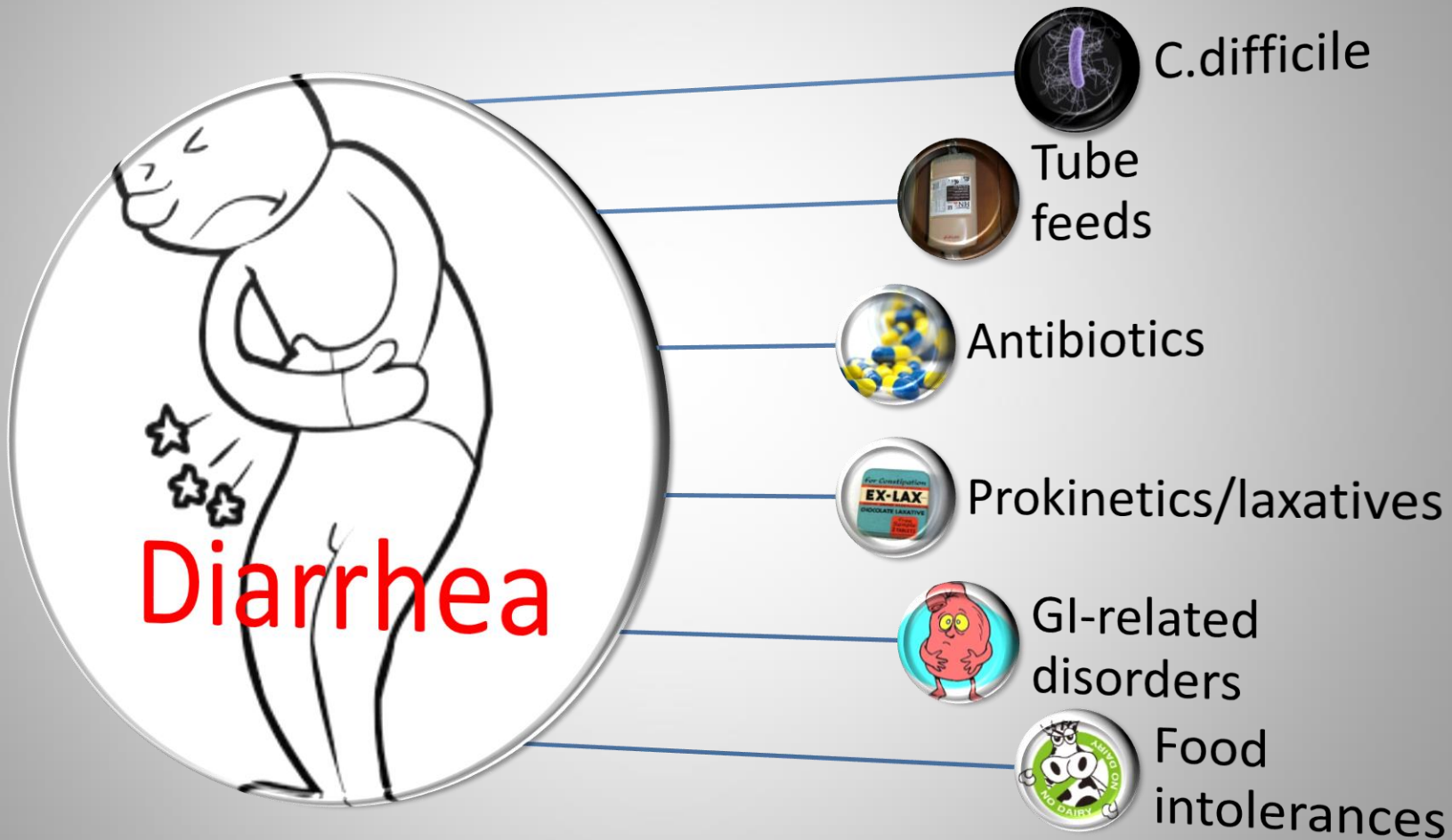
Merck: Economic Model of *C. difficile*

- Utilizing 2014 data, predicted 606,058 *C. difficile* episodes

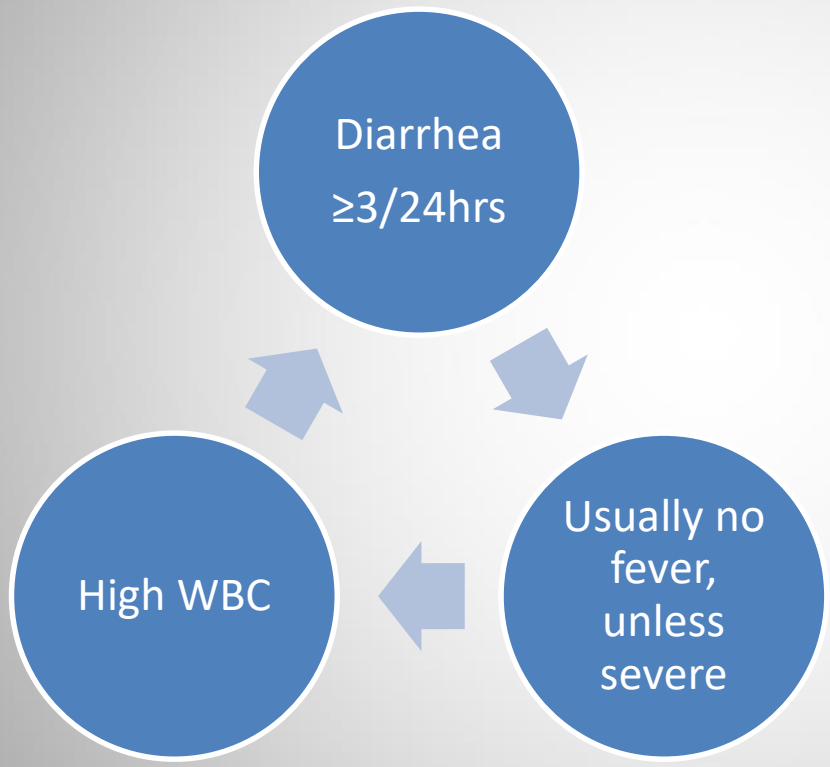


Desai et al. BMC Infectious Diseases (2016) 16:303

Differential Diagnosis: Diarrhea



Clinical Diagnosis



Positive Test

Laboratory Tests

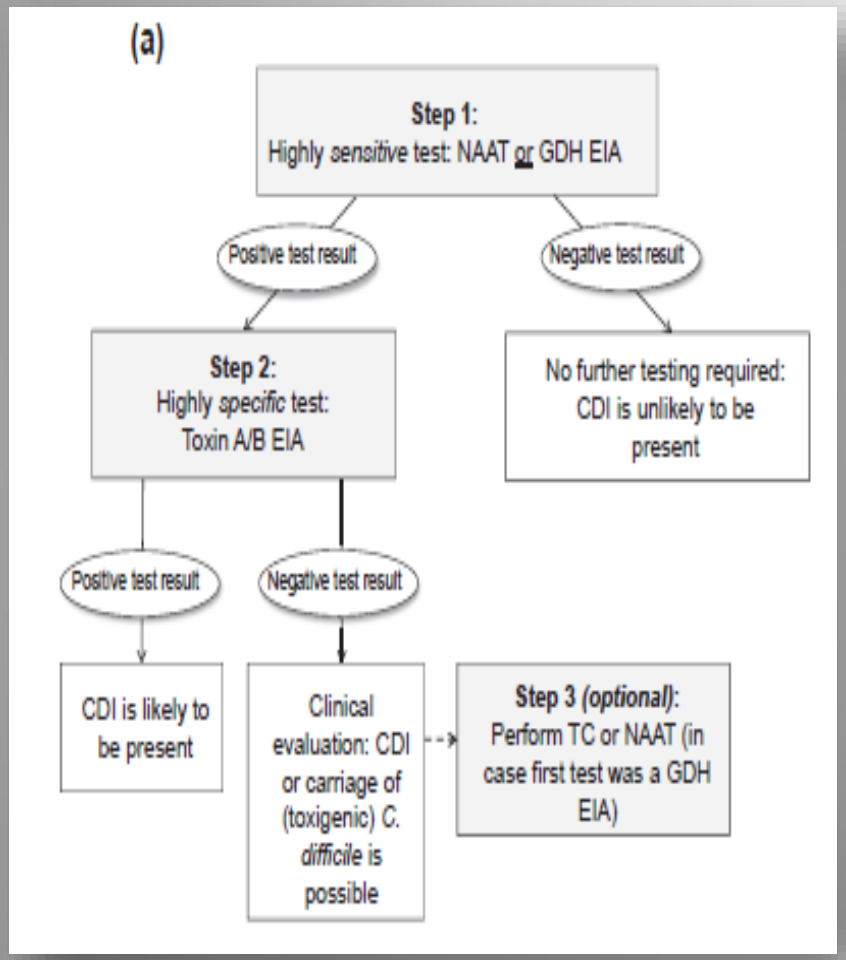
Test	Sensitivity	Specificity	Comments
Enzyme Immunoassay (EIA) for toxins A/B	63-94%	75-100%	Easy to test, cheap, quick turnaround
Culture	90-100%	98-100%	Labor-intensive, long turnaround time, cannot differentiate toxin producing vs. non-toxin
Cell Cytotoxicity Assay	67-100%	90-100%	Only detects toxin B, requires technical expertise, expensive, long turnaround time
Glutamate Dehydrogenase (GDH)	58-68%	94-98%	Easy to test, cheap, quick turnaround, need confirmatory test
Polymerase Chain Reaction (PCR)	92-97%	100%	Easy to test, quick turnaround, expensive

