Clinical Pearls in Infectious Diseases

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No conflict commercial interest

Clinical Pearls in *C. Difficile* Infections

Objectives

- Compare and contrast recommended and emergent treatment options for recurrent *C. difficile* infections
- Review the primary literature supporting current guidelines recommendations
- Evaluate changes in the most updated guideline recommendations

Clostridioides Difficile Infection (CDI)

- Gram positive, spore-forming, gram-positive bacteria
- Produces exotoxins that act upon epithelial cells, leading to tissue injury and diarrhea

Diagnosis

- **Clinical Diagnosis:**
  1. Diarrhea (≥3 in 24 hours), Megacolon or Severe Ileus

     PLUS

  2. Positive laboratory diagnostic test result

- Can be classified as:
  - Non severe infection
  - Severe infection (WBC ≥ 15,000 **or** Scr >1.5mg/dl)
  - Fulminant infection (Shock, ileus, megacolon)

CID 2018:66 (1 April) • McDonald et al

Bristol Stool Scale

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage, but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces (entirely liquid)

Stick Test!

https://www.researchgate.net/figure/The-Bristol-Stool-Form-Scale-This-scale-is-a-useful-tool-to-evaluate-stool-and-can_fig1_330943567 Accessed 10/23/2020

Initial Therapy

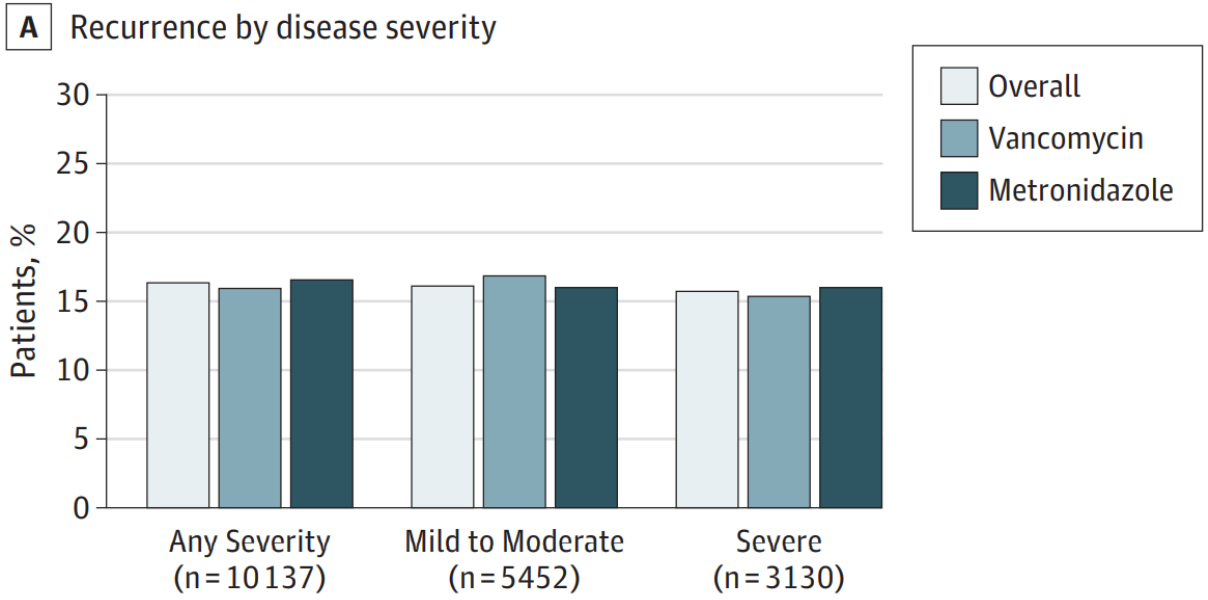
Disease Severity	2010 IDSA/SHEA Guidelines	2018 IDSA/SHEA Guidelines
Non-Severe (Mild to Moderate)	**Metronidazole** 500mg PO TID for 10-**14** days	Vancomycin 125mg PO QID for 10 days **OR** **Fidaxomicin** 200mg PO BID for 10 days (If other N/A: Metronidazole 500mg PO TID for 10days)
Severe	Vancomycin 125mg PO QID for 10-**14** days	Same as above (no metronidazole)
Fulminant (severe-complicated)	Vancomycin 500mg PO QID PLUS Metronidazole 500mg IV q8h (rectal vancomycin if ileus present)	Vancomycin 500mg PO QID **PLUS** Metronidazole 500mg **IV** q8h (rectal vancomycin if ileus present)

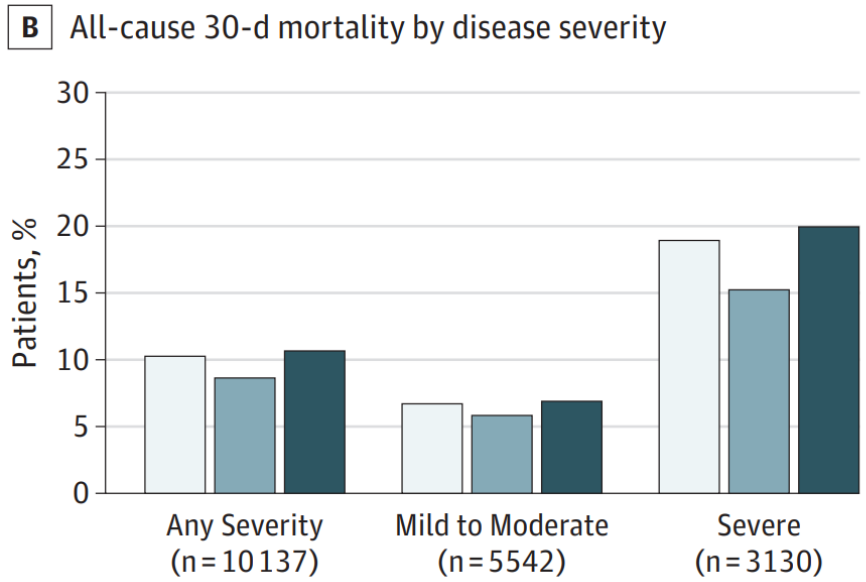
CID 2018:66 (1 April) • McDonald et al

Vancomycin vs Metronidazole

- Vancomycin was consistently showed improved outcomes when compared to metronidazole

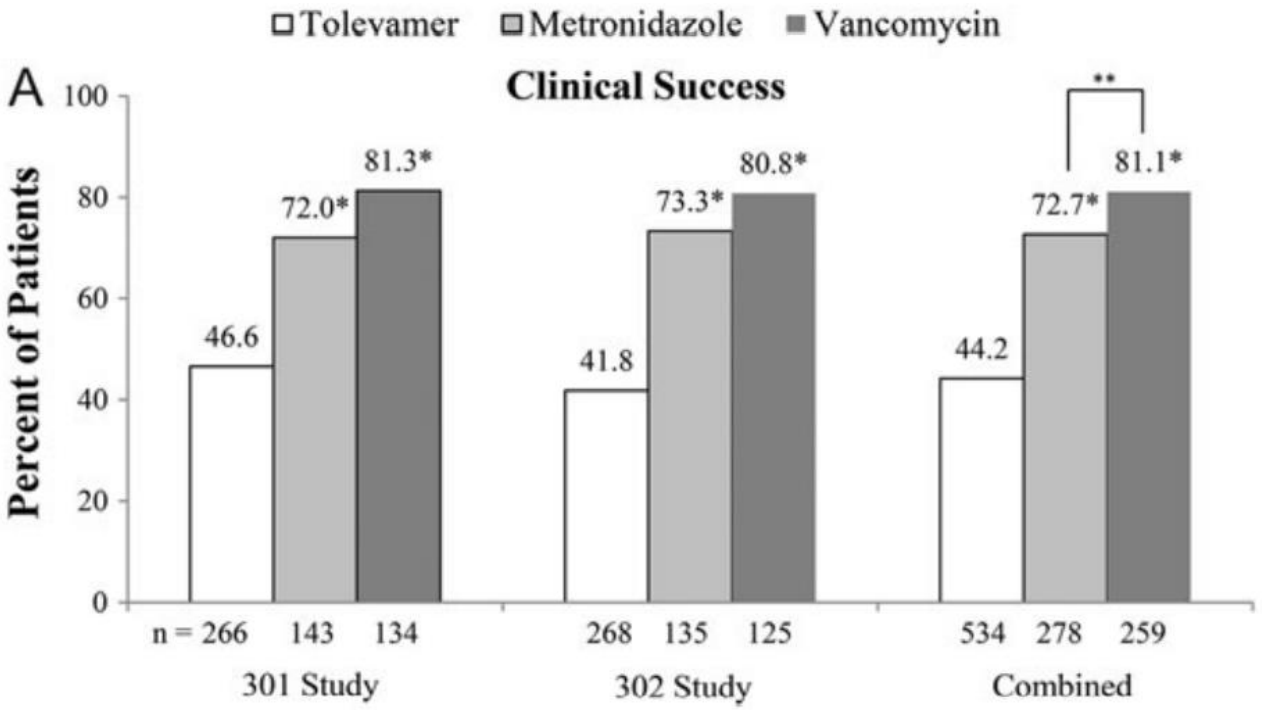
Clinical Cure	Mortality	Recurrence (at 8 weeks)
Increased (81 vs 73%)	Decreased (12.4% vs 8.6%)	Similar

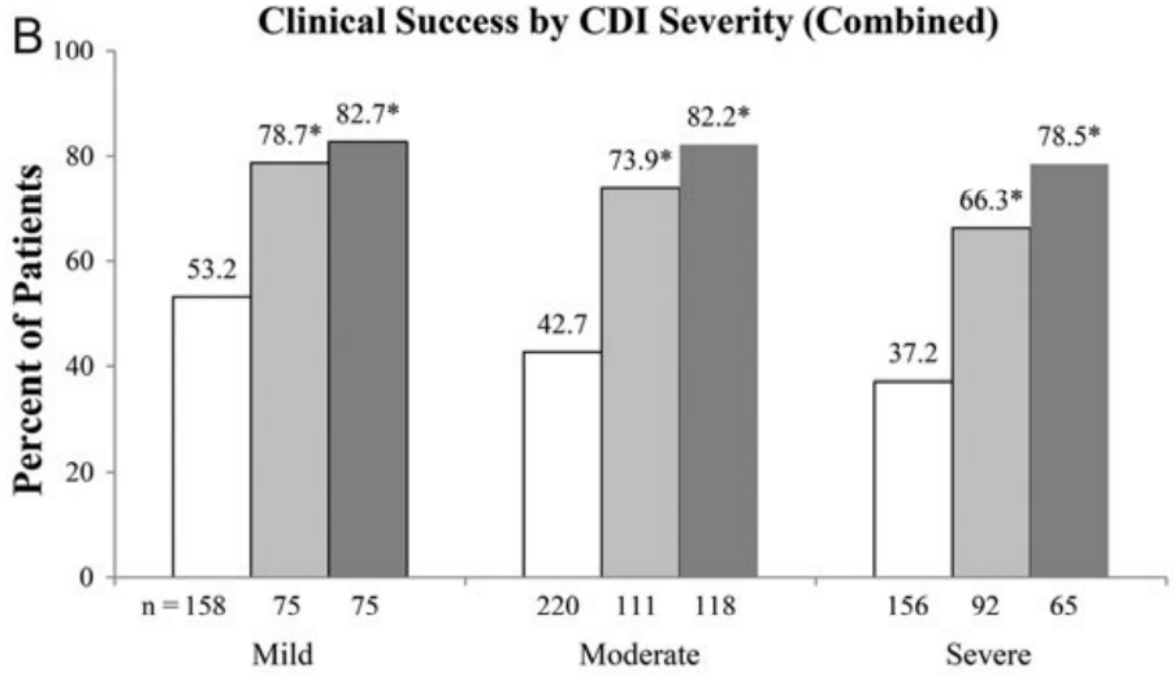




JAMA April 2017 Volume 177, Number 4

Vancomycin vs Metronidazole





CID 2014:59 (1 August) • Johnson et al

Question #1: Why did the recommendations for an initial episode of non-severe CDI change?

a) Vancomycin showed increased mortality
b) Vancomycin is better absorbed
c) Metronidazole has less propensity for drug interactions
d) Metronidazole showed decreased clinical cure rates

