

Staphylococcal Bacteremia

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Case 1

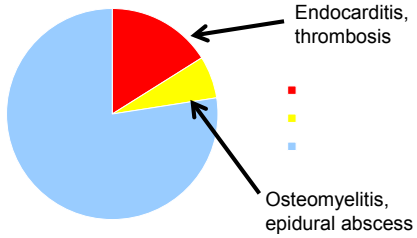
- 38 y/o man, new CHF, alcoholic cardiomyopathy, Hct = 13
- Given PRBCs, diuretics, afterload reducers
- HD 6: upper + lower endoscopy
- Post-procedure T = 39°C, blood cultures taken
- HD 7: afebrile but BC x2 = GPC in clusters; R forearm former IV site red, tender, indurated
- Vancomycin administered
- HD 8: BC isolate = MSSA; f/u BC sterile

Management Issues

- What is the risk of a poor outcome?
- What antibiotic should be used?
- What is the duration of therapy?

What is the risk of a poor outcome?

Complications in catheter-associated SAB



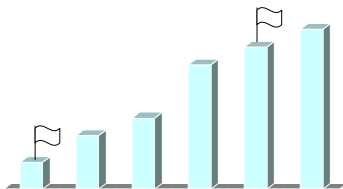
Raad, CID 14:75, 1992; Fowler CID 40:695, 2005; Thomas Int Med J 35:319, 2005

Independent Predictors of Complicated SAB

Predictor	Odds ratio
Positive f/u blood culture	5.6
Community onset	3.1
Persistent fever @ 72h	2.2
Skin lesions	2.0

Fowler, Arch Intern Med 163:2066, 2003

What is the risk of a poor outcome?



1 point each for skin findings, fever > 72h, community onset
4 points for positive blood culture @ 48-96h

Fowler, Arch Intern Med 163:2066, 2003

Predictors of Poor Outcome for *Staphylococcus aureus* Bacteremia

- Septic shock
- Persistent focus of infection
- Secondary focus of infection
- Prolonged bacteremia on therapy (>48-72h)
- Elderly patient (age \geq 60 years)
- MRSA
- Use of vancomycin instead of a β -lactam
- Duration of treatment < 10-14 days

Criteria for Antimicrobial Therapy of *Staphylococcus aureus* Bacteremia

1. Bactericidal activity
2. Non-toxic, well-tolerated
3. Parenteral administration, at least initially
4. Convenient dosing

What antibiotic should be used?

Regimen	Pros	Cons
Nafcillin or oxacillin 2 g q4h IV	Highly effective	Poorly tolerated, inconvenient
Cefazolin 2 g q8h IV	Effective	Inconvenient
Vancomycin 1 g q12h IV	Well tolerated, convenient	Less effective than β -lactams
Dicloxacillin or cephalexin 1 g qid PO	Convenient (oral)	Unknown efficacy, GI side effects, qid dosing

What antibiotic should be used?

	β -lactam (n = 110)	Vancomycin (n = 133)
Cure	84%	62%*
Relapse	4%	20%
Death	6%	12%

Fowler, CID 27:478-86, 1998

What is the duration of therapy?

7-10 or fewer days?

– Associated with high relapse, complication rates

10-14 days?

– Standard recommended duration

4-6 weeks?

– For endocarditis, osteomyelitis, complicated SAB

What was done?

- PICC placed
- Ceftriaxone 2g IV q24h for 14 days
- Home infusion therapy arranged

Case 2

- 27 y/o man with progressive pulmonary cocci and respiratory failure
- History of prior fluconazole
- Admitted to ICU, intubated
- Chest CXR shows extensive inflammatory changes and numerous cavitory lesions
- Sputum culture grow *C. immitis* and rare MRSA, no organisms seen on Gram stain
- Amphotericin B begun and patient slowly improves

Case 2

- On day 12 of therapy, new fevers, oxygenation requirements, which had been improving, plateau
- Sputum Gram stain: oral flora, GPC
- Sputum culture: MRSA
- 2 blood cultures positive for MRSA
- Vancomycin added, troughs of 15 $\mu\text{g/ml}$ achieved

Case 2

- Patient stabilizes for a few days then...
- CXR shows possible progression of infiltrates
- Persistently tachycardic and on pressure support respiratory rate = 35/min
- Requires frequent fluid boluses to maintain blood pressure
- Now what?

What therapy should be initiated?

