Ad Hoc Working Group to Reassess Daptomycin Breakpoint for Enterococci

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CLSI January 2018 Proposal for Daptomycin/Enterococci Breakpoints

- Susceptible: ≤1 µg/mL*
- Susceptible-Dose Dependent: 2-4 µg/mL**
- Resistant: ≥ 8 µg/mL

Comments:
*Based on a dosage regimen of 6 mg/kg/day in adults
**Increased daptomycin doses of 10-12 mg/kg are recommended for infections caused by these organisms, with potential consideration of combination therapy.

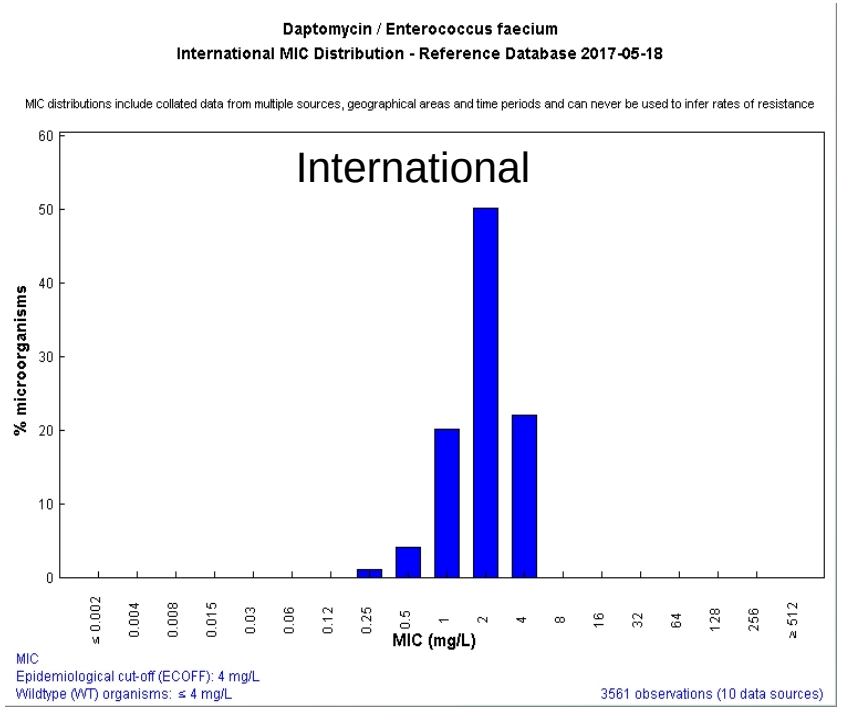
- AHWG vote: 5-0-0-4 (Approval)
- Breakpoint WG approved this 11-0-1-1 (Approval)
- Subcommittee vote: 7-6-0-0 (Did not pass)

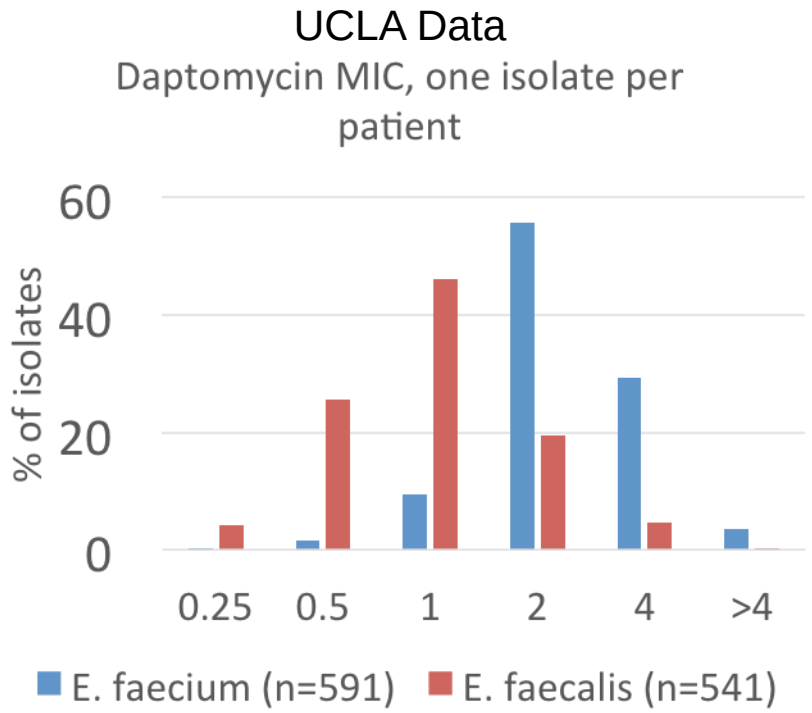
What concerns were raised in January that led to failure to obtain approval?

- **Safety** of recommending higher doses of daptomycin than what is in the FDA label
  - CK elevations and rhabdomyolysis
  - Eosinophilic pneumonitis?
- Should we separate ***E. faecium*** **breakpoints** from other enterococci and is so should we just have S-DD and R (instead of S, S-DD, and R)
- Other concerns:
  - For all infections? What about urinary tract infections?
  - Lack of clarity around “combination therapy”

Microbiologic data: MIC Distributions

ECV would be **4 µg/mL** for *E. faecium*





EUCAST MIC Distributions

Table 1: MIC distributions and epidemiological cut-off values (mg/L) for *Enterococcus* spp.

Organism	≤0.06	0.125	0.25	0.5	1	2	4	8	≥16	ECOFF
Enterococcus faecalis	51	166	765	8064	12321	3255	398	5	0	2
Enterococcus faecium	10	63	144	611	3228	14761	1495	23	5	4

Microbiologic Data: AST Testing: ***E. faecium***

UCLA: MIC ≥8 µg/mL **UCLA: MIC ≤1 µg/mL** Multicenter study: MIC 2-**4 µg/mL**

BMD MIC Distributions (n=3 labs, 3 media)

	1	5	6	9	12	13	15	21	26	31	2	7	14	18	22	23	28	34	39	40	17	19	20	29	3	30	32	36	4	8	10	11	16	24	25	27	33	35	37	38
≤0.12												1						6			2	1		1														3			
0.25								2				8						3				1		1			1														
0.5											3			1		1	1						1				1									1		1			
1													4	3	5								1		1						1			2						
1.5										1			3	5	4	3	3		2				1					1		1	2	1			1					
2							1			6	2		1			2	2		6	1	1	5	6		2			1		2	2	6	1	3	2				1	
3										2	3		1			2	2		1	5	4	2		1	4				4	5	2	2	7	4	5	5	5	5	5	4
4		1				1					1					1	1			3	2			4	1	2	2	2	4	1	2		1		1	1	1		1	4
8		1	1			3		3	3															2	1	6	4	4	1									1	2	1
16	4	7	4		1	4	3	4	1																	1	1	1								2		2		
>16	5		3	9	8	1	5		5																															

High MIC Group | Low MIC Group | Mid-MIC with LiaFSR mut'n | Mid-MIC without LiaFSR mut'n

- 84% of reads ≥8 µg/mL
- 94% if remove outlier

- 78% of reads ≤2 µg/mL
- 100% ≤4 µg/mL

Very difficult to reliably separate isolates with MICs in the 2-**4 µg/mL range**

Clinical Cutoff

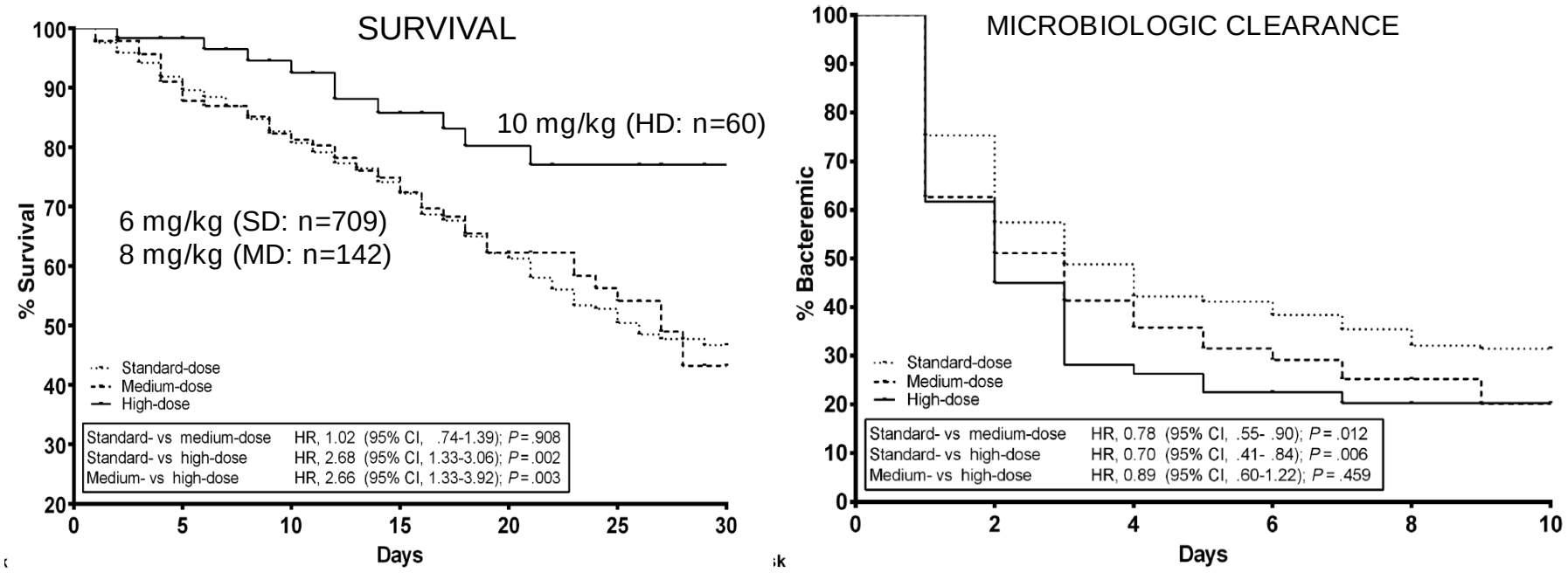
Are clinical outcomes worse with DAP MICs 3-4 µg/mL vs. ≤ 2 µg/mL for VRE.*faecium* bacteremia in patients treated with DAP?

	Study	N of patients (MIC 3-4/≤2) by AST method	Daptomycin dose	Comparison of Outcomes 3-4 vs. ≤2 µg/mL (N: %)
YES	Shukla et al. CID 2016	62 Etest: 31/31 BMD: 0/62	58%: ≥8 mg/kg	• Microbiologic failure • 71% (3-4) vs. 39% (≤2). *P*=0.01 (using Etest, not by BMD) • Association persisted in multivariate model • No mortality difference
YES	Moise et al. Clin Ther 2015	101 Variable: 31/70	10%: ≥8 mg/kg	• Clinical failure • 29% (3-4) vs. 10% (≤2). *P*=0.02
NO	Chaung et al. CID 2017	112 Etest: 40/72 BMD: 78/34	Median dose: 7.7 mg/kg	• No differences in microbiologic failure (*P*=0.8) or mortality between MIC 3-4 vs. MIC ≤2
NO	Casapao et al. AAC 2013	116 (not all BSI) Variable: 64/52	Median dose: 8.2 mg/kg	• No differences in clinical failure (*P*=0.4)
NO	Chong et al. Clin Ther 2016	42 (heme malignancies) Etest: 19/23	39% : >6 mg/kg	• No differences in microbiologic failure (*P*=0.4) or mortality (*P*=0.06-MIC 3-4 µg/mL: trend towards **decreased** mortality, although this group receive higher dapto dose)

Data do NOT consistently show this

Clinical Cutoff: Better Outcomes with Higher Doses of Daptomycin

- Observational study of 911 patients with VRE bacteremia (89% *E. faecium*) in 81 VA hospitals from 2004-2014 who were:
  - Treated with daptomycin at >5.5 mg/kg for ≥48 hours
  - Dapto MICs were ≤4 µg/mL (very limited MIC data: <5%)
  - No treatment with other VRE active agent
  - Standard dose (SD): 6 (±0.5) mg/kg/d; Medium dose (MD): 8 mg/kg/d; High dose (HD): ≥10 mg/kg/d (TBW)

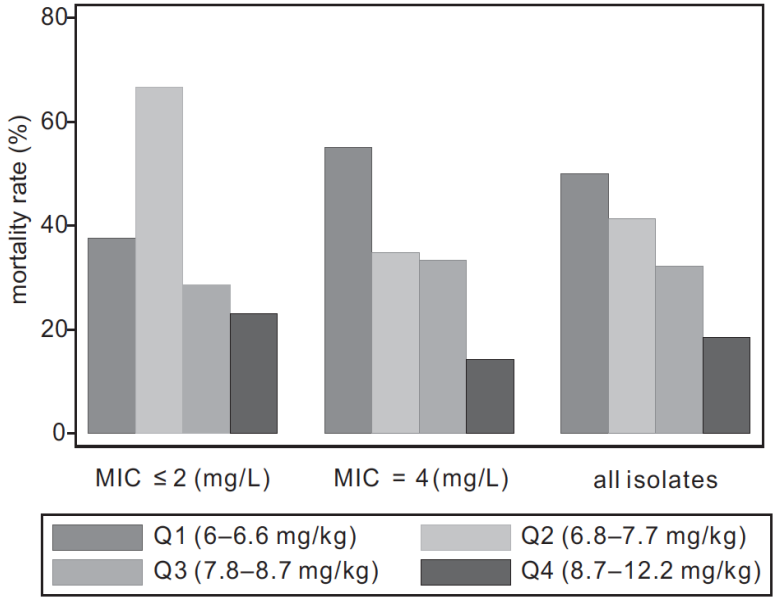


Britt NS, et al. CID 2017.

Effect of Daptomycin Dose on the Outcome of Vancomycin-Resistant, Daptomycin-Susceptible *Enterococcus faecium* Bacteremia

Yu-Chung Chuang,[1,2] Hsin-Yi Lin,[3] Pao-Yu Chen,[4] Chi-Ying Lin,[5] Jann-Tay Wang,[2,a] Yee-Chun Chen,[2] and Shan-Chwen Chang[2,a]

- Observational cohort study of 112 patients with VRE.*faecium* bacteremia in Taiwan from 2010-2015 who were:
  - Treated with daptomycin at ≥6 mg/kg for ≥72 hours
  - Dapto MICs were ≤ 4 µg/mL
- MICs by BMD and Etest
- Primary outcome: 14-day mortality



Dapto dose (mg/kg)	<7 mg/kg (n=36)	7-9 mg/kg (n=51)	>9 mg/kg (n=25)
14d mortality	50%	33%	20%

Table 2. Multivariable Logistic Regression Analysis of Factors Associated With 14-Day Mortality and the Daptomycin Dose Cutoffs

Variable	Multivariable Odds Ratio[a] (95% Confidence Interval)	*P* Value
Steroid use	7.39 (1.82–29.96)	.005
Pitt bacteremia score	1.26 (1.07–1.48)	.007
Platelet count (×10^4/µL)	0.93 (0.88–0.98)	.01
Daptomycin dose		
<7 mg/kg	Reference	
7–9 mg/kg	0.47 (0.16–1.40)	.18
≥9 mg/kg	0.09 (0.02–0.44)	.003

Chuang YC, et al. CID 2017.

Clinical Cutoff: Higher Doses?

