

# **Challenging Cases Involving Resistant Organisms: MRSA and MDR Acinetobacter**

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# Case 1

A 55 y.o. man presents with fever, chills and pain over his pacer site. His T is 102 F, BP is 100/70, P is 103. There is erythema over the pacer site and pain with palpation. Blood cultures grow MRSA with an MIC to vancomycin of 1. Therapy is started with vancomycin 1 gram IV q12 H (Cr = 0.9) and the pacemaker is removed. Despite a vancomycin trough of 15 mg/L, blood cultures continue to grow MRSA 4 days after the pacer is removed. TEE does not show evidence of endocarditis and workup for other metastatic foci of MRSA infection is negative. What antibiotic therapy do you recommend?

# Case 1

- A. Continue vancomycin
- B. Continue vancomycin and add rifampin
- C. Continue vancomycin and add gentamicin and rifampin
- D. Change to linezolid
- E. Change to daptomycin
- F. Continue vancomycin and add linezolid
- G. Continue vancomycin and add quinupristin/dalfopristin

# Questions to be Answered

- Is the patient failing vancomycin and why?
  - Normal length of bacteremia for MRSA?
  - Inadequate dose?
  - Presence of heteroresistance?
- What therapeutic options exist besides vancomycin monotherapy?
  - Addition of rifampin or gentamicin
  - Daptomycin
  - Linezolid
  - Quinupristin/dalfopristin
  - TMP/SMX
  - Clindamycin

# Expected Time to Clearance of MRSA Bacteremia

Disease Entity	Year	Median	Mean
Left-sided endocarditis (LIE)	1991	9 days	
Mixed right-sided endocarditis (RIE) and bacteremia	1992		5.4 days
Bacteremia	2004	3.5 days	6.4 days
Mixed bacteremia, LIE, RIE	2006	8-9 days	

Levine et al. *Ann Intern Med.* 1991;115:674-80.

Markowitz et al. *Ann Intern Med.* 1992;117:390-8.

Charles et al. *Clin Infect Dis.* 2004;38:448.

Fowler et al. *N Engl J Med.* 2006;355:653.

# Dosing of Vancomycin

- What's wrong with 1 gm q 12h?
  - Risk of underdosing in serious infections
- Recommended vancomycin troughs from recent guidelines:
  - MRSA pneumonia: 15-20 mg/L
  - CNS infection: 15-20 mg/L
  - MRSA bacteremia and endocarditis: 10-15 mg/L
- However, still difficult to find good evidence that higher troughs help

ATS/IDSA Guidelines for HAP/VAP. *Am J Resp Crit Care Med.* 2005;171:338.

IDSA Guidelines for Bacterial Meningitis. *Clin Infect Dis.* 2004;39:1267-84.

AHA Scientific Statement on Infective Endocarditis. *Circulation.* 2005; 111:e394-e433.

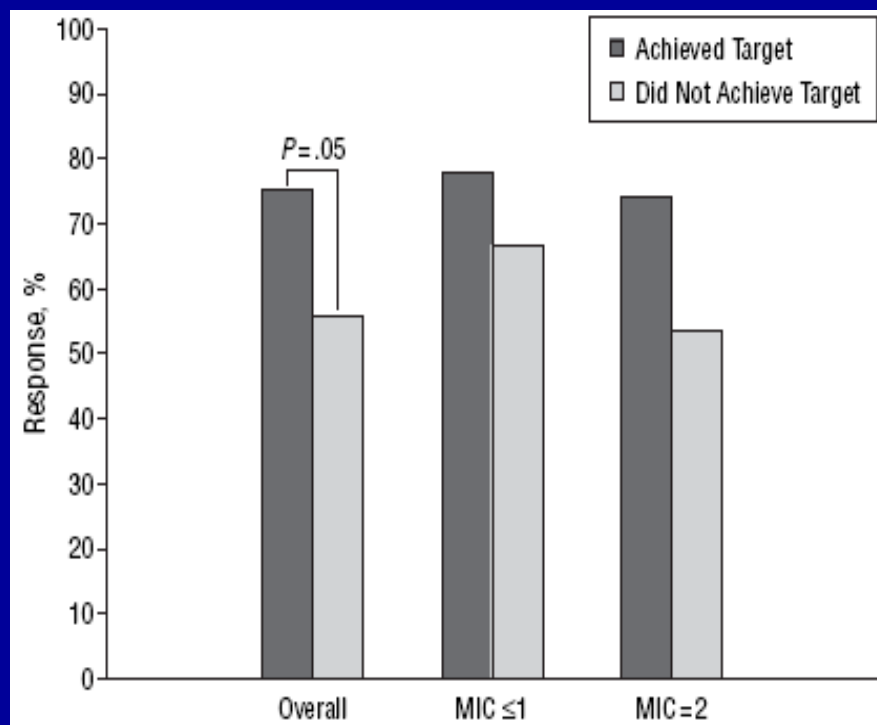
# Is Vancomycin Dosing Related to Outcome?

- Adult patients with nosocomial MRSA infection and  $\geq 72$  hours of vancomycin
- Outcomes: complete response (resolution of fever,  $\uparrow$  WBC, signs of infection), partial response (improvement), failure (no improvement, worsening, relapse, death)

