Report of the *Acinetobacter* spp. Ad-Hoc Working Group

CLSI AST June 2013 Meeting

Working Group Members

- James Lewis - Chair
- Dwight Hardy
- Joe Kuti
- Emil Lesho
- Clinton Murray
- Helio Sader
- Paige Waterman
- Steve Jenkins – Ad Hoc

Background

- Approval of doripenem Acinetobacter spp breakpoints at the June 2011 meeting
- Request from sponsor not to publish until imipenem and meropenem BPs were re-reviewed
- Ad-hoc WG formed Sept 2012

DORIPENEM MIC AND DISK DIFFUSION BREAKPOINT: June 2011 Meeting

Antimicrobial Agent	**(μg/mL)**			**Vote**
	S	**I**	**R**	**MIC – Approved 11 -0; 1 abstain.** **Disk - Approved 12-0** **Dosing comment: Interpretive criteria are based on a dosage regimen of 500 mg every 8 h.** **Approved 9-3** The sponsor requested that the new interpretive criteria for Doripenem/*Acinetobacter* spp. not be published in M100 until the other carbapenems breakpoints are reassessed.
Doripenem	**≤1**	**2**	**≥4**	

Additional Considerations from June 2011

- Historically, *Acinetobacter* MIC breakpoints have generally been the same as *Enterobacteriaceae*
- Decision based on the 1h infusion and not 4h infusion. 4h infusion not in the FDA label
- No clinical data at MIC = 2 presented for review (except for one complicated UTI) that would fit the subcommittee's definition of “I”.
- No data on the MICs that would result with carbapenemases in *Acinetobacter*.
- It is suspected that they could be as low as MIC = 4 with certain carbapenemases.

Additional Considerations from June 2011

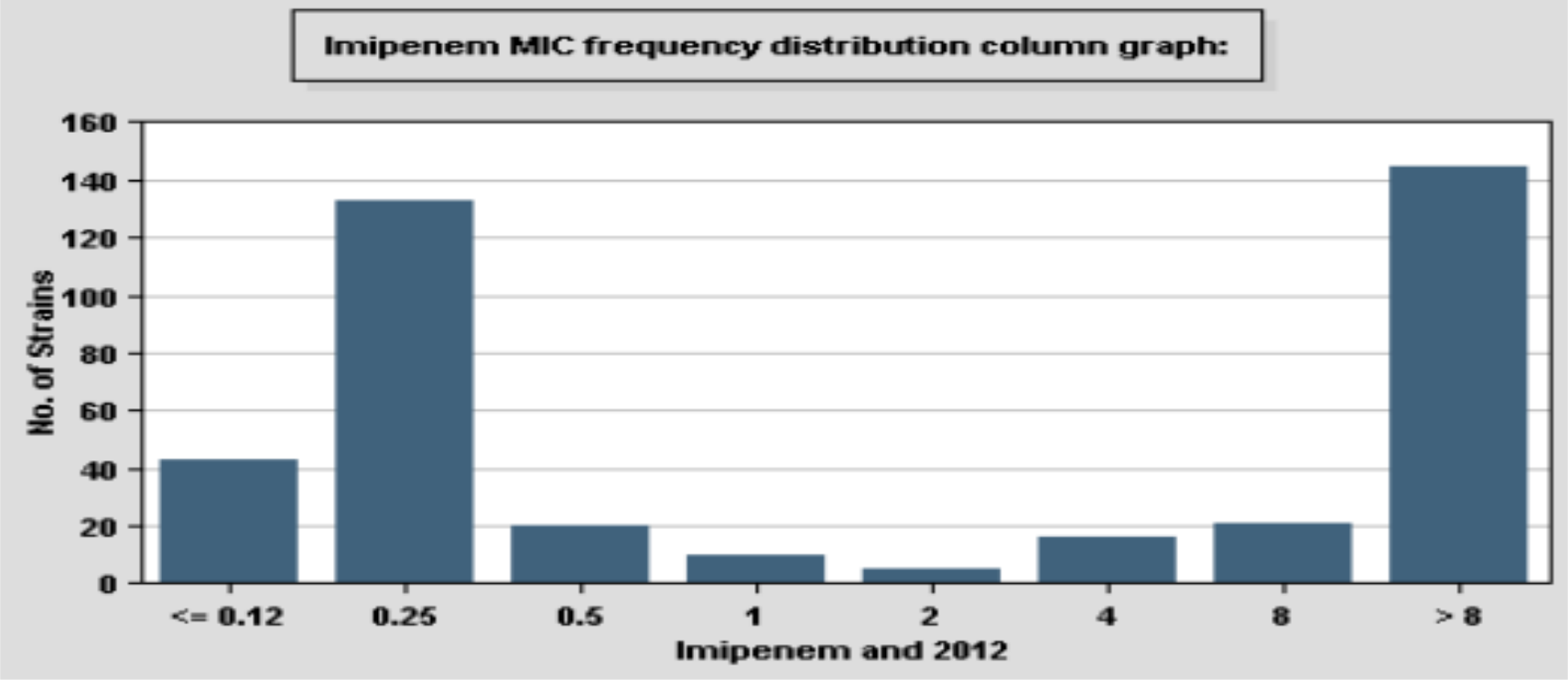
- "S" breakpoint selected (MIC = ≤1) covers all doses and modes of administration.
- No data that would allow to conclude that the "I" range should include the different dosage regiments.
- The target attainment rates for *Acinetobacter* are more like *Enterobacteriaceae*
- No data presented to validate this statement
- No animal model data was presented