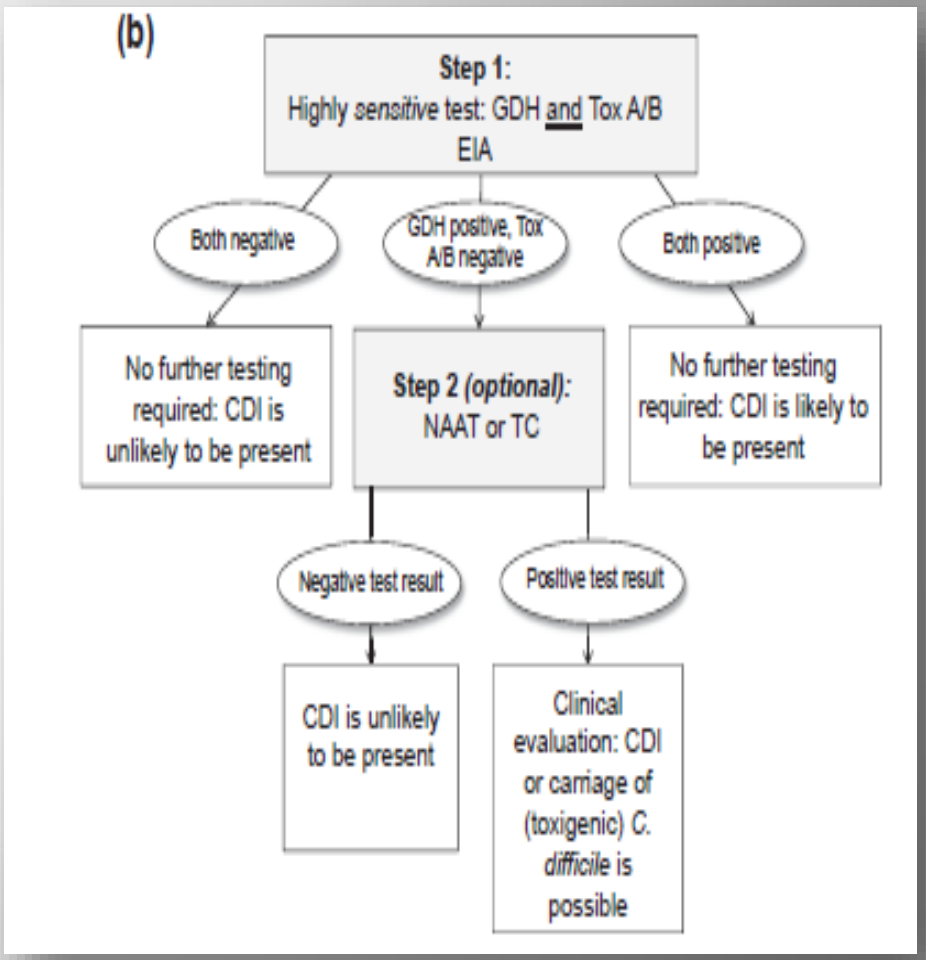
Infect Control Hosp Epidemiol 2010; 31(5):000-000

Current Issues Around Testing

- Focus is CO vs. HO
  - Diarrhea within 4 days of admit → CO → priority to get test
  - If test is not done within 72 hours of order → automatic discontinuation
  - Do not repeat test within 7-10 days, or for test of cure → SNF not accepting patients without test of cure
- Colonization vs. infection
  - PCR is "too" specific → too many patients lab-identified as *C. difficile* when not infected → over-reporting and over-treating
  - Labs evaluating GDH / EIA again, with PCR as confirmatory only as needed
  - Administration asking about testing for *C. difficile* colonization upon admit
- BI/NAP1/027
  - Not many labs have capabilities to test
  - Other rapid diagnostics with *C. difficile* testing
  - What are clinical implications?