Are outcomes improved with high-dose daptomycin (>=8 mg/kg) vs. FDA-label dose of daptomycin (6 mg/kg) for VRE bacteremia

	Study	N of patients per dose	Comparison of Outcomes
YES	Britt et al. CID 2017 (n=911)	• 6 mg/kg: 709 • 8 mg/kg: 142 • ≥10 mg/kg: 60	• Mortality in multivariate model: Improved survival with ≥10 mg/kg than with 6 or 8 mg/kg (HR 2.5; *P*=0.008). • Microbiologic clearance: ≥10 mg/kg and 8 mg/kg with improved clearance compared to 6 mg/kg (no difference betw. 8 and ≥10 mg/kg)
YES	Chuang et al. CID 2017 (n=112)	• 6-7 mg/kg: 36 • 7-9 mg/kg: 51 • ≥9 mg/kg: 25	• 14-day mortality in multivariate model: Decreased mortality with ≥9 mg/kg compared to 6-7 mg/kg (P=0.003) or 7-9 mg/kg (*P*=0.03). • No difference in microbiologic failure
YES?	Seaton et al. Adv Ther 2015 (EU-CORE registry)	Any enterococcal infection •≤6 mg/kg: 371 •>6 to <8: 32 •>8 mg/kg: 63	• Clinical success: Trend towards improved clinical success with higher dosages: • ≤6 mg/kg: 76% • >6 to <8 mg/kg: 78% • >8 mg/kg: 86%
YES?	Ye et al. J Med Micro Infect 2017	• ≥10 mg/kg: 18 • <10 mg/kg: 77 (n=95)	• Mortality: Trend towards improved 28-day survival with ≥10 mg/kg dose (*P*=0.15)
YES?	Cornell data (unpublished)	• 6 mg/kg • 8 mg/kg • ≥10 mg/kg	• Trend towards increased rates of microbiologic clearance with higher doses of daptomycin (when assessed by ideal or adjusted body weight; *P*=0.1). No difference in mortality (*P*=0.6)
NO	King et al. JAC 2011 (n=46)	• ≤6 mg/kg: 24 • >6 mg/kg: 22	• No difference in microbiologic cure (P=0.97) or mortality

Safety of High-Dose Daptomycin Clinical Trials

- Phase 1: Healthy volunteers
  1) N=36. 6, 8, 10, and 12 mg/kg similar to placebo[1]
  2) N=24. 6 and 8 mg/kg similar to placebo[2]
- Phase 2: Randomized clinical trials
  1) 10 mg/kg DAP (n=48) x 4 days vs. other abx for SSTI[3]
     - 10 mg/kg DPA: 4/48 (8%) with CK increase, none required hospitalization or considered serious
  2) 8 mg/kg DAP (n=25) vs. 6 mg/kg DAP (n=23) x 6 weeks vs. other abx for prosthetic joint infection
     - CK >500: 6 mg/kg DAP (16%), 8 mg/kg DAP (22%), other abx (8%)

[1]Dvorchik et al. AAC 2003.
[2]Benvenuto M, et al. AAC 2006.
[3]Katz DE, et al. Int J Clin Pract 2008.
[4]Byren I, et al. AAC 2012.

Safety of High-Dose Daptomycin
Observational Studies

Risk of CK elevations with high-dose daptomycin

Reference	≤ 6 mg/kg N (%CK elevations)	~7 mg/kg N (% CK elevation)	8 mg/kg N (%CK elevation)	9 mg/kg N (% CK elevation)	10 mg/kg N (%CK elevation)
Seaton Adv Ther 2015 (EU-CORE registry)	4892 (1.0%)	452 (2.0%)	645 (2.8%) (≥8 mg/kg)		
Chuang CID 2017	36 (5.6%)		51 (7.8%)	25 (4.0%): (≥9 mg/kg)	
Britt CID 2017	441 (1.4%)		103 (1.0%)		51 (0%)
Casapao AAC 2013			245 (3%) All asymptomatic		
Kullar Pharmacotx 2013				250 (1.2%)	
Durante-Mangoni IJAA 2016			102 (15%)-all but 2 mild and asymptomatic		

- EU-CORE: No increase in rhabdomyolysis, myositis, myalgia, or myopathy with higher daptomycin doses
- Eosinophilic pneumonia:
  - CORE (US) and EU-CORE: 4/11,557 patients (0.03%)[1]
  - Not thought to be a dose-dependent adverse reaction[2]

[1]Seaton RA, et al. Ann Clin Micro Antimicrob 2016.

[2]Hirai J, et al. J Infect Chemother 2017.

IDSA Guidelines
Recommendations for High-Dose Daptomycin

- MRSA bacteremia and endocarditis: “some experts recommend daptomycin at 8-10 mg/kg”
- Persistent MRSA bacteremia and vancomycin treatment failures: “High-dose daptomycin (10 mg/kg/day)”
- Native valve endocarditis caused by staphylococci: “Daptomycin ≥8 mg/kg”
- Endocarditis caused by ampicillin-resistant and vancomycin-resistant enterococci: “Daptomycin 10-12 mg/kg. If daptomycin is selected, then doses of 10-12 mg/kg may be considered”

Liu C, et al. CID 2011.
Baddour LM et al., Circulation 2015.

Animal PK-PD Target
Dr. Nicolau's neutropenic thigh model

(Inoculum of *E. faecium*: 10^8 CFU)

*f*AUC/MIC Required To Achieve		
Stasis	**1-Log Reduction**	**R^2**
0.00	**9.80**	**0.6879**

Like with Dr. Craig's model, stasis in untreated mice

Conclusion: fAUC/MIC target of 9.8 needed to achieve 1-log kill in the neutropenic thigh model, but concerns about suitability of model for *E. faecium*

Unpublished work: Kidd MJ, et al.

Clinical Exposure Targets

- No clinical trials to correlate patient exposures to outcomes in enterococcal infections
- Dr. Kuti et al. acquired data from investigators of published observational studies and modeled their estimated exposures and correlated with outcomes
  - Then identified estimated fAUC/MIC targets that were correlated with microbiologic clearance and survival

Outcome	**Survival (Monotherapy)**	**Survival (Combo therapy)**	**Microbiologic response**
fAUC/MIC target	27.4	20.0	12.3

Monte Carlo Simulation: PTA at PD Thresholds

MIC	Clinical: Survival (MonoTx) > 27.43	Clinical: Micro Response (MonoTx) > 20.01	Clinical: Survival (ComboTx) > 12.28	Neutropenic thigh model: 1-log kill ≥ 9.8
Daptomycin 6 mg/kg daily				
0.5	100.0%	100.0%	100.0%	100.0%
1	91.0-97.9%	99.1-100.0%	100.0%	100.0%
2	32.4-54.4%	63.0-82.5%	95.2-99.3%	99.3-100.0%
4	1.5-5.5%	8.4-20.1%	43.0-64.6%	64.8-83.8%
8	0.0%	0.0-0.3%	2.9-9.3%	9.4-22.1%
16	0.0%	0.0%	0.0%	0.0%

With 6 mg/kg dosing, susceptible breakpoint should be 1 or 2 µg/mL

Daptomycin 8 mg/kg daily				
0.5	100.0%	100.0%	100.0%	100.0%
1	98.7-99.9%	100.0%	100.0%	100.0%
2	60.7-80.4%	86.7-95.9%	99.7-100.0%	100.0%
4	7.3-18.1%	25.0-45.4%	70.9-87.5%	87.6-96.3%
8	0.0-0.2%	0.0-3.3%	11.7-26.4%	26.5-47.4%
16	0.0%	0.0%	0.1-0.9%	0.9-3.7%

Monte Carlo Simulation: PTA at PD Thresholds

MIC	Clinical: Survival (MonoTx) > 27.4	Clinical: Micro Response (MonoTx) > 20.0	Clinical: Survival (ComboTx) > 12.3	Neutropenic thigh model: 1-log kill ≥ 9.8
Daptomycin 10 mg/kg daily				
0.5	100.0%	100.0%	100.0%	100.0%
1	99.9-100.0%	100.0%	100.0%	100.0%
2	80.4-92.9%	95.9-99.5%	100.0%	100.0%
4	18.1-36.2	45.4-66.7%	87.5-96.2%	96.3-99.6%
8	0.2-2.0%	3.3-9.9%	26.4-47.2%	47.4-68.8%
16	0.0%	0.0%	0.9-3.7%	3.7-10.7%
Daptomycin 12 mg/kg daily				
0.25	100.0%	100.0%	100.0%	100.0%
0.5	100.0%	100.0%	100.0%	100.0%
1	100.0%	100.0%	100.0%	100.0%
2	91.0-97.9%	99.1-100.0%	100.0%	100.0%
4	32.4-54.4%	63.0-82.5%	95.2-99.3%	98.5-99.7%
8	1.5-5.5%	8.4-20.1%	43.0-64.6%	63.2-81.8%
16	0.0%	0.0-0.3%	2.9-9.3%	8.8-20.8%

With 10-12 mg/kg dosing, susceptible breakpoint should be 2 or 4 µg/mL

Concerns raised and how they were addressed

- Safety of higher doses of daptomycin:
  - Can not rule out a minor increase in CK elevations, but this potential small toxicity risk is minor compared to a likely mortality benefit
  - Eosinophilic pneumonitis not dose-related
  - IDSA Guidelines frequently recommend these doses
- Prefer to not separate *E. faecium* from other enterococci: concerns that labs may not always be able to reliably distinguish between enterococci
  - Don’t want to recommend high doses for infections with other enterococci; Data supporting this high dose are only for *E. faecium* with MICs 2-4 µg/mL

Proposal for Daptomycin/Enterococci Breakpoints

- Susceptible: ≤1 µg/mL*
- Susceptible-Dose Dependent: 2-4 µg/mL**
- Resistant: ≥ 8 µg/mL

Comments:

*Based on a dosage regimen of 6 mg/kg/day in adults.

**The S-DD category is based on a dosage regimen of 8-12 mg/kg in adults and is intended for serious infections due to *Enterococcus* spp. Consultation with an infectious diseases specialist is recommended.

BPWG Actions:
Vote: 8 Yes; 0 No; 1 Abstain
AHWG Vote – Unanimous “Yes”

- The same breakpoints are being recommended with added comments:
- Susceptible ≤1 mg/ml *
- S-DD = 2-4 mg/ml **
- R ≥8 mg/ml
- *Based on a dosage regimen of 6 mg/kg/day in adults.
- **The S-DD category is based on a dosage regimen of 8-12 mg/kg in adults and is intended for serious infections due to *Enterococcus* spp. Consultation with an infectious diseases specialist is recommended.

Evaluation of Ceftaroline Breakpoints for *Staphylococcus aureus*

Helio S. Sader, M.D.

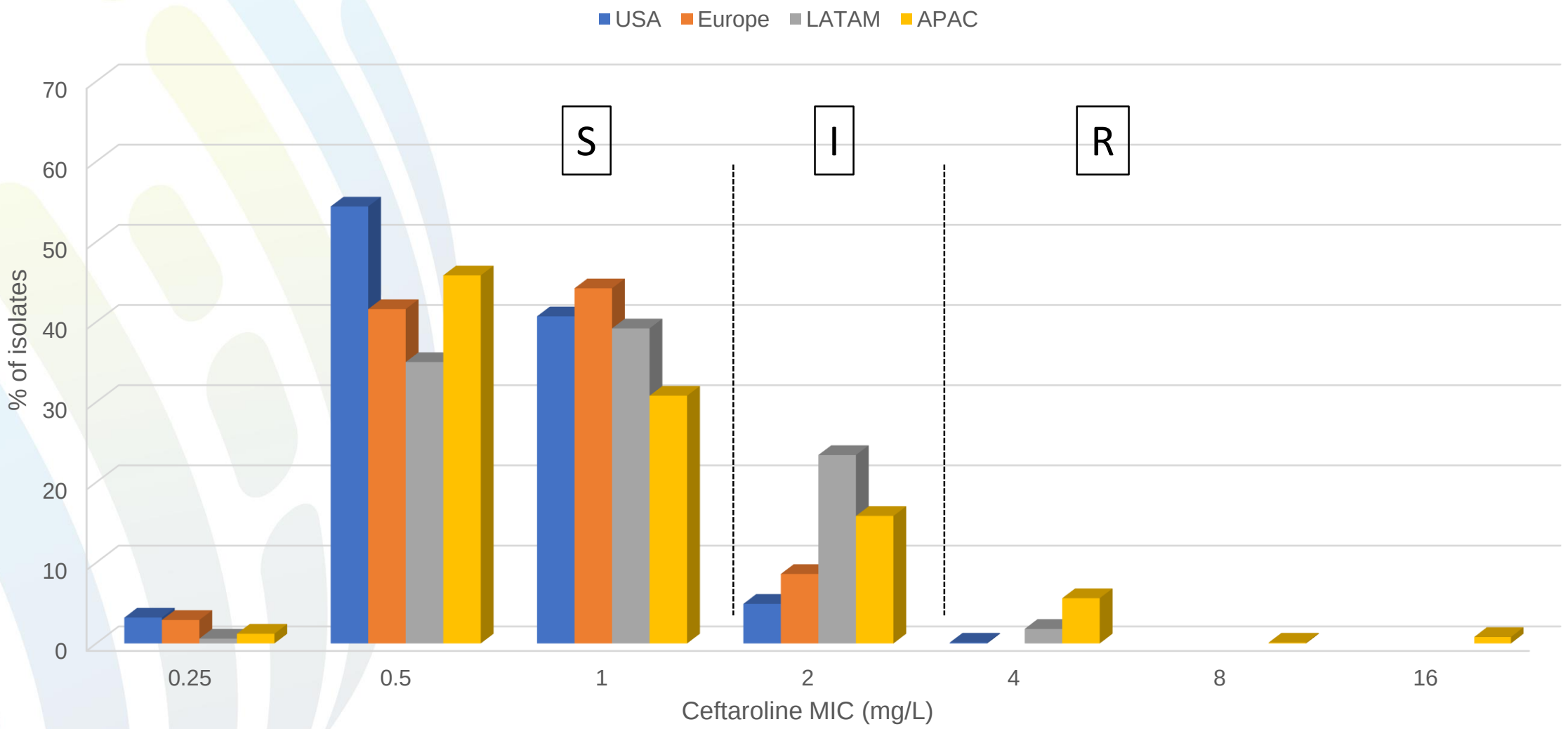
JMI Laboratories

North Liberty, Iowa USA

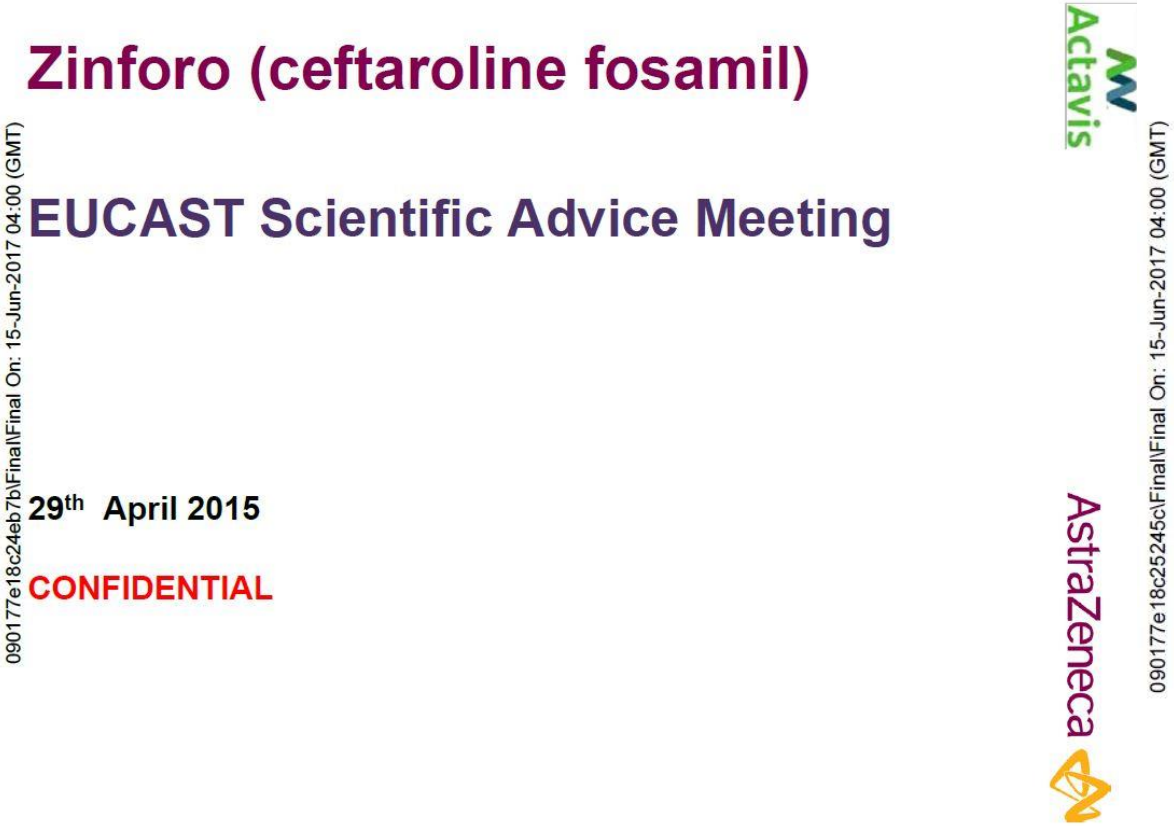
Conclusions from previous meeting (1)

- There was a direct correlation between disk-MIC discrepancy rates and the proportion of ceftaroline nonsusceptible isolates in the collection:
  - **Error rates are elevated (>10% Mi and/or >1% VM) when the collection had >15% ceftaroline-nonsusceptible isolates**
- Current CLSI/US FDA disk breakpoints (≥24 mm/≤20 mm for S/R) appeared appropriate to reduce discrepancy errors
- An optimal correlation between disk and broth microdilution methods **cannot** be achieved with current MIC breakpoints in geographic regions/medical centers with >15% ceftaroline-nonsusceptible MRSA isolates

Ceftaroline activity tested against MRSA stratified by geographic region (SENTRY Program, 2016-2017)



Additional data provided by Pfizer



New data — after current CLSI/US FDA breakpoints established

- **Study D3720C00001 (COVERS)**
  The COVERS study was conducted to evaluate the efficacy of ceftaroline fosamil 600 mg q8h 2h infusion in patients with more considerable disease or systemic upset.

