



Limitations of PK-PD in Clinical Trials: Focus on Vancomycin MIC and MRSA Infection

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Disclosures

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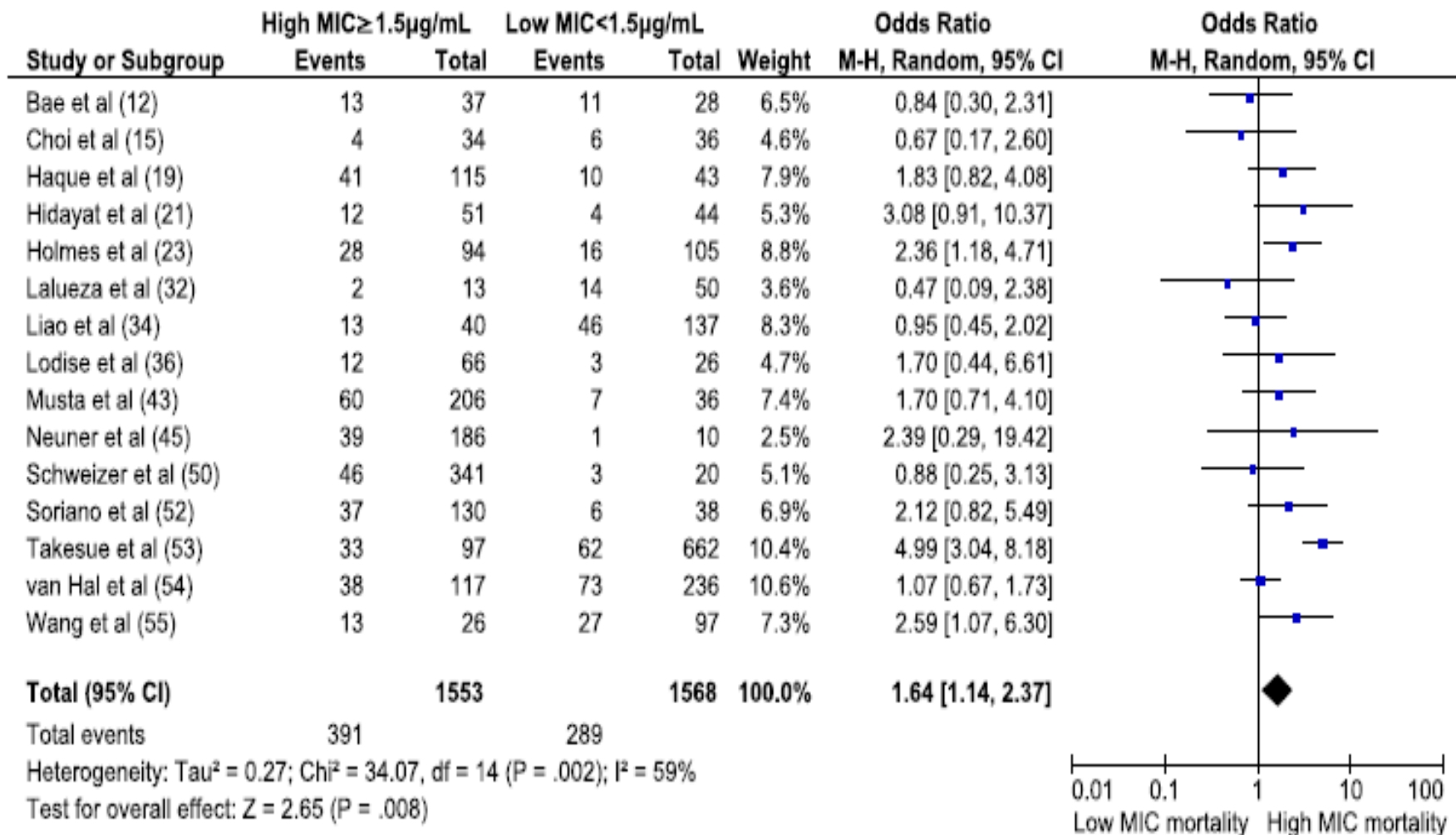
Points of this Talk

- Association of Vanco MIC & Outcome in MRSA: Present, Complex, and Potentially Not Causal
- Clinical Benefit of $AUC/MIC > 400$: Unestablished

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MRSA Infection with Vanco MIC $\geq 1.5\mu\text{g/mL}$ Associated with Mortality



Factors Associated with Treatment Outcomes

■ MSSA

- vancomycin [vs beta-lactams] ¹⁻⁴
- vancomycin MIC > 1.5 (independent of tx) ¹¹
 - even when treated with beta-lactam (flucloxacillin)