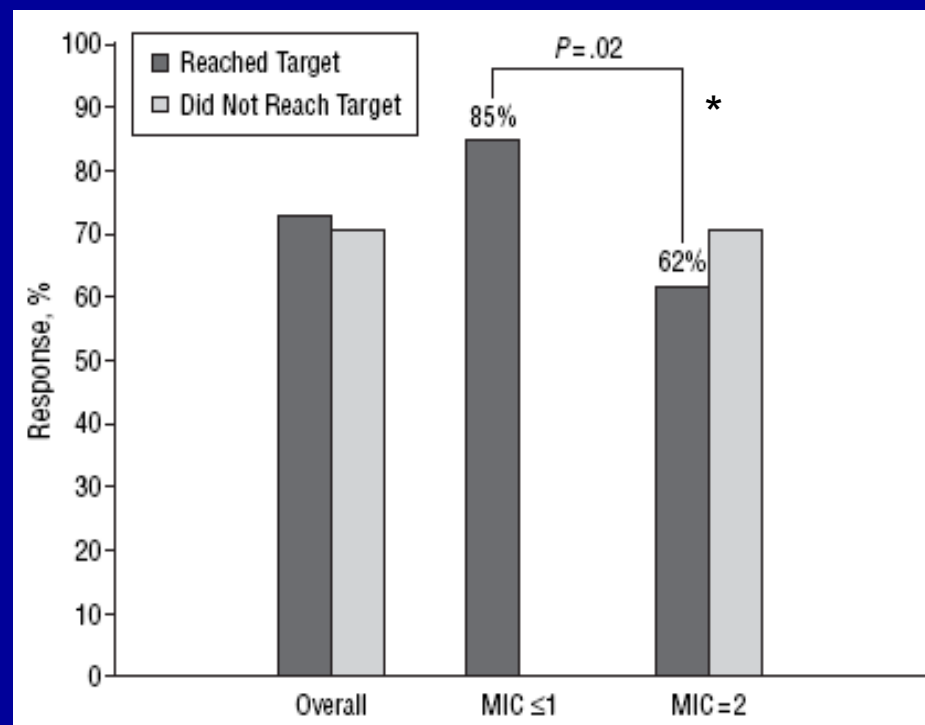
	High MIC (n = 51)	Low MIC (n = 44)
Sputum source	49%	55%
<b>Blood source</b>	<b>35%</b>	<b>14%</b>
Wound source	16%	27%

# Is Vancomycin Dosing Related to Outcome?

## Response at 72 Hours



## Response at End of Treatment



\*Also true for subgroup with pneumonia/BSI

Independent predictors of poor response: high MIC and APACHE score

A subset of isolates were found to have tolerance to vancomycin (MBC/MIC ≥ 32) or heteroresistance

# Heteroresistance in MRSA

- MRSA strains susceptible to vancomycin (MIC < 4) but containing subpopulations of organisms with MICs in the intermediate range (4-32)
- Routine screening for heteroresistance not done
- Associated with vancomycin treatment failure, initially low serum vancomycin levels, and high bacterial load
- BUT, frequency in US isolates is low
  - Found in 13.6% of isolates in patients with persistent ( $\geq 10$  days) or recurrent ( $\geq 30$  days) MRSA bacteremia

Charles et al. *Clin Infect Dis.* 2004;38:448.

Khosrovaneh et al. *Clin Infect Dis.* 2004;38:1328-30.

# Addition of Rifampin to Vancomycin

- Addition of rifampin has not been shown to improve outcomes in MSSA or MRSA bacteremia or native valve IE
  - 42 pts with MRSA native valve IE randomized to vanco or vanco/rifampin for 28 days (600 daily)
  - No difference in outcome
  - Mean duration of bacteremia longer in combination therapy group (9 vs 7 days)
- Thoughts:
  - To avoid emergence of resistance, better to wait until blood cultures have cleared before adding rifampin
  - Consider value of preservation of rifampin in case prosthetic material is ever introduced

# Addition of Gentamicin to Vancomycin

- Addition of synergistic gentamicin has not been shown to improve outcomes in MSSA or MRSA bacteremia or native valve IE
- Studied in IDUs and non-IDUs with MSSA NVIE who received 2 weeks of gent
  - IDU {
    - Faster defervescence and normal WBC
    - No difference in clearance of bacteremia or mortality
  - Non IDU {
    - No difference in defervescence or mortality
    - Clearance of bacteremia faster w/ gent: **2.8 vs 4.1 days**
- Authors recommended 3-5 days of initial, low dose gentamicin based on this finding

Abrams et al. *Ann Intern Med.* 1979;90:789;  
Korzeniowski & Sande. *Ann Intern Med.* 1982;97:496.

# Is Synergistic Gentamicin Safe?

- Secondary analysis from daptomycin SAB/SAIE trial suggest that even low dose, short course gentamicin is associated with nephrotoxicity
  - Pts received daptomycin at 6 mg/kg daily or standard therapy (ASP or vancomycin, both with initial low dose gentamicin for a median of 4 or 5 days, respectively)
  - Some patients in both arms received gentamicin before enrollment (median of 2 days)
- More renal adverse events reported in standard therapy arm (7% vs. 18%)
  - Most pronounced in the elderly and in diabetics
- More laboratory evidence of nephrotoxicity among pts who received gentamicin