- **Data suggesting that the current breakpoint for *S. aureus* bisects the normal distribution**
  - Based on surveillance and molecular epidemiology data
  - This impacts performance of the 5 µg disk

- **Dose ranging hollow fibre study**
  - Addition to data from previous in vivo and in vitro studies has allowed for a more robust definition of PK/PD targets.
  - Stasis, 1-log, and 2-log kill PK/PD targets for *S. aureus* have been updated to take all data into account.

- **Population PK modelling and PTA simulation**
  - Additional data from patients with cSSTI has been used to update the population model and probability of target attainment (PTA) analyses using the updated PK/PD targets.

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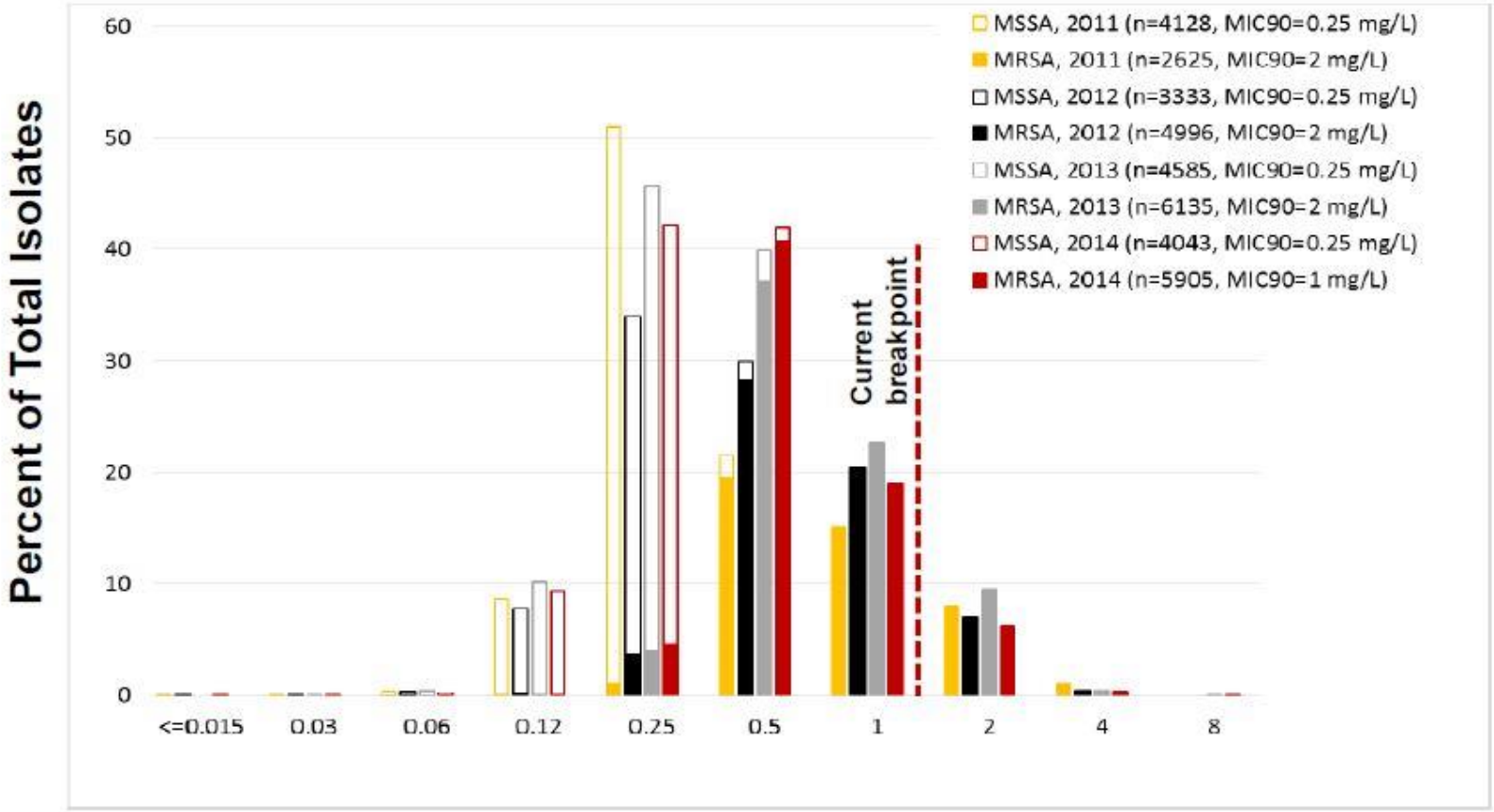
S. aureus Ceftaroline MIC distribution by year
(in USA, Europe, Latin America, and Asia/Pacific)



The ceftaroline MIC distribution for *S. aureus* is consistent over 4 years and test predominantly in the 0.12-2.0 mg/L range.

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New ceftaroline PK/PD data in hollow fibre infection model

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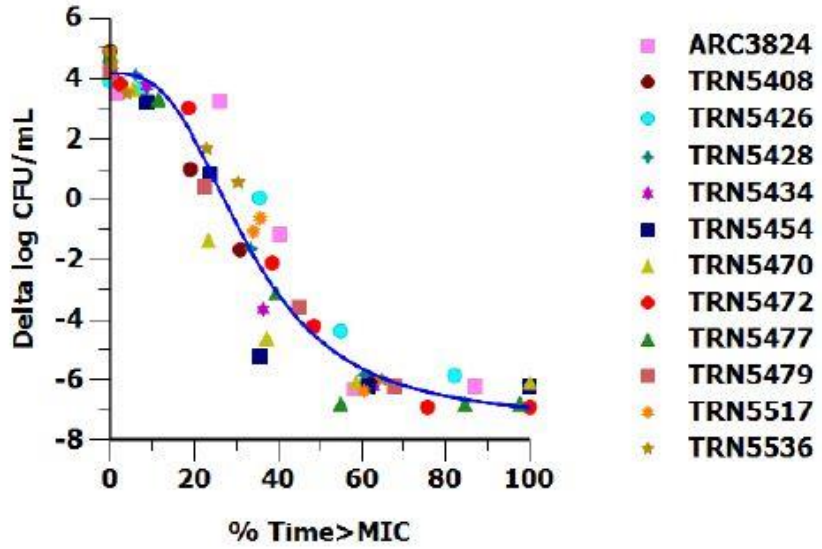
PK/PD target of ceftaroline MRSA isolates with MICs 2 to 4 mg/L explored by dose ranging using a q8h regimen for 24 hours.

A total of 12 MRSA isolates with diverse molecular characteristics were studied.

Across the 12 isolates, mean ceftaroline *f*T>MIC of 29%, 32% and 35% achieved stasis, 1-log and 2-log kill, respectively

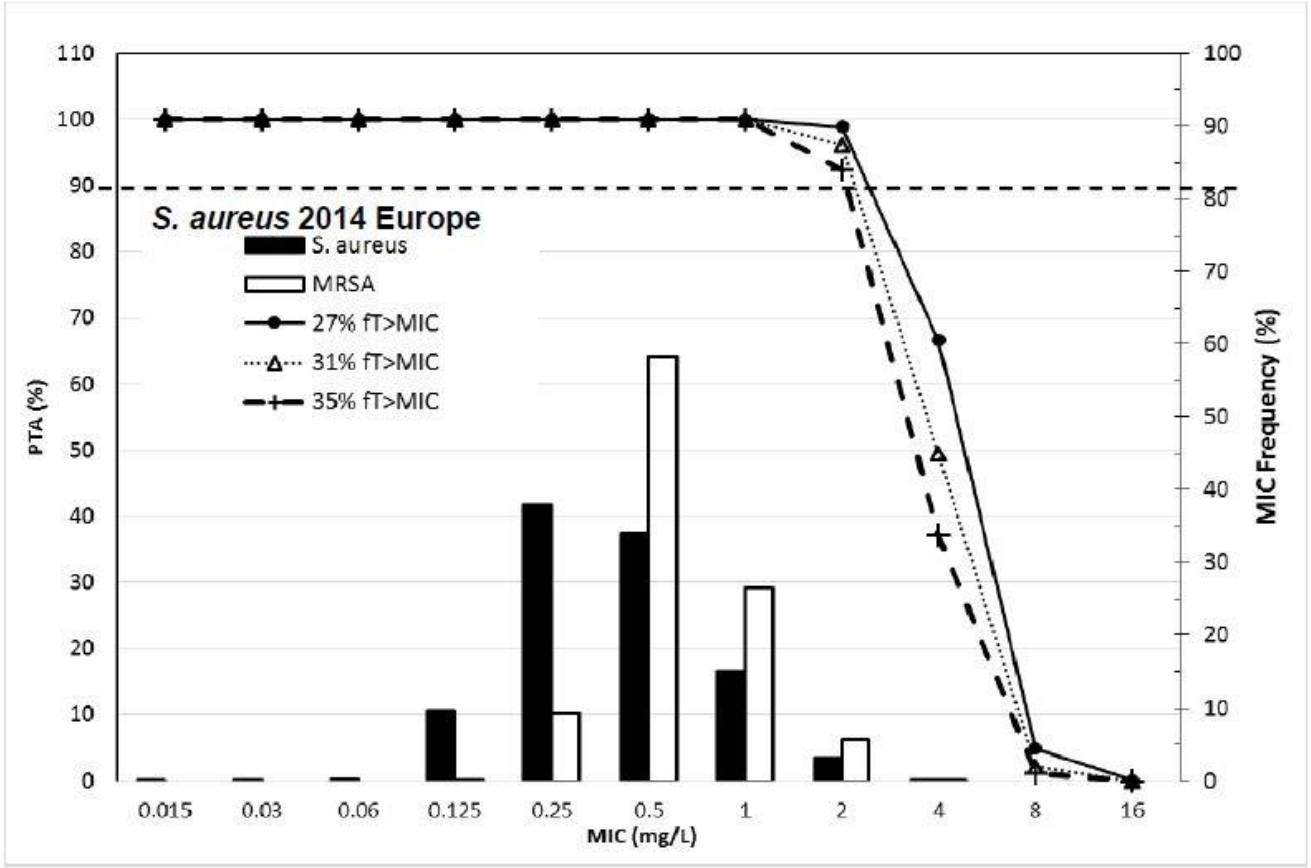
Results consistent with previous in vivo and in vitro data generated for *S. aureus* isolates

Results using q8h dosing as used here and q12h dosing used in previous in vitro experiments showed consistency



Overall, for stasis, 1-log and 2-log kill ceftaroline *f*T>MIC target is 27%, 31% and 35%, respectively

Using new targets PTA analysis for 600 mg q12h for *S. aureus* versus surveillance frequency distribution in Europe



Ceftaroline fosamil dose of 600 mg q12h 1h infusion achieves >95% and >90% PTA against 1-log kill and 2-log kill targets respectively for *S. aureus* up to an MIC of 2 mg/L.

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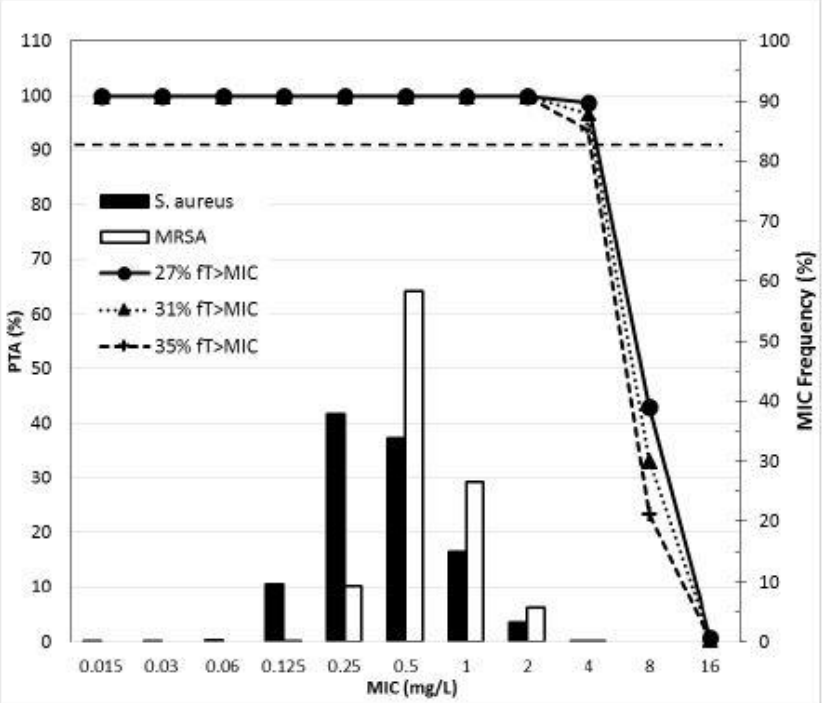
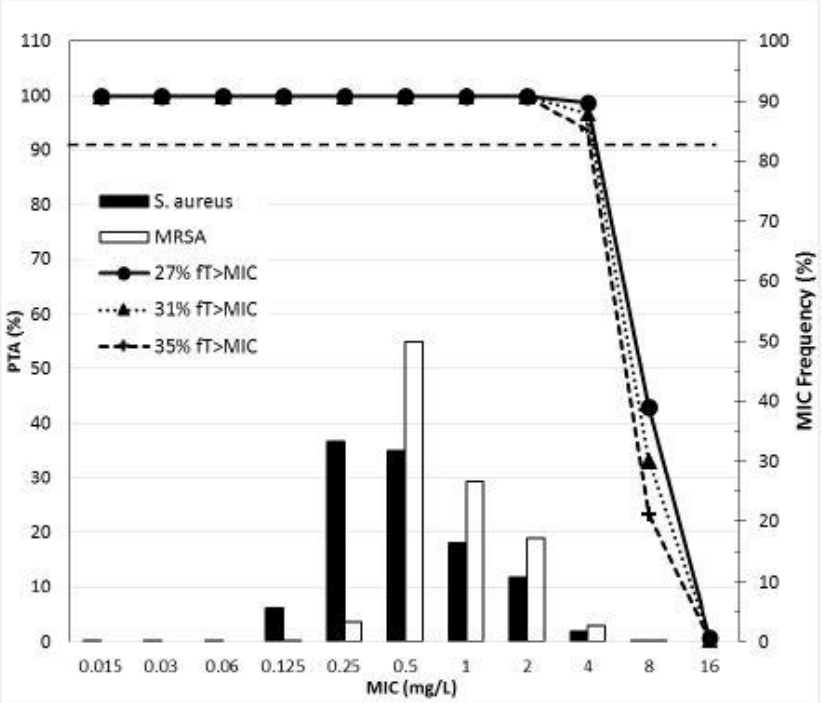
New PTA analysis for 600 mg q8h for *S. aureus* versus surveillance frequency distribution

Europe (2014)



Asia / Pacific (2014)



Ceftaroline fosamil dose of 600 mg q8h 2h infusion achieves >95% and >90% PTA against new 1-log kill and 2-log kill targets respectively for *S. aureus* up to an MIC of 4 mg/L.