■ MRSA

- prior vancomycin use¹⁶
- vancomycin cidal (vs static) ¹⁶
- tPMP-1¹⁶
- USA 300 strain ¹⁵
- high vancomycin MICs ^{5-10, 15}
- heteroresistance ¹³
- infection site¹²
- Agr dysfunction ¹⁴
- APACHE II \geq 14 ¹⁵
- AUC/MIC ¹⁷⁻¹⁹

1. Chang FY et al. Medicine (Baltimore) 2003;82:333-9. 2. Stryjewski ME et al. Clin Infect Dis 2007;44:190-6. 3. Lodise TP et al. Antimicrob Agents Chemother 2007;51:3731-3. 4. Gentry CA et al. Pharmacotherapy 1997;17:990-7. 5. Musta AC et al. J Clin Microbiol 2009;47:1640-4. 6. Lodise TP et al. Antimicrob Agents Chemother 2008;52:3315-20. 7. Soriano A et al. Clin Infect Dis 2008;46:193-200. 8. Hsu DI et al. Int J Antimicrob Agents 2008;32:378-85. 9. Sakoulas G et al. J Clin Microbiol 2004;42:2398-402. 10. Wang JL et al. BMC Infect Dis 2010;10:159. 11. Holmes NE et al. J Infect Dis. 2011;204:340-347. 12. Walraven CJ et al. J Antimicrob Chemother. 2011;doi:10.1093/jac/dkr301. 13. Maor Y et al. J Infect Dis. 2009;199:619-24. 14. Fowler VF et al. J Infect Dis. 2004;190:1140-9. 15. Moore C et al. Antimicrob Agents Chemother. 2011;55:4581-4588. 16. Moise PA et al. J Inf Dis. 2010;201:233-40. 17. Brown J et al. Antimicrob Agents Chemother. 2012;56(2):634-8. 18. Moise Broder PA et al. Clin Pharmacokinet. 2004;43(13):925-42. 19. Kullar R. Clin Infect Dis. (2011) 52(8): 975-981.

The Problem with MRSA Outcome Studies

THE BLIND MEN AND THE ELEPHANT (A Hindoo Fable)

IT was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

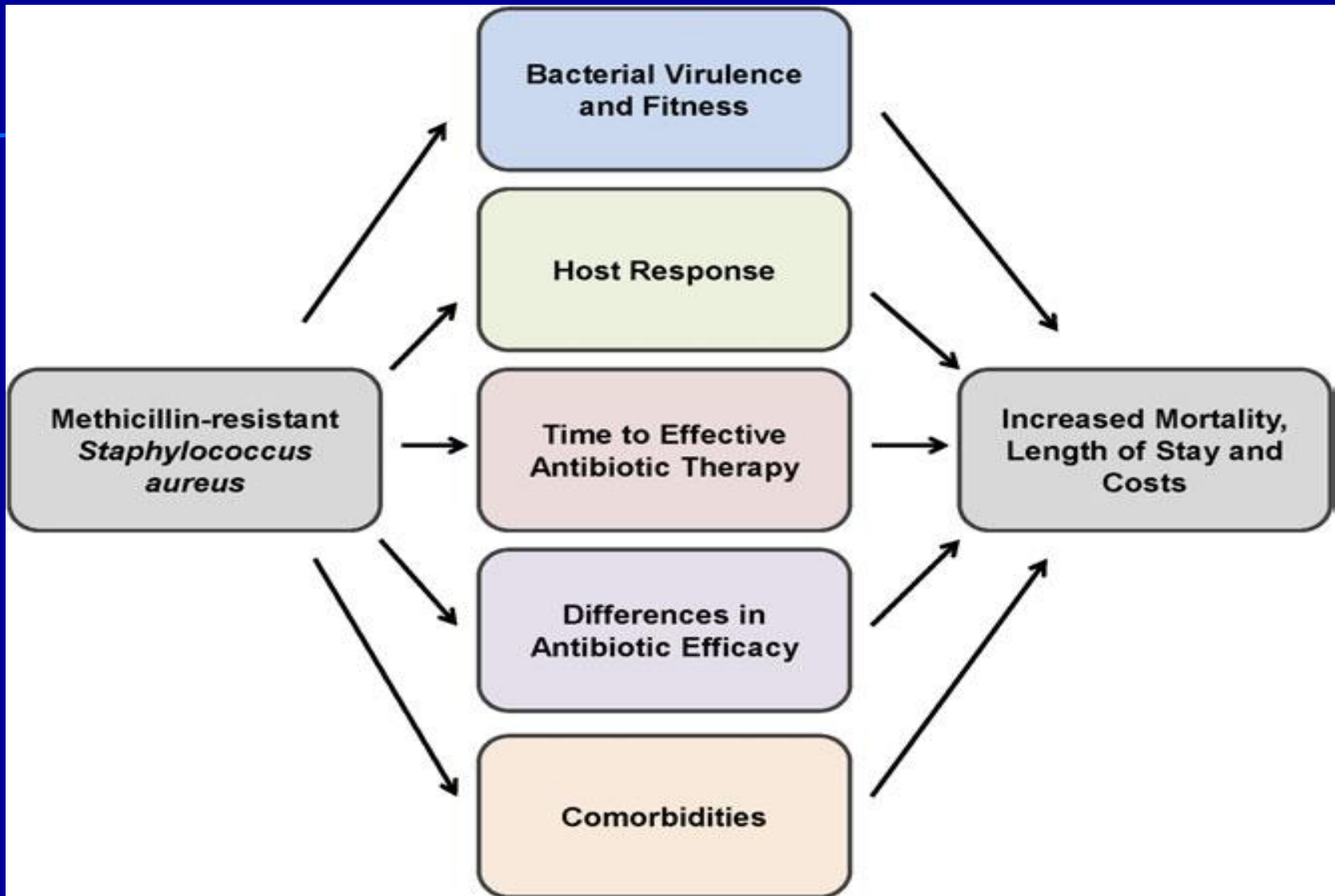
The *First* approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"