Recurrent CID

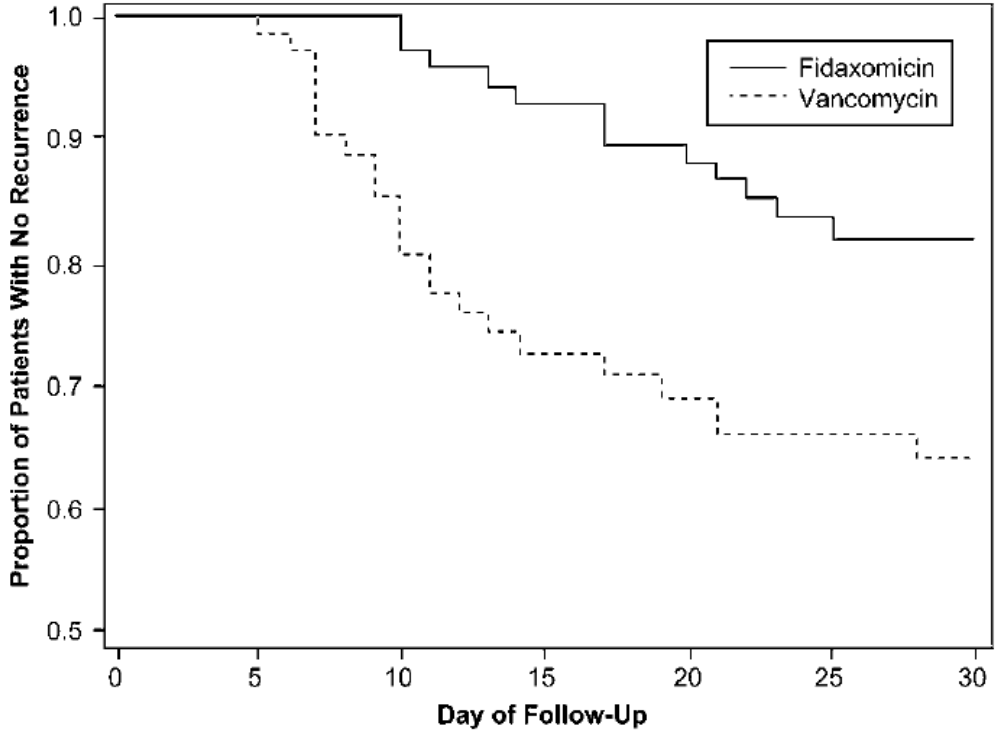
Symptom onset **AND** positive assay following an episode with positive assay result in the **last 2-8 weeks**

Disease Severity	2010 IDSA/SHEA Guidelines	2018 IDSA/SHEA Guidelines
First Recurrence	**Same as initial episode**	If metronidazole was used first: **Vancomycin** 125mg PO QID for 10 days **followed by** **Vancomycin pulse/taper** **OR** If vancomycin was used first: **Fidaxomicin** 200mg PO BID for 10 days
Second Recurrence	Vancomycin pulse/taper	**Vancomycin pulse/taper** **OR** **Fidaxomicin** 200mg PO BID for 10 days **OR** **Vancomycin** 125mg PO QID for 10 days **followed by** **Rifaximin** 400mg PO daily for 20 days **OR** **Fecal microbiota transplantation (FMT)**

CID 2018:66 (1 April) • McDonald et al

Fidaxomicin vs Vancomycin

- Fidaxomicin
  - Narrow spectrum
  - More potent
  - May halt sporulation
  - May suppress toxin production



Clinical Cure	Mortality	Recurrence (at 8 weeks)
Similar	Similar	Decreased (~14.5 *vs* ~25.3 %)

CID 2012:55 (Suppl 2) • Cornely et al

Fidaxomicin vs Vancomycin

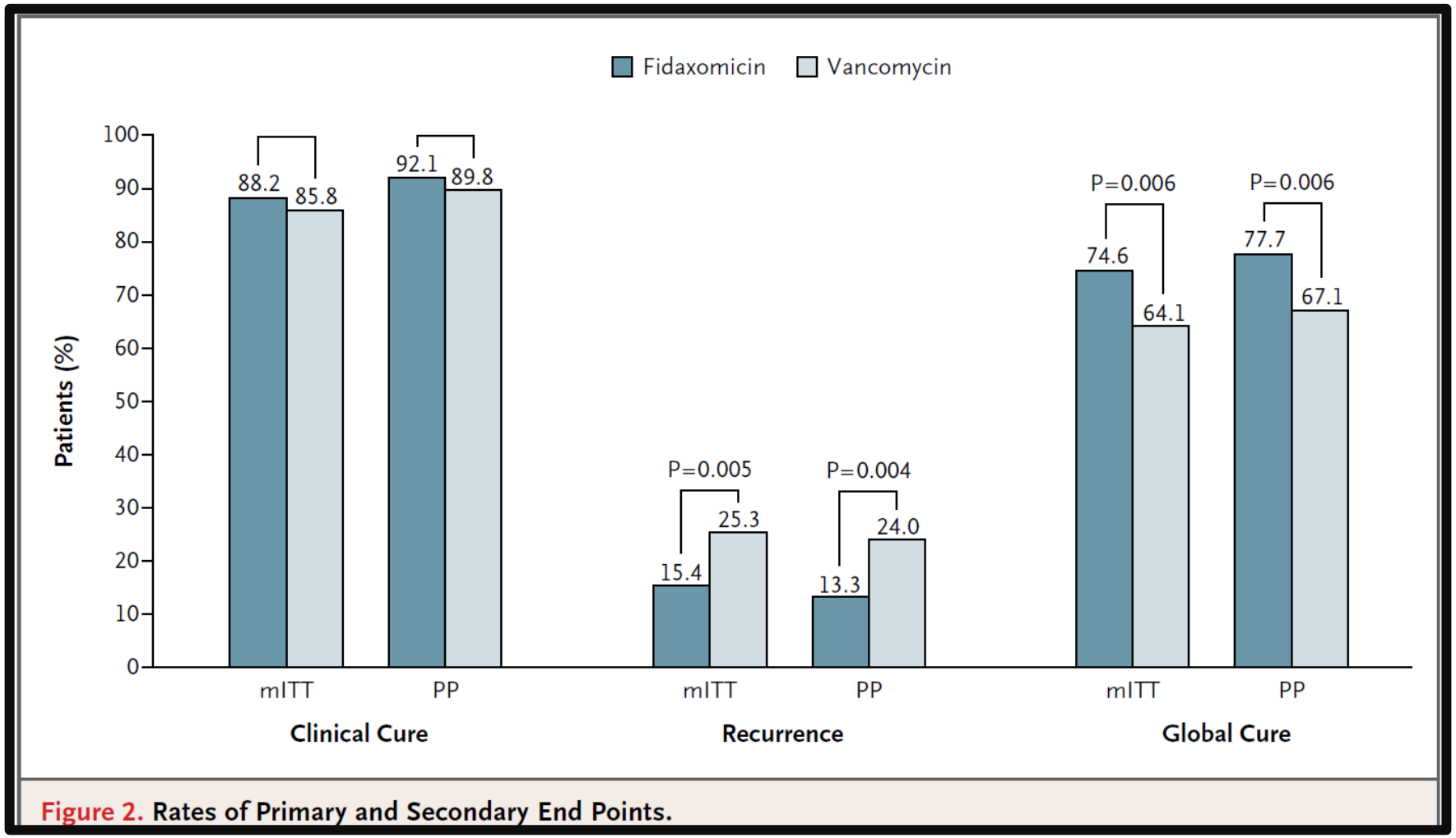


Figure 2. Rates of Primary and Secondary End Points.

N Engl J Med 2011; 364:422-431

Vancomycin Taper

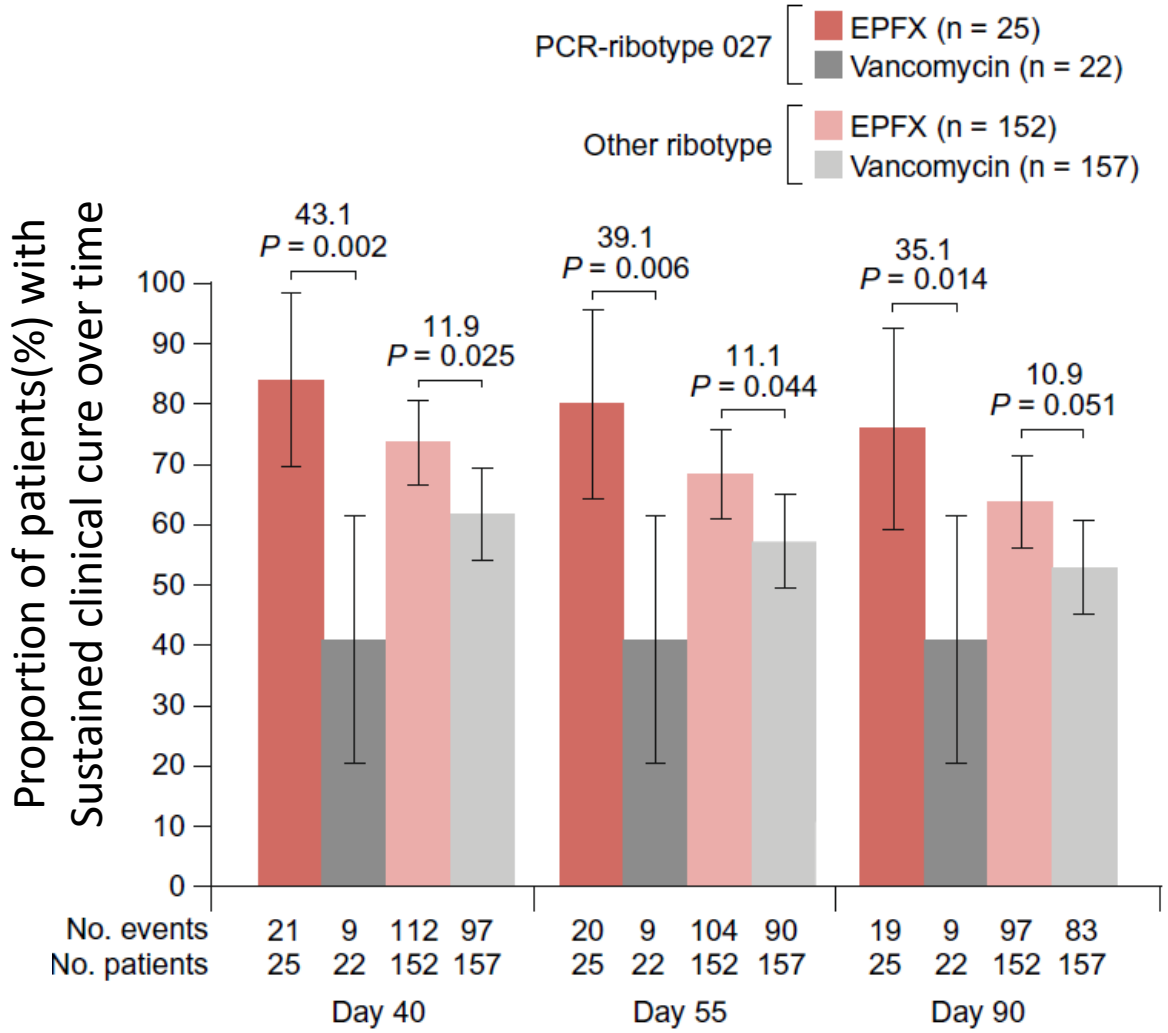
- Vancomycin pulsed-tapered regimen (dose: 125mg oral):

- Very limited data
- Rationale: Kills *C. diff* as it germinates from spores
- Non- RCT (n=163, recurrent CDI)
  - Vancomycin-tapered regimen (n= 29) recurrence rates of 31%
  - Vancomycin pulsed regimen (n= 7) recurrence rates were 14%
  - Other regimen: recurrence rate of 45%

Am J Gastroenterol. 1985;80(11):867
Am J Gastroenterol. 2002;97(7):1769
Clin Infect Dis. 2017;64(3):265. Epub 2016 Nov 9.