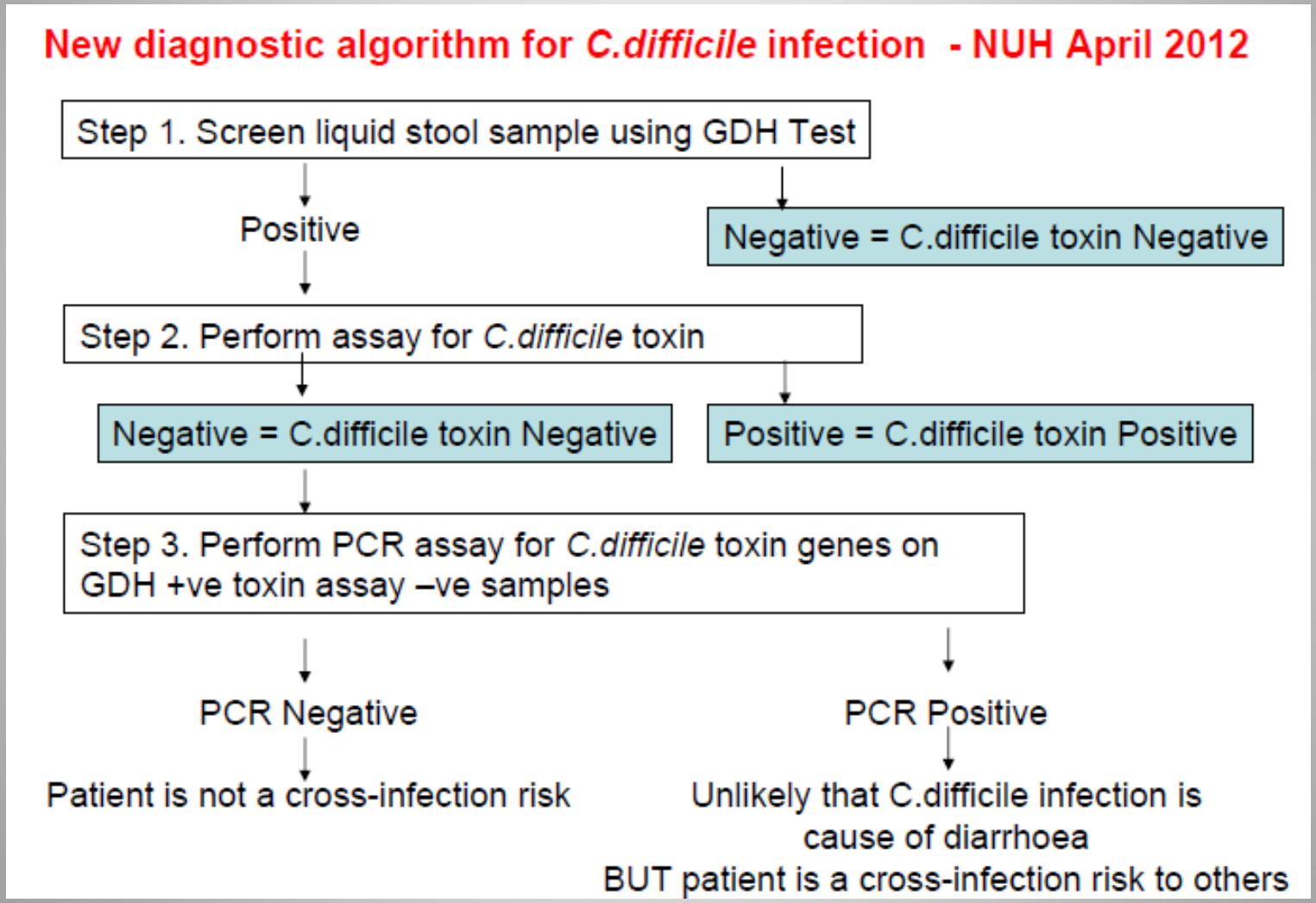
ESCMID 2016 Diagnostic Guidelines for *C. difficile*





M.J.T. Crobach et al. / Clinical Microbiology and Infection 22 (2016) S63–S81

3-Step Testing



https://www.nuh.nhs.uk/media/1069241/new_cdiff_testing_and_reporting.pdf

EIA vs. 2 Step vs. PCR Study

- Cedars Sinai evaluated differences in testing methodologies from 2008-2011

Dec 2008-Nov 2009: EIA Toxin A/B	Dec 2009-Apr 2010: GDH + PCR	May 2010: PCR, repeat within 7 days cancelled by lab
14.2% (+) result	17.5% (+) result (23.2% increase, p = 0001)	20% (+) result (41.1% vs. EIA, P,0.0001), 14.6% vs. 2ST, p = 0.02)
32.3h time to test result	26.5h time to test result	17h time to test result
Ave # treatment days: 2.12 days	No difference in empiric treatment vs. EIA	Ave # treatment days: 1.65 days (22.2% reduction, p<0.0001)
4+ days of CDI treatment: 25%	Patients with GDH (+), PCR (-) received more empiric therapy (58.6% with >4 days of tx)	4+ days of CDI treatment: 18.7% (p<0.0001)

Clin Microbiol Infect 2014; 20: 65–69

C. DIFFICILE – ANTIMICROBIAL STEWARDSHIP AND TREATMENT

2010 SHEA/IDSA Guidelines for *C. difficile*

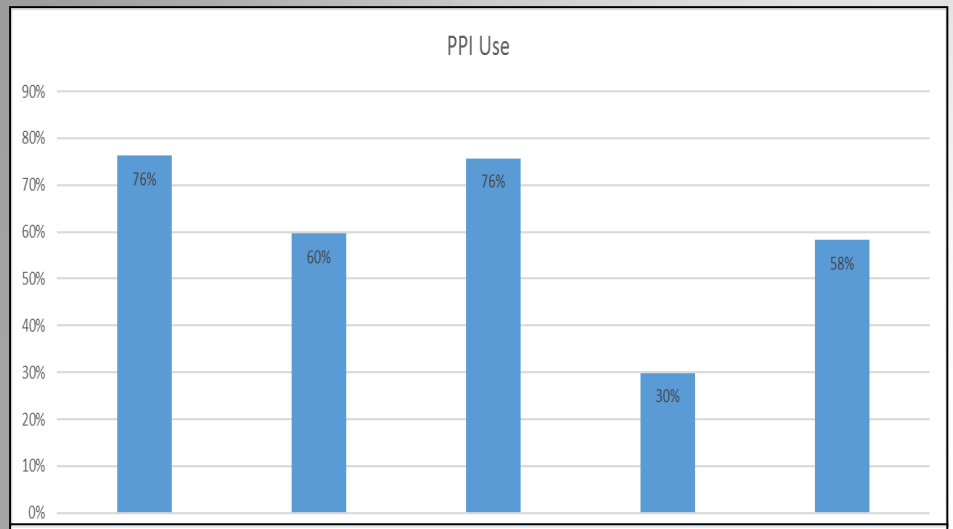
TABLE 3. Recommendations for the Treatment of *Clostridium difficile* Infection (CDI)