The *Second*, feeling of the tusk,
Cried, "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The *Third* approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"

The *Fourth* reached out an eager hand,
And felt about the knee,
"What most this wondrous beast is like
Is mighty plain," quoth he;
"'Tis clear enough the Elephant
Is very like a tree!"

Complex Relationship Between MRSA & Mortality



Vancomycin MIC-Mortality Association:

- Present in patients who never received vancomycin

Holmes *J Infect Dis* 2011; 204: 340

Cervera ICAAC 2012 Abst #K1122

- \uparrow Vancomycin MIC = \downarrow Virulence *In vivo*

Cameron *J Infect Dis* 2012; 205: 1677

Peleg *J Infect Dis* 2009; 199: 532.

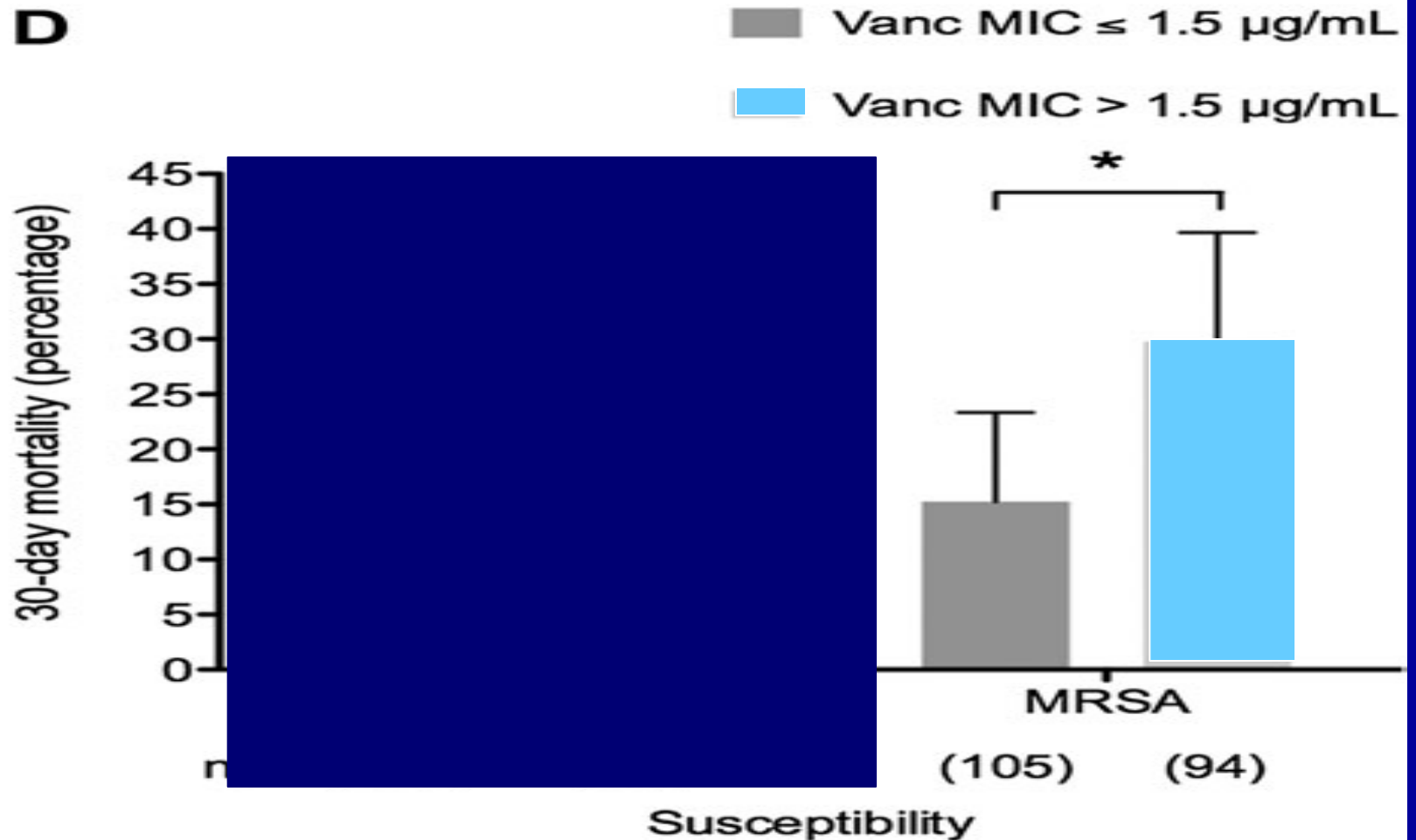
- \uparrow Vancomycin MIC = \downarrow Mortality in Clinic