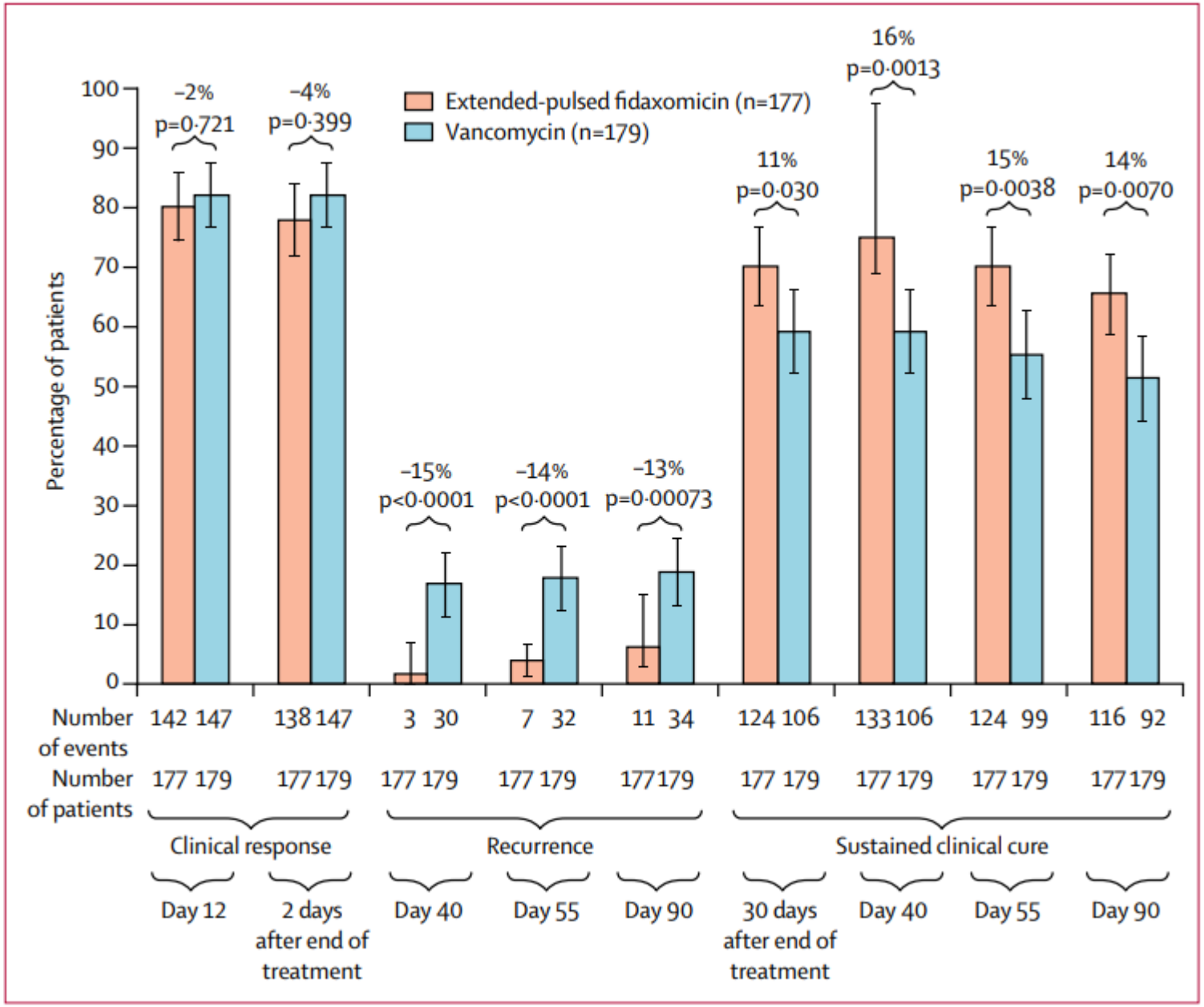
Fidaxomicin: Extended-Pulsed Regimen

- Fidaxomicin 200mg
  - Day 1 to 5: twice daily
  - Day 7 to 25: every other day
- Same total amount of tablets
- Demonstrated greater sustained clinical response and decreased recurrence rates *vs* standard vancomycin



Eur J Clin Microbiol Infect Dis. 2019; 38(6): 1187–1194

EXTEND: Randomized, controlled, open-label, phase 3b/4 trial



Lancet Infect Dis 2018; 18: 296–307

Question #2: When compared to vancomycin, what clinical outcomes were observed with fidaxomicin?

a) Greater mortality benefit
b) Increased hospitalizations
c) Decreased recurrence rates
d) Decreased hepatotoxicity

Bezlotoxumab

- Monoclonal antibody that targets *C. difficile* toxin B
- Does not directly attack or kill *C. difficile*
- Should be cautious in patients with heart failure
- The main benefit seen is in reducing the risk of recurrence

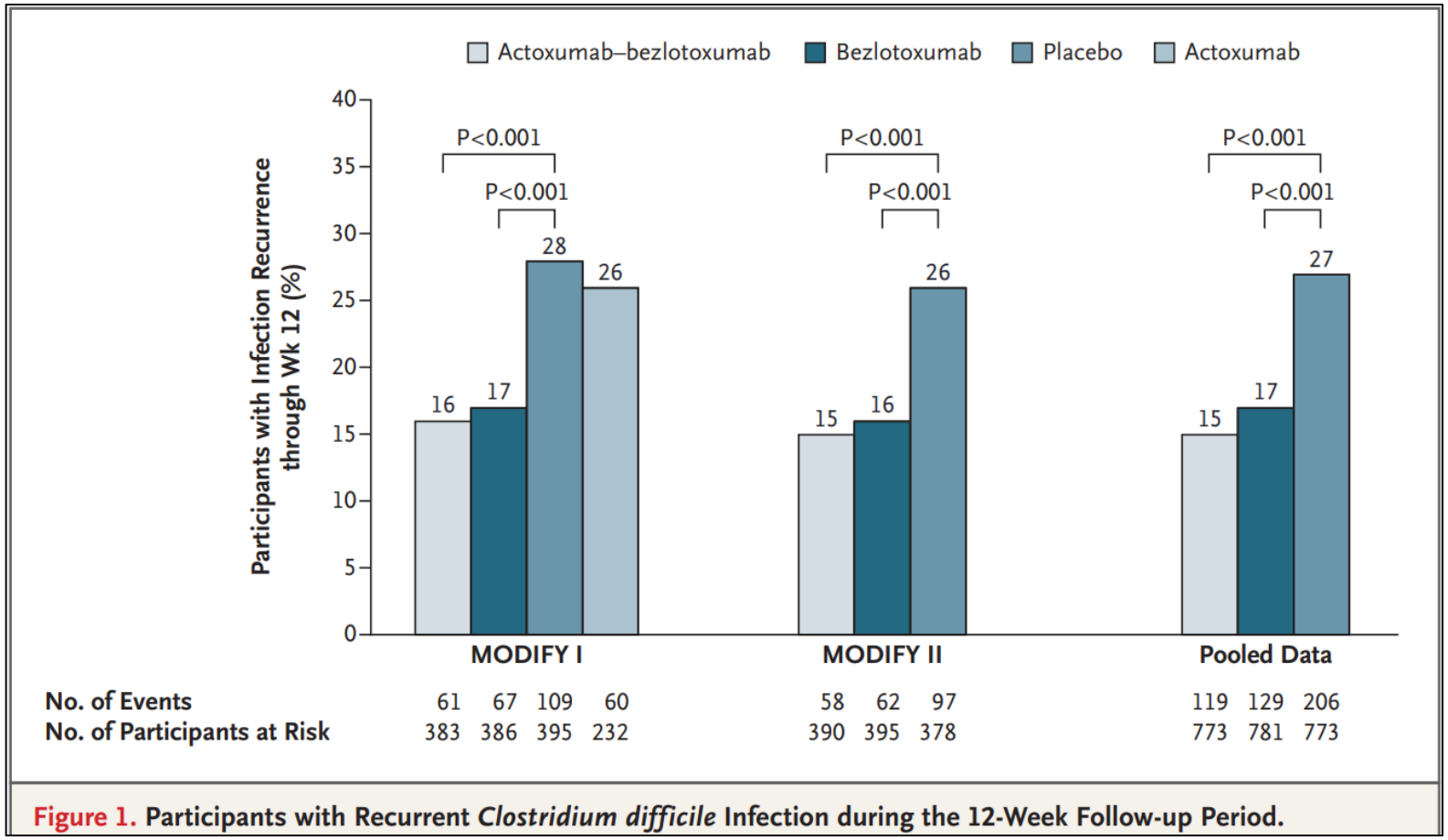


Figure 1. Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period.

N Engl J Med 2017; 376:305-317

Fecal Transplant

- Very encouraging results in small studies
  - Very logical and theoretically correct approach
- Very limited comparative data
- Very heterogeneous methodologies
  - How to dose?
  - What route?
  - When to administer?
  - Risk of infection with other pathogens

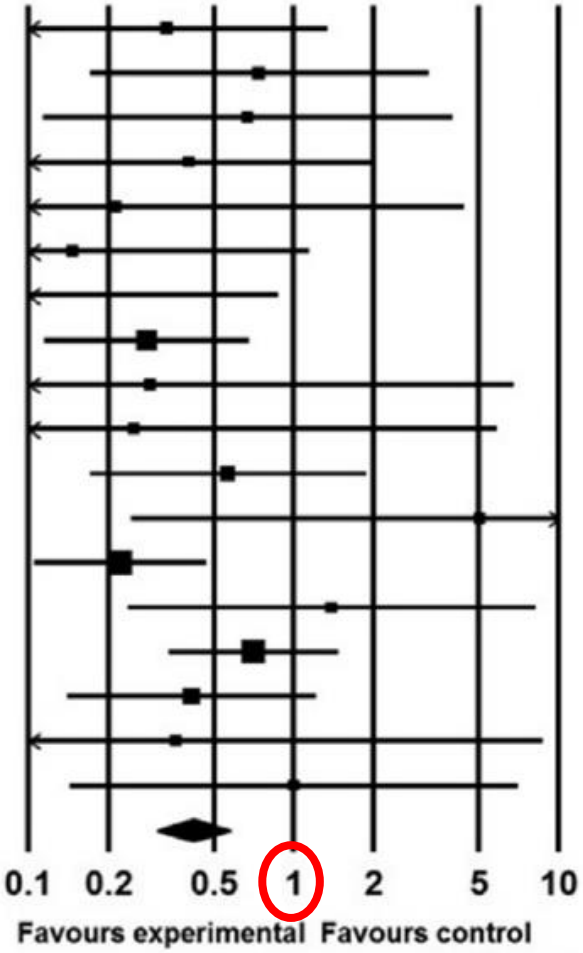
Gastroenterology. 2019;156(5):1324. Epub 2019 Jan 2