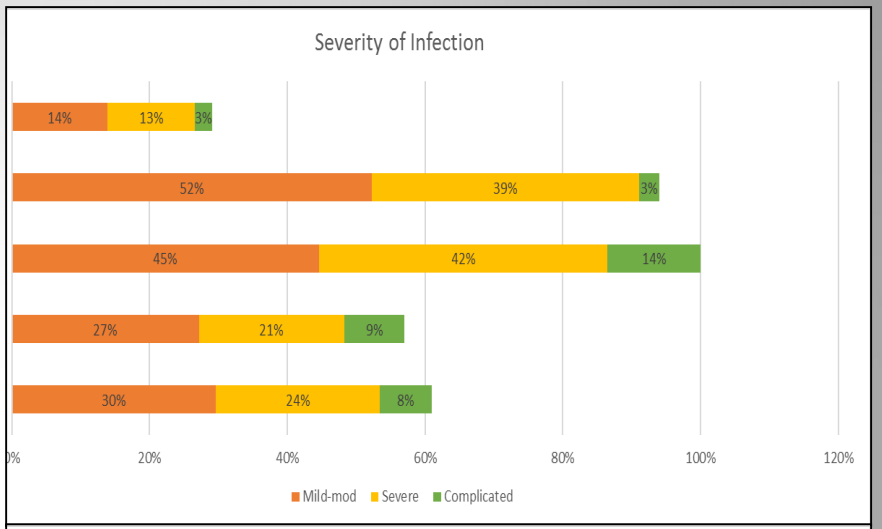
Clinical definition	Supportive clinical data	Recommended treatment	Strength of recommendation
Initial episode, mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/μL or lower and a serum creatinine level less than 1.5 times the premorbid level	Metronidazole, 500 mg 3 times per day by mouth for 10–14 days	A-I
Initial episode, severe[a]	Leukocytosis with a white blood cell count of 15,000 cells/μL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level	Vancomycin, 125 mg 4 times per day by mouth for 10–14 days	B-I
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin	C-III
First recurrence	…	Same as for initial episode	A-II
Second recurrence	…	Vancomycin in a tapered and/or pulsed regimen	B-III

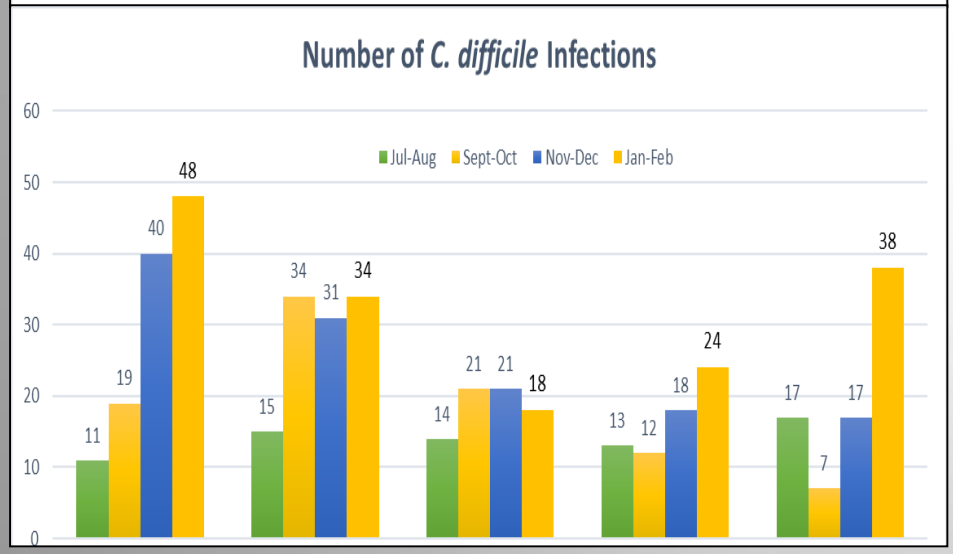
[a] The criteria proposed for defining severe or complicated CDI are based on expert opinion. These may need to be reviewed in the future upon publication of

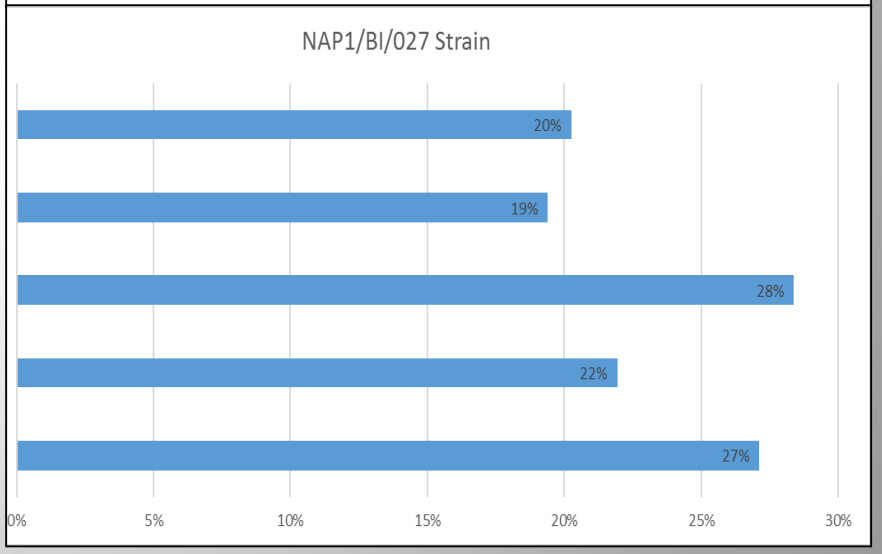
 CDI.

CDI Stewardship Metrics









Stewardship Thoughts Around NAP1/BI/027

- Known to increase 027 strain with FQ exposure → decrease FQ use
- Known hypervirulence with potential worse patient outcomes
  - What about 078 strain?
- Most probable treatment: vancomycin PO → does this increase VRE?
  - Fidaxomicin did not show better outcomes in 027
  - Metronidazole in 027 → clinical outcomes unsure
  - Surotomycin – possibly better for 027?
- Clinical implications unsure → most likely IC issue rather than clinical

J Antimicrob Chemother. 2007Jul;60(1):83-91. Epub 2007 May 5.

Fidaxomicin

Table 1. Demographic and Baseline Clinical Characteristics of the Patients in the Modified Intention-to-Treat and Per-Protocol Populations.*

Characteristic	Modified Intention-to-Treat Population			Per-Protocol Population		
	Fidaxomicin (N=287)	Vancomycin (N=309)	Total (N=596)	Fidaxomicin (N=265)	Vancomycin (N=283)	Total (N=548)
Age (yr)	60.3±16.9	62.9±16.9	61.6±16.9	59.9±17.1	62.7±17.0	61.3±17.1
Female sex (%)	57.1	54.7	55.9	57.4	54.8	56.0
Unformed stools per day (no.)	8.1±4.2	8.3±5.4	8.2±4.8	8.2±4.3	8.4±5.5	8.3±4.9
Inpatient (%)	58.2	60.5	59.4	55.1	57.2	56.2
Lack of response to metronidazole (%)	4.5	5.5	5.0	4.9	5.7	5.3
Treatment for *C. difficile* infection in previous 24 hr (%)	38.3	39.8	39.1	37.4	38.5	38.0
Previous episode of *C. difficile* infection (%)	16.7	17.5	17.1	16.2	17.0	16.6
BI/NAP1/027 strain (%)†	37.5	38.6	38.1	35.3	36.4	35.9