van Hal *PLoS One* 2011; 6:e21217

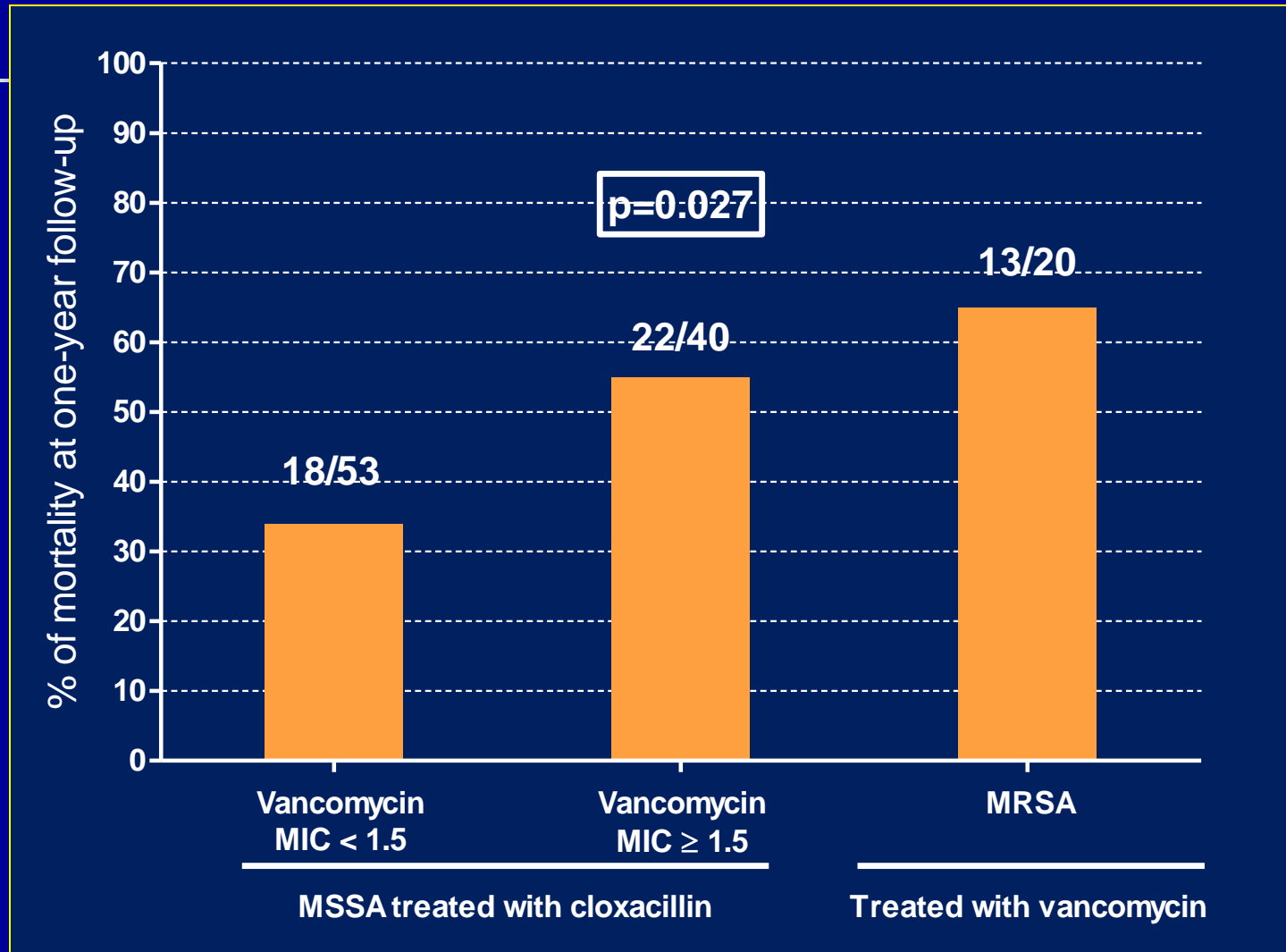
Cameron *Clin Infect Dis* 2011; 53: 576.