Probiotics

- Slightly better data for primary prevention than for secondary prevention

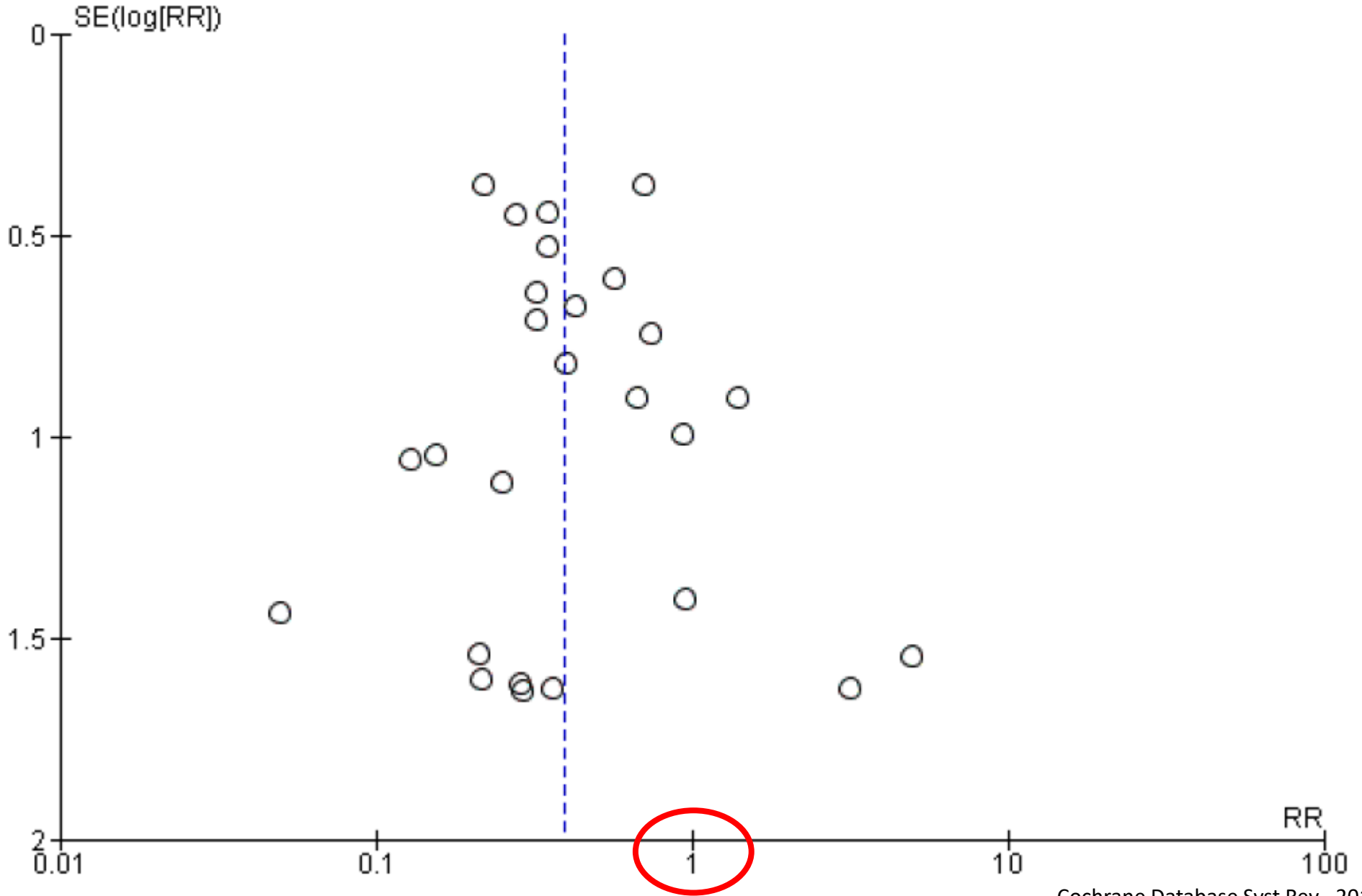
- Still many unknowns
  - Types/strains
  - Dosing
  - When to start/stop
  - Risk of bacteremia

Study name	Events / total		Relative weight	Risk ratio
	Probiotics	Control		
Surawicz 1989	3 / 116	5 / 64	5.30	0.33
McFarland 1995	3 / 97	4 / 96	4.80	0.74
Thomas 2001	2 / 133	3 / 134	3.30	0.67
Plummer 2004	2 / 69	5 / 69	4.02	0.40
Can 2006	0 / 73	2 / 78	1.14	0.21
Beausoleil 2007	1 / 44	7 / 45	2.46	0.15
Hickson 2007	0 / 57	9 / 56	1.30	0.05
Rafiq 2007	5 / 45	22 / 55	13.16	0.28
Wenus 2008	0 / 34	1 / 29	1.04	0.29
Safdar 2008	0 / 23	1 / 17	1.05	0.25
Miller 2008a	4 / 95	7 / 94	7.26	0.57
Miller 2008b	2 / 157	0 / 159	1.13	5.06
Gao 2010	9 / 171	20 / 84	18.82	0.22
Pozzoni 2012	3 / 106	2 / 98	3.32	1.39
Allen 2013	12 / 1470	17 / 1471	19.16	0.71
Ouwehand 2014	6 / 304	7 / 146	9.01	0.41
Wong 2014	0 / 76	1 / 82	1.02	0.36
Ehrhardt 2016	2 / 146	2 / 146	2.74	1.00
Summary estimate				0.42



Gastroenterology 2017;152:1889–1900

Figure 5. Funnel plot of comparison: 1 C. difficile associated diarrhea, outcome: 1.1 Incidence CDAD: complete case.



Cochrane Database Syst Rev . 2017 Dec 19;12(12):CD00609

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with probiotics				
Incidence CDAD: complete case	Study population		RR 0.40 (0.30 to 0.52)	8672 (31 RCTs)	⊕⊕⊕◯ MODERATE [1]	Note: Risk with control calculated by pooled event rate across control groups
	40 per 1,000	16 per 1,000 (12 to 21)				
CDAD (baseline risk 0-2%)	Study population		RR 0.77 (0.45 to 1.32)	5845 (15 RCTs)	⊕⊕⊕◯ MODERATE [2]	
	11 per 1,000	8 per 1,000 (5 to 14)				
CDAD (baseline risk 3-5%)	Study population		RR 0.53 (0.16 to 1.77)	373 (3 RCTs)	⊕⊕◯◯ LOW [3,4]	
	38 per 1,000	20 per 1,000 (6 to 67)				
CDAD (baseline risk >5%)	Study population		RR 0.30 (0.21 to 0.42)	2454 (13 RCTs)	⊕⊕⊕◯ MODERATE [5]	
	116 per 1,000	35 per 1,000 (24 to 49)				
Incidence of *C. difficile* infection: complete case	Study population		RR 0.86 (0.67 to 1.10)	1214 (15 RCTs)	⊕⊕⊕◯ MODERATE [6]	

Cochrane Database Syst Rev . 2017 Dec 19;12(12):CD00609

Are New Therapies Worth It?...

- Conflicting data on cost-effectiveness

- Who should we target?
  - Elderly
  - Immunosuppressed
  - Proton Pump Inhibitor use
  - Severe CDI PLUS renal failure

Same group who is likely to benefit from other preventive strategies (e.g. **Probiotics**)

CID 2018:66 (1 April) • McDonald et al

Possible BIG Change Coming Soon!

- In patients with an initial CDI episode, should fidaxomicin be used rather than vancomycin?
  - Recommendation: **For patients with an initial CDI episode, we suggest using fidaxomicin rather than a standard course of vancomycin**
  - 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 if fidaxomicin is not available.

Clinical Pearls: Infections by Gram Negative Organisms

Objectives

- Describe the epidemiology of resistant gram-negative organisms (GNO) in the United States
- Review new possible antibiotic options for resistant GNOs
- Examine the primary literature behind current recommendations for treatment duration in the management of GNO infections

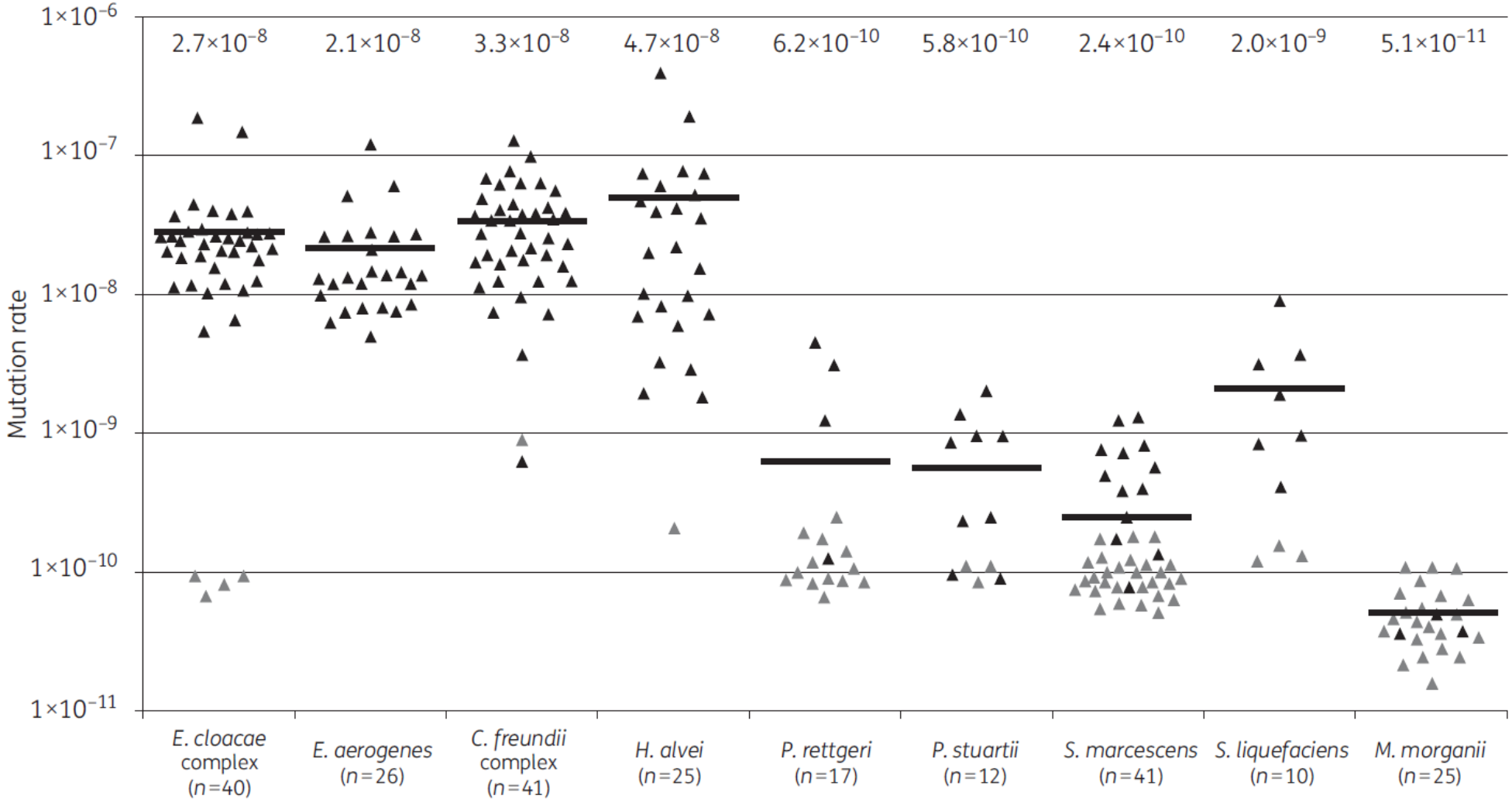
GNO Examples

- *(PESSECKY) Proteus*, *Escherichia*, *Shigella*, *Salmonella, Enterobacter*, *Citrobacter*, *Klebsiella*, *Yersinia*

- *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Burkholderia cepacia*, *Stenotrophomonas.*

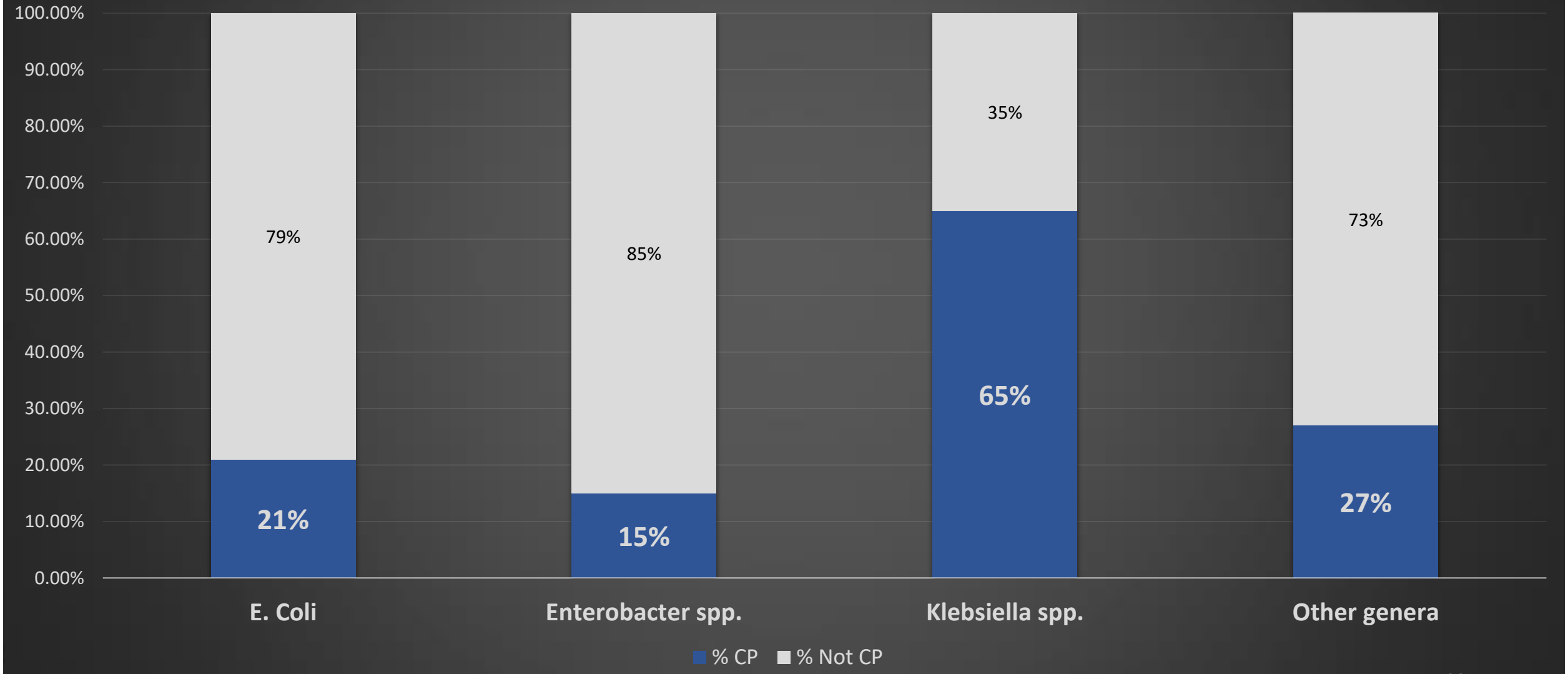
- *(SPICE)* ***Serratia marceces,*** **Pseudomonas aeruginosa**, **Indole-positive *Proteus*, *Citrobacter freundii, Enterobacter cloacae***, and *Morganella morganii*

Not All GNOs Are Created Equal



J Antimicrob Chemother 2018; 73: 1530–1536

% of CRE that are Carbapenemase Producing (CP)
AR Lab Network 2017 - 2018



Data Presented at ID week 2019. Not yet published.