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Clinical data

- **Clinical efficacy data in patients with cSSTI and *S. aureus* with a ceftaroline MIC ≥2 mg/L are limited**
  - 5 ceftaroline-treated patients across 3 Phase 3 cSSTI trials (plus MRSA extension) 2172 randomised patients (4 in q12h and 1 in q8h)
- **It is difficult to enrol patients with pathogens at the upper end of the MIC distribution**
  - cSSTI disease definitions and protocol inclusions/exclusions favour enrolment of newly hospitalized patients with community-acquired infections
  - MIC distribution of trial isolates are “left-shifted” compared to surveillance isolates
- **Reliance solely on clinical data causes breakpoints to lag behind emergence of more resistant pathogens, thus clinicians’ guidance may be lacking for treatment of patients at greatest need**

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EUCAST version 8.0 (2018)

Ceftaroline, *S. aureus* (indications other than pneumonia)	1[5]	2[5,6]	5	20[D]	17[D,E]
Ceftaroline, *S. aureus* (pneumonia)	1[5]	1[5]	5	20[D]	20[D]

5/D. Methicillin-susceptible isolates can be reported susceptible to ceftaroline without further testing.
6/E. Resistant isolates are rare.

EUCAST version 8.0 (2018)

Ceftaroline	0.6 g x 2 iv over 1 hour	0.6 g x 3 iv over 2 hours	***S. aureus* in complicated skin and skin structure infections:** There is some PK-PD evidence to suggest that isolates with MICs of 4 mg/L could be treated with high dose.

EU SmPC for ceftaroline fosamil reflects new breakpoint and dose recommendations

Table 1 Dosage in adults and adolescents (aged from 12 to < 18 years with bodyweight ≥ 33 kg) with CrCL > 50 mL/min

Infection	Dosage	Frequency	Infusion time (minutes)	Duration of treatment (days)
cSSTI[a]	600 mg	Every 12 hours	60	5-14
CAP	600 mg	Every 12 hours	60	5-7

[a] Based on pharmacokinetic and pharmacodynamic analyses the recommended dose regimen for treatment of cSSTI due to *S. aureus* for which the ceftaroline MIC is 2 or 4 mg/L is 600 mg every 8 hours using 2 hour infusions. See sections 4.4 and 5.1.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for susceptibility testing are presented below.

Organisms	MIC breakpoints (mg/L)	
	Susceptible (≤ S)	Resistant (R>)
Staphylococcus aureus	1[1]	>2[2]
Streptococcus pneumoniae	0.25	0.25
Streptococcus Groups A, B, C, G	Note[3]	Note[3]
Haemophilus influenzae	0.03	0.03
Enterobacteriaceae	0.5	0.5

1. Refers to dosing of adults or adolescents (from 12 years and 33 kg) with ceftaroline every 12 hours using 1-hour infusions (see section 4.2). Note that: There are no clinical trial data regarding the use of ceftaroline to treat CAP due to S. aureus with ceftaroline MICs > 1 mg/L
2. Refers to dosing of adults or adolescents (from 12 years and 33 kg) with ceftaroline every 8 hours using 2-hour infusions to treat cSSTI (see section 4.2). *S. aureus* with ceftaroline MICs ≥ 4 mg/L are rare. PK-PD analyses suggest that dosing of adults or adolescents (from 12 years and 33 kg) with ceftaroline every 8 hours using 2-hour infusions may treat cSSTI due to *S. aureus* for which the ceftaroline MIC is 4 mg/L.
3. Infer susceptibility from susceptibility to benzylpenicillin.

EU SmPC, July 2017

Timing for submission of q8h dose*

EU Markets		EU SmPC Dependent Markets (follows SmPC)		EU Independent Markets (follows Core Data Sheet)	
High dose approval effective April 2017		High dose to be submitted in 2018**		High dose to be submitted in 2018**	
Austria	Italy	Algeria	Lebanon	Argentina	Malaysia
Belgium	Latvia	Bahrain	Morocco	Aruba	Mexico
Bulgaria	Lithuania	Ghana	Nigeria	Australia	New Zealand
Croatia	Luxenberg	Hong Kong	Norway	Brazil	Nicaragua
Cyprus	Malta	Iceland	Qatar	Chile	Panama
Czech Republic	Netherlands	Israel	Serbia	Colombia	Philippines
Denmark	Poland	Jordan	Tunisia	Costa Rica	Russia
Estonia	Portugal	Kazakhstan	UAE	Curacao	Saudi Arabia
Finland	Romania	Kuwait		Dominican Republic	Singapore
France	Slovakia			Ecuador	South Africa
Germany	Slovenia			Egypt	Switzerland
Greece	Spain			El Salvador	Taiwan
Hungary	Sweden			Guatemala	Thailand
Ireland	United Kingdom			India	Trinidad & Tobago
				Indonesia	Turkey
				Iraq	Uruguay
				Lichtenstein	Venezuela
				Macao	

* There are no plans to seek approval of the 600 mg q8h dose in the United States

** Tentative

Ceftaroline WG proposal

Organism	MIC breakpoints (mg/L)		
	Susceptible	**SDD[a]**	**Resistant**
S. aureus	≤1 mg/L	2-4 mg/L	≥8 mg/L

Organism	Zone diameter breakpoints (mm)		
	Susceptible	**SDD[a]**	**Resistant**
S. aureus	≥25	20-24	≤19

[a] SDD is based on 600 mg q8 infused over 2 hours in adults.

Passed 6 - 0

Motion that outreach group be contacted to promote education around the reasoning for this change and its applicability outside the U.S.
Passed 6-0

- **BP WG-- A motion was made and seconded to approve the proposed breakpoints.**
- Vote: 6 Yes; 2 No; 1 Abstain.

Meeting Materials for CLSI BP SC - Cefiderocol (FDC, S-649266) -

June, 2018

Breakpoint proposal

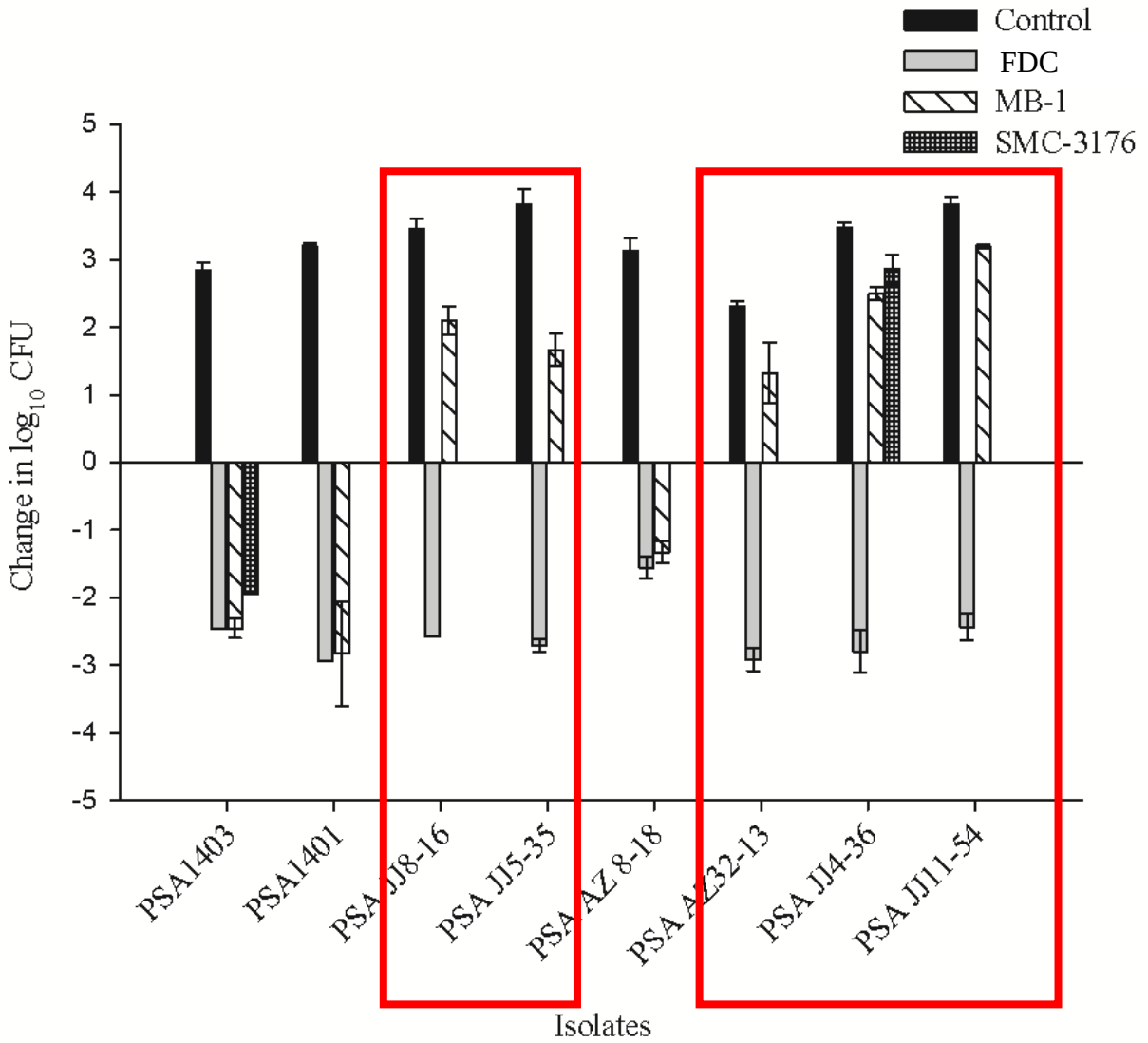
Susceptible and intermediate breakpoint is proposed to be 4 and 8 μg/mL, respectively.

- Human clinical trials for cUTI patients have not provided evidence for breakpoint determination for carbapenem resistant strains of *Enterobacteriaceae* and *P. aeruginosa*, and *A. baumannii* and *S. maltophilia*.
- BP is mainly proposed based on the non-clinical studies.

	Breakpoint MIC (μg/mL)		
	Susceptible	Intermediate	Resistant
Enterobacteriaceae	≤4	8	≥16
P. aeruginosa	≤4	8	≥16
A. baumannii	≤4	8	≥16
S. maltophilia	≤4	8	≥16

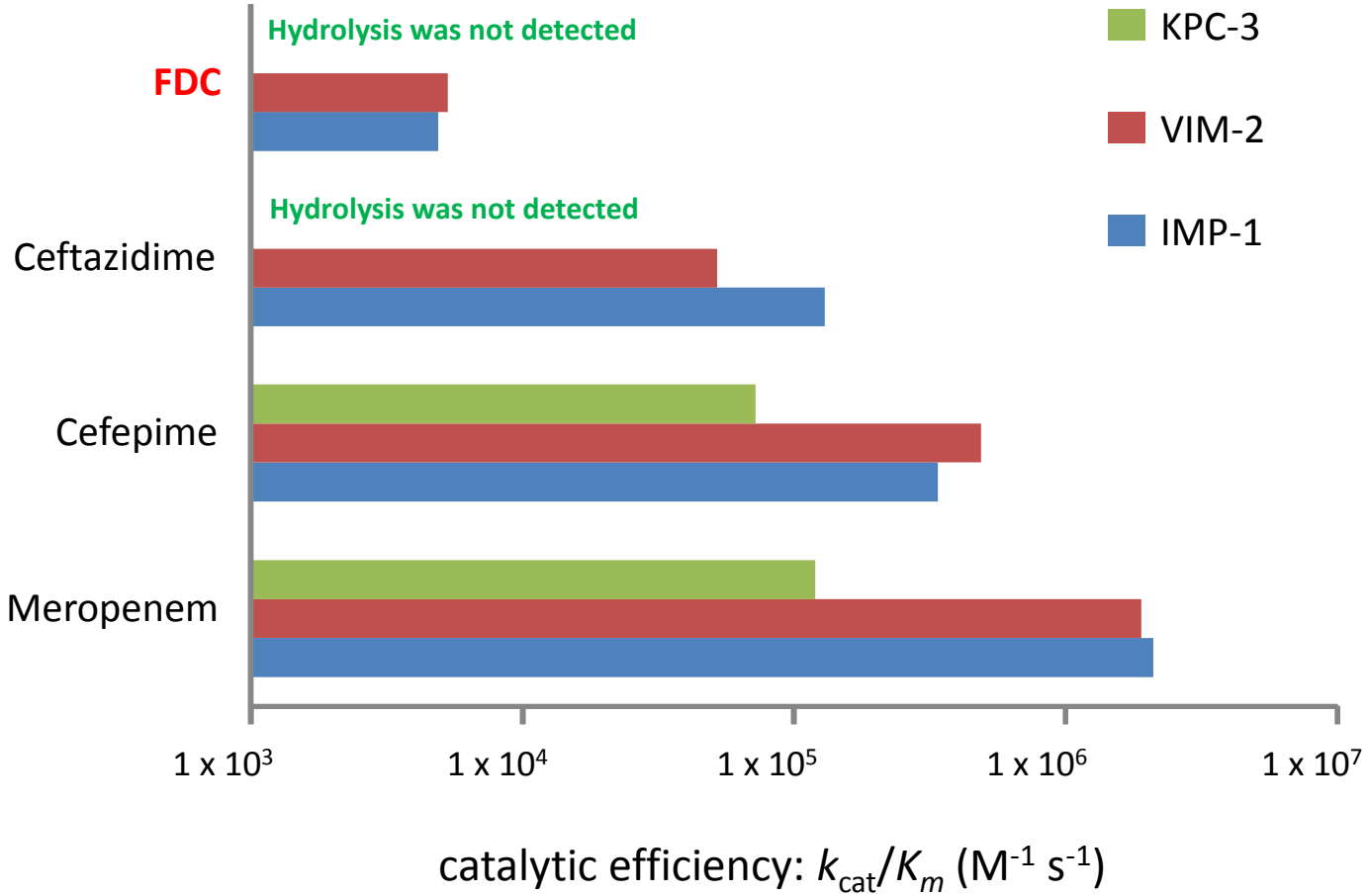
No Adaptive Resistance for FDC

Therapeutic Efficacies of FDC, MB-1, and SMC-3176 in Murine Thigh Infection Model Caused by *P. aeruginosa* under the Conditions Mimicking the Human Exposures

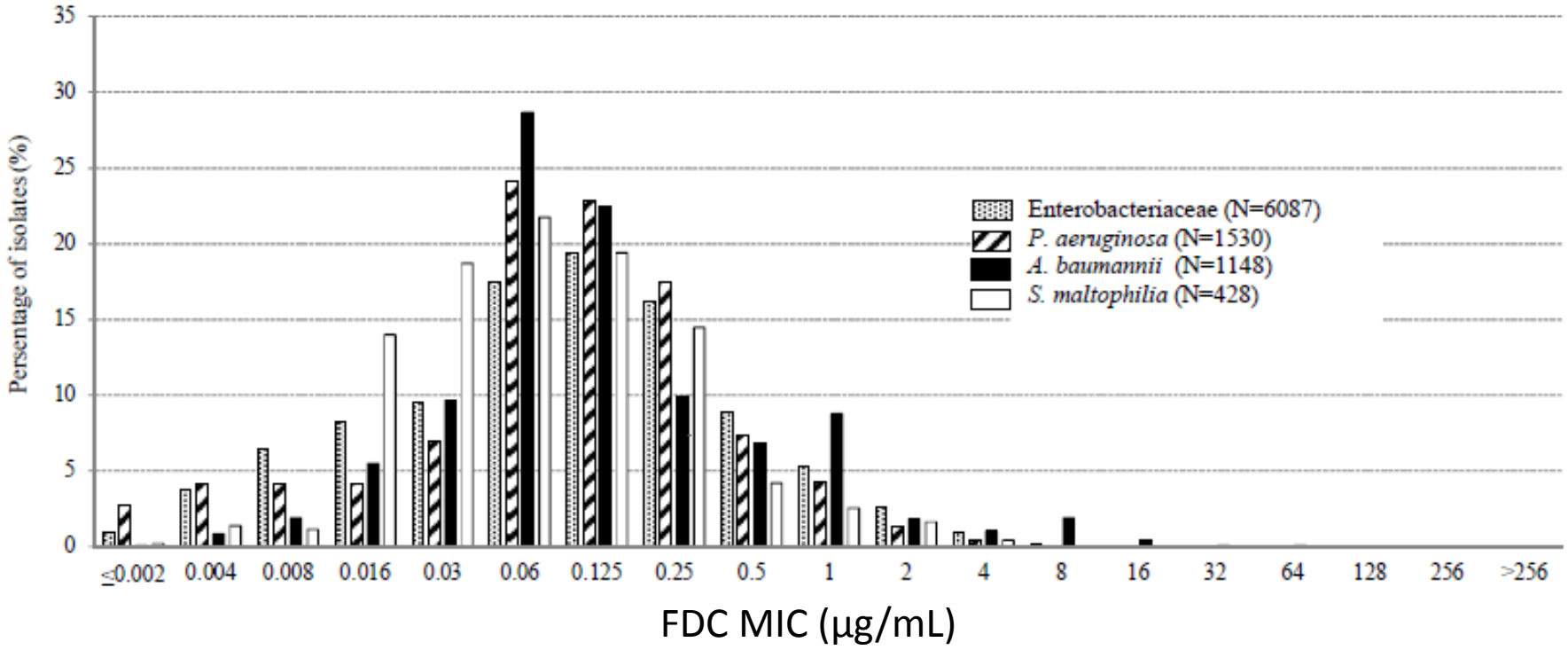


Mechanisms to Overcome Carbapenem Resistance (2)