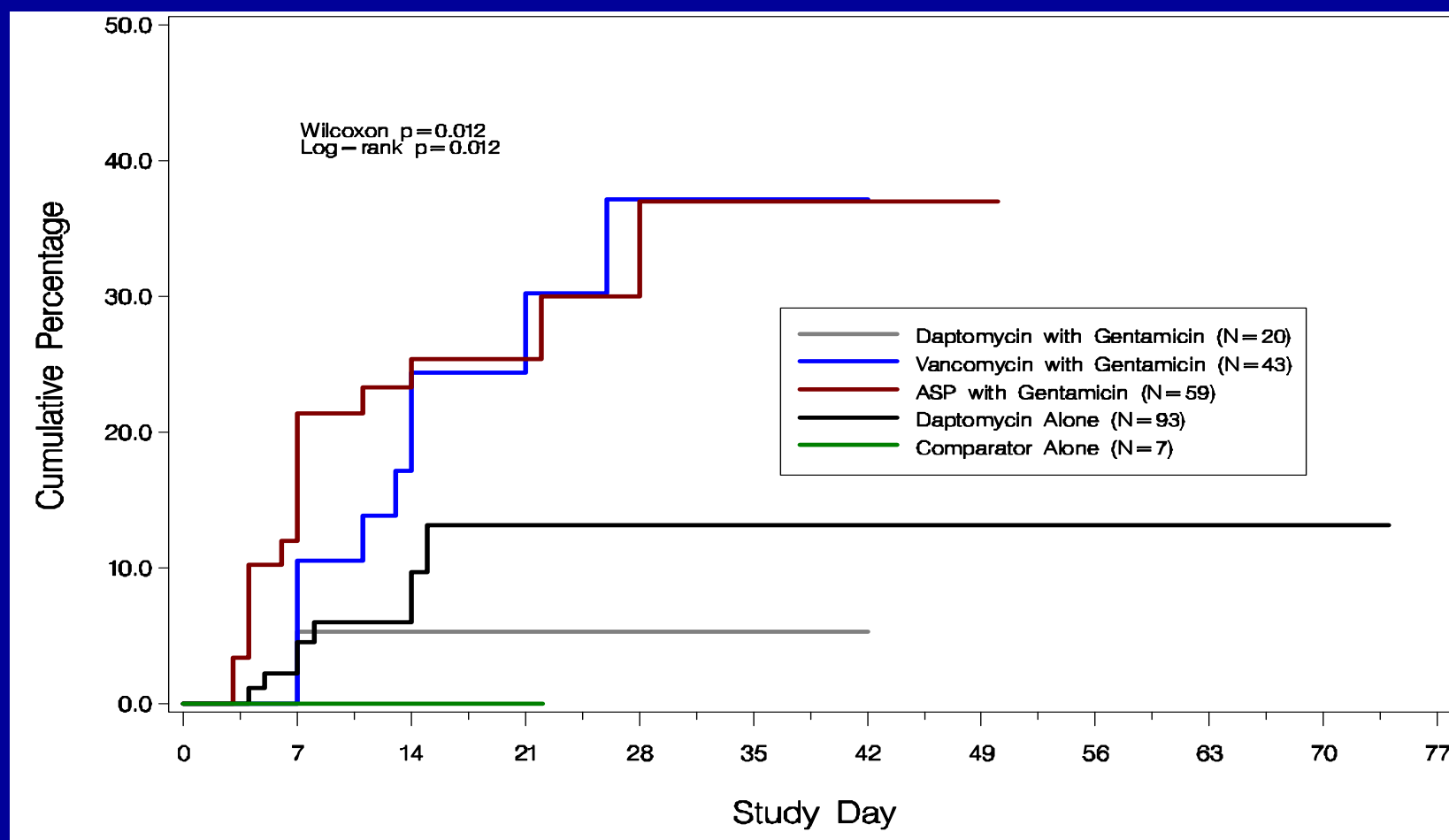
# Incidence of Decrease in CrCl in Patients who Received Low-dose Gentamicin

	Received Gentamicin (n=122)	No Gentamicin (n=100)	P value
Clinically significant decrease in CrCl*	27 (22%)	8 (8%)	.005
Sustained 50% decrease in CrCl†	7 (6%)	0	.02
Sustained 25% decrease in CrCl†	26 (21%)	9 (9%)	.02

\*Decline in CrCl to < 50 mL/min if the baseline was ≥ 50 mL/min or decrease in CrCl of ≥ 10 mL/min if the baseline was < 50 mL/min

†Reduction on two or more consecutive measurements of CrCl

# Time to Clinically Significant Decrease in CrCl\*



\*Decline in CrCl to  $< 50$  mL/min if the baseline was  $\geq 50$  mL/min or decrease in CrCl of  $\geq 10$  mL/min if the baseline was  $< 50$  mL/min

# Addition of Gentamicin to Vancomycin

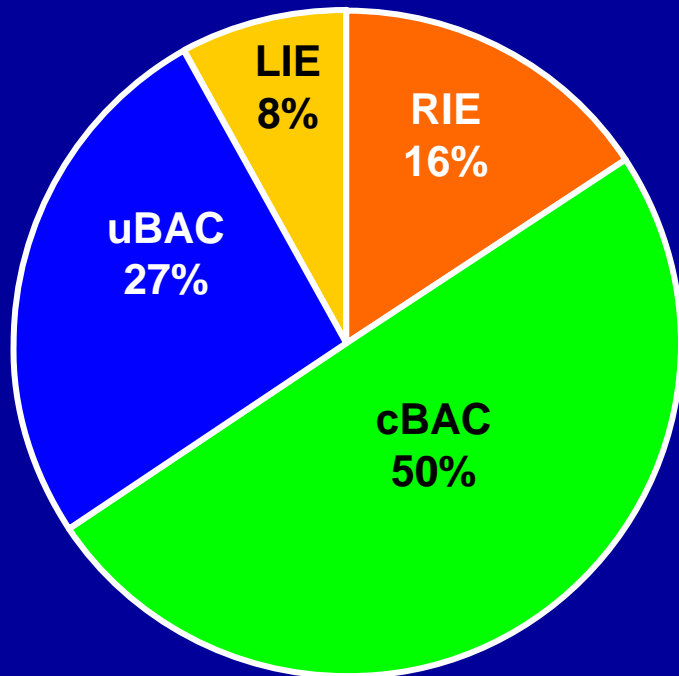
- I recommend not using synergistic gentamicin in the management of *S. aureus* bacteremia and native valve endocarditis
  - Particularly in pts with diabetes, renal or neurologic impairment, or the elderly
- Many MRSA isolates are not susceptible to gentamicin

# Daptomycin SAB/IE Study

- Open-label, non-inferiority study, 8/02-2/05
  - 120 pts received daptomycin at 6 mg/kg daily
  - 115 pts received standard therapy (ASP or vancomycin, both with initial low dose gentamicin)
- 1° endpt: success at TOC 6 wks after EOT
- Exclusions: intravascular foreign material, CrCl < 30, known pneumonia or osteo
- All pts had TEE
- Diagnoses and outcomes determined by an independent external adjudication committee (IEAC)
- No differences in baseline characteristics
- 38% of patients had MRSA bacteremia