Comparison in Spectrum of Activity

Agent	AmpC/ ESBL	Serine Carbapenemase (e.g. KPC)	Metallo-Beta Lactamase (e.g. NDM)	*P. aeruginosa*	*Acinetobacter spp.*
Ceftolozane/Tazobactam (Zerbaxa®)	+	-	-	+	-
Ceftazidime/Avibactam (Avycaz®)	+	**+ (OXA-48)**	-	+/-	-
Meropenem/Vaborbactam (Vabomere®)	+	+	-	-	-
Imipenem/c/Relebactam (Recarbrio)	+	+	-	+	-
Cefiderocol (Fetroja®)	+	+	+	+	+

Avycaz®- CAZ/AVI and CRE (CRACKLE Study)

Prospective Observational Study

- Ceftazidime/Avibactam (n=38)
- Colistin (n=99)

Table 4. Treatment Characteristics

Characteristic	Patients, No. (%)[a] Ceftazidime-Avibactam (n = 38)	Colistin (n = 99)	All (N = 137)	*P* Value
Time to treatment, median (IQR), d[b]	3 (2–4)	2 (1–4)	3 (1–4)	.22[c]
Duration of treatment, median (IQR), d	10 (5–26)	10 (4–18)	10 (5–19)	.52[d]
Additional antibiotics				
None	14 (37)	6 (6)	20 (15)	<.001[e]
Tigecycline	12 (32)	60 (61)	72 (53)	.002[e]
Amikacin	6 (16)	23 (23)	29 (21)	.34[e]
Gentamicin	12 (32)	14 (14)	26 (19)	.02[e]
TMP/SMX	4 (11)	12 (12)	16 (12)	.80[e]
Carbapenem	11 (29)	59 (60)	70 (51)	.001[e]
Fosfomycin	1 (3)	3 (3)	4 (3)	>.99[c]

Clin Infect Dis. 2018 Jan 6;66(2):163-171

Avycaz®- CAZ/AVI and CRE (CRACKLE Study)

Type of infection				.59[b]
Bloodstream	15 (39)	48 (48)	63 (46)	
Pneumonia	9 (24)	21 (21)	30 (22)	
Urinary tract	6 (16)	13 (13)	19 (14)	
Wound	6 (16)	8 (8)	14 (10)	
Other	2 (5)	9 (9)	11 (8)	
Type of CRE				>.99[f]
Klebsiella pneumoniae	37 (97)	96 (97)	133 (97)	
Enterobacter sp.	1 (3)	3 (3)	4 (3)	
Susceptibility (susceptible/tested)				
Colistin	23/30 (77)	63/68 (93)	86/98 (88)	.04[f]
Ceftazidime-avibactam	18/19 (95)	5/5 (100)	23/24 (96)	>.99[f]

CPEs were KPC-2 (n=28) and KPC-3 (n=24) ONLY!

Clin Infect Dis. 2018 Jan 6;66(2):163-171

Avycaz®- CAZ/AVI and CRE (CRACKLE Study)

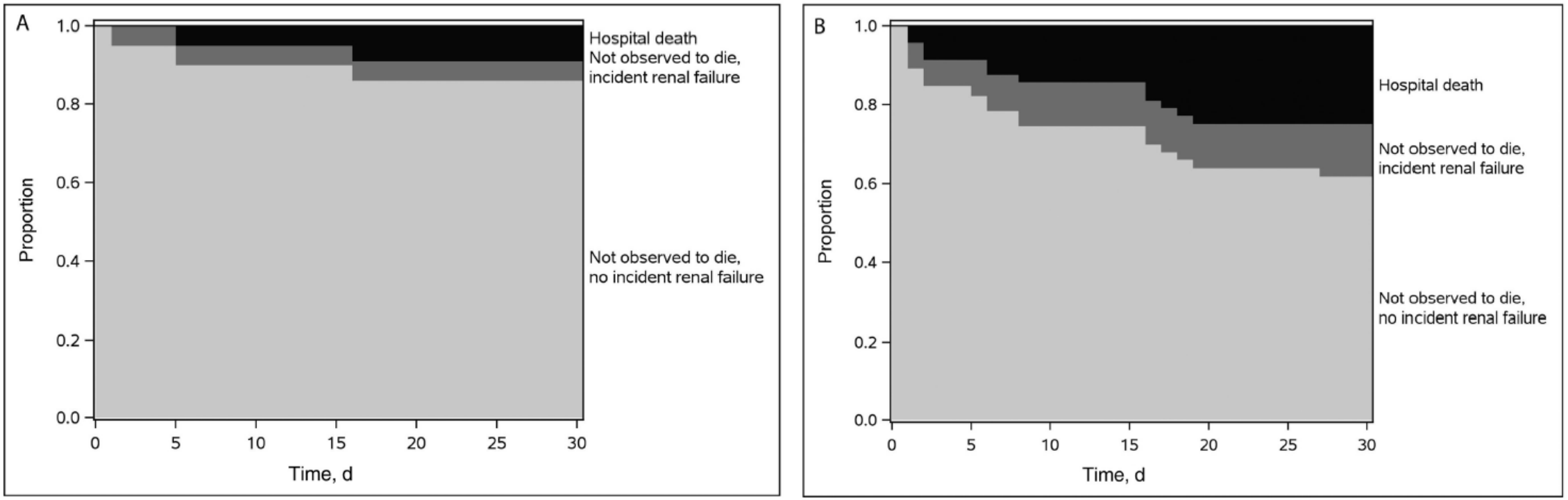


Figure 2. Inverse probability of treatment weighting (IPTW)–adjusted safety over time: renal failure (n = 72; restricted to patients at risk for incident renal failure, without renal failure at treatment initiation). *A,* Ceftazidime-avibactam group (n = 26). *B,* Colistin group (n = 46).

Vabomere®- MER/VAB and CRE (TANGO II)

Randomized Multinational Open-label Study

- Meropenem/ Vaborbactam (n=32)
- Best Available Therapy (n=15)

Infection type, *n* (%)			
Bacteremia	14 (43.8)	8 (53.3)	22 (46.8)
cUTI/AP	12 (37.5)	4 (26.7)	16 (34.0)
HABP/VABP	4 (12.5)	1 (6.7)	5 (10.6)
cIAI	2 (6.3)	2 (13.3)	4 (8.5)
Baseline pathogen, *n* (%)[b]			
Klebsiella pneumoniae	29 (90.6)	12 (80.0)	41 (87.2)
Escherichia coli	3 (9.4)	1 (6.7)	4 (8.5)
Enterobacter cloacae sp.	1 (3.1)	2 (13.3)	3 (6.4)
Proteus mirabilis	0 (0)	2 (13.3)	2 (4.3)
Serratia marcescens	1 (3.1)	1 (6.7)	2 (4.3)
Enrolled as confirmed CRE, *n* (%)	23 (71.9)	14 (93.3)	37 (78.7)
Enrolled as suspected CRE, *n* (%)	9 (28.1)	1 (6.7)	10 (21.3)

>72% of *K. pneumoniae* were KPC producers!

Infect Dis Ther (2018) 7:439–455

Vabomere®- MER/VAB and CRE (TANGO II)

Table 2 Efficacy endpoints among all patients with confirmed CRE infections (mCRE-MITT)

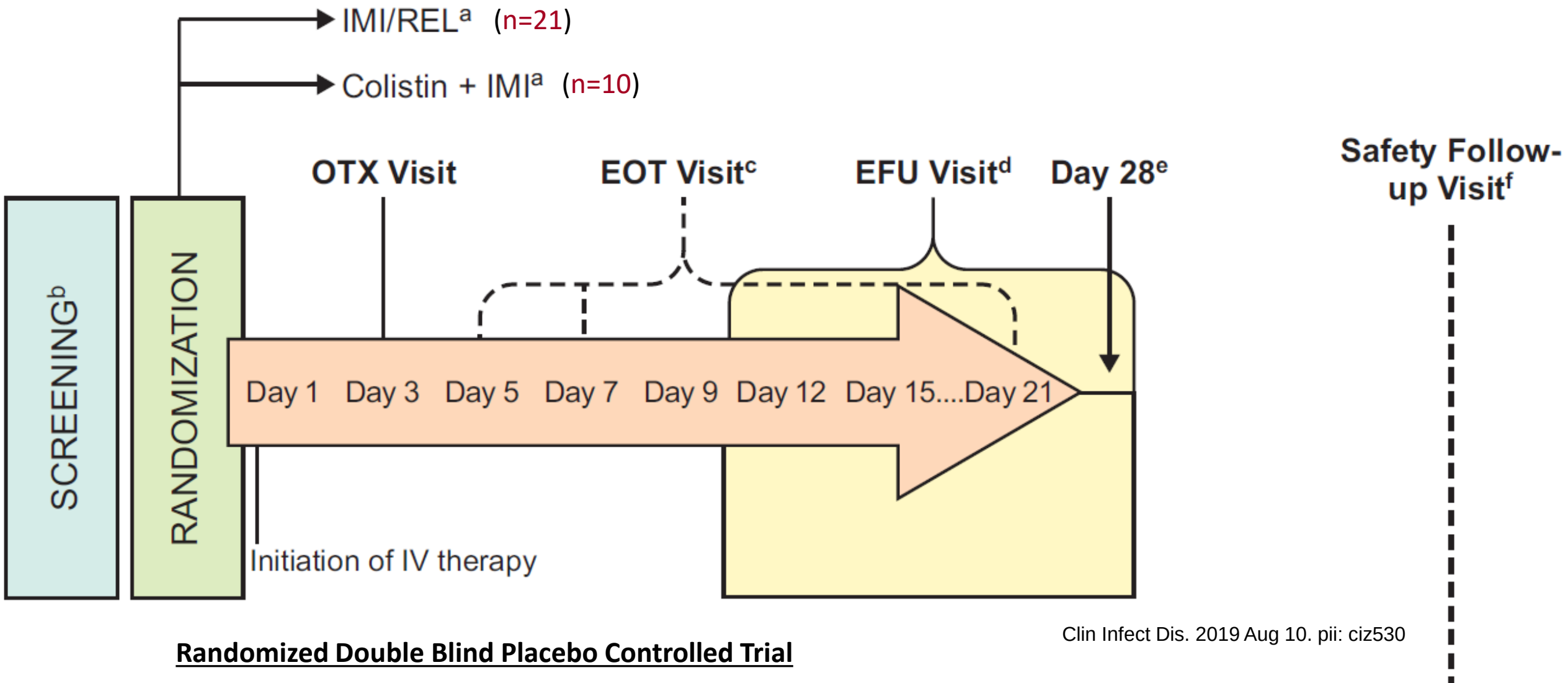
	M–V (*n* = 32) *n* (%)	BAT (*n* = 15) *n* (%)	Difference[a] (95% CI)	*P* value	Relative difference[b]
Efficacy endpoints					
Clinical cure at EOT	21 (65.6)	5 (33.3)	32.3 (3.3–61.3)	0.03	97.0
Clinical cure at TOC	19 (59.4)	4 (26.7)	32.7 (4.6–60.8)	0.02	122.5
Microbiologic cure[c] at EOT	21 (65.6)	6 (40.0)	25.6 (− 4.1 to 55.4)	0.09	64.0
Microbiologic cure[c] at TOC	17 (53.1)	5 (33.3)	19.8 (− 9.7 to 49.3)	0.19	59.5
Day-28 mortality	5 (15.6)	5 (33.3)	− 17.7 (− 44.7 to 9.3)	0.20	− 53.2