1. Daptomycin 6 mg/kg IV once daily
2. Add gentamicin + rifampin to vancomycin
3. Add clindamycin to vancomycin
4. Linezolid 600 mg twice daily
5. Daptomycin + linezolid

Linezolid

FDA Approved Indications

- Vancomycin-resistant *E. faecium* infections
- Nosocomial pneumonia (MRSA or MSSA)
- Community-acquired pneumonia
- Skin, skin-structure infections, complicated (MRSA or MSSA) or uncomplicated

Daptomycin: Place in Therapy

- Complicated skin and skin structure infections (4 mg/kg)
- Bacteremia and right-sided endocarditis (6 mg/kg)
- NOT PNEUMONIA: inferior to ceftriaxone in CAP

Best answer....

Linezolid 600 mg twice daily

Case 3

Case 3

- 57 y/o man, fevers, aching all over
- Exam
 - VS: 39.5, 130/70, 140, 18
 - 2/6 systolic murmur
 - Tender, 1 cm hemorrhagic lesions both great toes
- Labs:
 - WBC = 22,000, remainder unremarkable
 - CXR: normal
 - Blood cultures pending
- RX: Vancomycin + ceftriaxone

Hospital Course

Day	Tmax	BC	Vanco MIC	Management Questions 1. Would you change antibiotics? 2. If so, to what? 3. And if so, when?
1	39.5	1/1 +	1	
2	38.3	4/4 +	2	
3	39.8	1/2 +	0.5	
4	39.2	4/4 +	2	
5	38.4	1/2 +	1	
8	37.1	2/2 +	0.5	

Choose the answer that best indicates what you would do.

1. Continue vancomycin as a single agent.
2. Add gentamicin to vancomycin on day 5 or 7.
3. Add rifampin to vancomycin on day 5 or 7.
4. D/C vanco, switch to alternative on day 8.
5. D/c vanco, switch to alternative on day 5.

Management Issues

- What is the appropriate dosing for vancomycin?
- Is this a vancomycin failure?
- What is the reason for failure?
- How does the MIC affect the decision?
- At what point in therapy should one consider changing therapy?

What is Persistent SAB?

Duration of Positive Blood Cultures on Therapy

Study	Regimen	MSSA*	MRSA*
Korzenowski, 1982**	Naf	3	--
	Naf + gent	2	--
Levine, 1991**	Vanco	--	7
	Vanco + rif	--	9
Fowler, 2006**	Vanco or naf + 4d gent	3	9
	Daptomycin	4	8
Khatib, 2006	Beta-lactam, vanco	3	4
Neuner, 2010	Vanco	--	2

*Median or mean duration of positive blood cultures in days
**Endocarditis

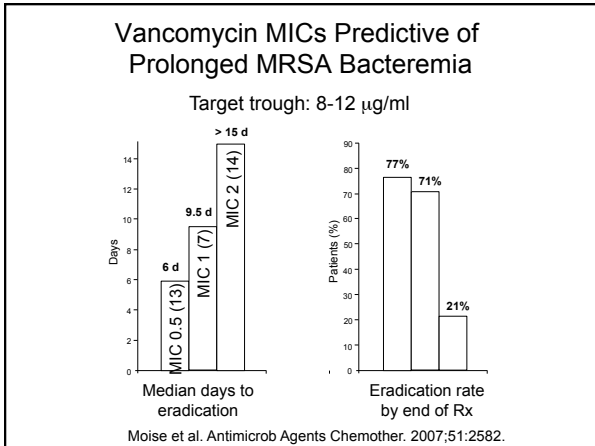
Persistent Bacteremia: Risk Factors

Study	Khatib ScanJID 2006	Hawkins Arch IM 2007	Neuner DMID 2010	Yoon JAC 2010
Design, N	Cohort 245	Case-control 236	Cohort 196	Case-control 63
Scope	MSSA, MRSA	MSSA, MRSA	MRSA	MRSA
Persistence	> 3d	>7d v < 3d	> 5d	>7d v <3d
Predictors	•Endovascular source •Cardiac prosthesis •Metastatic foci •DM •Vancomycin	• Endocarditis •CVC/foreign body •Metastatic foci •MRSA •Renal failure	•Endocarditis •Metastatic foci •Septic shock •Vanco MIC = 2 (6/120 v 12/76)	•Retained device •Metastatic foci •Vanco MIC = 2 (4/32 v 14/31)
Not predictors	Fever, MRSA		Vanco trough, AUC, AUC/MIC	Vanco trough

Vancomycin MIC Breakpoints in *S. aureus*

	Old	New
Susceptible	≤ 4	≤ 2
Intermediate	8-16	4-8
Resistant	≥ 32	≥ 16

Clinical and Laboratory Standards Institute January 2006.