Imipenem: *Acinetobacter* spp.
Validated: sentryMICValidated
North America
2012

Results from the SENTRY Program North America, 2012

Total: 393

MIC	<= 0.12	0.25	0.5	1	2	4	8	> 8	MIC_{50}	MIC_{90}
Count	43	133	20	10	5	16	21	145	1	>
Percent	10.94	33.84	5.09	2.54	1.27	4.07	5.34	36.90		
Cum Pct	10.94	44.78	49.87	52.42	53.69	57.76	63.10	100.00		



Slides and data courtesy of Helio Sader/JMI Laboratories

Meropenem: *Acinetobacter* spp.

Validated: sentryMICValidated

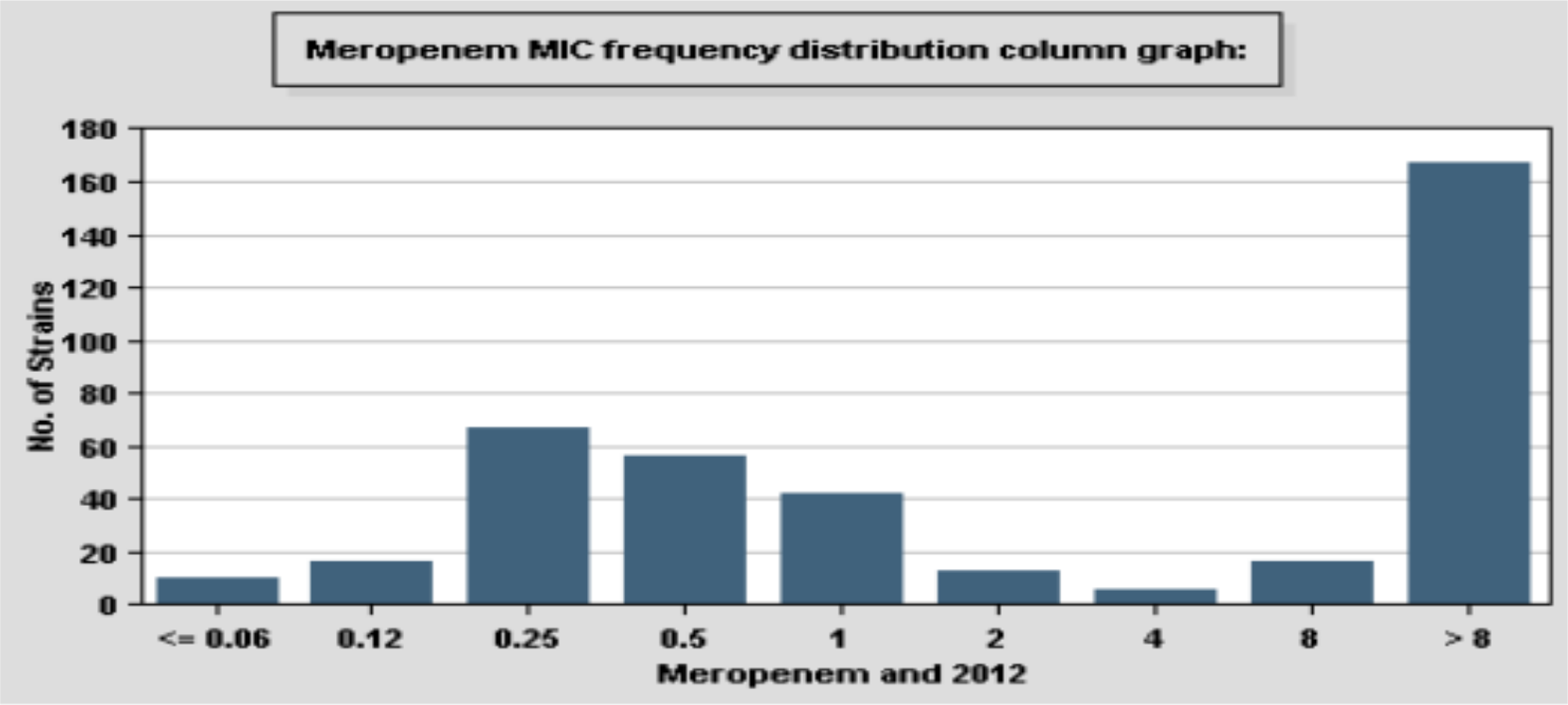
North America

2012

Results from the SENTRY Program North America, 2012

Total: 393

MIC	<= 0.06	0.12	0.25	0.5	1	2	4	8	> 8	MIC_{50}	MIC_{90}
Count	10	16	67	56	42	13	6	16	167	2	>
Percent	2.54	4.07	17.05	14.25	10.69	3.31	1.53	4.07	42.49		
Cum Pct	2.54	6.62	23.66	37.91	48.60	51.91	53.44	57.51	100.00		



Slides and data courtesy of Helio Sader/JMI Laboratories

Doripenem: *Acinetobacter* spp.