	M–V (*n* = 23) *n* (%)	BAT (*n* = 15) *n* (%)	Difference[a] (95% CI)	*P* value	Relative difference[b]
Sensitivity analysis of clinical cure at TOC and all-cause mortality at day 28 across all infection types (mCRE-MITT) excluding prior antibiotic failure[d]					
Clinical cure at TOC	16 (69.6)	4 (26.7)	42.9 (13.7–72.1)	0.004	160.7
Day-28 all-cause mortality	1 (4.3)	5 (33.3)	− 29.0 (− 54.3 to -3.7)	0.02	− 87.1

	M–V (*n* = 32) *n* (%)	BAT (*n* = 15) *n* (%)	Difference[a] (95% CI)	*P* value	Relative Difference[b]
Exploratory analysis of risk–benefit profile of meropenem–vaborbactam compared to best available therapy					
Day-28 all-cause mortality or nephrotoxicity[e]	8 (25.0)	6 (40.0)	− 15.0 (− 44.0 to 14.0)	0.31	− 37.5
Clinical failure or nephrotoxicity[f]	10 (31.3)	12 (80.0)	− 48.7 (− 74.6 to − 22.9)	< 0.001	− 60.9
Day-28 all-cause mortality or renal AEs[g]	6 (18.8)	9 (60.0)	− 41.2 (− 69.5 to − 13.0)	0.004	− 68.7
Clinical failure or renal AEs[h]	9 (28.1)	12 (80.0)	− 51.9 (− 77.4 to − 26.3)	< 0.001	− 64.9

Infect Dis Ther (2018) 7:439–455

Recarbrio®- IMI/RELE and CRE (RESTORE-IMI)



Randomized Double Blind Placebo Controlled Trial

Clin Infect Dis. 2019 Aug 10. pii: ciz530

Recarbrio®- IMI/RELE and CRE (RESTORE-IMI)

Primary diagnosis			
HAP, n (%)	1 (4.8)	1 (10.0)	2 (6.5)
VAP, n (%)	7 (33.3)	2 (20.0)	9 (29.0)
cUTI (urinary tract abnormalities), n (%)	5 (23.8)	3 (30.0)	8 (25.8)
cUTI (acute pyelonephritis), n (%)	6 (28.6)	2 (20.0)	8 (25.8)
cIAI, n (%)	2 (9.5)[a]	2 (20.0)[b]	4 (12.9)
Bacteremia[c]			
Yes, n (%)	1 (4.8)	1 (10.0)	2 (6.5)
No, n (%)	5 (23.8)	2 (20.0)	7 (22.6)
Unknown, n (%)[c]	15 (71.4)	7 (70.0)	22 (71.0)
Qualifying causative pathogens			
Citrobacter freundii, n (%)	1 (4.8)	0 (0.0)	1 (3.2)
Enterobacter cloacae, n (%)	1 (4.8)	0 (0.0)	1 (3.2)
Klebsiella oxytoca, n (%)	0 (0.0)	1 (10.0)	1 (3.2)
Klebsiella pneumoniae, n (%)	3 (14.3)	1 (10.0)	4 (12.9)
Pseudomonas aeruginosa, n (%)	16 (76.2)	8 (80.0)	24 (77.4)

Clin Infect Dis. 2019 Aug 10. pii: ciz530

Recarbrio®- IMI/RELE and CRE (RESTORE-IMI)

β-lactamases[d]			
Class A			
Older spectrum β-lactamases			
SHV[e]	2 (9.5)	1 (10.0)	3 (9.7)
TEM	7 (33.3)	3 (30.0)	10 (32.3)
Extended spectrum β-lactamases			
CTX-M	7 (33.3)	4 (40.0)	11 (35.5)
SHV[e]	1 (4.8)	0	1 (3.2)
VEB	0	0	0
Serine carbapenemases			
KPC	4 (19.0)	1 (10.0)	5 (16.1)
Class C			
Chromosomal AmpC			
PDC	16 (76.2)	8 (80.0)	24 (77.4)
Plasmid-mediated AmpC			
ACT	0	0	0
CMY	1 (4.8)	0	1 (3.2)
DHA	1 (4.8)	0	1 (3.2)
Class D			
OXA-48	0	1 (10.0)	1 (3.2)

Clin Infect Dis. 2019 Aug 10. pii: ciz530

Recarbrio®- IMI/RELE and CRE (RESTORE-IMI)

Table 2. Primary and Secondary Prospective Efficacy Endpoints (in the Modified Microbiologic Intent-to-Treat Population) and Secondary Prospective Safety Endpoints (in the Safety Population)

	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference[a]	
Endpoint	n	% (95% CI)[b]	n	% (95% CI)[a]	%	%	90% CI
Primary endpoint							
Favorable overall response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	–7.3	(–27.5, 21.4)
Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	7/8	87.5 (50.8, 99.9)	2/3	66.7		20.8	
Complicated intraabdominal infection	0/2[d]	0.0	0/2[e]	0.0		0.0	
Complicated urinary tract infection	8/11	72.7 (42.9, 90.8)	5/5	100.0 (51.1, 100.0)		–27.3 (–52.8, 12.8)	
Secondary endpoints							
Favorable clinical response (day 28)	15[f]	71.4 (49.8, 86.4)	4[g]	40.0 (16.7, 68.8)	31.4	26.3	(1.3, 51.5)
28-day all-cause mortality	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	–20.5	–17.3	(–46.4, 6.7)
Treatment-emergent nephrotoxicity[h]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)		–45.9 (–69.1, –18.4)	

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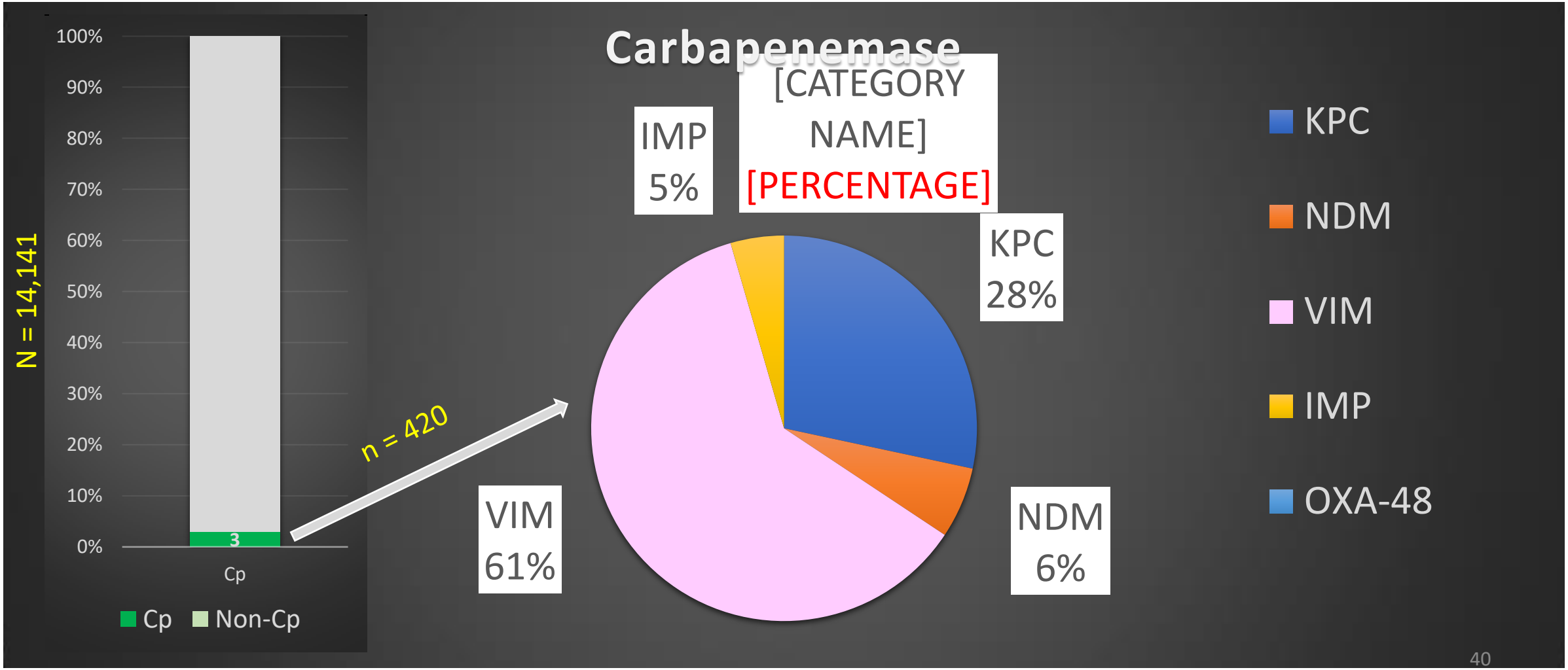
Prevalence of Carbapenem Resistance Mechanisms in P. aeruginosa in the US



Data Presented at ID week 2019. Not yet published.

Mechanisms of Carbapenem Resistance in Non-Enterobacterales

Organism	Mechanism of Resistance	Notes
MDR- *Pseudomonas Aeruginosa* (MDR-PsA)	Membrane permeability Efflux pumps Biofilm Beta-lactamase (MBLs, KPC**, AmpC, ESBLs[OXA]**)	Ceftolozane/tazobactam may retain activity against many of these isolates
CR – *Acinetobacter baumannii* (CRAB)	Porin mutations Altered PBPs Beta-lactamase (Carbapenemase →MBLs, OXA)	Other potential alternatives are toxic/limited (colistin, tigecycline, minocycline)

Ceftolozane/Tazobactam (Zerbaxa®)

- Less affinity for AmpC hydrolysis
- Weak substrate for efflux pumps
- Not affected by OprD loss

- FDA Indications
  - Hospital Acquired Pneumonia and Ventilator-associated Pneumonia
  - Complicated UTI
  - Complicated Intra-abdominal infections (W/ metronidazole)

- Dosing Regimens:
  - **HAP/VAP: 3g IV every 8 hours (ASPECT-NP trial)**
  - cUTI/cIAI: 1.5g IV every 8 hours
    - May required dose adjustments in renal impairment