# Final Diagnosis

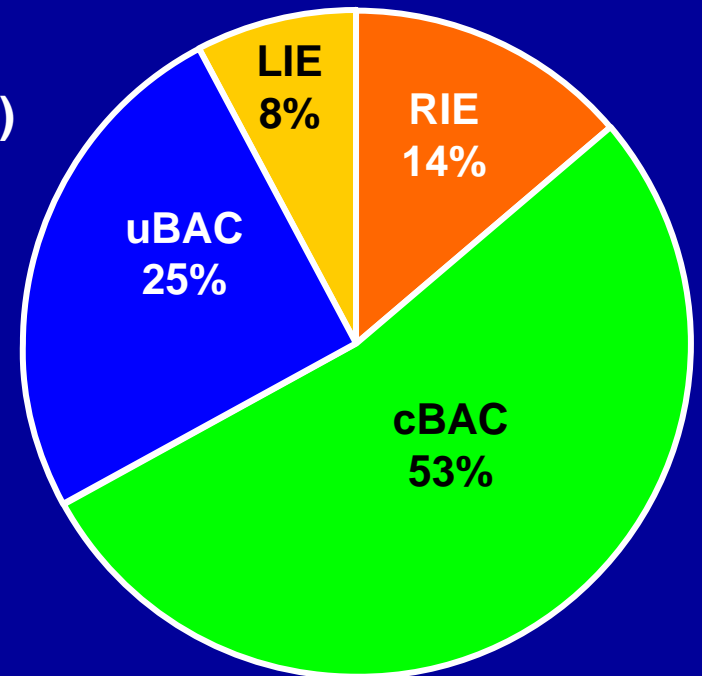
**Daptomycin Group**  
N = 120



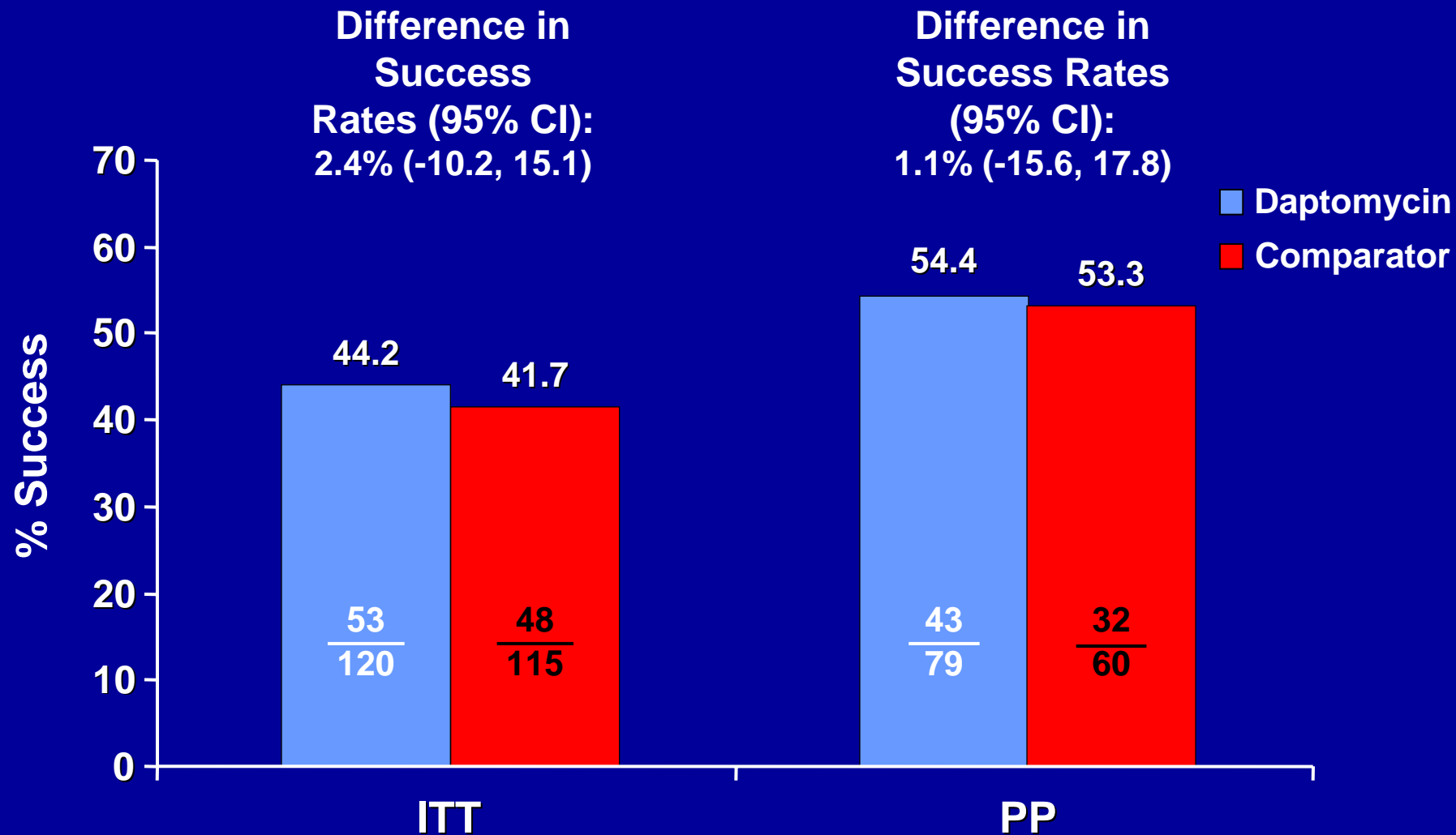
Overall  
Final Diagnosis  
N = 235

uBAC = 61 (26%)  
cBAC = 121 (51%)  
RIE = 35 (15%)  
LIE = 18 (8%)