- Higher stability to both serine- and metallo-type carbapenemases than carbapenems and cephalosporins



FDC MIC Distribution of 9,205 Gram-Negative Clinical Isolates From SIDERO-WT-2014



99.6% of all isolates susceptible to FDC at ≤4 µg/mL

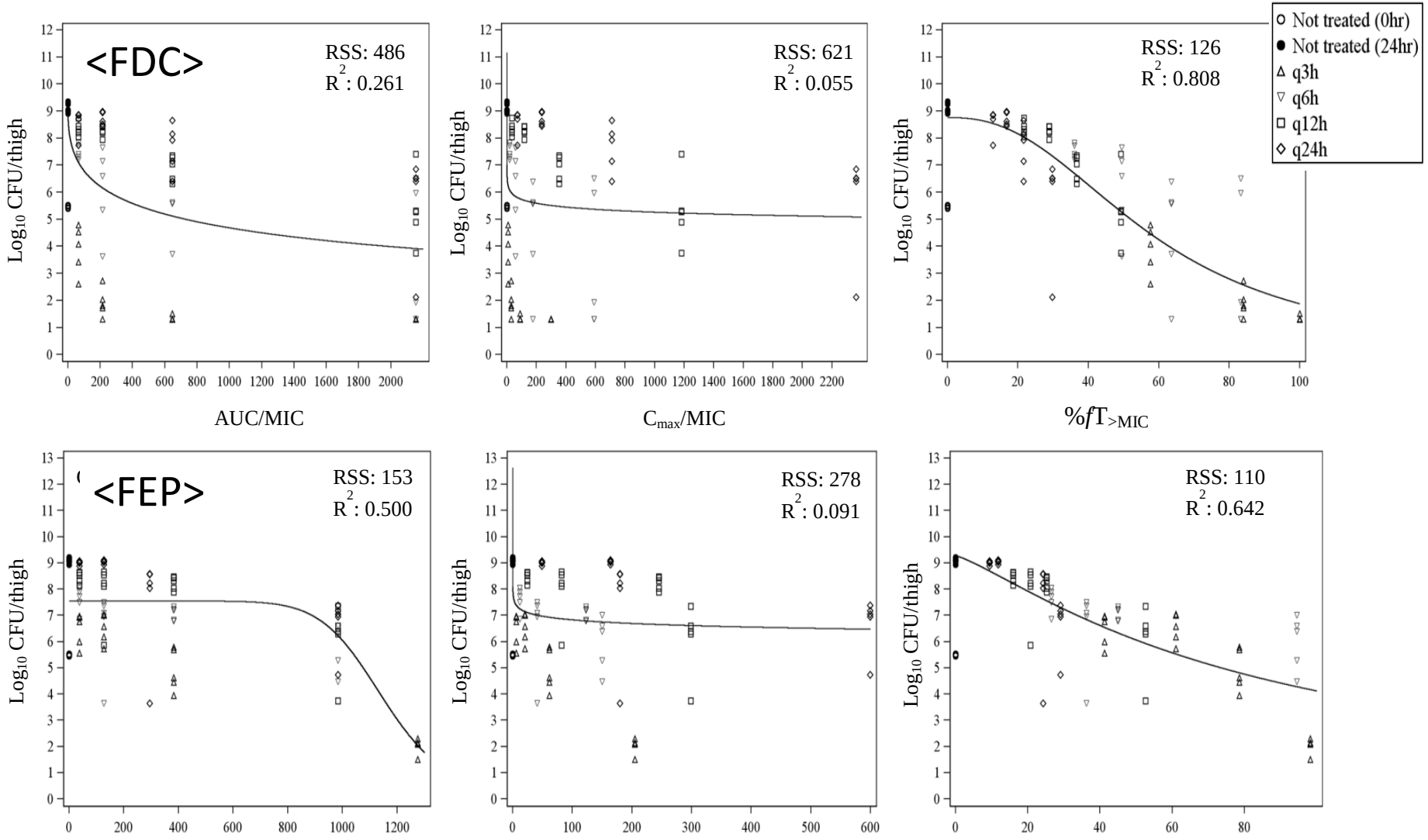
MIC Distribution against Carbapenemase Producers from SIDERO-WT-2014

	No. isolates	Number of isolates at cefiderocol MIC (μg/mL)												
		≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128
KPC	72	1	1	8	14	11	16	14	7					
GES	12			2	4	3	1		1	1				
IMP	4						1	3						
VIM	57		1	3	18	7	13	11	4					
NDM	14						4	2	3	5				
OXA-23	543	22	177	154	63	40	55	10	7	13	2			
OXA-24/40	124	10	26	39	10	13	14	5	1	3	1	1	1	
OXA-48-like	27	1	2	4	3	4	4	5	4					
OXA-58	13			6	2	3	2							
Carbapenemase-negative CarbNS strain	332	62	81	65	55	34	23	6	6					
Total		96	288	281	169	115	133	56	33	22	3	1	1	96

OXA-48 like: OXA-48, OXA-162, OXA-181, OXA-244

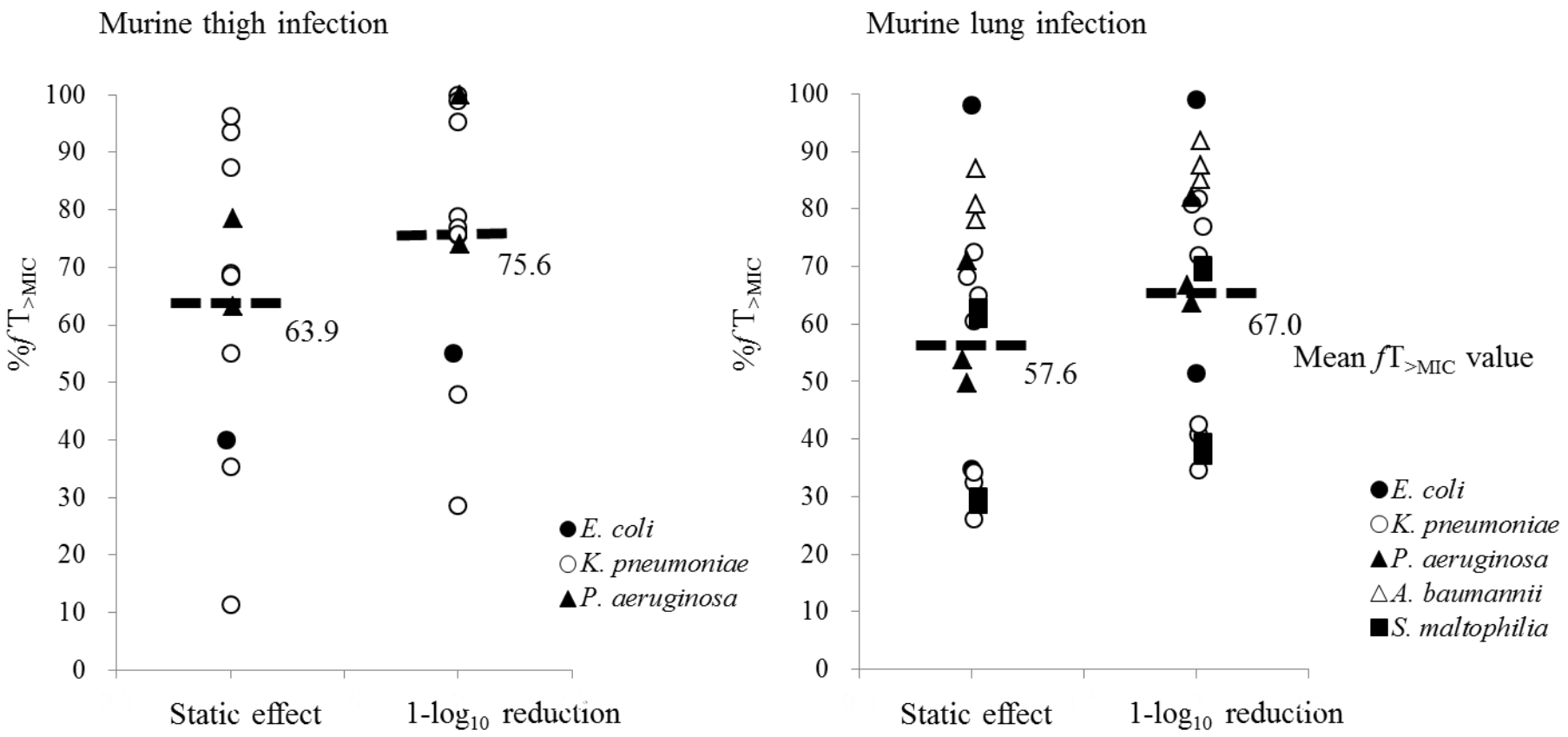
- No clear relationship between specific carbapenemase production and cefiderocol resistance
- High MIC trend was observed for NDM producers

Dose Fractionation Study using Murine Thigh Infection Models



$T_{>MIC}$ was shown to be appropriate PK/PD index to predictive efficacy

%$fT_{>MIC}$ in ID-CAMHB Required for Efficacy in Murine Thigh and Lung Infection Models for Each Strain



Neutropenic murine thigh and lung infection model

- Treatment: 2, 5, 8, 11, 14, 17, 20 ,23 hour post infection (8 times)
- Dissection: 24 hour post infection

In Vivo Pharmacodynamics of Ceftobiprole against Multiple Bacterial Pathogens in Murine Thigh and Lung Infection Models

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2008, p. 3492–3496

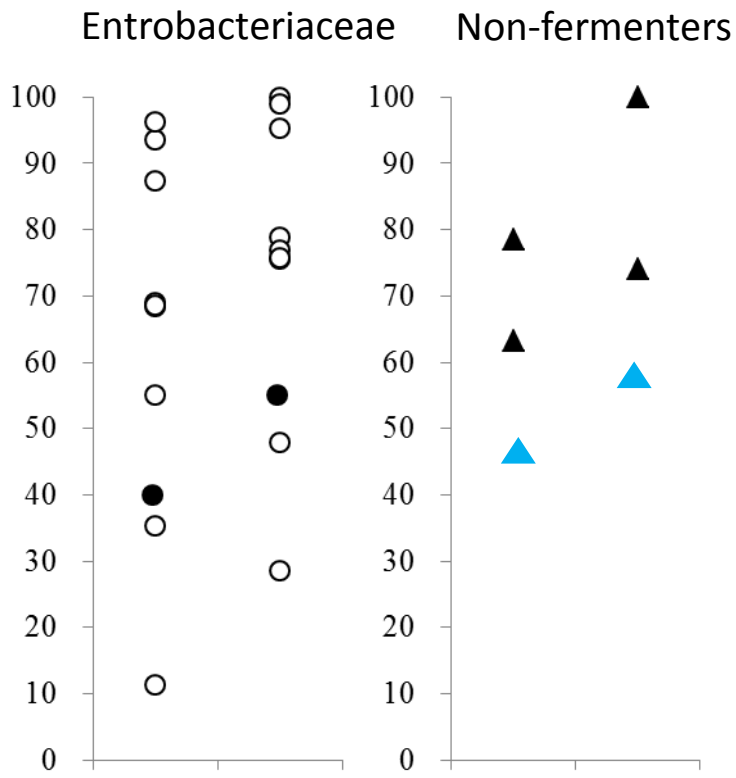
TABLE 1. Comparative efficacies of ceftobiprole against various pathogens[a]

Organism	MIC (μg/ml)	Static dose (mg/kg) and dosing interval	Static-dose $T > MIC$ (% of dosing interval)	2-Log kill dose (mg/kg) and dosing interval	2-Log kill dose $T > MIC$ (% of dosing interval)
S. pneumoniae strains					
ATCC 10813	0.03	0.180 every 6 h 0.307 every 6 h	19.4	0.552 every 6 h 0.450 every 6 h	24.8
MNO-418	0.015	0.238 every 6 h	21.3	0.624 every 6 h	31.8
CDC 145	0.25	0.956 every 6 h	15.2	3.27 every 6 h	23.0
CDC 1293	0.5	2.72 every 6 h	16.3	3.55 every 6 h	18.4
CDC 1329	0.25	2.93 every 6 h	22.2	5.51 every 6 h	27.0
CDC 673	1.0	6.68 every 6 h	18.5	29.0 every 6 h	29.7
Total (mean ± SD)			18.8 ± 2.7		25.8 ± 4.8
S. aureus strains					
ATCC 33591	1.0	7.91 every 6 h	19.1	15.3 every 6 h	24.4
MRSA WIS-1	1.0	16.1 every 6 h	25.0	53.9 every 6 h	39.1
MRSA 11888	2.0	22.6 every 6 h	22.5	40.2 every 6 h	27.4
MRSA 12248	2.0	29.2 every 6 h	24.5	50.5 every 6 h	31.6
MRSA 22115	1.0	16.9 every 6 h	25.4	34.4 every 6 h	29.6
ATCC 22923	0.5	2.03 every 6 h	14.1	10.3 every 6 h	26.5
ATCC 29213	0.5	3.78 every 6 h	18.9	15.4 every 6 h	29.9
ATCC Smith	0.5	4.21 every 6 h	19.6	9.60 every 6 h	25.9
Total (mean ± SD)			21.1 ± 3.9		29.3 ± 4.6
Enterobacteriaceae					
E. coli ATCC 25922	0.06	8.25 every 6 h 10.4 every 6h	41.9	42.4 every 6 h 44.7 every 6 h	57.8
K. pneumoniae ATCC 43816	0.06	6.61 every 6 h 8.57 every 6 h	41.2	43.8 every 6 h 47.5 every 6 h	59.2
E. cloacae 2249	2.0	22.2 every 3 h	44.6	155 every 3 h	100
E. cloacae 4567	0.5	3.28 every 3 h	35.6	4.67 every 3 h	40.9
Total (mean ± SD)			40.8 ± 3.8		64.5 ± 25.1
P. aeruginosa ATCC 27853	2.0	25.2 every 3 h	46.7	110 every 3 h	98.8

[a] The R^2 for the individual organisms varied from 0.932 to 0.999 (mean of 0.983).