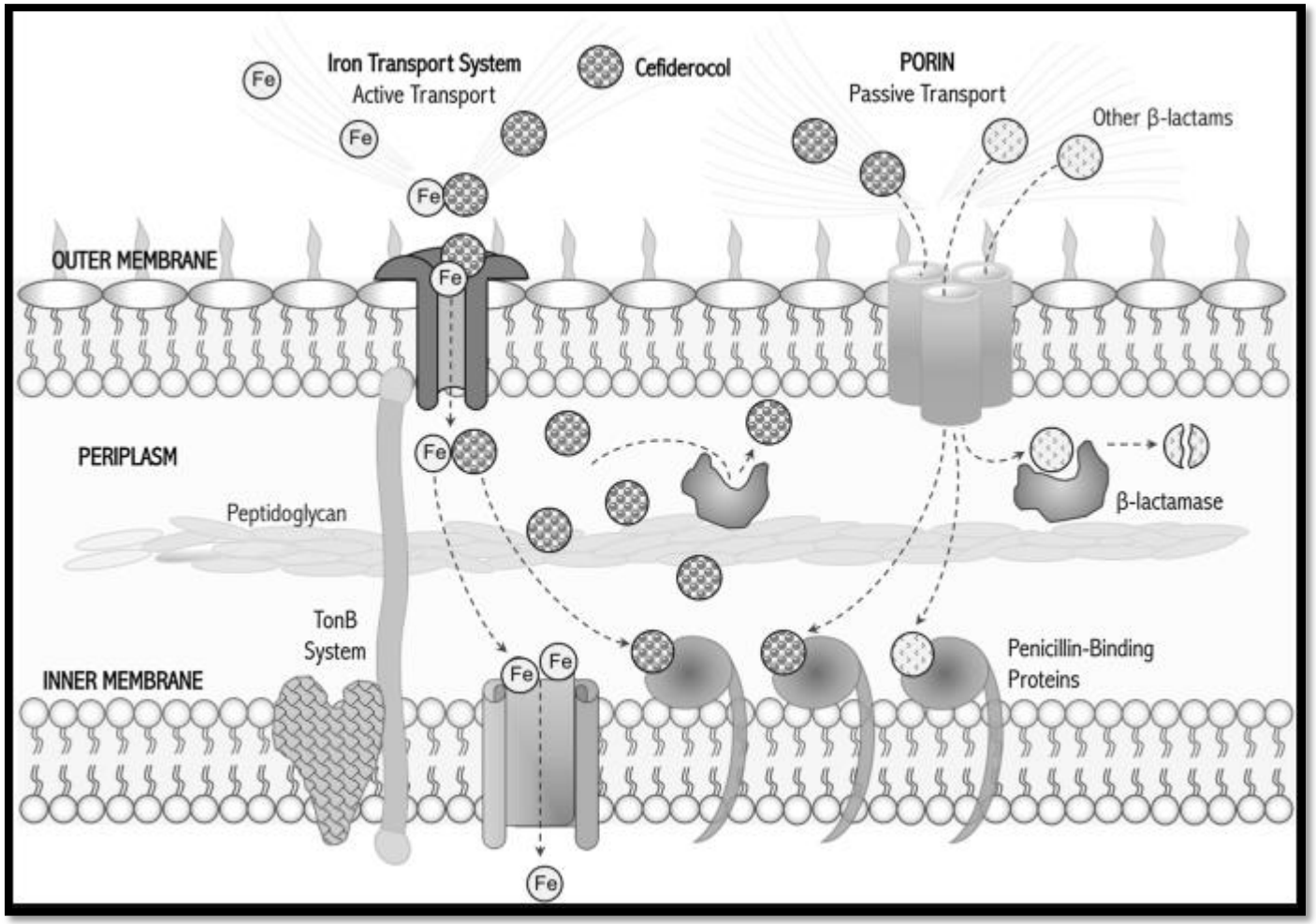
Ceftolozane/Tazobactam Spectrum

- Key Coverage
  - ESBLs
  - MDR *P. aeruginosa*
- Lacks in coverage
  - CP-CRE
  - *Acinetobacter* spp.

Agents	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S (CLSI)
Sader HS et al. (1909 MDR **PsA** from US in 2017)			
Ceftolozane/tazobactam	0.5	2	97.5
Ceftazidime/avibactam	2	8	96.9
Piperacillin/tazobactam	4	128	77.5
Ceftazidime	2	32	82.5
Cefepime	4	16	82.4
Meropenem	0.5	16	76
Humphries et al. (309 beta-lactam-resistant **PsA** from LosAngeles, CA)			
Ceftolozane/tazobactam	-	-	72.5
Ceftazidime/avibactam	-	-	61.8
Piperacillin/tazobactam	-	-	20.7
Ceftazidime	-	-	24.6
Cefepime	-	-	25.9
Meropenem	-	-	15.9

Humphries RM et al. AAC 2017.
Sader HS et al. AAC 2018.

Fetroja® - Cefiderocol



Drugs volume 79, pages271–289(2019)

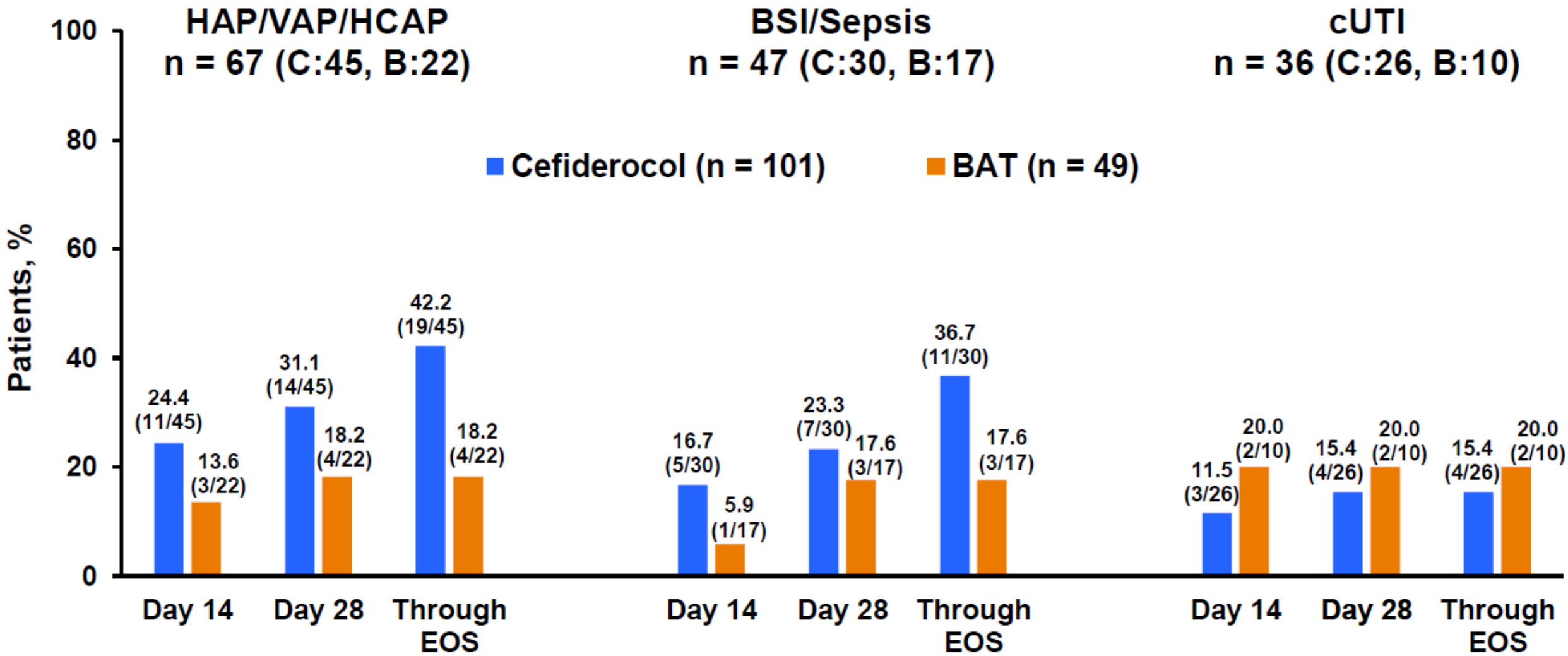
Fetroja® - Cefiderocol and CRE

Trial	Comparator	Trial Design	Dosing	Infection Type	Endpoint
APEKS-cUTI	**Imipenem 1g q8h**	RCT-DB-P (non-inferiority)	2g IV q8h	cUTIs	Response at TOC 73% v 55%
APEKS-NP	**Meropenem 2g q8h**	Phase III	2g IV q8h	HAP, VAP	All-cause mortality 12.4% vs 11.6% (non-inferior)
CREDIBLE-CR	BAT	Phase III	2g IV q8h	Any	All-cause mortality **18.8%** vs 12.2%

The **CREDIBLE-CR study** (HABP/VABP, cUTI, and BSI due to CRO) were randomized to receive cefiderocol or BAT, of which 66% were colistin-based regimens. The study **all-cause mortality rate was higher in the cefiderocol group compared to the BAT** group at Day 14 (18.8% versus 12.2%) and Day 28 (24.8% versus 18.4%) respectively. "The greatest mortality difference disfavoring Cefiderocol was noted in the **HABP/VABP subgroup, followed by the BSI/sepsis subgroup**".

https://www.fda.gov/media/131705/download Accessed 11/27/19

CREDIBLE-CR All-Cause Mortality by Infection Site (Safety Population)



https://www.fda.gov/media/131705/download Accessed 11/27/19

MDR-GNR Treatment Summary

- Carbapenem Resistant ***E. coli*** or ***K. pneumoniae***
  - Think Carbapenemase
  - Trx: Ceftazidime/Avibactam or Meropenem/Vaborbactam

- MDR – ***Pseudomonas***
  - Think Porins, Efflux pumps with AmpC/ESBLs
  - Trx: Ceftolozane/Tazobactam (maybe Imipenem/c/Relebactam)

- MDR- *Acinetobacter baumaniii*
  - Do not think of C/A, C/t, M/V, or I/c/R (non-OXA-48 oxacillinases, permeability)
  - Trx: “tetracycline”, cefiderocol, polymyxin-based combination therapy

Oral Carbapenem Coming Soon?

- Sulopenem is a carbapenem that has both oral and IV formulations

- DB-RCT (N =1671) Women with uncomplicated-UTI
  - Oral Sulopenem twice daily x5d *vs* Oral Ciprofloxacin twice daily x3d

  - Primary endpoint: Overall success (clinical and microbiologic success)
    - Solupenem: 62.6% (92 of 147 patients)
    - Ciprofloxacin: 36% (50 of 139 patients)
    - Percentage difference of 26.6% (95% CI, 15.1-37.4; *P* <.001)

  - Most frequent AEs:
    - diarrhea (7.3% vs 7.6%)
    - nausea (3.4% vs 4%)
    - headache (2.2% in both arms)

https://www.contagionlive.com/view/sure-1-trial-results-of-sulopenem-vs-ciprofloxacin. Accessed 11/3/20

Question #3: Which of the following agents has shown improved in-vitro susceptibility against CR – *Acinetobacter baumannii* (CRAB)

a) Ceftazidime-avibactam (Avycaz®)
b) Ceftolozane-tazobactam (Zerbaxa®)
c) Cefiderocol (Fetroja®)
d) Meropenem-vaborbactam (Vabomere®)

Most Common Infections Caused by GNO

- Urinary tract infections (UTI)
- Hospital acquired pneumonia (HAP)
- Ventilator acquired pneumonia (VAP)
- Intra-abdominal infections (IAI)

- Bacteremia is very common in the healthcare setting

Stewardship: Shorter = Better

Diagnosis	Short (d)	Long (d)	Result	#RCTs
CAP	3-5	5-14	Equal	10
VAP	8	15	Equal	2
Pyelo	5 or 7	10 or 14	Equal	7
Intra-abd	4	10	Equal	2
GNB Bacteremia	7	14	Equal	2*
AECB & Acute Bac Sinusitis	≤5	≥7	Equal	>25
Cellulitis	5-6	10	Equal	4**
Chronic Osteomyelitis	42	84	Equal	2
Septic Arthritis	14	28	Equal	1
Ortho Implant w/removal	28	42	Equal	1
Neutropenic Fever	AFx72 h	+ANC>500	Equal	1
P. vivax Malaria	7	14	Equal	1

*GNB bacteremia also in UTI/cIAI RCTs; **3 cellulitis RCTs equal, 1 (low dose oral flucox) ↑relapses; refs at https://www.bradspellberg.com/shorter-is-better

FDA approves safety labeling changes for fluoroquinolones

Information by Drug Class

Human Immunodeficiency Virus (HIV)

[7-26-16] Today, the FDA has approved labeling changes for antibacterial drugs called fluoroquinolones, including an updated Boxed Warning, and advising that the serious side effects associated with fluoroquinolones generally outweigh the benefits for patients with acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB) and uncomplicated urinary tract infections (UTIs) who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Content current as of:
07/26/2016

https://www.fda.gov/drugs/information-drug-class/fda-approves-safety-labeling-changes-fluoroquinolones . Accessed 11/3/2020

Urinary Tract Infections (UTI)

Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis

Randomized, double-blind, placebo-controlled trial

- Ciprofloxacin 500mg BID x7d (n=73)
- Ciprofloxacin 500mg BID x14d (n=83)

	Ciprofloxacin for 7 days	Ciprofloxacin for 14 days	Difference (90% CI)	Non-inferiority test p value
Short-term efficacy	73	83		
Cure	71 (97%)	80 (96%)	−0·9% (−6·5 to 4·8)	0·004
Clinical failure or recurrent symptomatic urinary tract infections	2 (3%)	3 (4%)	..	
Cumulative efficacy	73	84		
Cure	68 (93%)	78 (93%)	−0·3% (−7·4 to 7·2)	0·015
Clinical failure or recurrent symptomatic urinary tract infections	5 (7%)	6 (7%)	..	