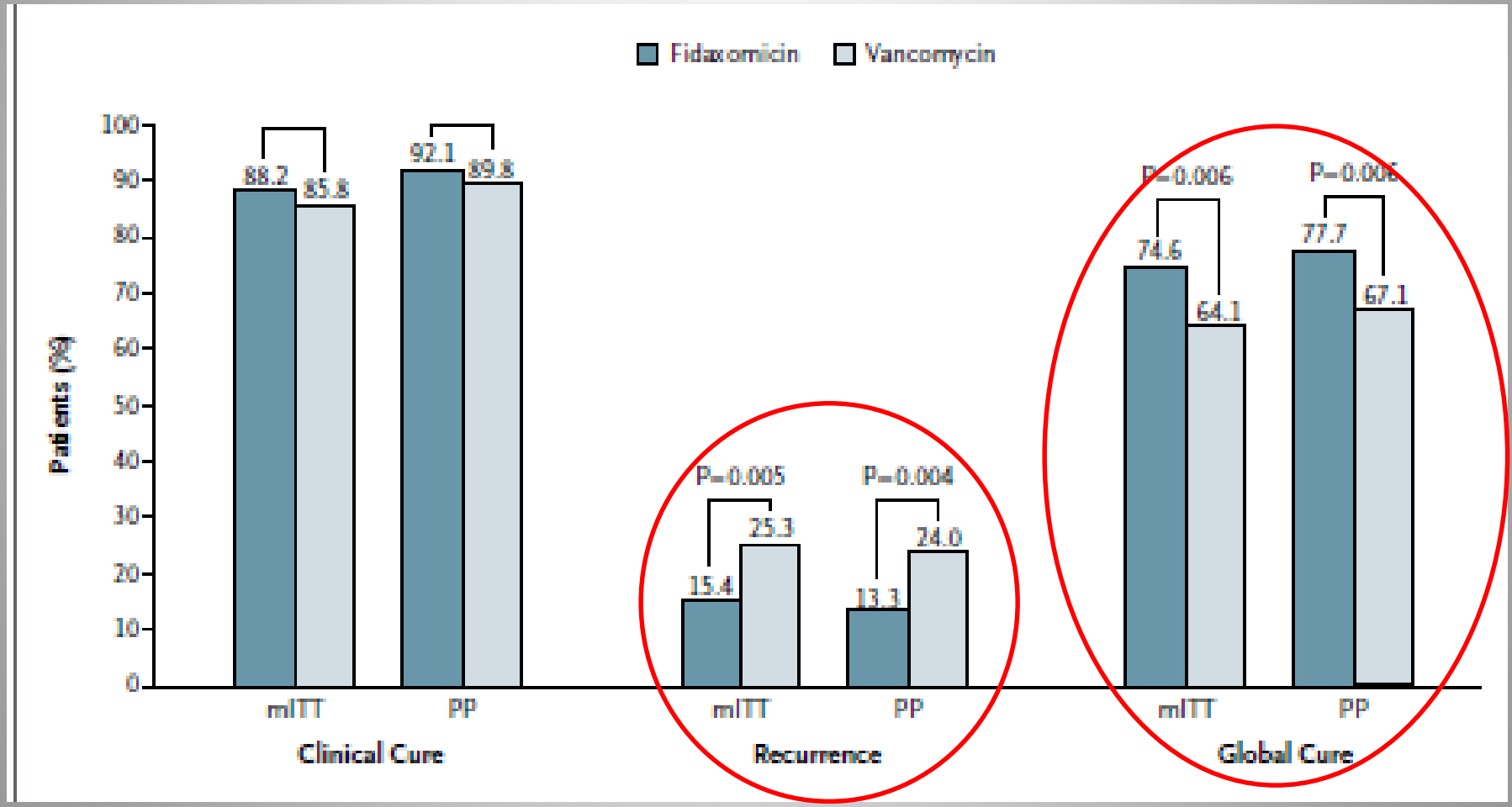
Table 2. Rates of Clinical Cure at the End of Therapy, According to Subgroups, in the Modified Intention-to-Treat and Per-Protocol Populations.*

Subgroup	Modified Intention-to-Treat Population		Per-Protocol Population	
	Fidaxomicin	Vancomycin	Fidaxomicin	Vancomycin
	number/total number (percent)			
Age				
<65 yr	150/165 (90.9)	134/157 (85.4)	145/152 (95.4)	132/145 (91.0)
≥65 yr	103/122 (84.4)	131/152 (86.2)	99/113 (87.6)	122/138 (88.4)
Hospital status				
Inpatient	136/167 (81.4)	146/187 (78.1)	128/146 (87.7)	136/162 (84.0)
Outpatient	117/120 (97.5)	119/122 (97.5)	116/119 (97.5)	118/121 (97.5)
Previous episode of *C. difficile* infection				
No	211/239 (88.3)	217/255 (85.1)	203/222 (91.4)	209/235 (88.9)
Yes	42/48 (87.5)	48/54 (88.9)	41/43 (95.3)	45/48 (93.8)
Treatment for current episode of *C. difficile* infection in previous 24 hr				
Yes	88/110 (80.0)	97/123 (78.9)	85/99 (85.9)	92/109 (84.4)
No	165/177 (93.2)	168/186 (90.3)	159/166 (95.8)	162/174 (93.1)
Severity of disease				
Mild	59/64 (92.2)	68/80 (85.0)	56/59 (94.9)	63/71 (88.7)
Moderate	102/111 (91.9)	88/106 (83.0)	99/105 (94.3)	84/97 (86.6)
Severe	92/112 (82.1)	109/123 (88.6)	89/101 (88.1)	107/115 (93.0)
Strain type				
NAP1/BI/027	59/75 (78.7)	67/83 (80.7)	56/65 (86.2)	61/72 (84.7)
Non–NAP1/BI/027	117/125 (93.6)	121/132 (91.7)	115/119 (96.6)	119/126 (94.4)
Lack of response to metronidazole before study				
Yes	13/13 (100.0)	15/17 (88.2)	13/13 (100.0)	14/16 (87.5)
No	240/274 (87.6)	250/292 (85.6)	231/252 (91.7)	240/267 (89.9)
Concomitant systemic antimicrobial therapy				
Yes	67/83 (80.7)	72/94 (76.6)	63/71 (88.7)	67/80 (83.8)
No	186/204 (91.2)	193/215 (89.8)	181/194 (93.3)	187/203 (92.1)