Guidelines

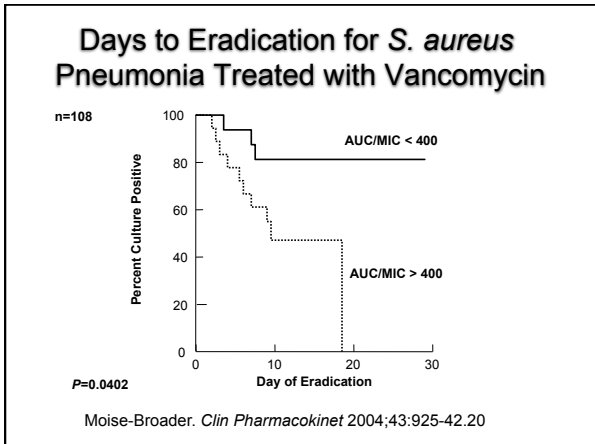
ATS: Am J Resp Crit Care Med. 2004;171;338-416.

American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA WAS APPROVED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2004 AND THE IDSA GUIDELINE COMMITTEE, OCTOBER 2004

- Vancomycin 15 mg/kg q12h
- Recommended trough: 15-20 µg/ml
 - No data offered to support that 15 mg/kg will achieve troughs 15-20 µg/ml or that higher troughs will improve performance

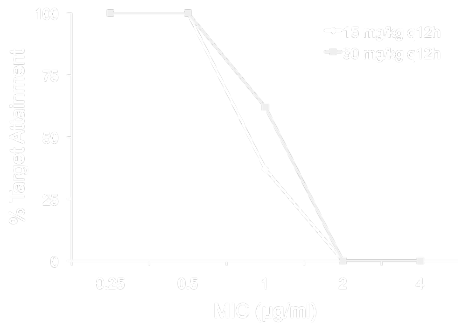


MIC and Probability to Obtain Target Attainment

1. Trough $\sim 10 \mu\text{g/ml}$
15 mg/kg q 12 h, 70 kg individual, nl RF
 $\text{AUC}_{24} = 318 \pm 111 \mu\text{g}/24\text{h/ml}$
2. Trough $\sim 20 \mu\text{g/ml}$
30 mg/kg q 12 h, 70 kg individual, nl RF
 $\text{AUC}_{24} = 418 \pm 152 \mu\text{g}/24\text{h/ml}$

Jeffries MN et al. *Critical Care Med.* 2006;130:947
Mohr J & Murray B. *Clin Infect Dis.* 2007 44:1536

MIC and Probability of Target Attainment



Limitations of Current MIC Methods

- Compared to CLSI reference broth microdilution, Etest yields one dilution higher vancomycin MIC
 - Etest: MIC of $2 \mu\text{g/ml}$ reported in 20-37% of isolates
 - Microdilution: MIC of $2 \mu\text{g/ml}$ reported in 3% of isolates
- MRSA USA300 (reference microdilution MIC = $1 \mu\text{g/ml}$) sent to > 2000 laboratories as the CAP challenge organism:
 - Microscan and BD Phoenix: Majority MIC = $2 \mu\text{g/ml}$
 - Vitek: Majority MIC as ≤ 0.5 or $2 \mu\text{g/ml}$
 - Vitek 2: Most accurate method, majority MIC = $1 \mu\text{g/ml}$
- No commercially available methods detect hVISA

Prakash V AAC 2008; Personal communication, Ronald Jones

How Should the Vancomycin MIC Be Used to Guide Therapy?

- An alternative to vancomycin is recommended for the treatment of isolates with a vancomycin MIC $> 2 \mu\text{g/mL}$ (e.g., VISA, VRSA)
- Due to the limitations of susceptibility testing, clinical and microbiologic correlation with MIC results is recommended if MIC ≤ 2

Management of Persistent MRSA Bacteremia on Vancomycin Therapy

- Median time to clearance of MRSA bacteremia is 7-9 days
- Persistent bacteremia around day 7 of therapy should prompt assessment to determine if a change in therapy is indicated:
 - Search for and remove other foci of infection
 - Evaluate clinical response
 - Assess micro data (vanco MIC, results of f/u bld cx)

Consider change if:

- 1) Unsatisfactory clinical response, regardless of MIC or
- 2) Vanco MIC = 2



No change if:

- 1) Clinically responding *and*
- 2) Vanco MIC < 2

1 2 3 4 5 6 7 8 9 10 11 12 13
Day of vancomycin therapy

Vancomycin Alternatives

- Trimethoprim-sulfamethoxazole
- Quinupristin/dalfopristin (Synercid™)
- Linezolid (Zyvox™)
- Daptomycin (Cubicin™)
- Tigecycline (Tygacil™)
- Telavancin (Vibativ™)
- Ceftaroline (Teflaro™)

Additives

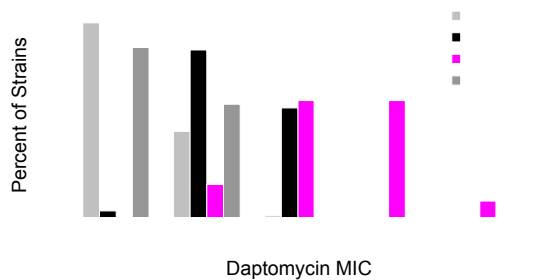
- Rifampin
- Gentamicin
- Beta-lactams
- TMP-SMX
- Linezolid, daptomycin, quinupristin/dalfopristin

What ID Consultants Would Do for Persistent MRSA Bacteremia

	MIC = 2 μ g/ml 441 respondents	MIC = 4 μ g/ml 439 respondents
Continue vanco only	39 (9%)	8 (2%)
Continue vanco, add...	319 (72%)	127 (29%)
Gent	154	56
Rif	242	86
Lz, Dapto, or Q/D	38	47
D/C vanco, start...	83 (19%)	304 (69%)
Dapto	54	172
Linezolid	46	159
Q/D	9	20

Hageman CID 43:e42, 2006

Daptomycin MIC Distribution for Vancomycin Non-Susceptible Strains



Data on file. Cubist Pharmaceuticals; Sader, Antimicrob Agents Chemother. 2006;50:2330.

Do we have the right dose for daptomycin?

- Dose was chosen based on concerns for toxicity, not guarantee of efficacy
- Daptomycin has concentration dependent killing
- Higher dose may provide protection against emergence of resistance
- IDSA guidelines committee recommends that if daptomycin is used for treatment failure, it be used at a dose of 10 mg/kg/d

Telavancin

- Vancomycin derivative
- Active in vitro and in animal models against vancomycin non-susceptible strains (VISA, not VRSA)
- FDA approved at a dose of 10 mg/kg/d for treatment of complicated SSTI

Anti-MRSA Beta-lactams

	Ceftaroline	Ceftobiprole
Prodrug	fosamil	medocaril
PBP 2a IC50	1 µg/ml	0.5 µg/ml
MRSA MIC90	2 µg/ml	2 µg/ml
MSSA MIC90	0.25 µg/ml	0.5 µg/ml
Beta-lactamase susceptibility profile	ESBLs, carbapenemases, ampC	ESBLs, carbapenemases, ampC

Zhanel, et al. Drugs 2009; 69: 809; Vidailiac & Rybak, Pharmacother. 2009;29:511

Vancomycin or Linezolid Combinations

Regimen	Organism	Model	Key Results
Vanco + gent ¹	MRSA	In vitro, animals, humans	Toxic, efficacy not improved
Vanco + rif	MRSA	In vitro, animals, humans	Antagonistic in vitro, prolongs bacteremia in endo; benefit in osteo, foreign body infection, VAP?
Vanco + naf ¹	MRSA-VISA	Rabbit endo	Efficacy ↑
Linezolid + erta ²	MRSA	Rabbit endo	Efficacy ↑

¹Climo AAC 1992; ²Jacquiline AAC 2006

Daptomycin

Regimen	Organism	Model	Key Findings
Hi dose dapto ¹	Dapto NS MRSA	Rabbit endo	Hi dose > standard dose dapto
Hi dose dapto ²	MRSA	Rat, tissue cage	Hi dose > standard dose dapto
Dapto + rif ²	MRSA	Rat, tissue cage	Dapto + rif > Dapto
Dapto + rif ³	MRSA	Rabbit endo	Dapto + rif antagonistic; efficacy not ↑
Dapto + rif ⁴	MRSA	Fibrin clot	Rif antagonistic, efficacy not ↑; dapto > vanco