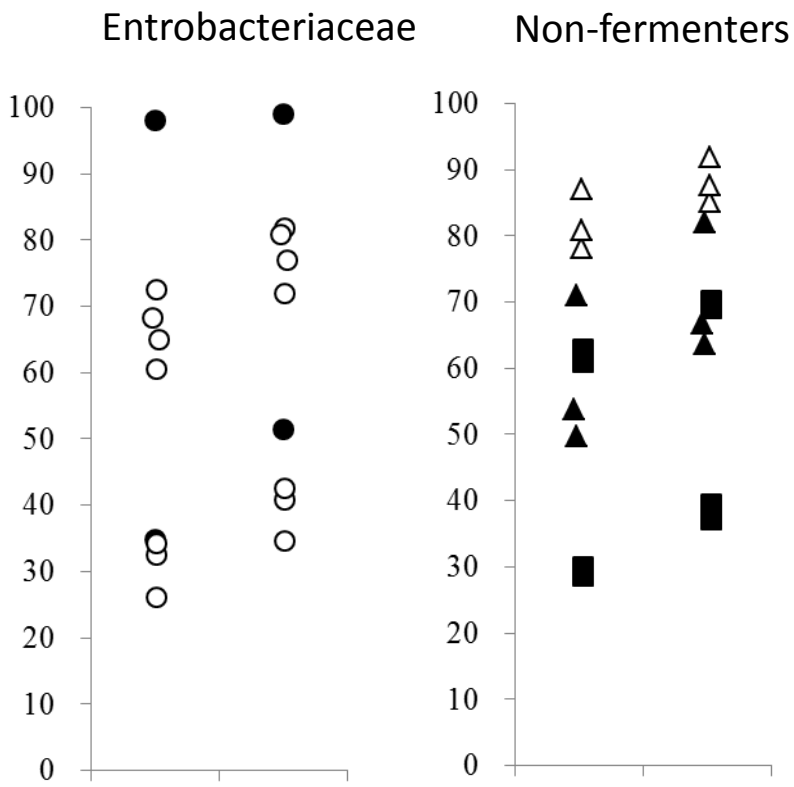
*f*T>MIC in ID-CAMHB Required for Efficacy in Murine Thigh and Lung Infection Models for Each Strain (Updated)

Murine thigh infection
(5 carba S + 7 carba R)



- ● *E. coli* 1 strain
- ○ *K. pneumniae* 9 strains (3KPC, 3 NDM)
- ▲ *P. aeruginosa* 2 strans (1 IMP) + 1 strain

Murine lung infection
(all carba R)



- ● *E. coli* 2 strains (1 KPC, 1 NDM)
- ○ *K. pneumniae* *7* strains (3 KPC, 4 NDM)
- ▲ *P. aeruginosa* 3 strains (1 IMP, 1 VIM)
- △ *A. baumannii* 3 strains (1 OXA-23, 1 OXA-24)
- ■ *S. maltophilia* 4 strains

$\%fT_{>MIC}$ in ID-CAMHB Required for Efficacy in Murine Thigh and Lung Infection Models

Organisms (Number of Strains used for each infection models)	**$\%fT_{>MIC}$ (Mean ±SD)**			
	Thigh Infection		Lung Infection	
	Static	1-$\log_{10}$ reduction	Static	1-$\log_{10}$ reduction
E. coli, *K. pneumoniae* (N = 10 thigh, 9 lung)	62.5 ± 27.4	73.3 ± 23.3	54.7 ± 24.1	64.4 ± 22.5
P. aeruginosa (N = 2 thigh, 3 lung)	70.8 ± 10.8	87.1 ± 18.3	58.1 ± 11.3	70.8 ± 9.8
A. baumannii (N = 0 thigh, 3 lung)	not done	not done	82.0 ± 4.6	88.1 ± 3.4
S. maltophilia (N = 0 thigh, 4 lung)	not done	not done	45.6 ± 18.9	53.9 ± 18.1
Total (N = 12 thigh, 19 lung)	63.9 ± 25.2	75.6 ± 22.5	57.6 ± 21.7	67.0 ± 20.2

PTA for 75% $fT_{>MIC}$

Highlighted > 90% PTA

Renal Function	Regimen	MIC (µg/mL)						
		0.25	0.5	1	2	4	8	16
Augmented	2 g q6 hour	100	100	99.8	98.8	93.0	70.1	23.7
Normal	2 g q8 hour	100	100	99.6	97.6	90.1	61.2	16.8
Mild	2 g q8 hour	100	100	100	99.6	96.6	83.0	37.4
Moderate	1.5 g q8 hour	100	100	100	100	99.3	92.0	52.1
Severe	1 g q8h our	100	100	100	100	99.7	97.5	71.1
ESRD	0.75 g q12 hour	100	100	100	99.9	99.8	95.4	59.7

Augmented: CrCL 120 to 200 mL/min. Normal: 90 to < 120. Mild: 60 to < 90. Moderate: 30 to < 60. Severe: 15 to < 30. ESRD: 5 to < 15.
Body weight was assumed to be log-normal distributed with geometric mean of 75 kg and CV of 20%.

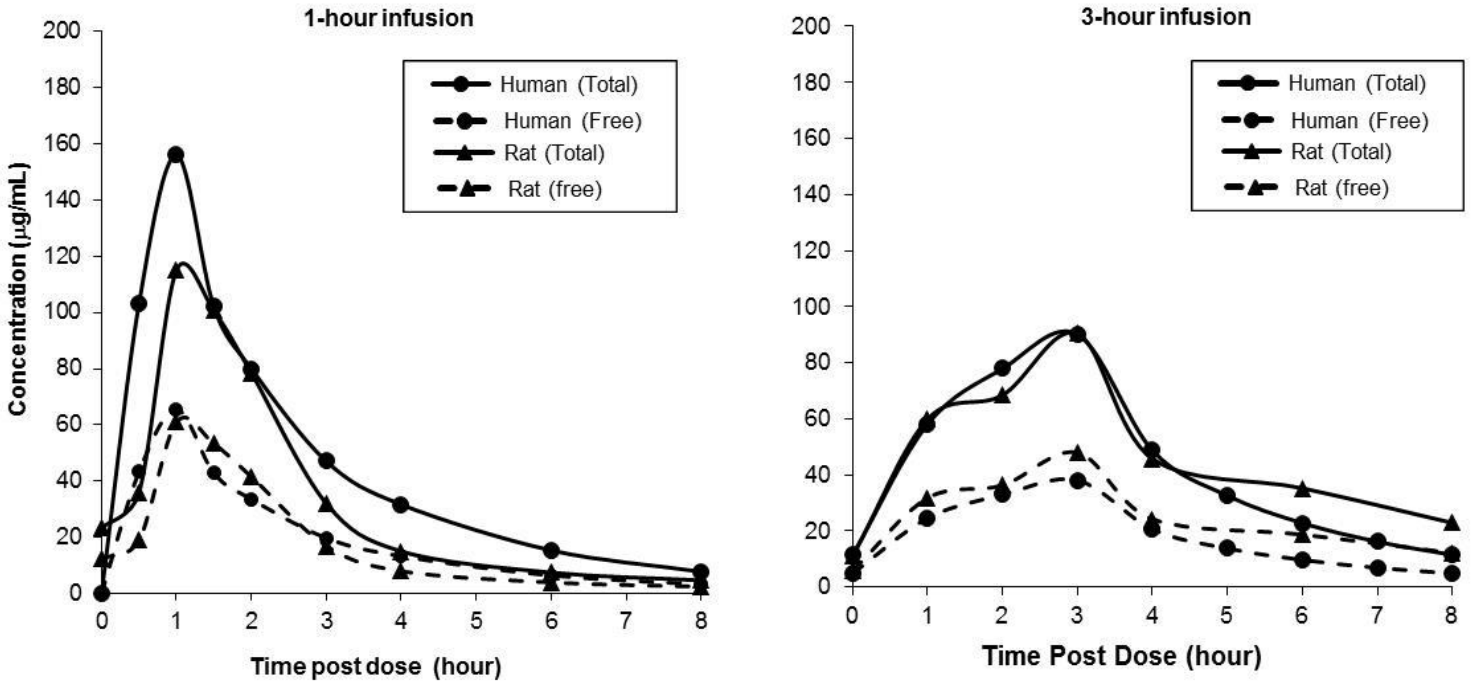
The PTA for 75% $fT_{>MIC}$ against up to 4 µg/mL at the dose regimens was more than 90% for all renal function groups.

Additional Non-clinical PD Evaluation under Human PK

- In addition to standard murine thigh/lung infection models for the evaluation on PK/PD parameters, two types of non-clinical infection models were conducted to evaluate the non-clinical pharmacodynamic evaluation by recreating human plasma PK in animal infection models

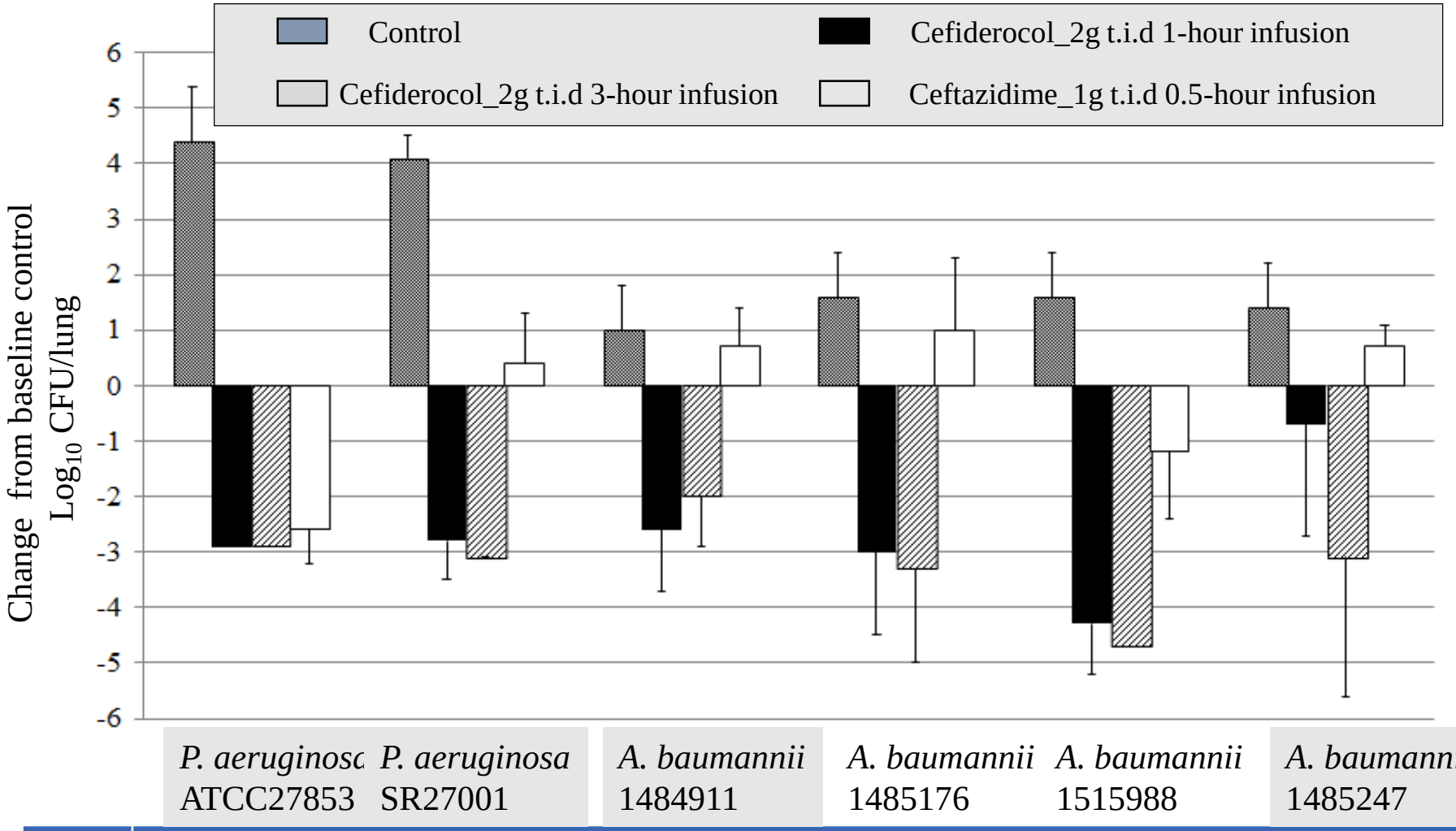
1. Rat lung infusion models
   - Normal rat lung infection models
   - Human plasma PK of free FDC concentrations was recreated in rat by the intravenous administration of FDC by using the implanted cannulae into the jugular vein rats as continuous infusions.
   - Ceftazidime (1 g TID 0.5h infusion) and meropenem (1g TID bolus) was used as control
2. Murine thigh infection models
   - neutropenic murine thigh infection models with impaired renal impairment by uranyl nitrate
   - Human plasma PK of free FDC concentrations was recreated by the frequent intravenous administration of FDC
   - Cefepime and meropenem by 2 g TID 3h infusion were used as control

Reproducing Human Plasma PK Profiles in Infected Rats by Intravenous 2 g Administration of FDC



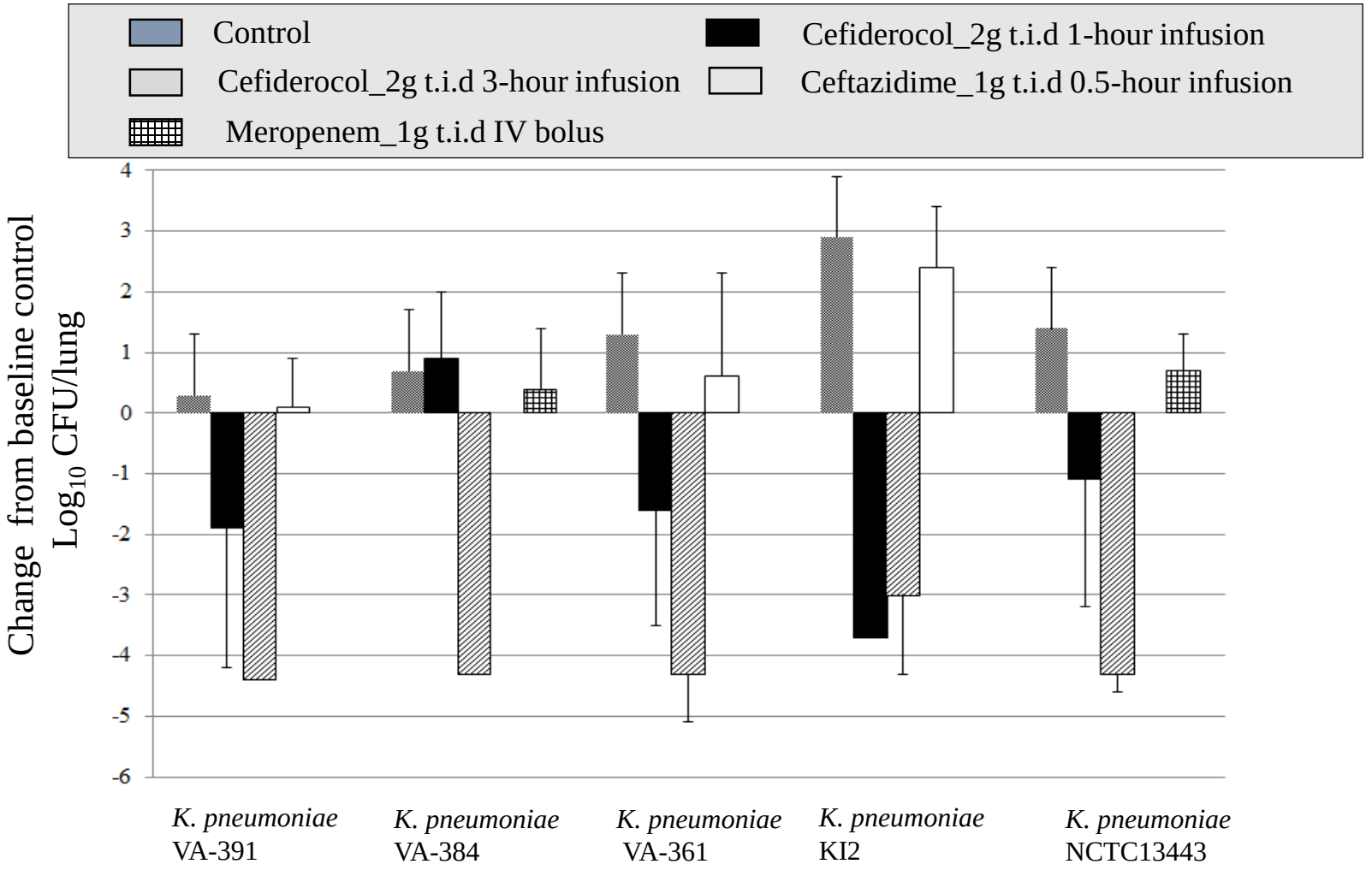
MIC (µg/mL)	$\%fT_{>MIC}$ (rat)	
	1-hour infusion	3-hour infusion
2	100	100
4	75	100
8	50	78
16	41	50
32	25	13

Efficacy of FDC Against Rat Lung Infection Models Reproducing Human PK Profile; *P. aeruginosa* and *A. baumannii*