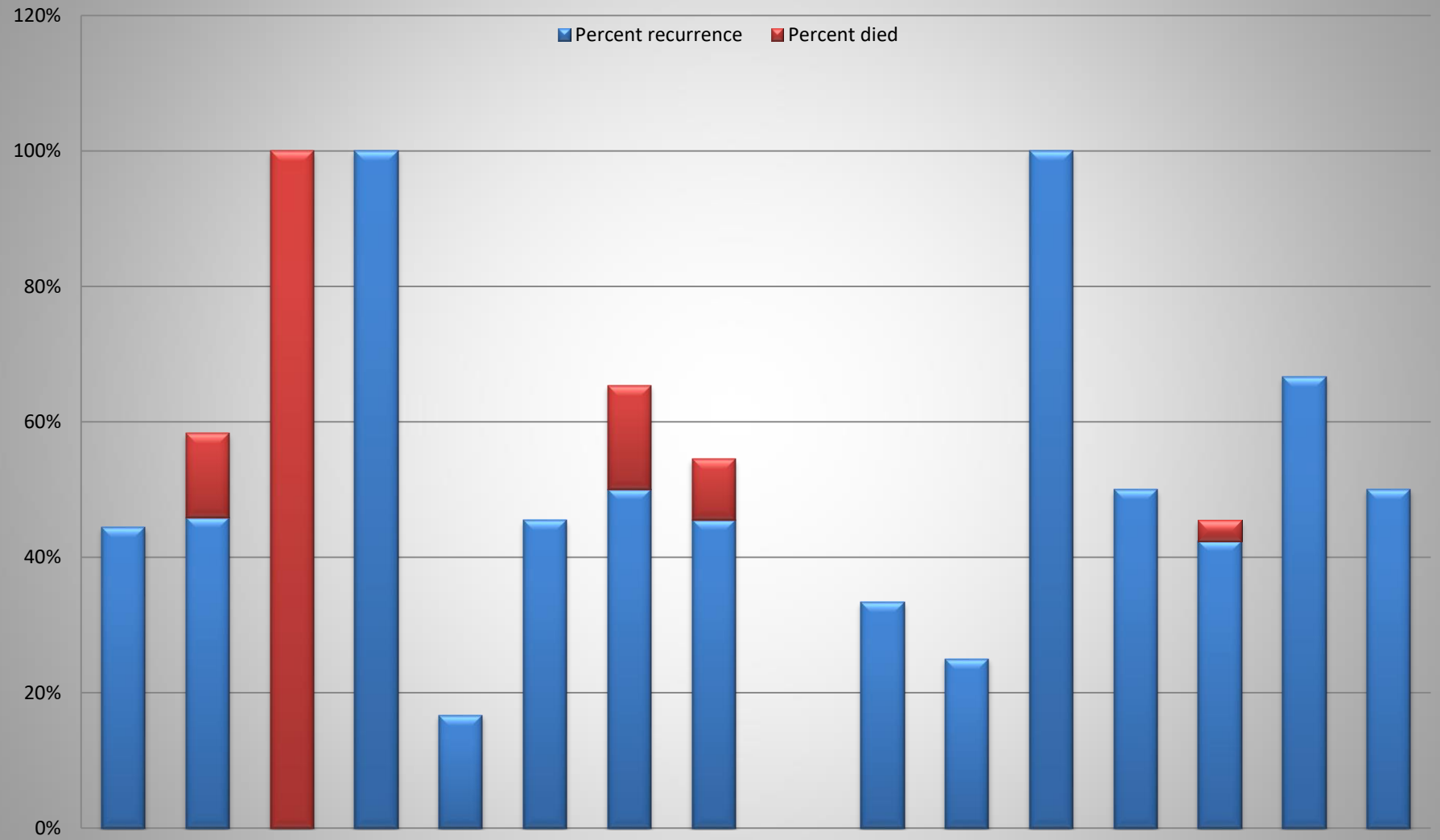
Table 3. Rates of Recurrence of *C. difficile* Infection, According to Subgroups, in the Modified Intention-to-Treat and Per-Protocol Populations.

Subgroup	Modified Intention-to-Treat Population			Per-Protocol Population		
	Fidaxomicin	Vancomycin	PValue	Fidaxomicin	Vancomycin	PValue
	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
Treatment for current episode of *C. difficile* infection in previous 24 hr						
Yes	16/88 (18.2)	25/97 (25.8)	0.22	13/73 (17.8)	19/81 (23.5)	0.39
No	23/165 (13.9)	42/168 (25.0)	0.01	15/138 (10.9)	34/140 (24.3)	0.003
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

Fidaxomicin Global Cure



Fidaxomicin MUE



Fecal Transplant

CONSENT FOR
MICROBIOTIC TRANSFER OF FECALLY
DERIVED BACTERIA

1. **CONSENT FOR PROCEDURE**

A. I understand my diagnosis/condition is Clostridium difficile infection.

B. I hereby authorize _____ and his/her associates or assistants but not limited to residents or fellows who are at this healthcare facility to perform the following procedure: Microbiotic Transfer of Fecally Derived Bacteria

C. The (physician/provider) has fully explained to me the above procedure the anticipated benefits, materials risks, alternative therapies, potential problems during recuperation and likelihood of achieving my goals. I have been given an opportunity to ask questions and all my questions have been answered fully and satisfactorily.

D. Understanding of this form. I confirm that I have read this form, fully understand its contents, and that all the blank spaces have been completed prior to my signing. I understand that no guarantees or assurances have been made to me concerning the results intended from the procedure above.

E. I understand the following:

1. I have been made aware of certain risks and consequences that are associated with this particular procedure. These include:

a) Donors are screened and undergo testing for many common communicable diseases to ensure that the procedure is done as safely as possible, but that it is not possible to test donors for all possible organisms and some infections may be undetectable.

OpenBiome

Order Information

E. ORDER INFORMATION		
ITEM	**DESCRIPTION**	**UNIT PRICE**
FMP250	FMT Lower Delivery	$385
FMP30	FMT Upper Delivery	$385
FMPCapG3	FMT Capsule G3 (physician orientation required before first order)	$535
Standard S&H	Flat Shipping & Handling fee per shipment, waived on orders of 10 units or more	$150
Same-day Shipping	Order must be received before 3pm ET Mon-Thur. Availability not guaranteed	Additional $50
First Overnight	Approximate 8am local delivery time, compared to approximate 10:30am Standard delivery time	Additional $100

Current Issues Around Fecal Transplant

- How many doses need to be administered?
- Optimal route of administration?
- Frozen vs. Fresh samples?
- Bowel prep ± vancomycin taper?
- Follow-up?