Validated: sentryMICValidated

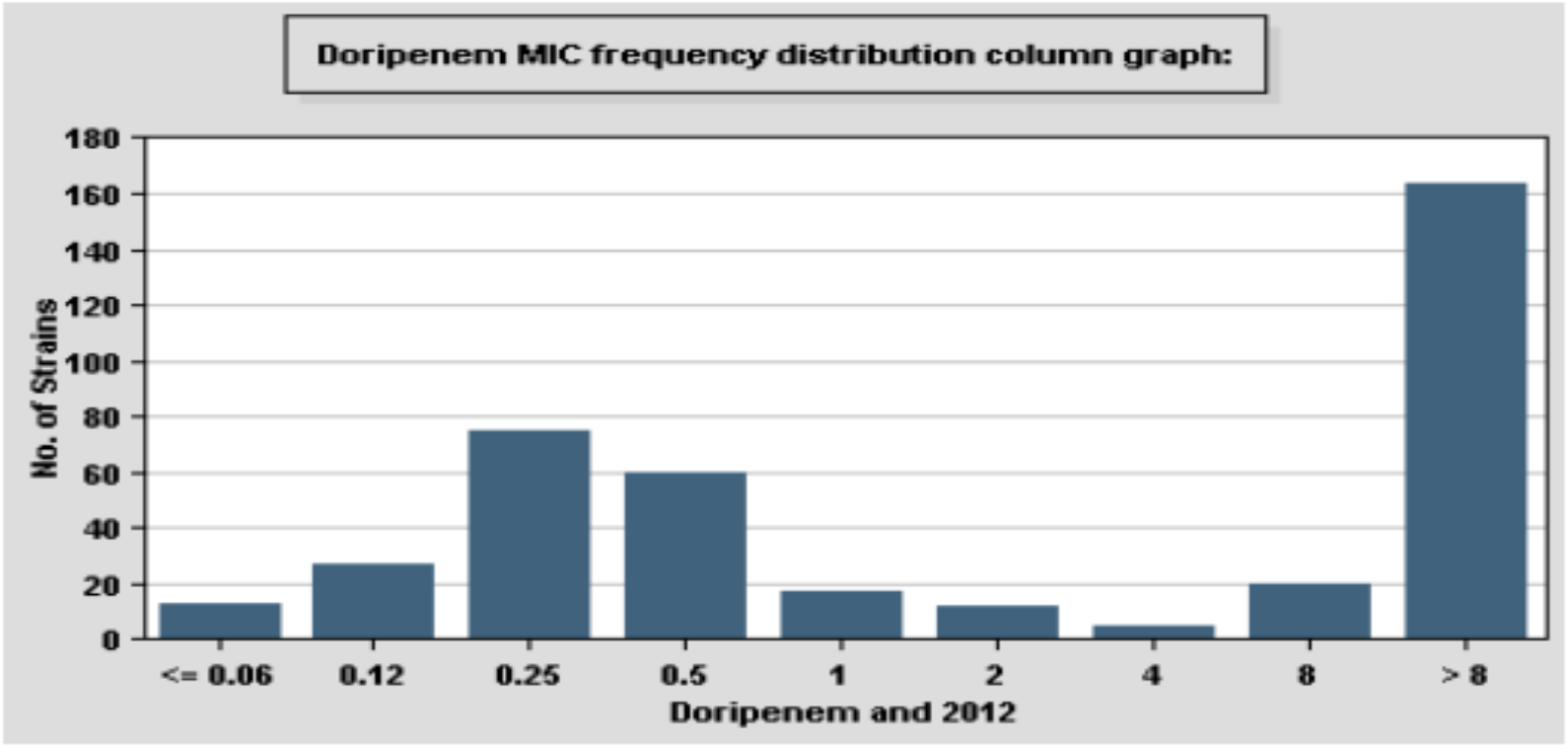
North America

2012

Results from the SENTRY Program North America, 2012

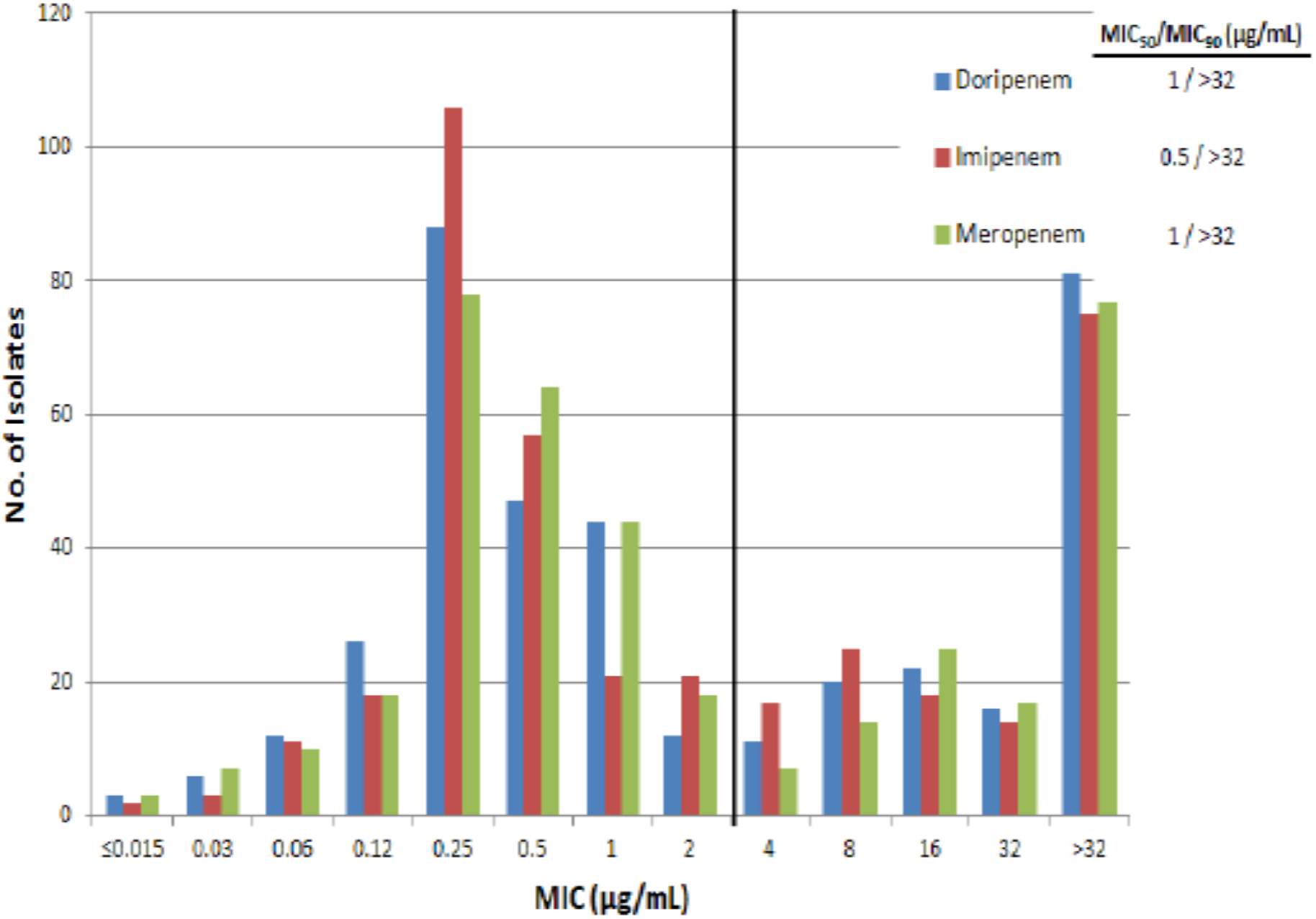
Total: 393

MIC	<= 0.06	0.12	0.25	0.5	1	2	4	8	> 8	MIC_{50}	MIC_{90}
Count	13	27	75	60	17	12	5	20	164	2	>
Percent	3.31	6.87	19.08	15.27	4.33	3.05	1.27	5.09	41.73		
Cum Pct	3.31	10.18	29.26	44.53	48.85	51.91	53.18	58.27	100.00		



Slides and data courtesy of Helio Sader/JMI Laboratories

Figure 6. *Acinetobacter spp.* TRUST 13 (2009) Carbapenem MIC Distribution (n=388)



MICs and Resistance Mechanisms

- 108 isolates of *A. baumanii* from San Antonio Military Medical Center 2006-2008: no isolates with OXA-23 or OXA-24 had mero, imi, or dori MICs ≤4.
- 350 isolates from Walter Reed National Military Medical Center. No carbapenemases at an MIC ≤4mcg/mL

