Staphylococcal Disease

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Coagulase-negative staphyloccci
(S. epidermidis)

- Commensal, not invasive, rarely disseminates
- Rarely pathogenic in normals
- Spectrum of disease
  - Catheter-associated bacteremia
  - Prosthetic device (joint, valve), pacemaker, device-related infections
  - Neonatal sepsis
- Virulence factors
  - Biofilm (ica locus, among others)
  - Multiple drug resistant (reservoir for S. aureus)

Staphylococcus lugdunensis

- Coagulase negative
  - Actually “free” coagulase negative (negative tube coagulase test)
  - May produce bound coagulase (positive slide coagulase test)
- Spectrum of disease: virulent, aggressive
  - Bacteremia, NV and PV endocarditis
  - Bone and joint infection
  - Pacemaker, other device-related infections
- Susceptible to many antibiotics (rare mecA positive)

Types of S. aureus Diseases

- Carriage (not a disease, normal flora)
  - 30% rate
  - Transmission by direct contact
  - Prevented by good hand washing
- Spectrum of disease
  - Local infection: abscess, cellulitis, folliculitis, impetigo
  - Toxin-mediated disease
    - Staphylococcal food poisoning (preformed toxin, not an infection)
    - Toxic shock syndrome
    - Bullous impetigo, scalded skin syndrome
  - Invasive infection, sepsis: bacteremia, endocarditis, osteomyelitis, septic arthritis, pneumonia, complicated skin/soft tissue infections
Case 1

Mr. B is a 21 college student and varsity basketball player. He presents to you with an exquisitely painful raised 5 cm lesion which is fluctuant in the center and surrounded by erythema extending 5 cm beyond the raised lesion. He is otherwise healthy. He is afebrile and other vital signs are normal. What is the best single answer?

1. Perform incision and drainage.
2. Perform incision and drainage and start cephalexin.
3. Perform incision and drainage and start TMP-SMX + cephalexin.
4. Perform incision and drainage and start linezolid.
5. Perform incision and drainage and administer a dose of vancomycin.

Most Common CA-MRSA Skin Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
<td>59%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>42%</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>7%</td>
</tr>
<tr>
<td>Impetigo</td>
<td>3%</td>
</tr>
</tbody>
</table>

Rare cause of necrotizing fasciitis

Fridkin, et al, NEJM 2005;352:1436

Abscess, Cellulitis

Abscess

“Spider Bite” Lesion/ Cellulitis
Role of MRSA
Data for Community-Onset SSTIs

Virtually all USA300 (Clin Infect Dis 53:144, 2011)

Summary

- Get a culture if antibiotics are prescribed
- Incision and drainage for abscesses is probably sufficient in most cases, especially in OP therapy
  - Use of an antibiotic to which the isolate is susceptible may provide a marginal benefit in a minority of cases
- Cellulitis is tricky…if purulent drainage, likely S. aureus (treat with antibiotics)

Agents of Choice for SSTIs

- Trimethoprim-sulfamethoxazole (~90% “S”)
  - 1 or 2 DS bid (no difference except in obesity
  - Caveat: activity against GAS not proven
- Doxycycline (minocycline) (~90% “S”)
  - 100 mg bid
  - Caveat: susceptibility of GAS unknown
- Clindamycin (~90% “S”)
  - 300 mg tid
  - Caveat: constitutive and inducible resistance (D-test)
- Vancomycin, linezolid, daptomycin, telavancin, ceftaroline
  - Therapeutically equivalent, differing principally in cost
  - Overkill except for more severe SSTIs

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Invasive Infection
(Bacteremia in 75%)

What about MRSA?
Data for community-onset BSIs, US Military Healthcare System
(JAMA 308:50, 2012)

Case 2
38 y/o man, new CHF, alcoholic cardiomyopathy, Hct = 13. He is transfused and on hospital day 3 an upper + lower endoscopy performed. Post-procedure T = 38°C. The site of the previous IV, d/c’d post-procedure is tender and red. Two peripheral blood cultures are drawn and vancomycin is begun empirically. The next day he is afebrile and 1 blood culture is growing GPC in clusters.