Hospital Protocols for Fecal Transplant

- UNC: https://www.med.unc.edu/gi/faculty-staff-website/patient-education/1FecalTransplantProtocols.pdf
- U of Indiana: http://medicine.iupui.edu/gast/programs/fecal-microbiota
- Stanford (using Openbiome): http://med.stanford.edu/bugsanddrugs/guidebook/jcr:content/main/panel_builder_1454513702/panel_0/download_1985839819/file.res/OpenbiomeFMTprotocol_6-1-15.pdf
- Johns Hopkins: http://www.hopkinsmedicine.org/gastroenterology_hepatology/clinical_services/advanced_endoscopy/fecal_transplantation.html
- UW: https://www.uwhealth.org/healthfacts/dhc/7878.pdf
- Cleveland Clinic: https://health.clevelandclinic.org/2014/05/despite-the-ick-factor-fecal-procedure-works-wonders/

Bezlotoxumab (Zinplava)

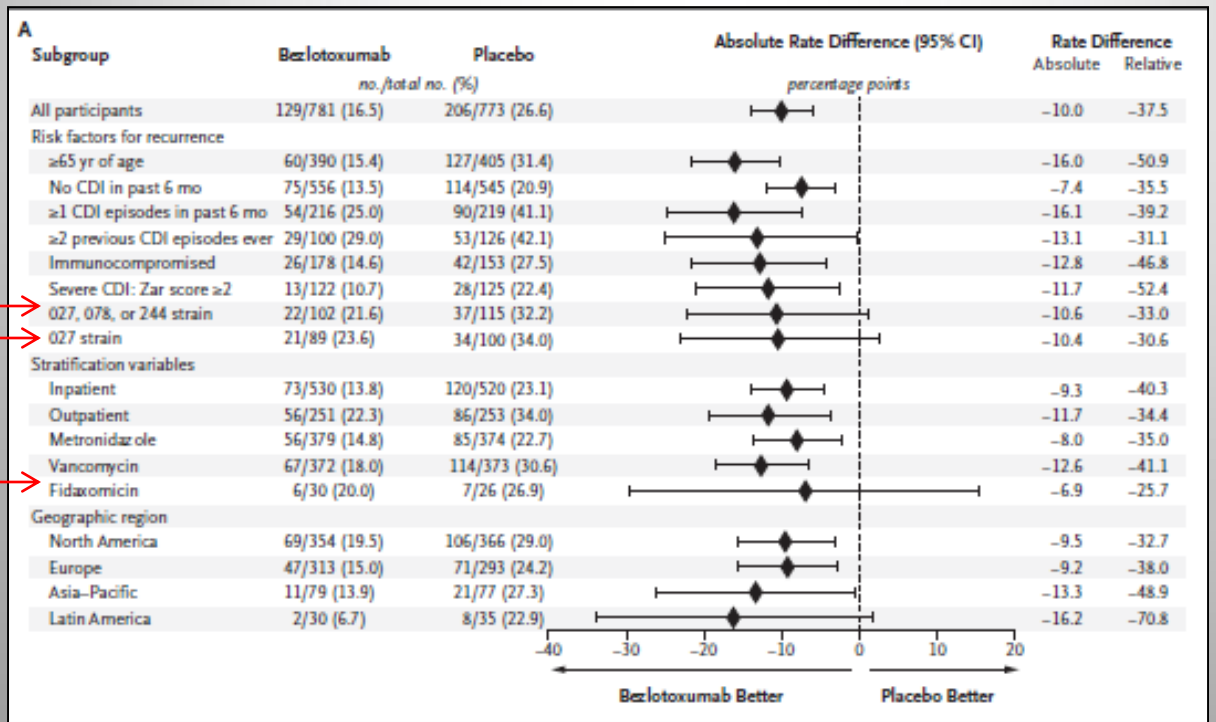
- Actoxumab neutralize toxin A, bezlotoxumab neutralize toxin B
  - Fully human monoclonal antibodies

- **MODIFY I and II** trials: 322 sites, 30 countries, Nov 1, 2011-May 22, 2015
- Primary Outcome: recurrence within 12 weeks in mITT
  - Tx: PO metronidazole, PO vancomycin/fidaxmicin +/- IV metronidazole x 10-14d
  - Day 1, 60-min infusion: 1:1:1 bezlotoxumab 10mg/kg vs. actoxumab+bezlotoxumab 10mg/kg each vs. NS
  - >90% power to detect 9-10% difference in recurrence

N Engl J Med 2017;376:305-17

Bezlotoxumab (Zinplava) Results

- 2559 patients in mITT, 2174 patients completed 12 weeks
  - Median age: 66 years, 86% white, 56% women, 68% inpatient
  - Tx: 47% metronidazole, 48% vancomycin, 4% fidaxomicin
- NNT to prevent 1 recurrence:: 10
  - Age >65yo or previous CDI: NNT 6



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Subgroup	Bezlotoxumab	Placebo	Absolute Rate Difference (95% CI)	Rate Difference Absolute	Rate Difference Relative
	no./total no. (%)		percentage points		
All participants	129/781 (16.5)	206/773 (26.6)		−10.0	−37.5
Risk factors for recurrence					
≥65 yr of age	60/390 (15.4)	127/405 (31.4)		−16.0	−50.9
No CDI in past 6 mo	75/556 (13.5)	114/545 (20.9)		−7.4	−35.5
≥1 CDI episodes in past 6 mo	54/216 (25.0)	90/219 (41.1)		−16.1	−39.2
≥2 previous CDI episodes ever	29/100 (29.0)	53/126 (42.1)		−13.1	−31.1
Immunocompromised	26/178 (14.6)	42/153 (27.5)		−12.8	−46.8
Severe CDI: Zar score ≥2	13/122 (10.7)	28/125 (22.4)		−11.7	−52.4
027, 078, or 244 strain	22/102 (21.6)	37/115 (32.2)		−10.6	−33.0
027 strain	21/89 (23.6)	34/100 (34.0)		−10.4	−30.6
Stratification variables					
Inpatient	73/530 (13.8)	120/520 (23.1)		−9.3	−40.3
Outpatient	56/251 (22.3)	86/253 (34.0)		−11.7	−34.4
Metronidazole	56/379 (14.8)	85/374 (22.7)		−8.0	−35.0
Vancomycin	67/372 (18.0)	114/373 (30.6)		−12.6	−41.1
Fidaxomicin	6/30 (20.0)	7/26 (26.9)		−6.9	−25.7
Geographic region					
North America	69/354 (19.5)	106/366 (29.0)		−9.5	−32.7
Europe	47/313 (15.0)	71/293 (24.2)		−9.2	−38.0
Asia–Pacific	11/79 (13.9)	21/77 (27.3)		−13.3	−48.9
Latin America	2/30 (6.7)	8/35 (22.9)		−16.2	−70.8

N Engl J Med 2017;376:305-17

Table 3 : Results of Clinical Cure, CDI Recurrence and Global Cure (FAS) in Study P001

	Acto plus Bezlo n=383	Actoxumab n=232	Bezlotoxumab n=386	Placebo n=395
Clinical Cure	286 (74.7) -8.2 (-13.9, -2.4) **p=0.0057**	169 (72.8) -10.0 (-16.8, -3.2) p=0.0031	299 (77.5) -5.3 (-10.9, 0.3) p=0.0622	327 (82.8)
CDI Recurrence	61 (15.9) -11.6 (-17.3, -5.9) **p<0.0001**	60 (25.9) -1.7 (-8.8, 5.4) p=0.6368	67 (17.4) -10.1 (-15.9, -4.3) **p=0.0006**	109 (27.6)
Global Cure	225 (58.7) 3.5 (-3.4, 10.4) p=0.3165	109 (47.0) -8.3 (-16.4, -0.3) p=0.0470	232 (60.1) 4.8 (-2.1, 11.7) p=0.1647	218 (55.2)