Data are number (%), unless otherwise indicated.

Table 3: **Clinical outcomes in the per-protocol population**

Women (aged ≥18 years) who were not pregnant and had a presumptive diagnosis of acute

Lancet 2012; 380: 484–90

Duration of Therapy: UTIs

- Uncomplicated Cystitis
  - Nitrofurantoin: 5 days
  - Trimethoprim-sulfamethoxazole: 3 days
  - **Fluoroquinolones: 3 days**
  - Beta-lactams: 5 to 7 days

- Pyelonephritis
  - **Fluoroquinolones: 5 to 7 days**
  - Trimethoprim-sulfamethoxazole: 7 to 10 days
  - **Beta-lactams: 10 to 14 days**

CID, VoL 52, 5, March 2011, Pag e103–e120

Hospital Acquired Pneumonia (HAP) and Ventilator Acquired Pneumonia (VAP)

Pneumonia (HAP/VAP)

Antipseudomonal Beta-Lactam	Anti-MRSA Agent	Second Antipseudomonal Agent (e.g. FQ, AG,…)
In all patients	IV ABx in last 90 days	IV ABx in last 90 days
	High risk for mortality	High risk for mortality
	MRSA rate >10-20%	Pseudomonal resistance rate >10-20%

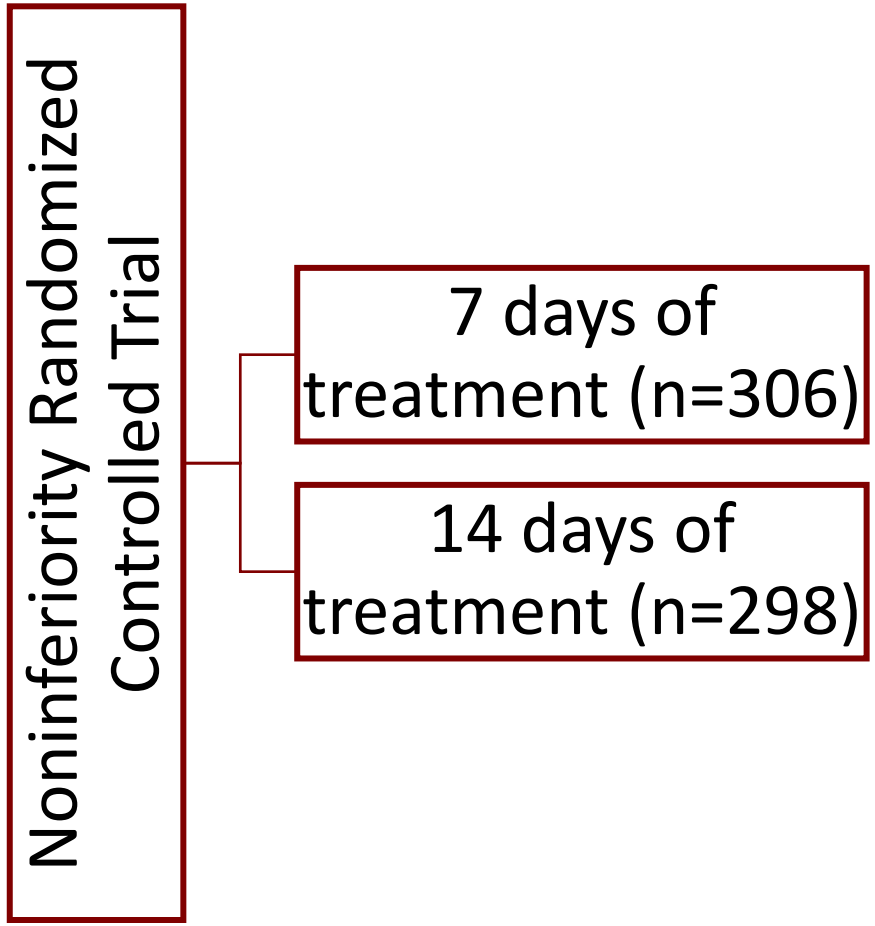
- Duration of treatment: 7 days

Risk factors for MDR VAP: Prior IV ABx use within 90 d, Septic shock at time of VAP, ARDS preceding VAP, ≥5 days of hospitalization prior to VAP, Acute renal replacement therapy prior to VAP.
High risk for mortality: Septic shock or need for ventilatory support.

CID 2016, 63; e61–e111

Bacteremia

Seven Versus 14 Days of Antibiotic Therapy for **Uncomplicated** Gram-negative Bacteremia



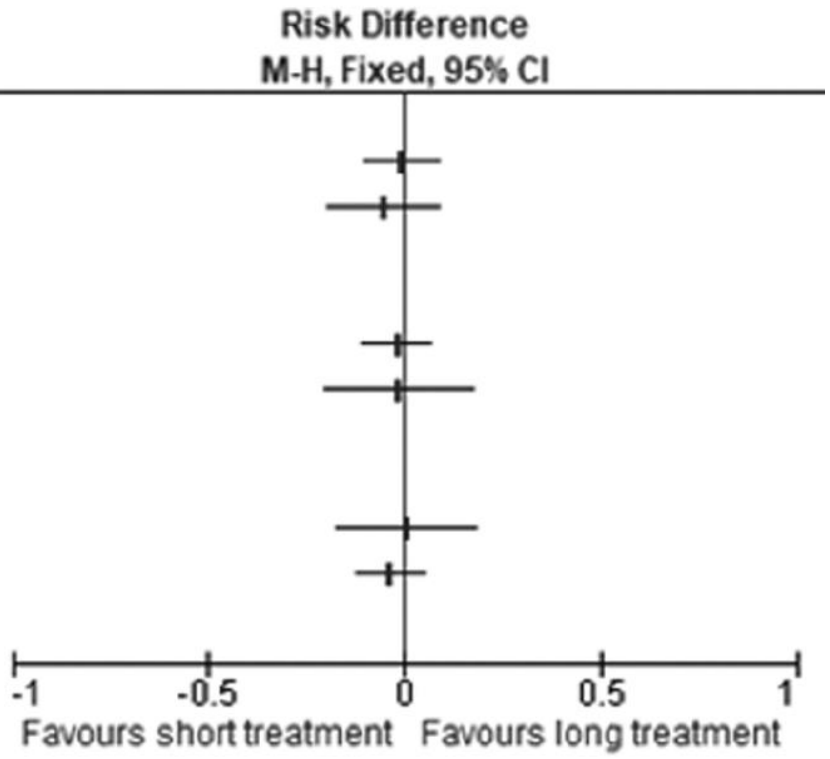
Outcome	Short Arm (7d) (n=306)	Long Arm (14d) (n=298)	P value
Primary Outcome	140 (45.8)	144 (48.3)	.527
90-d all cause mortality	36 (11.8)	32 (10.7)	.702
Readmission	119 (38.9)	127 (42.6)	.363
Relapse bacteremia	8 (2.6)	8 (2.7)	.957
14-d mortality	7 (2.3)	4 (1.3)	.288
28-d mortality	14 (4.9)	13 (4.4)	.753

Patients with GNB at day 7 of antibiotic therapy, if hemodynamically stable and afebrile for at least 48 hours.

CID, Vol 69,7,Oct 2019, Pag 1091–1098

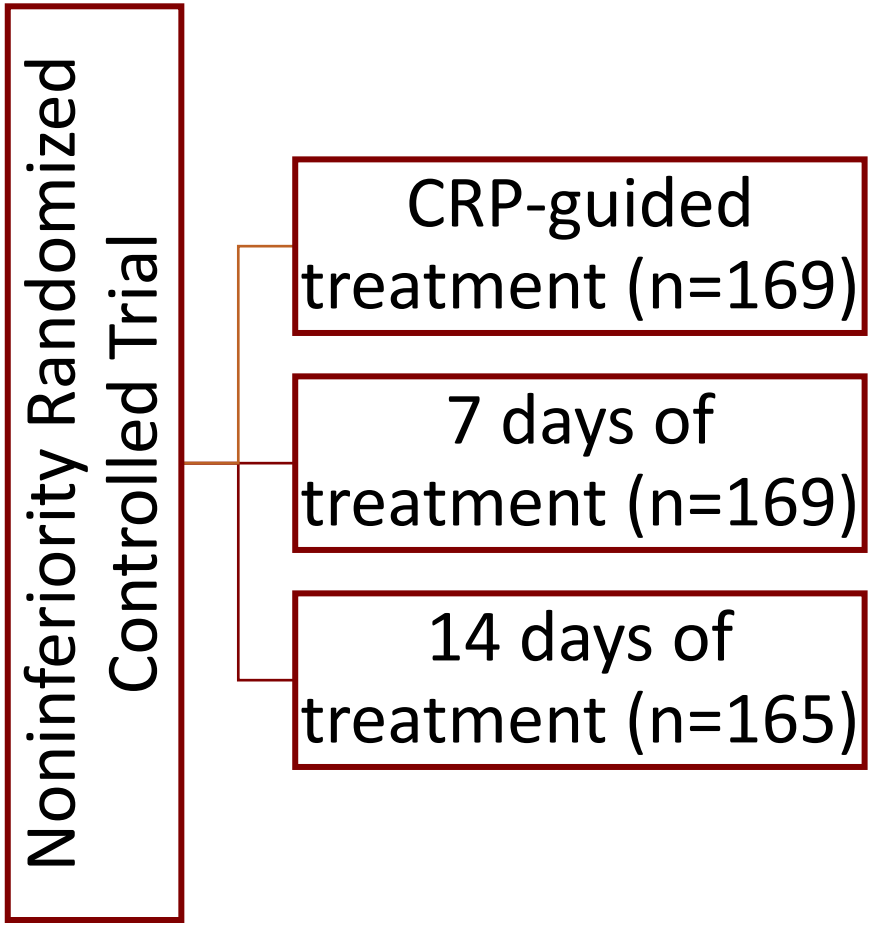
Primary outcome according to patient subgroups

Subgroup	Short Events	Short Total	Long Events	Long Total	Risk Difference M-H, Fixed, 95% CI
.1 Bacteremia source					
UTI	92	212	88	199	-0.01 [-0.10, 0.09]
non-UTI	48	94	56	99	-0.06 [-0.20, 0.09]
.2 Empirical antibiotic treatment					
Covering empirical	112	260	109	242	-0.02 [-0.11, 0.07]
Non-covering empirical	28	46	35	56	-0.02 [-0.21, 0.17]
.3 Multi-drug resistance					
MDR	39	58	34	51	0.01 [-0.17, 0.18]
Non-MDR	101	248	110	247	-0.04 [-0.13, 0.05]



CID, Vol 69,7,Oct 2019, Pag 1091–1098

Effect of C-Reactive Protein–Guided Antibiotic Treatment Duration in Patients With **Uncomplicated** Gram-Negative Bacteremia



Outcome	CRP-guided treatment (n=169)	7 days of treatment (n=169)	14 days of treatment (n=165)
Clinical success through day 30	160 (97.6)	155 (93.4)	154 (94.5)
Clinical success through day 60	146 (94.2)	141 (89.8)	146 (92.4)
Clinical success through day 90	133 (93.0)	135 (89.4)	137 (89.5)

Patients with fever or hemodynamic instability in the 24 hours prior to recruitment, NFGNB, recurrent, or complicated infections (eg, abscess, endocarditis) were not eligible.

JAMA. 2020;323(21):2160-2169. doi:10.1001/jama.2020.634

Question #4: New data from retrospective and prospective suggests that in the management of uncomplicated gram-negative bacteremia, duration of treatment may be as short as:

a) 14 days
b) 3 days
c) 7 days
d) 21 days

Takeaway points

- CREs are increasingly common and >50% are not CPE (carbapenemase producers)
- The spectrum of activity of new agents vary significantly
- Cefiderocol is a promising agent, but PK/PD may need optimization
- New studies suggest that treatment duration of infections caused by GNOs, may be shorter than previously thought
- Treatment of uncomplicated bacteremia caused by GNOs may be a short as 7 days

Clinical Pearls in Infectious Diseases

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