Case 2 – Scenario 1
Assume that the blood culture is positive for coagulase-negative staph, methicillin-susceptible.
1. Not trust the results and treat with vancomycin and treat for 7-10 days.
2. Believe the results and treat with cefazolin for 7-10 days.
3. Discharge the patient and treat orally with cephalaxin for 7-10 days.
4. Stop the vancomycin and discharge the patient with no further therapy.
Case 2 – Scenario 2

Assume that the blood culture is positive for S. aureus, methicillin-susceptible. You would
1. D/c vancomycin and discharge the patient.
2. Continue vancomycin for 14 days.
3. D/c vancomycin, treat with cefazolin for 7 days.
4. D/c vancomycin, treat with cephalaxin for 10 days.
5. D/c vancomycin, treat with cefazolin for 14 days

Case 3

Mr. Q is a 27 y/o AIDS patient admitted 10 days ago for cryptococcal meningitis. A PICC was placed and liposomal amphotericin was begun. 5 days ago two blood cultures were drawn, one from a peripheral vein and the other from the PICC, for a temperature of 38°C. Vancomycin was started empirically. The peripheral blood culture has no growth but the PICC culture grew MRSA after 2 days. The patient had only the one fever. You are asked how long to treat the patient. Your recommendation is to
1. Complete a 7 day course of therapy
2. Complete a 14 days course of therapy
3. Complete a 28 day course of therapy
4. Discontinue the vancomycin

Diagnosis of Intravenous Catheter-Related BSI

• No broth cultures of tip, no “routine” cultures
• Dx of catheter-related infection requires a positive peripheral blood culture PLUS
  – Semi-quantitative roll-plate tip culture with > 15 cfu/5 mm segment (i.e., colonization) OR
  – Paired blood culture drawn through the line
    • Differential time to positivity of 2 h (catheter first) OR
    • Quantitative blood cultures: CFU (catheter) is ≥ 3x greater than CFU (peripheral venous blood)

Interpreting Blood Culture Results

• Coagulase-negative staph
  – Most common blood culture isolate (~40%)
  – Only 10-15% represent true bacteremia
• Staphylococcus aureus
  – Second most common isolate (~15%)
  – 93% represent true blood stream infection
• Other organisms with high contamination rates
  – Viridans strep (55%)
  – Corynebacterium (88%)
  – Bacillus, Micrococcus, Propionibacterium species (all > 90%)
Criteria for True BSI with CoNS

- Signs or symptoms of infection
- Two or more positive blood cultures
- Positive cath tip roll plate culture + positive blood culture
- Positive paired blood cultures through catheter and peripheral vein
  - Cath cfu > 3 x blood cfu
  - Cath culture positive 2 h before peripheral blood culture

Criteria for True BSI with CoNS (Gold standard of identical genotypes (74 of 101 cases))

- Single positive culture should be presumed to be a contaminant
- Two or more positive blood cultures plus
  1. Positive w/in 48h, temp > 38, chills, hypotension
     Sens = 91%, Spec = 11%, NPV = 30%
  2. No. 1 + identical antibiograms
     Sens = 76%, Spec = 26%, NPV = 27%
  3. No. 1 + identical species
     Sens = 91%, Spec = 52%, NPV = 67%
  4. Identical species
     Sens = 100%, Spec = 48%, NPV = 100%

Therapy of True CoNS BSI

- Antibiotic
  - MRCS: vancomycin 15 mg/kg q12h
  - MSCS: beta-lactam
- Duration
  - No therapy: line out, no hardware, intravascular device, pre-treatment blood cultures negative
  - 3-5 days or 5-7 days: line out
  - 10-14 days: line in and in combo with lock therapy