Probability of Target Attainment by MIC Value: Inflated Variance

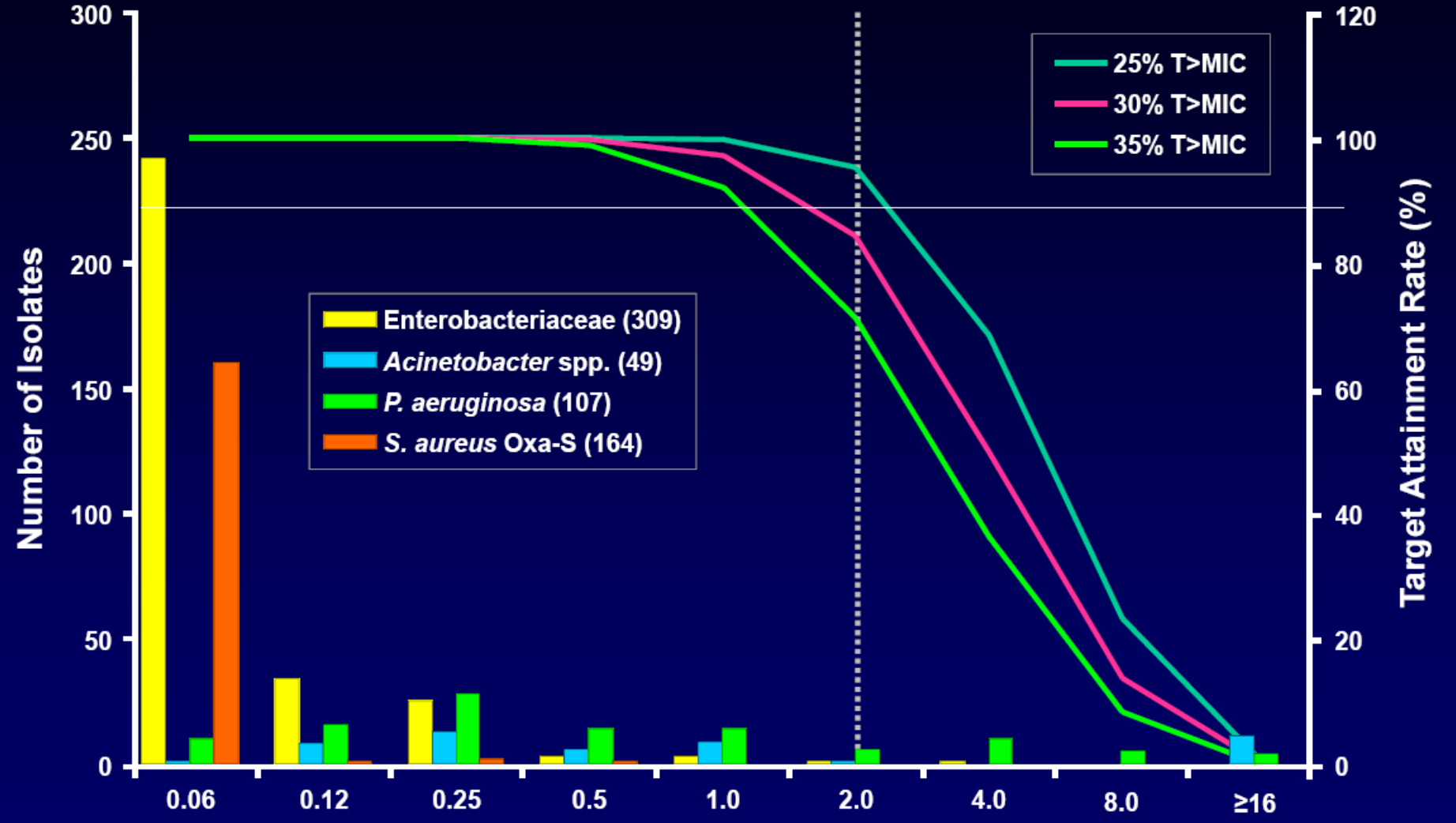
Imipenem 500mg Q6h	*f %T >MIC ≥ 30*	*f %T >MIC ≥ 35*	*f %T >MIC ≥ 40*	*f %T >MIC ≥ 45*
1	0.976	0.946	0.914	0.881
2	0.894	0.840	0.780	0.718

Meropenem 1g Q8h	*f %T >MIC ≥ 30*	*f %T >MIC ≥ 35*	*f %T >MIC ≥ 40*	*f %T >MIC ≥ 45*
1	0.969	0.927	0.874	0.794
2	0.886	0.806	0.715	0.609