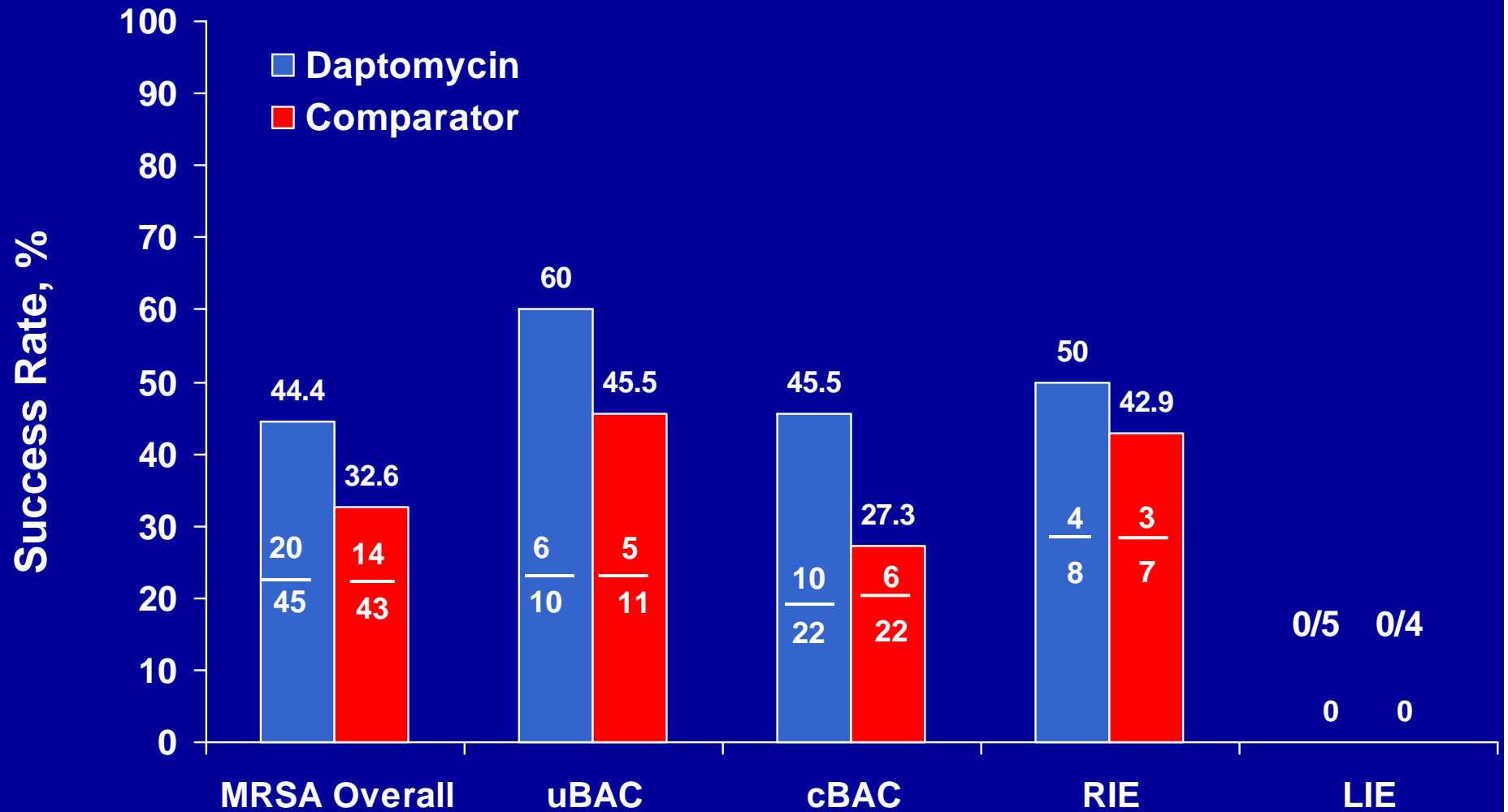
**Comparator Group**  
N = 115



# Primary Endpoint: Success at Test of Cure Visit



# MRSA—Success at TOC by Final Diagnosis



# Left Sided Endocarditis (ITT)

	Daptomycin N = 9 n (%)	Comparator N = 9 n (%)
<hr/>		
Adjudication Committee Success		
End of Therapy	4 (44.4)	3 (33.3)
Test of Cure	1 (11.1)	2 (22.2)
MRSA	0/5	0/4
MSSA	1/4 (25.0)	2/5 (40.0)
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Survival	6 (66.7)	4 (44.4)
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# All Reasons for Failure at Test of Cure (ITT)

	Daptomycin N = 120 n (%)	Comparator N = 115 n (%)
<b>Overall failure</b>	<b>67 (55.8)</b>	<b>67 (58.3)</b>
Reason for failure (more than 1 reason may be indicated for each patient)		
<b>Persisting or relapsing <i>S aureus</i> infection</b>	<b>19 (15.8)</b>	<b>11 (9.6)</b>
Death	13 (10.8)	13 (11.3)
Clinical failure w/o persisting/relapsing <i>S aureus</i>	4 (3.3)	4 (3.5)
<b>Treatment-limiting adverse events</b>	<b>8 (6.7)</b>	<b>17 (14.8)</b>
Non-study antibiotics	20 (16.7)	16 (13.9)
No blood culture	9 (7.5)	12 (10.4)
Nonevaluable (eg, withdrew consent, left AMA)	9 (7.5)	14 (12.2)

# Cases With Emergence of Reduced Susceptibility to Daptomycin

	Final Diagnosis	Baseline Pathogen	Duration of Therapy (days)	Baseline MIC ( $\mu\text{g/mL}$ )	Highest MIC ( $\mu\text{g/mL}$ )	Clinical Summary
1	LIE	<b>MRSA</b>	7	0.25	2	Mitral/aortic IE
2	LIE	<b>MRSA</b>	8	0.5	2	Mitral IE, stroke
3	cRIE	MSSA	20	0.25	4	Tricuspid IE, large pulmonary emboli, tunnel infection
4	cBAC	<b>MRSA</b>	14	0.25	2	IV port infection
5	cBAC	<b>MRSA</b>	23	0.25	2	Septic arthritis
6	cBAC	<b>MRSA</b>	35	0.5	2	Undiagnosed retroperitoneal abscess