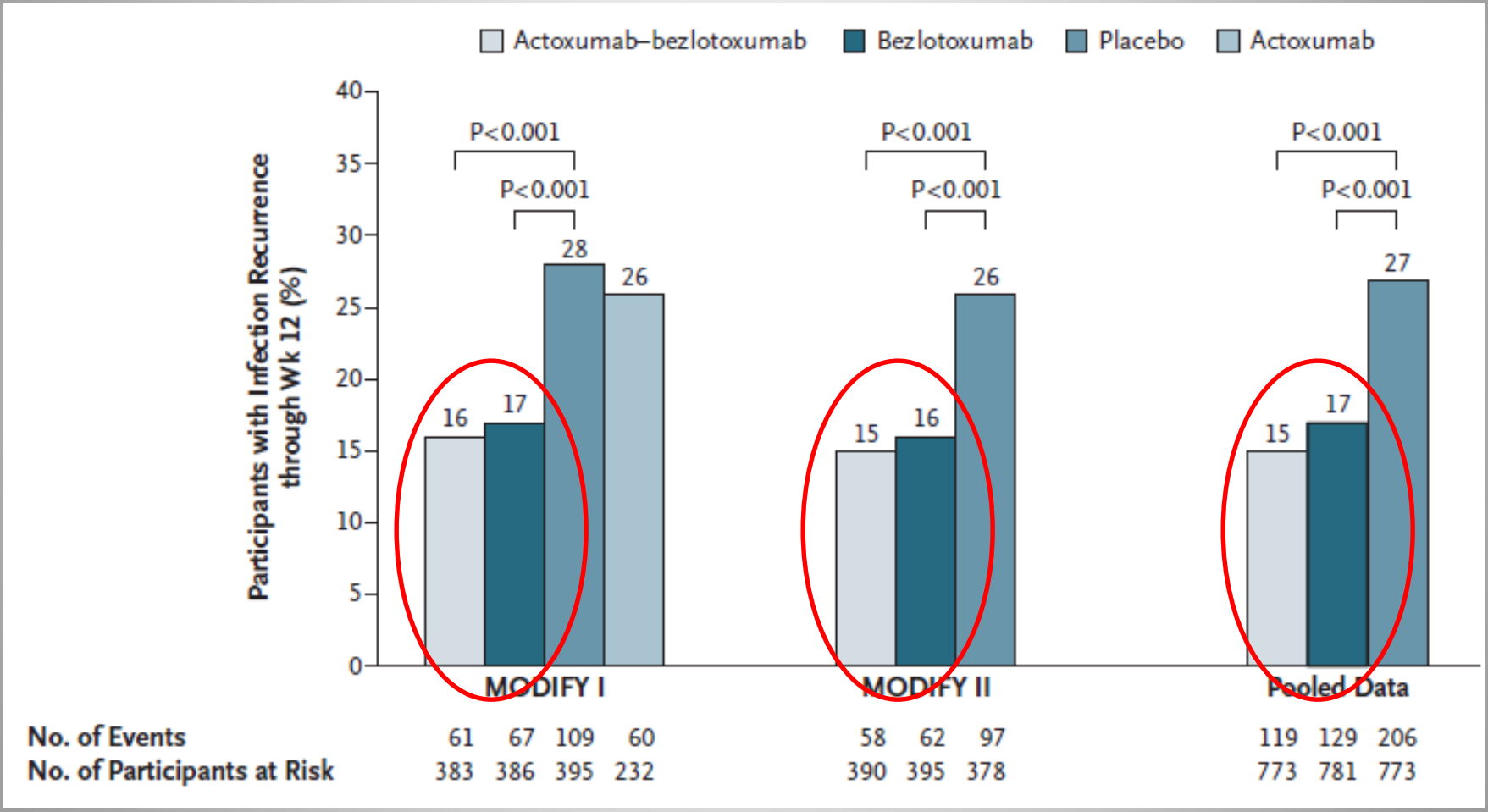
Difference (95% CI) for monoclonal antibody - placebo

Table 4: Results of Clinical Cure, CDI Recurrence and Global Cure (FAS) in Study P002

	Acto plus Bezlo (n=390)	Bezlotoxumab (n=395)	Placebo (n=378)
Clinical Cure	282 (72.3) -5.5 (-11.6, 0.6) p=0.0801	326 (82.5) 4.8 (-0.9, 10.4) p=0.0973	294 (77.8)
CDI Recurrence	58 (14.9) -10.7 (-16.3, -5.1) **p=0.0002**	62 (15.7) -9.9 (-15.5, -4.2) **p=0.0006**	97 (25.7)
Global Cure	224 (57.4) 5.2 (-1.7, 12.2) p=0.1386	264 (66.8) 14.6 (7.8, 21.4) **p<0.0001**	197 (52.1)

Difference (95% CI) for monoclonal antibody – placebo

Recurrent *C. difficile* Infection, 12 weeks



N Engl J Med 2017;376:305-17

Table 2. Clinical Adverse Events in the As-Treated Population in Both Trials.

Time Period and Event	Actoxumab plus Bezlotoxumab (N=777)	Bezlotoxumab (N=786)	Actoxumab (N=235)	Placebo (N=781)
	number of participants (percent)			
During the 24 hours after infusion				
Infusion-specific reaction*	62 (8.0)	81 (10.3)	26 (11.1)	59 (7.6)
Treatment stopped because of an adverse event	0	1 (0.1)	1 (0.4)	0
During the 4 weeks after infusion				
One or more adverse events	455 (58.6)	485 (61.7)	158 (67.2)	478 (61.2)
Serious adverse event	123 (15.8)	156 (19.8)	65 (27.7)	167 (21.4)
Death	28 (3.6)	32 (4.1)	14 (6.0)	32 (4.1)
Drug-related adverse event†	50 (6.4)	59 (7.5)	17 (7.2)	46 (5.9)
Serious drug-related adverse event‡	5 (0.6)	4 (0.5)	3 (1.3)	2 (0.3)
Most common adverse events§				
Abdominal pain	32 (4.1)	34 (4.3)	15 (6.4)	34 (4.4)
Diarrhea	46 (5.9)	47 (6.0)	13 (5.5)	45 (5.8)
Nausea	47 (6.0)	52 (6.6)	28 (11.9)	39 (5.0)
Vomiting	24 (3.1)	31 (3.9)	10 (4.3)	21 (2.7)
Fatigue	21 (2.7)	18 (2.3)	11 (4.7)	12 (1.5)
Pyrexia	31 (4.0)	36 (4.6)	11 (4.7)	27 (3.5)
C. difficile infection¶	27 (3.5)	23 (2.9)	20 (8.5)	48 (6.1)
Urinary tract infection	24 (3.1)	32 (4.1)	13 (5.5)	35 (4.5)
Headache	33 (4.2)	35 (4.5)	14 (6.0)	24 (3.1)
During the 12 weeks after infusion				
Serious adverse event‖	212 (27.3)	231 (29.4)	104 (44.3)	255 (32.7)
Death	51 (6.6)	56 (7.1)	27 (11.5)	59 (7.6)

Nevada Antimicrobial Stewardship
HAI Caucus 2017

Updates on *C. difficile* Testing and Treatment

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