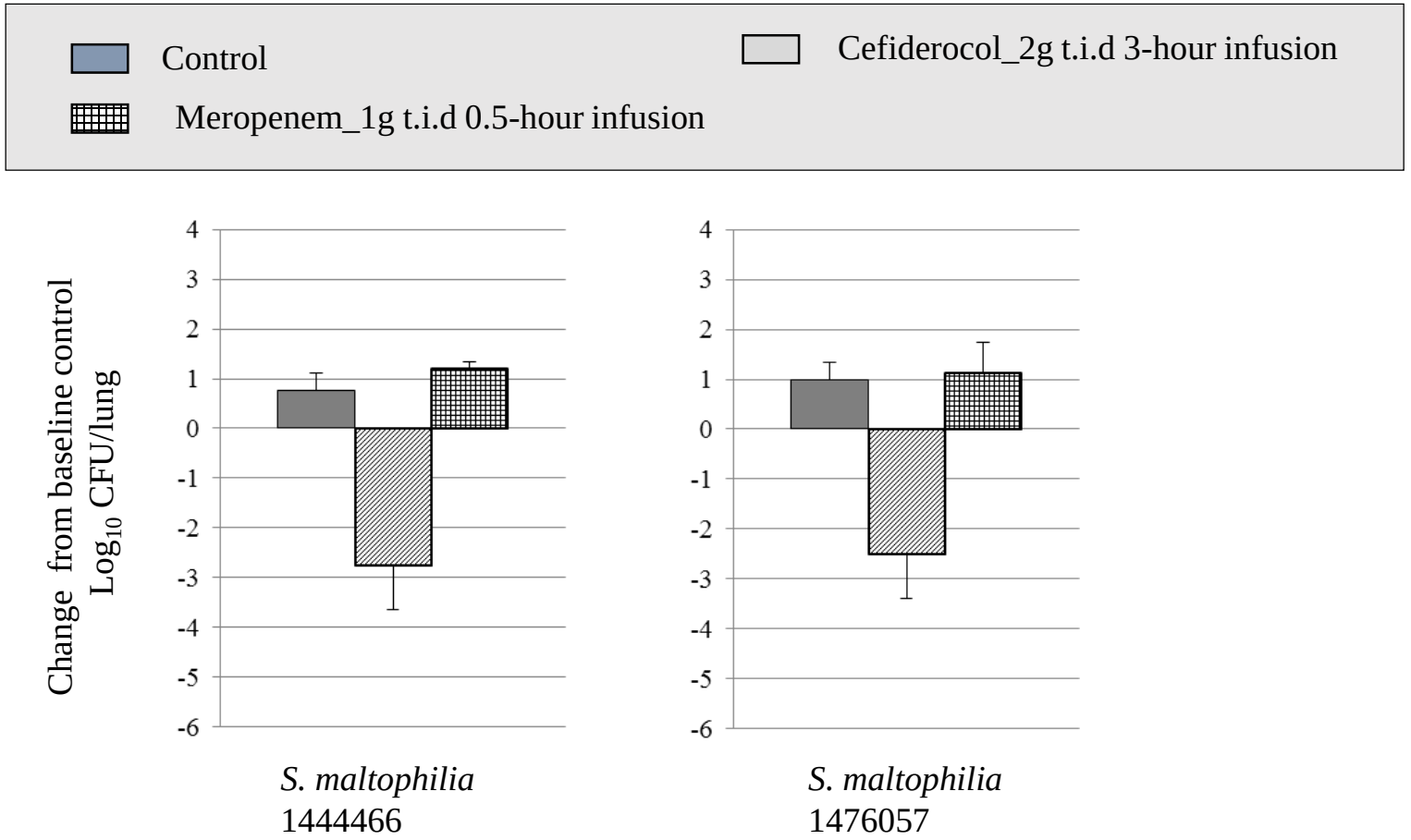
	MIC (µg/mL)					
FDC	0.5	2	0.25	0.125	0.125	2
CAZ	2	>32	>32	>32	>32	>32

Efficacy of FDC Against Rat Lung infection Models Reproducing Human PK Profile: *K. pneumoniae*



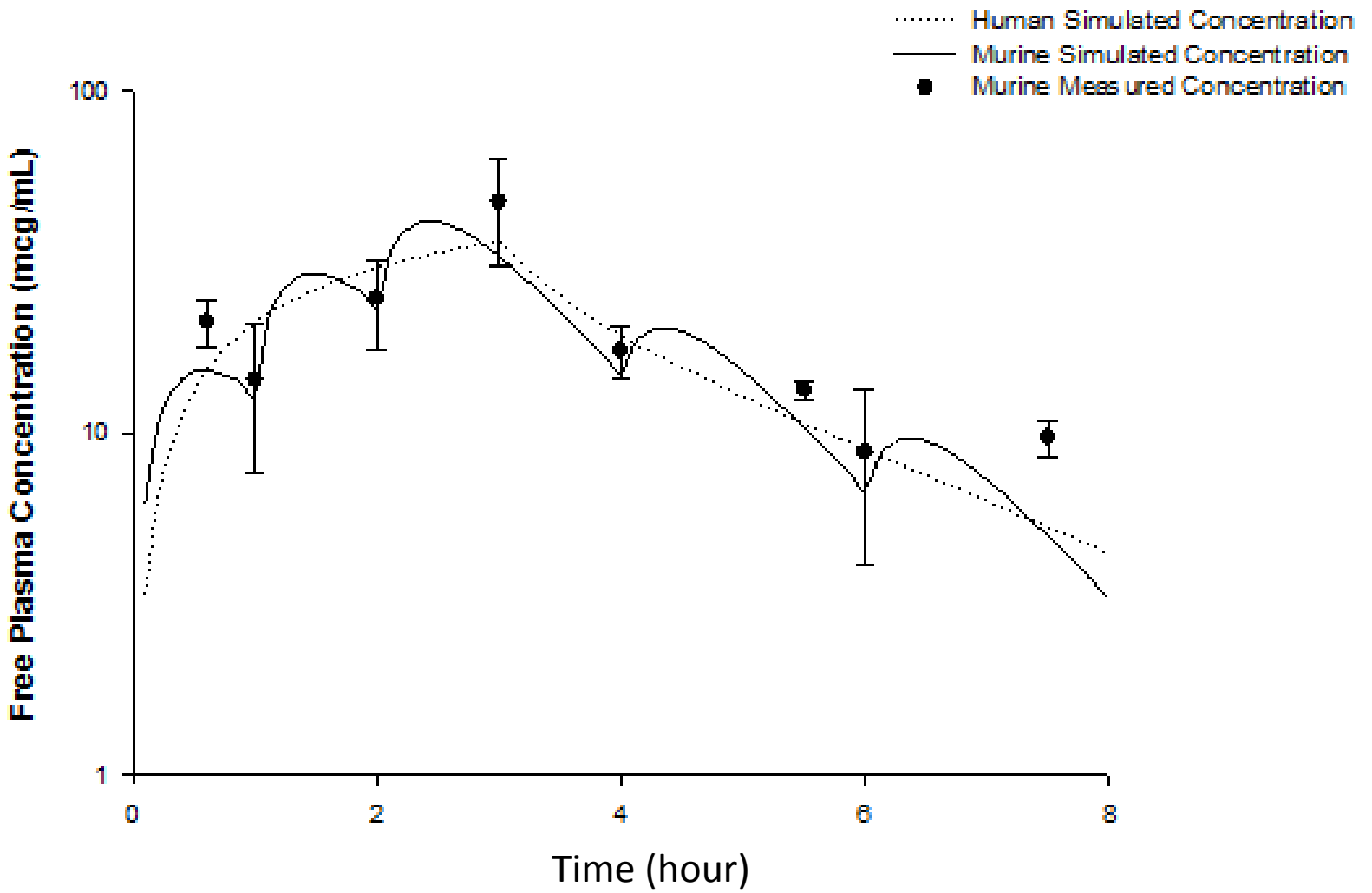
	MIC (µg/mL)				
FDC	4	4	4	8	16
CAZ	>32	>32	>32	>32	>32
MEM	16	>32	16	>32	>32

Efficacy of FDC Against Rat Lung Infection Models Reproducing Human PK Profile: *S. malthophilia*

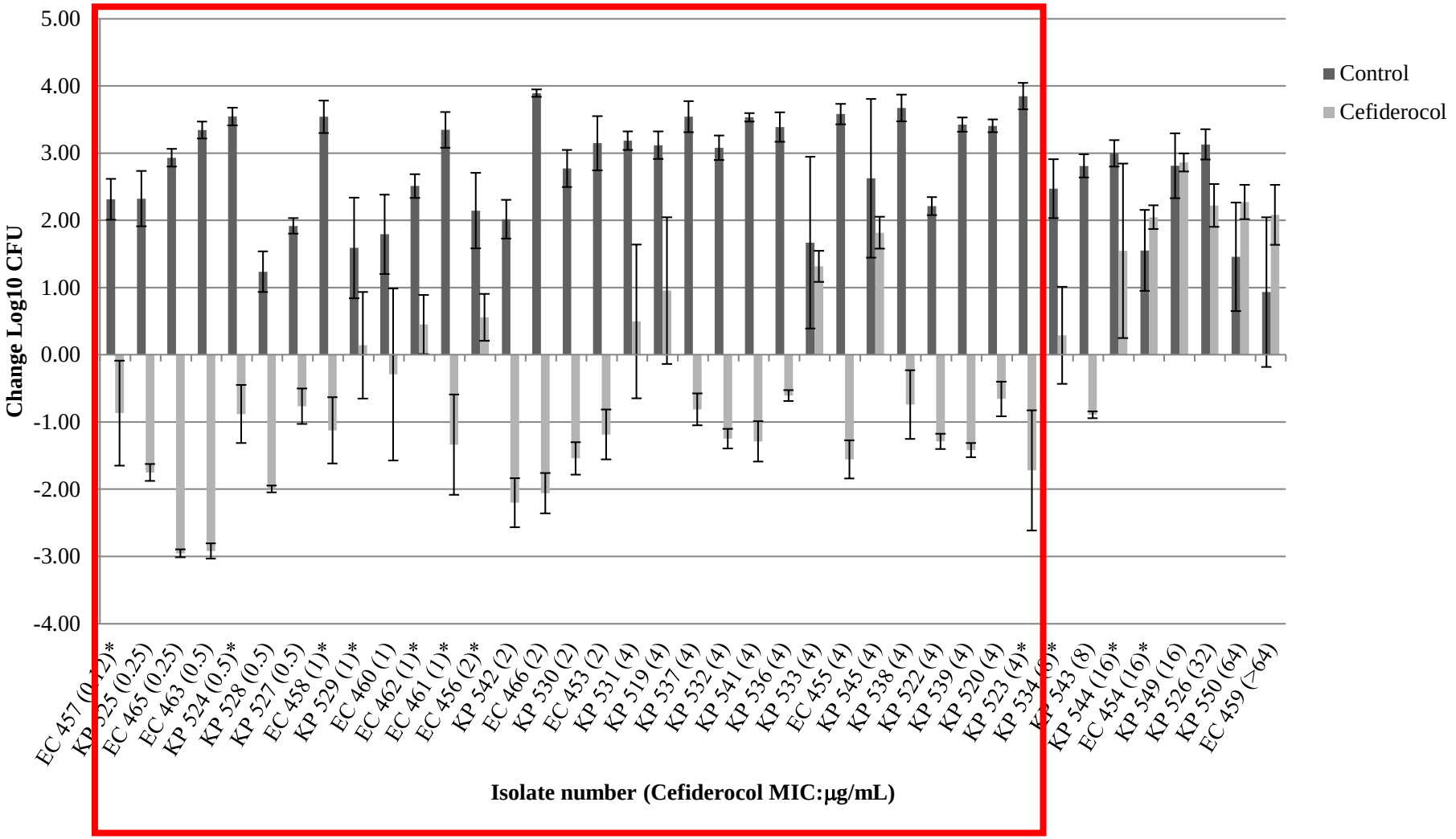


	MIC (µg/mL)	
FDC	0.06	0.5
MEM	64	128

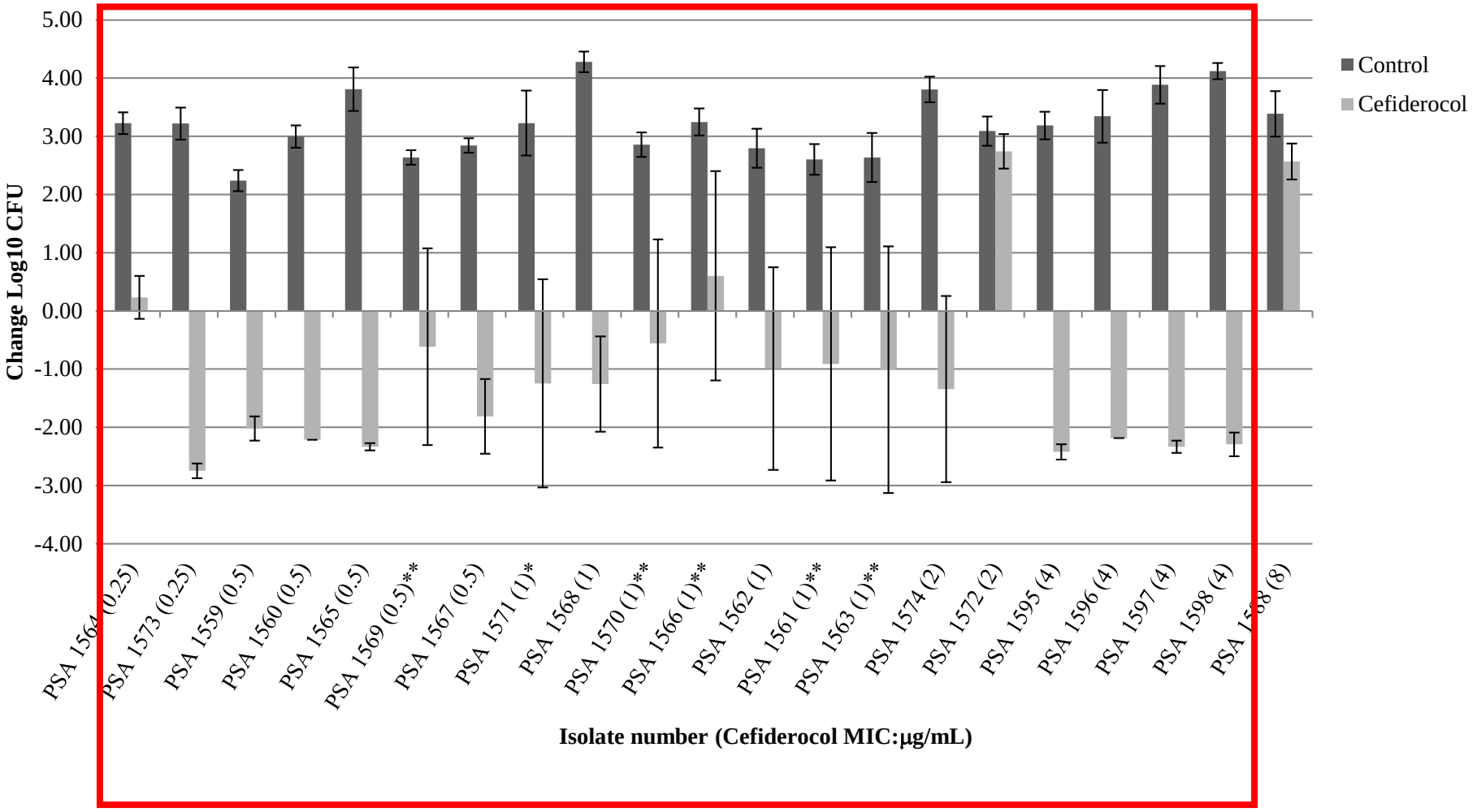
Reproducing Human Plasma PK Profiles in Infected Mouse by Intravenous 2 g Administration of FDC