# Correlation between Vancomycin and Daptomycin Resistance in *S. aureus*?

**Table 1. Effect of increasing vancomycin MICs on daptomycin susceptibility for *Staphylococcus aureus* isolates.**

Vancomycin MIC, $\mu\text{g}/\text{mL}$	No. (%) of isolates	
	Daptomycin MIC $\leq 1 \mu\text{g}/\text{mL}$	Daptomycin MIC $\geq 2 \mu\text{g}/\text{mL}$
$\leq 2$	812 (97)	30 (3)
4	11 (20)	43 (80)
8–16	1 (7)	15 (93)
$\geq 32$	5 <sup>a</sup> (100)	0 (0)

Cui et al. *Antimicrob Agents Chemother.* 2006;50:1079; Patel et al. *Clin Infect Dis.* 2006;42:1652; Sakoulas et al. *Antimicrob Agents Chemother.* 2006;50:1581.

# Use of Daptomycin for SAB/IE

- Doses up to 12 mg/kg safe in healthy volunteers
  - If renal function is normal, I start with 8 mg/kg daily
  - Case report of successful therapy in pacemaker-induced *S. aureus* mitral valve IE complicated by persistent bacteremia from a coronary stent
    - Dose: 12 mg/kg per day for 41 days
- Given emergence of resistance on therapy, use with caution in pts with undrained source or metastatic site of infection
- Follow CPK, especially if using in pts with CrCl < 30 or high dose
- Inactivated by pulmonary surfactant → high failure rates when used for treatment of pneumonia
  - Seems to be OK for septic pulmonary emboli

Benvenuto et al. *Antimicrob Agents Chemother.* 2006;50:3245.

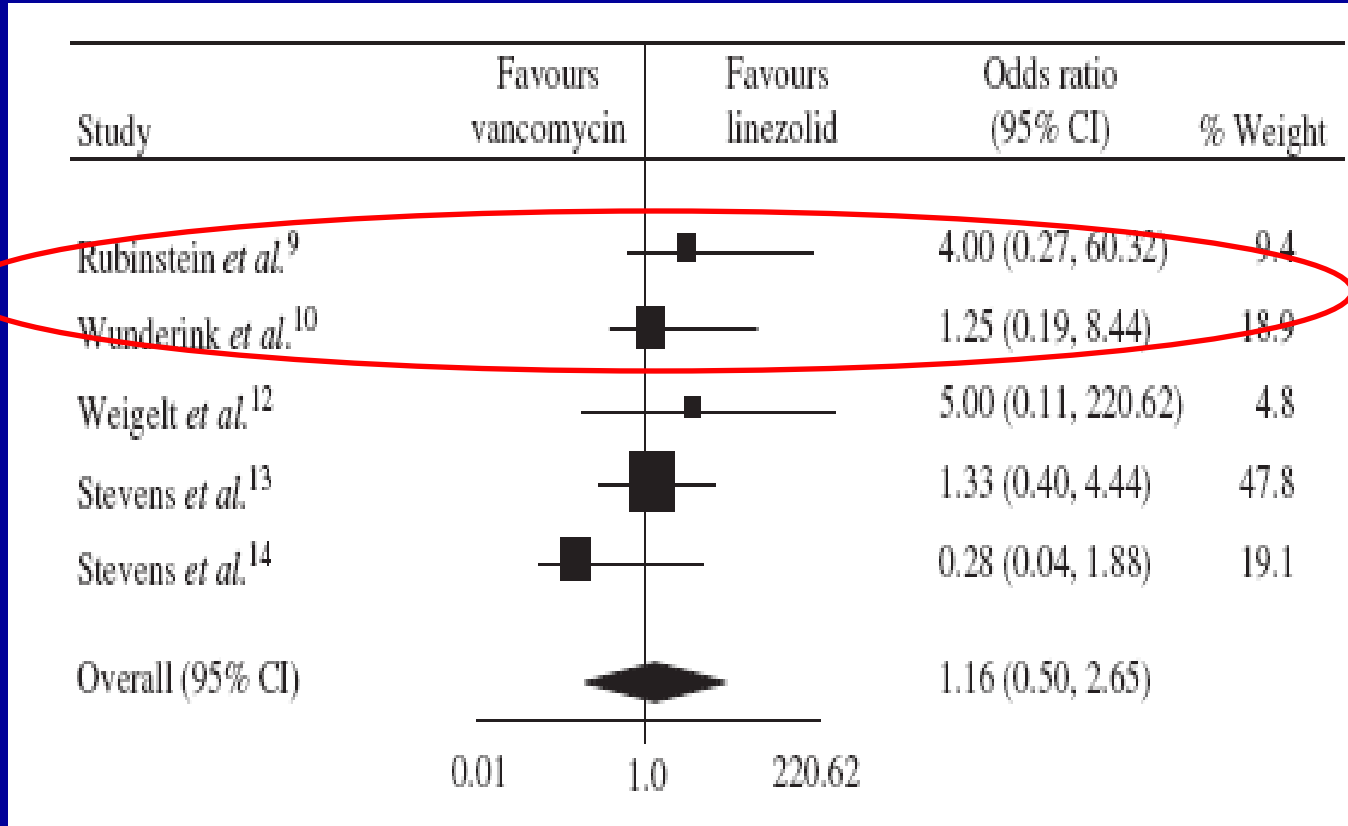
Cunha BA et al. *Heart Lung.* 2006;35:207-11.

# Linezolid and MRSA Bacteremia

- Mechanism of action: inhibition of bacterial protein synthesis at ribosome (bacteriostatic)
- Stories of success in MRSA bacteremia
  - 9/15 (60%) receiving linezolid vs 7/10 (70%) receiving vanco for MRSA infections (bacteremia subgroup)
  - 6/12 (50%) of pts with hVISA bacteremia/IE
- Stories of failure in MRSA bacteremia and IE
- Side effects: bone marrow suppression, serotonin syndrome

Ben Mansour et al. *Eur J Clin Microbiol Infect Dis.* 2003;22:372; Howden et al. *Clin Infect Dis.* 2004;38:521; Ruiz et al. *Clin Infect Dis.* 2002;35:1018; Sperber et al. *Clin Infect Dis.* 2003;36:675; Stevens et al. *Clin Infect Dis.* 2002;34:1481.