¹Moore AAC 2003; ²Garrigos AAC 2010; ³Miro AAC, 2009; ⁴LaPlante AAC 2009

Daptomycin

Regimen	Organism	Model	Key Findings
Dapto + gent ¹	MRSA	Fibrin clot	Efficacy not ↑
Dapto + gent ²	MRSA	Rabbit endo	Efficacy not ↑
Dapto + cefepime ³	Dapto NS MRSA	Fibrin clot	Efficacy variable
Dapto + linezolid ³	Dapto NS MRSA	Fibrin clot	Efficacy variable
Dapto + TMP-SMX ³	Dapto NS MRSA	Fibrin clot	Efficacy ↑
Dapto + naf ³	Dapto NS MRSA	Fibrin clot	Efficacy variable
Dapto + oxa ⁴	Dapto NS MRSA	Rabbit endo	Efficacy ↑

¹LaPlante AAC 2009; ²Miro AAC, 2009; ³Steed AAC 2010; ⁴Yang AAC 2010

Vancomycin vs TMP-SMX
Matched Case-control Study of SAB

	TMP-SMX (n=38)	Vancomycin (n=76)
Length of stay (d)	21.5	25
Persistent + BC	2 (5%)	5 (7%)
Relapses	1 (3%)	9 (12%)
30 d mortality	13 (34%)	31 (41%)

Goldberg JAC 2010

Linezolid Salvage for Persistent Bacteremia

Strategy	Attempts (N)	% Neg BC @ 72h	Success
Add rif or gent to vanco	12	2 (17%)	0
Switch to linezolid	16	12 (75%)	14 (88%)

Jang CID 2009

Linezolid Salvage for Persistent SAB

Primary Regimen	Salvage success	Mortality	Days + BC	Vanco levels	MIC = 2
Vanco	0/12	10/19	12 ± 4	16 ± 19	N=1
Vanco only		6/14	12 ± 4		
+ rif ± gent		4/5	17 ± 3		
Linezolid	14/16	4/16	26 ± 39	19 ± 5	N=2
Linezolid only		2/7	33 ± 55		
+ penem		2/9	20 ± 10		

Jang CID 2009

Vanco levels (± s.d.) and MIC in µg/ml; days and vanco levels are mean + s.d.

Case Reports of Salvage Therapy for SAB

- **Daptomycin + rifampin** (Ahmed Ann Pharmacother 2010)
 - 19 days of MRSA bacteremia (occult, post-cystoscopy)
 - Vnco 10 d, Dapto 9 d, emergence of dapto NS isolate (MIC =2)
 - Resolution with addition of rifampin
- **Linezolid + rifampin** (Schwalm Can JID 2004)
 - Vanco + rif failure (bone and joint)
- **Telavancin**
 - 15 days of bacteremia, emergence of VISA (Marcos AAC 2010)
 - Pacemaker, epidural abscess, initial vanco MIC = 2
 - Daptomycin failure, emergence of dapto NS isolate (MIC=2)
 - 8 days of bacteremia, MRSA (Nace JAC 2010)
 - TCV endocarditis
 - Negative blood cultures after 1 day of telavancin

Treatment of Bacteremia and Other Serious Staph Infections

- Use a beta-lactam for MSSA infections whenever possible
- Vancomycin has issues....
 - High clinical and microbiological failure rate (25-50%)
 - May be nephrotoxic at the higher doses required to achieve recommended troughs of 15-20 µg/ml (Lodise, AAC 52:1330, 2008)
- No alternative agents(s) has been shown to be superior to vancomycin alone
 - In fact, they have been found to be "not inferior"

Summary

- Define and eliminate source of bacteremia
- Document clearance of bacteremia with follow-up blood cultures
- Use of vancomycin for MRSA
 - Few data supporting utility of drug combinations
 - Precisely define the vancomycin MIC
 - Maintain vancomycin troughs of 15-20 µg/ml
 - Treatment failures are common
- Switch to alternative agents in non-responders
 - Do not "add on" to vancomycin, switch
 - Use a drug combination whenever possible
 - If daptomycin is used
 - Check daptomycin MIC
 - Dose daptomycin at 10 mg/kg and in combination
 - Role of newer agents unknown

Hospital Course

Day	Tmax	BC	Vanco MIC	Other info
1	39.5	1/1 +	1	Vanco started
2	38.3	4/4 +	2	TEE = AV veg
3	39.8	1/2 +	0.5	Vanco _T = 20 µg/ml
4	39.2	4/4 +	2	Stable
5	38.4	1/2 +	1	Δ to dapto 10 mg/kg + gent 3 mg/kg/d
8	37.1	2/2+	1	Stable
10	37.1	2/2 -	n/a	Stable