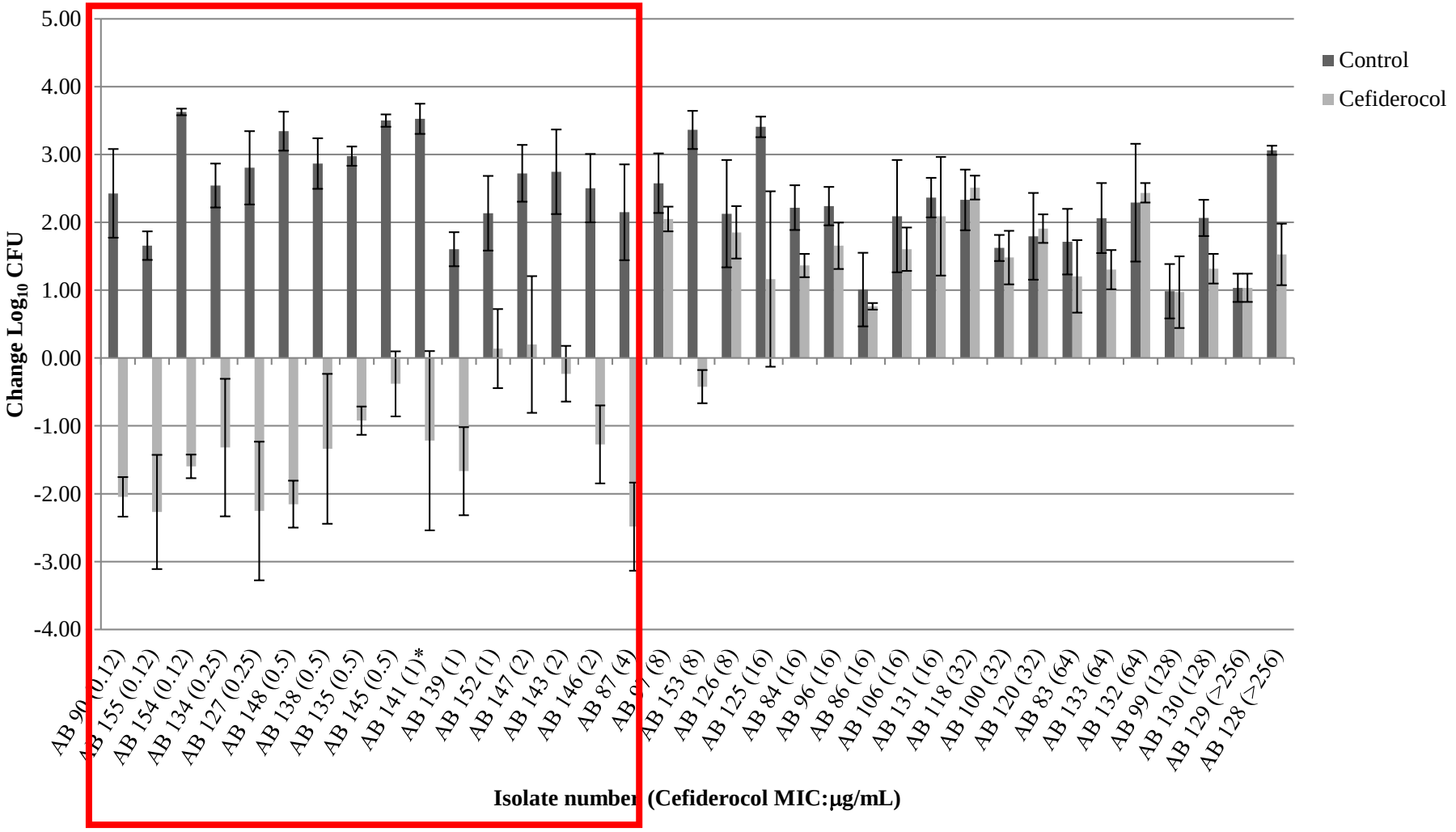
Efficacy of FDC against *Enterobacteriaceae* with Diverse MIC in Neutropenic Mice Thigh Infection Model



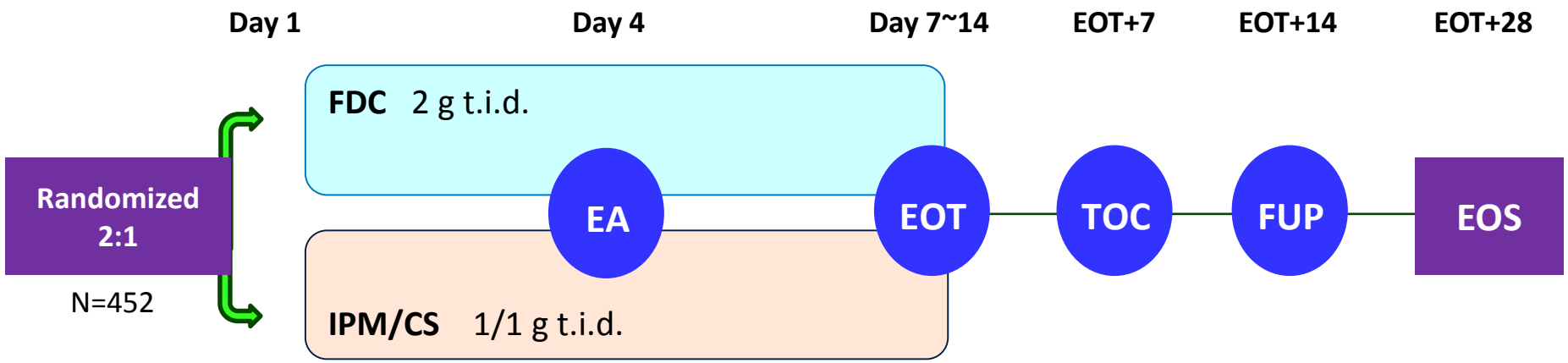
Efficacy of FDC against *P. aeruginosa* with Diverse MIC in Neutropenic Mice Thigh Infection Model



Efficacy of FDC against *A. baumannii* with Diverse MIC in Neutropenic Mice Thigh Infection Model



APEKS-cUTI was a non-inferiority study vs high dose IPM/CS



- **Multicenter, double-blind, randomized, non-inferiority trial**
  - **2-sided 95% confidence interval, non-inferiority margin 15%**
- **<u>Primary endpoint</u>: composite clinical and microbiological response at TOC in MITT population**
- **<u>Secondary endpoint</u>: Microbiological response at TOC in MITT population**

MITT: patients who received at least 1 dose and have a baseline Gram-negative uropathogen

NB: No oral antibiotic step-down permitted

SCR: screening, EA: early assessment, EOT: end of treatment, TOC: test of cure,
FUP: follow up, EOS: end of study

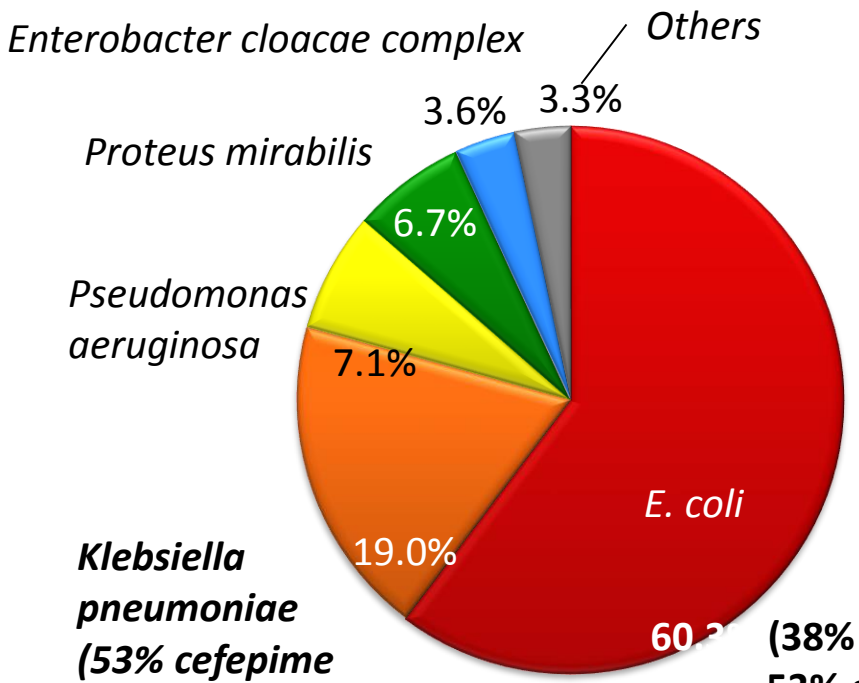
APEKS-cUTI Targeted “at risk” Population for MDR cUTI

- Key Inclusion
  - Hospitalized subjects with either cUTI with or without pyelonephritis or Acute Uncomplicated Pyelonephritis (AUP)
    - ➢ AUP was limited to up to 30%
- Key Exclusion
  - Positive urine culture of Gram-negative uropathogen resistant to IPM
  - More than 2 baseline uropathogens or confirmed fungal UTI
  - Patient receiving hemodialysis or peritoneal dialysis

- Allow patients with immunosuppression, immunosuppressive drugs, renal transplants
- Allow mild to moderate renal failure (CrCl >20)

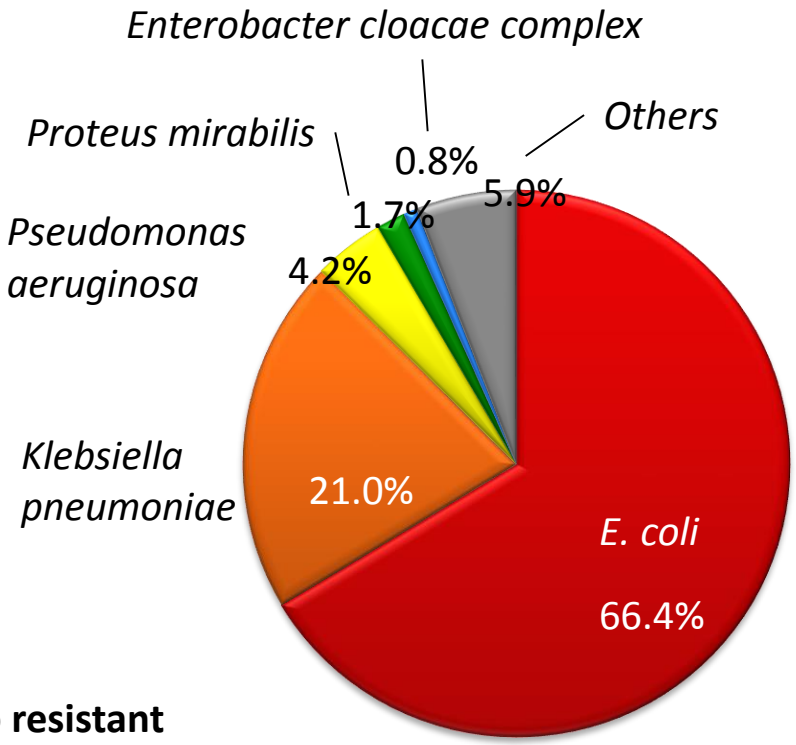
Baseline Uropathogens (MITT Population)

FDC (N=252)



Klebsiella pneumoniae (53% cefepime and levo resistant)

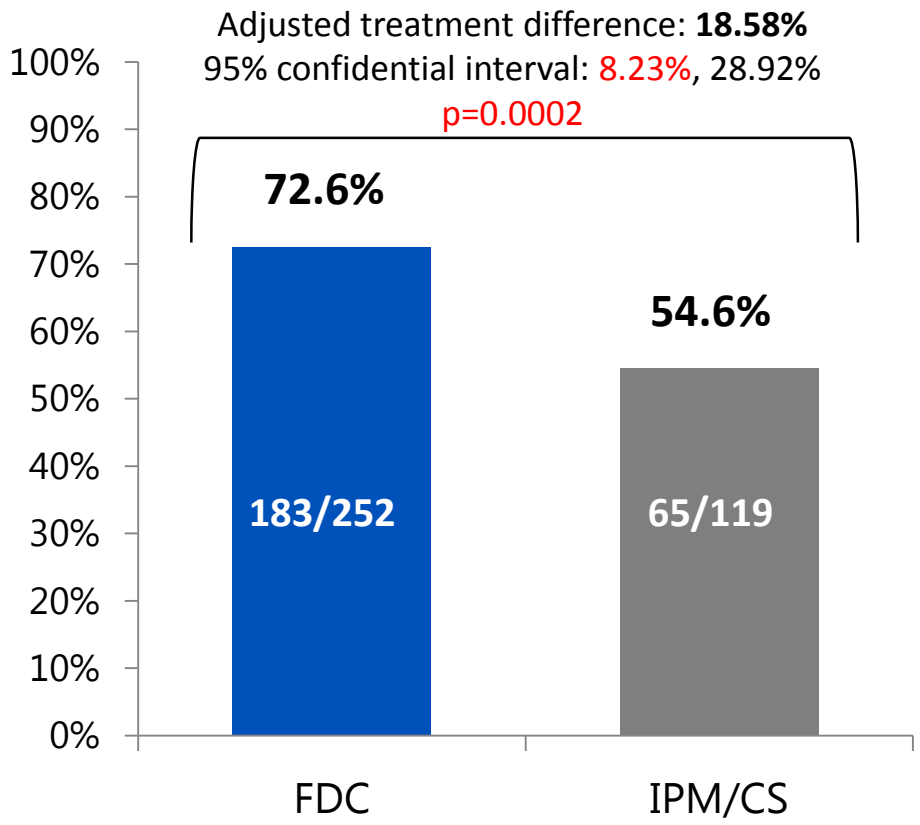
IPM/CS (N=119)



(38% Levo resistant 53% cefepime resistant)

APEKS-cUTI Demonstrated Non-inferiority to IPM/CS

Primary Endpoint
Composite Outcome at TOC
(Clinical Response and Microbiological Response)



Secondary Endpoint

Secondary Endpoint	FDC % (N/n)	IPM/CS % (N/n)
	Treatment Difference (95% CI)[a]	
	p-Value[b]	
Clinical response at TOC	**89.7%** (226/252)	**87.4%** (104/119)
	2.39 (-4.66, 9.44)	
	p= 0.2530	
Microbiological response at TOC	**73.0%** (184/252)	**56.3%** (67/119)
	17.25 (6.92, 27.58)	
	p= 0.0005	

Treatment difference (FDC minus IPM/CS) is the adjusted estimate of the difference in the responder rate between the 2 treatment arms. The adjusted difference estimates and the 95% CIs (2-sided) are calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratified factor at baseline (cUTI with or without pyelonephritis vs. acute uncomplicated pyelonephritis)
One-sided p-value is in favor of cefiderocol

Clinical & Microbiological Outcome by Baseline MIC: *Enterobacteriaceae*

MIC in μg/mL	Clinical Outcome	Microbiological Outcome
All Tested	203/226 (89.8%)	172/226 (76.1%)
≤0.004	22/24 (91.7%)	19/24 (79.2%)
0.008	12/13 (92.3%)	10/13 (76.9%)
0.015	19/19 (100%)	19/19 (100%)
0.03	23/26 (88.5%)	21/26 (80.8%)
0.06	30/32 (93.8%)	24/32 (75.0%)
0.12	35/40 (87.5%)	31/40 (77.5%)
0.25	22/29 (75.9%)	18/29 (62.1%)
0.5	15/16 (93.8%)	11/16 (68.8%)
1	13/13 (100%)	11/13 (84.6%)
2	8/9 (88.9%)	5/9 (55.6%)
4	4/4 (100%)	3/4 (75.0%)
8	0/1 (0%)	0/1 (0%)
>8	0	0

Clinical & Microbiological Outcome by Baseline MIC: *P. aeruginosa*

MIC in μg/mL	Clinical Outcome	Microbiological Outcome
All Tested	12/15 (80.0%)	7/15 (46.7%)
≤0.004	1/1 (100%)	1/1 (100%)
0.008	1/1 (100%)	1/1 (100%)
0.015	0	0
0.03	3/4 (75.0%)	2/4 (50.0%)
0.06	2/3 (66.7%)	0
0.12	3/3 (100%)	2/3 (66.7%)
0.25	1/2 (50.0%)	1/2 (50.0%)
0.5	0	0
1	0	0
2	1/1 (100%)	0/1 (0%)
4	0	0
8	0	0
>8	0	0

BPWG Vote: 5 Yes, 0 No, 3 Abstain

	MICs (mg/ml)		
	Susceptible	Intermediate	Resistant
Enterobacteriaceae	≤4	8	≥16
Pseudomonas aeruginosa	≤4	8	≥16
Acinetobacter baumannii	≤4	8	≥16
Stenotrophomonas maltophilia	≤4	8	≥16