# Linezolid for SAB



**Pneumonia**

**SSSI**

**Mixed**

**Mixed**

- > 3200 pts in 5 studies: 144 SAB (4.5%), 64 MRSA
- Micro outcome defined from primary source
- No long-term follow-up, routine monitoring

**Shorr *et al.* *J Antimicrob Chemother.* 2005;56:923.**

# New Linezolid Warning

- An imbalance in mortality was seen in patients treated with linezolid relative to vancomycin/dicloxacillin/oxacillin in an open-label study in seriously ill patients with intravascular catheter-related infections [78/363 (21.5%) vs. 58/363 (16.0%); odds ratio 1.426, 95% CI 0.970, 2.098]
- This observed imbalance occurred primarily in linezolid-treated patients in whom either Gram-negative pathogens, mixed Gram-negative and Gram-positive pathogens, or no pathogen were identified at baseline, but was not seen in patients with Gram-positive infections only
- Linezolid is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections

# Quinupristin/Dalfopristin for SAB

- Minimal data to support use in MRSA bacteremia and IE
- Study of patients with MRSA infections failing prior therapy (n = 90)
  - 44%, bone and joint; 17%, soft tissue; 12%, IE
  - 48% of patients had bacteremia
- Clinical success rates in bacteremia patients
  - 70.5% in all treated group
  - 55.6% in clinically and bacteriologically evaluable group
- Clinical success in IE patients
  - 54.4% in all treated group
  - 0% in clinically and bacteriologically evaluable group

# TMP-SMX for MRSA in IVDU

	TMP-SMX (n = 43)	Vancomycin (n = 58)
MRSA	49%	45%
MSSA	51%	55%
<i>Infection category</i>		
<b>TV IE</b>	<b>26%</b>	<b>21%</b>
<b>Thrombophlebitis</b>	<b>21%</b>	<b>17%</b>
<b>Pseudoaneurysm</b>	<b>5%</b>	<b>9%</b>
<b>Bacteremia</b>	<b>5%</b>	<b>3%</b>
<b>Bone and joint</b>	<b>16%</b>	<b>16%</b>
<b>Skin and soft tissue</b>	<b>28%</b>	<b>34%</b>

# TMP-SMX and MRSA

- Dose: 320/1600 iv bid (= 2 DS po bid)
- Cure rate:
  - 86% for TMP-SMX
  - 98% for vancomycin
- All 47 patients with MRSA infection were cured; all treatment failures occurred in patients with MSSA
- In vitro, TMP-SMX exhibits rapid bactericidal activity against CA-MRSA strains

Markowitz et al. *Ann Intern Med.* 1992;117:390.

Kaka AS et al. *J Antimicrob Chemo.* 2006;58:680-3.

# Clindamycin and MRSA Bacteremia

- Reports of relapse in pre-MRSA era
  - Associated with inducible macrolide-lincosamide-streptogramin B (MLS<sub>B</sub>) resistance
- In rabbit model of IE, at higher doses (equivalent to 900 mg IV q 6-8 h in humans), clindamycin was as effective as nafcillin in eradicating *S aureus* from aortic valve vegetations
  - Serum bactericidal titers closely correlated with the mean serum levels
- Cannot be recommended as monotherapy

Scheld et al. *Antimicrob Agents Chemother.* 1982;21:646;  
Watanakunakorn. *Am J Med.* 1976;60:419.

# Other New Agents

- Tigecycline
  - Peak serum concentrations do not exceed 1  $\mu\text{g}/\text{mL}$ ; may be a problem in treatment of bacteremia
- Lipoglycopeptides
  - Dalbavancin
    - Half life: 9-12 days
    - Small study in CA-BSI
  - Telavancin
    - Bacteremia studies planned
  - Oritavancin
- Ceftibiprole and ceftaroline
  - Cephalosporins with MRSA activity (high affinity for PBP-2a)

## Case 2

- A 75 y.o woman S/P CABG presents with an infected saphenous vein graft harvest site. Gram stain shows GNR and she is started on piperacillin/tazobactam. The wound continues to expand and culture grows *Acinetobacter baumannii*. The pt is taken for wound debridement. What antibiotic therapy do you recommend?

Gentamicin	R
Tobramycin	R
Amikacin	I
Aztreonam	R
Ceftriaxone	R
Cefepime	R
Piperacillin	R
Pip/tazo	R
Ciprofloxacin	R
TMP-SMX	R
Meropenem	R

## Case 2

- A. Ampicillin/sulbactam
- B. Colistin
- C. Tigecycline
- D. Imipenem
- E. Amikacin

# ***Acinetobacter baumannii* and Sulbactam**

- Study from Barcelona: 1000 bed hospital with ongoing *A. baumannii* outbreak (>1100 pts!)
- Pt with non-life threatening infection (defined by CDC criteria) received sulbactam (3 g/day) or amp/sulbactam (3 g/6 g/day in 3 doses)
- Clinical outcomes: cure (eradication of all presenting signs and symptoms), improvement, failure (no improvement in 72 hrs)
- Bacteriologic outcomes: eradication, persistence

# ***Acinetobacter baumannii* and Sulbactam**

- 42 patients (18 sulbactam, 24 amp/sulbactam)
- Types of infection: surgical wounds and soft tissue (20), UTI (7), bacteremia (2), tracheobronchitis/pneumonia (13)
- Results:
  - 35/41 (85%) cured, 4/41 (10%) improved, 2/41 (5%) failed
  - 97% eradicated