Doripenem 500mg Q8h	*f %T >MIC ≥ 30*	*f %T >MIC ≥ 35*	*f %T >MIC ≥ 40*	*f %T >MIC ≥ 45*
1	0.983	0.949	0.889	0.769
2	0.860	0.727	0.565	0.372

***Source: Ambrose and Bhavnani. CLSI Meeting Agenda Book June 2009**

Fractional Target Attainment[a]: Doripenem 500 mg q8h 1h infusion against NP isolates (DOR-09, -10)



[a]PK 2007 model: Nandy (2010) AAC 54:2354-59
includes NHV, cUTI and NP patients

Animal Model PK/PD Data

- No data available

Clinical Outcomes vs MIC data for *Acinetobacter* spp. Infections

- No data available

Favorable Outcome and T>MIC Data: *Acinetobacter spp.* / DOR 500 mg (q8, 1h)

MIC in µg/ml	Favorable Clinical Outcome – All Studies Combined (%)	Favorable Microbiological Outcome --All Studies Combined (%)	T>MIC[a] 25%	T>MIC 30%	T>MIC 35%	T>MIC 40%
All tested	28/30 (93)	26/30 (87)				
≤0.03	2/2 (100)	2/2 (100)	100	100	100	100
0.06	0	0	100	100	100	100
0.12	5/5 (100)	5/5 (100)	100	100	100	100
0.25	4/4 (100)	4/4 (100)	100	100	99.98	99.62
0.5	3/3 (100)	3/3 (100)	99.6	99.24	98.5	97.66
1	10/11 (91)	9/11 (82)	96.64	95.02	92.18	89.68
2	1/1 (100)	0/1 (0)	83.2	76.82	70.02	63.84
4	0	0	41.36	34.18	29.22	25.12
8	0	0	5.76	4.36	3.5	2.84
16	1/1 (100)	1/1 (100)				
32	0	0				
>64	2/3 (67)	2/3 (67)				

[a]Based on PK 2011 Model

EUCAST 2013 *Acinetobacter* spp. Breakpoints

Carbapenems	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Doripenem	1	4	10	21	15
Ertapenem	-	-		-	-
Imipenem	2	8	10	23	17
Meropenem	2	8	10	21	15

Current FDA Breakpoints

Imipenem	**Minimum Inhibitory Concentrations (µg/mL)**		
Pathogen	**S**	**I**	**R**
Enterobacteriaceae	≤1	2	≥4
Pseudomonas aeruginosa	≤2	4	≥8
Acinetobacter spp.	≤4	8	≥16

Meropenem	**Minimum Inhibitory Concentrations (mcg/mL)**		
Pathogen	**S**	**I**	**R**
Enterobacteriaceae	≤1	2	≥ 4
Pseudomonas aeruginosa	≤ 4	8	≥ 16

*Note – generic meropenem label not updated reflects *Acinetobacter* BP of 4

*Doripenem FDA *Acinetobacter* spp. BP = 1

Merrem and Primaxin Prescribing Information - http://dailymed.nlm.nih.gov – Accessed 5/2013

CLSI 2013 Breakpoints

P. aeruginosa

Drug/Dose	S	I	R
Imipenem 500mg q6h	2	4	8
Meropenem 1g Q8h	2	4	8
Doripenem 500mg q8h	2	4	8

Enterobacteriaceae

Drug/Dose	S	I	R
Imipenem 500mg q6h	1	2	4
Meropenem 1g Q8h	1	2	4
Doripenem 500mg q8h	1	2	4

Thoughts from the Working Group

- Appears to be clear population break for each drug at an MIC of 1 or 2
- No good animal data
- No good clinical data
- Do no harm – given the paucity of antibiotics for *Acinetobacter* spp. don't go too low
- Emphasize dose used for breakpoint setting and duration of infusion

Working Group Conclusion

- By a vote of 8-0 the WG proposes a susceptible breakpoint of ≤2mcg/mL for all 3 carbapenems at the specified doses.
- Intermediate = 4mcg/mL, Resistant ≥ 8.