Vancomycin vs. Beta-Lactams

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens compared</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler, et al (Clin Infect Dis 27:478, 1998)</td>
<td>Vanco vs beta-lactam</td>
<td><strong>Lower cure rate (62% vs 84%) with vanco</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Higher death rate (12% vs 6%) with vanco</strong></td>
</tr>
<tr>
<td>Schweizer, et al (BMC Infect Dis 11:279, 2011)</td>
<td>30 mortality with MSSA for: 1. Naf or cefazolin vs 2. Vanco + naf or cefazolin vs 3. Vanco</td>
<td><strong>Lowest mortality for 1 vs 2 vs 3 (3% vs. 7% vs 20%)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Naf vs vanco: adjusted HR=0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Switch to naf after vanco stay on vanco: adjusted HR=0.31</td>
</tr>
</tbody>
</table>
### Cefazolin vs. Nafcillin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cefazolin (n=41)</th>
<th>Nafcillin (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days resolution of fever (mean ± sd)</td>
<td>4.1 ± 3.8</td>
<td>5.4 ± 9.5</td>
<td>NS</td>
</tr>
<tr>
<td>Death or clinical failure @ 4 wk (n)</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Death or clinical failure @ 12 wk (n)</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Relapse @ 12 wk</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Death @ 12 wk</td>
<td>1</td>
<td>5</td>
<td>0.22</td>
</tr>
<tr>
<td>Rx stopped for adverse drug event</td>
<td>0</td>
<td>7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Predictors of Complicated *Staphylococcus aureus* Bacteremia
- Community-onset
- Septic shock
- Persistent or secondary focus of infection
- Prolonged bacteremia on therapy (>48-72h)
- Fever > 3 days on therapy
- Elderly patient (age ≥ 60 years)
- MRSA
- Use of vancomycin instead of a β-lactam
- Duration of treatment < 10-14 days

### Duration of Therapy: *S. aureus* Bacteremia

<table>
<thead>
<tr>
<th>Duration</th>
<th>Indications</th>
</tr>
</thead>
</table>
| 14 days  | • Fever resolves by day 3  
• Sterile blood culture after 2-3 days  
• Easily removed focus of infection  
• No metastatic infection (e.g., osteo)  
• Negative echo, no evidence of endocarditis  
• No predisposing valvular abnormalities  
• No implanted prosthetic devices  
• (No DM, immunosuppression) |
| 4-6 weeks| • Failure to meet one or more of above criteria  
• Osteomyelitis, endocarditis, epidural abscess, septic arthritis (3 wk), pneumonia (3-4 wk), complicated UTI |

### Case 2 – Scenario 1

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Case 3
Mr. Q is a 27 y/o AIDS patient admitted 10 days ago for cryptococcal meningitis. A PICC was placed and liposomal amphotericin was begun. 5 days ago two blood cultures were drawn, one from a peripheral vein and the other from the PICC, for a temperature of 38°C. Vancomycin was started empirically. The peripheral blood culture has no growth but the PICC culture grew MRSA after 2 days. The patient had only the one fever. You are asked how long to treat the patient. Your recommendation is to
1. Complete a 7 day course of therapy
2. Complete a 14 days course of therapy
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4. Discontinue the vancomycin

Case 4
Mr. Q is a 53 year old diabetic. He was hospitalized four weeks ago for hyperosmolar coma and was readmitted a week ago for fevers to 39°C. A CT scan showed findings consistent with a 4 cm psoas abscess. Three blood cultures were drawn and empirical therapy begun with vancomycin and piperacillin-tazobactam. All three blood cultures grew MRSA with a vancomycin MIC of 2 by microbroth dilution. TEE is negative. Treatment was de-escalated to vancomycin alone with documented trough concentration of 15 µg/ml. One of two blood cultures obtained on day 5 of therapy now is reported as positive for Gram-positive cocci in clusters. Which of the following is the most likely explanation for the persistently positive blood culture?
1. Vancomycin resistance MRSA strain
2. Treatment failure due to the MIC = 2
3. Undrained psoas abscess
4. Subtherapeutic levels of vancomycin
5. Contamination of the blood culture with coag-neg staph