# Colistin

- Colistin has no activity against *Proteus*, *Serratia*, *Providentia*, *Burkholderia*, GN or GP cocci
- Broth dilution titers  $\leq 2 \mu\text{g/mL}$  accepted as susceptible
- Antibacterial action: cell membrane disrupted by binding of drug to phospholipids
- Concentration dependent
- Dose: 5 mg/kg/day divided into 2 doses
- Major toxicities
  - Renal impairment
  - Neuromuscular blockade
  - Neurotoxicity (many different manifestations)

# Colistin for PAE and *A. baumannii*

- 60 infections 1993-4:  
35% MDR PAE, 65%  
MDR-AB
- Mean baseline Cr was  
 $1.5 \pm 1.5$  mg/dL
- 27% of pts with NL and  
58% of pts with abnormal  
renal function had  
worsening function
- No neuromuscular or  
neurologic problems

Infection	No. (%) of infections	No. (%) with good outcome
Pneumonia	20 (33)	5 (25)
Urinary tract infection	12 (20)	10 (83)
Primary bloodstream infection	9 (15)	7 (78)
CNS infection	5 (8)	4 (80)
Surgical site infection	5 (8)	3 (60)
Peritonitis	4 (7)	2 (50)
Catheter-related infection	4 (7)	3 (75)
Otitis media	1 (2)	1 (100)
Total	60 (100)	35 (58)

# Colistin for PAE

No. (%) with  
Good outcome

- 23 infections
  - 10 colistin only
  - 13 colistin + amikacin or antiPAE PCN
- Favorable outcome in 14/23 (61%)
- No difference with mono or combo therapy
- 21/23 pts on dialysis before starting
- 1/23 with suspected neurotoxicity

Type of infection	No. of patients
Pneumonia	18 <b>10 (56%)</b>
Bacteremia	8
Wound	3 <b>1 (33%)</b>
Intra-abdominal	6 <b>5 (83%)</b>
Peritonitis	2
Abscess	2
Cholangitis	2
Endocarditis	1
Multiple types <sup>a</sup>	5

<sup>a</sup> Three patients had pneumonia and intra-abdominal infection; 2 patients had pneumonia and wound infection.

# Tigecycline

- Mechanism of action
  - Bacteriostatic glycyclcycline that inhibition of bacterial protein synthesis at ribosome
  - Engineered to overcome TCN resistance (Efflux of drug from inside cell & protection of ribosomes)
- In vitro activity against MSSA, MRSA, VRE, GNR, Acinetobacter, anaerobes
- Poor activity against Pseudomonas (90% of strains have MICs  $\geq 4$ ), Proteus, Providentia
- Dose 100 mg x 1 then 50 mg IV Q12 H
- Dose adjustment in liver failure (25 mg instead of 50 mg)

# Tigecycline—FDA Approvals

- Complicated skin and skin structure infections
  - Compared to vancomycin/aztreonam for deep soft tissue (63%), major abscess (28%), cellulitis (59%)
  - 833 (422/411) pts received a mean of 8 days of Rx
  - Cure at test of cure visit: 87% vs 89% (test for non-inferiority,  $p < .001$ )
- Complicated intra-abdominal infections
  - Compared to imipenem for abscess, perforated appendix, viscus, or diverticulitis, complicated cholecystitis
  - 1262 (631/631) pts received a mean of 8 days of Rx
  - Cure at test of cure: 87% vs 87% (test for non-inferiority,  $p < .001$ )

Ellis-Grosse et al. *Clin Infect Dis.* 2005;41:S341-53.

Babinchak et al. *Clin Infect Dis.* 2005;41:S354-66.

# Tigecycline-Issues

- Susceptibility breakpoints
  - *S. aureus*  $\leq$  .5  $\mu\text{g/mL}$
  - Streptococcus and enterococcus  $\leq$  .25  $\mu\text{g/mL}$
  - Enterobacteriaceae  $\leq$  2  $\mu\text{g/mL}$
  - Anaerobes  $\leq$  4  $\mu\text{g/mL}$
- Peak serum concentrations do not exceed 1  $\mu\text{g/mL}$ ; may be a problem in treatment of bacteremia
- Side effects
  - N/V in 25-30% of pts
  - No photosensitivity, rash rare
  - If TCN allergic then assume Tigecycline allergic

Paterson DL. *Curr Opin in Pharmacology*. 2006;6:486.  
Stein GE and Craig WA. *Clin Infect Dis*. 2006;43:518-24.

# Desperation

**Table 1. Enhanced activity of antibiotic combinations against multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: in vitro and clinical evidence.**

Pathogen (type of evidence), antibiotic combination	Reference(s)
<i>P. aeruginosa</i> (in vitro)	
Ticarcillin, tobramycin, rifampin	[8]
Cephalosporins, quinolones	[21]
Ceftazidime, colistin	[22]
Macrolides, tobramycin, trimethoprim, rifampin	[20]
Polymyxin B, rifampin	[19]
Polymyxin B, imipenem	[11]
<i>A. baumannii</i> (in vitro)	
Polymyxin B, imipenem	[11]
Polymyxin B, rifampin	[11]
Polymyxin B, imipenem, rifampin	[16]
Polymyxin B, cecropin	[41, 42]
Polymyxin B, rifampin, ampicillin-sulbactam	[12]
Polymyxin B, rifampin, imipenem	[16]
Colistin, rifampin	[13, 15]
<i>A. baumannii</i> and <i>P. aeruginosa</i> (clinical)	
Cefepime, amikacin	[25]
Polymyxin B plus 1 or more of the following: a carbapenem, aminoglycoside, quinolone, or $\beta$ -lactam	[26]

# Final Thoughts

- *S. aureus* bacteremia is a bad disease
  - Its treatment relies on making good diagnostic and management decisions in the face of a suboptimal armamentarium of effective antibiotics
  - There are some interesting new agents on the horizon
- Treatment options for multi-drug resistant Gram negative infections are very limited
  - No new agents for these infections will be available in the next 5-10 years
  - Our only hope is to prevent emergence (through good antibiotic use) and transmission (through good infection control)