Vancomycin MIC Associated with 30 Day Mortality in MSSA Bacteremia

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Vancomycin MIC Associated with 1 Year Mortality in MSSA Left-Sided Endocarditis



Take Home Pay: Vancomycin MIC & Outcome

- Present
- Complex
- Not Necessarily Causal

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- Clinical Benefit of $AUC/MIC \geq 400$: Unestablished

The Recommendation

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

MICHAEL RYBAK, BEN LOMAESTRO, JOHN C. ROTSCHAFFER, ROBERT MOELLER JR., WILLIAM CRAIG, MARIANNE BILLETER, JOSEPH R. DALOVISIO, AND DONALD P. LEVINE

Am J Health-Syst Pharm. 2009; 66:82-98

Based on these study results, an AUC/MIC ratio of ≥ 400 has been advocated as a target to achieve clinical effectiveness with vancomycin.

Data for AUC/MIC and Clinical Outcome: No Consensus

Summary of Studies comparing AUC/MIC to Clinical Outcome in Patients with *S. aureus* Infection

	Design	Infection type	MIC	Outcome	Finding
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Association between Outcome and AUC/MIC

Moise-Broder ¹	Retrospective n=50 (Van Rx)	HAP/VAP MR/MSSA	BMD	Clinical & Microbiological Success	AUC/MIC \geq 350 Asstd with "Clinical Success": OR 7.19; 95% CI: 1.9-27.3
Kullar ²	Retrospective n=320	MRSA Bacteremia	BMD	Composite: - 30-d death, - SAB>7d - Symptoms	AUC/MIC<421 Asstd with failure (61.2% v. 48.6%; p=0.038) No Difference: - Median AUC/MIC - % MIC>1)
Brown ³	Retrospective n=50	MRSA IE/ Bacteremia	Etest	Attributable Mortality (n=8)	AUC ₂₄ /MIC <211 Associated with Attributable Mortality OR: 10.4 (3.89-16.77)

No Association between Outcome and AUC/MIC

Neuner ⁴	Retrospective n=222	MRSA Bacteremia	Etest	Persistent MRSAB (n=19)	No significant association between AUC/MIC and Persistent MRSAB
Holmes ⁵	Prospective N=182	<i>S. aureus</i> Bacteremia	BMD	30d Mortality (n=38)	No assn of AUC/MIC>400 and better outcome

¹Clin Pharmacokin 2004; 43:925; ²CID 2011; 52:975; ³ AAC 2012; 56: 634; ⁴DMID 2010; 67:228; ⁵ICAAC11 #A1681

AUC/MIC \geq 400 Did Not Improve Outcome in MRSA Endocarditis Model

- 3 MRSA isolates with MIC 0.5, 1, and 2ug/mL each used to infect rabbits at control, regular dose, and high dose vanco (n=45 rabbits/isolate)
- After 2 days of VAN neither sterilization rate nor reduction in bacterial density in vegetations improved with Cmin levels of 15-20 mg/L or with AUC/MIC index \geq 400.

Take Home Pay for $AUC/MIC \geq 400$

- Clinical studies: no consensus
- Recent *in vivo* model: negative
- It is time to go beyond Monte Carlo Simulations and retrospective case control study design
- If the treatment effect is as big as the retrospective studies suggest, a large sample size in the definitive trial is unnecessary.

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