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?
Recommended Vancomycin Dosing

- For serious infections (pneumonia, bacteremia)
  - 15-20 mg/kg IV q8-12h (loading dose of 25-30 mg/kg)
  - Target trough concentrations of 15-20 µg/ml; target AUC₂₄/MIC = 400 (or > 211?)
  - Adjust for renal function, actual body weight
- For less serious infections (SSTI):
  - 15 mg/kg q12h (1 gm q12h)
  - Routine measurement of trough not necessary


Vancomycin MIC Breakpoints in S. aureus

<table>
<thead>
<tr>
<th></th>
<th>Old</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>&lt; 4</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8-16</td>
<td>4-8</td>
</tr>
<tr>
<td>Resistant</td>
<td>≥ 32</td>
<td>≥ 16</td>
</tr>
</tbody>
</table>

Clinical and Laboratory Standards Institute January 2006.

Vancomycin MICs by Method

- Definitions vary: >3d or >5d or >7d
- What factors are consistently identified as being correlated?
  - Endocarditis, endovascular source
  - Metastatic infection
  - Retained catheter or foreign body
  - Use of vancomycin instead of β-lactam for MSSA
- Controversy over vancomycin MIC > 1 µg/ml (E-test)


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 µg/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)

### Day of vancomycin therapy

<table>
<thead>
<tr>
<th>Day</th>
<th>Consider change if:</th>
<th>No change if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1) Unsatisfactory clinical response, regardless of MIC &lt; 2</td>
<td>1) Clinically responding and 2) Vanco MIC &lt; 2</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2) Vanco MIC = 2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
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<td>7</td>
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<td>11</td>
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<tr>
<td>12</td>
<td></td>
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<tr>
<td>13</td>
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</tr>
</tbody>
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Vancomycin Alternatives with MRSA Activity

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>FDA approved for MRSA pneumonia, SSTI</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Contraindicated for pneumonia</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>CAP indication only (not MRSA or MSSA)*</td>
</tr>
<tr>
<td>Telavancin</td>
<td>No CAP, HAP, or VAP indication</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>CAP indication only (not MRSA)</td>
</tr>
<tr>
<td>Quinupristin-dalfopristin</td>
<td>Not FDA approved for MRSA</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>Not FDA approved for MRSA, inferior to vancomycin for MSSA bacteremia*</td>
</tr>
</tbody>
</table>

* Meta-analysis of RCT's, non-inferiority design, found 0% excess mortality and 2% excess non-cure rates with tigecycline vs comparators (Clin Infect 54:1699, 2012)
Additives

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

Possible Combinations

- Approx 80 to 100 possible combinations
  - 21 two-drug combos among primary alternatives (28 if vanco included)
  - 14 two-drug combos with rifampin or gentamicin (16 if vanco included)
  - 49 three-drug rif + gent combos (57 if vanco included)
  - 3 beta-lactam two-drug combos (+ vanco, + dapto, or + linezolid) (at least)
- Data-free zone!!

Linezolid

Linezolid Salvage for Persistent Bacteremia

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Attempts (N)</th>
<th>% Neg BC @ 72h</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add rif or gent to vanco</td>
<td>12</td>
<td>2 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>Switch to linezolid</td>
<td>16</td>
<td>12 (75%)</td>
<td>14 (88%)</td>
</tr>
</tbody>
</table>
### VISA and VRSA MICs (µg/ml)

<table>
<thead>
<tr>
<th></th>
<th>VISA (n=33)</th>
<th>VRSA (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>% NS</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4-8</td>
<td>100</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>1-8</td>
<td>70</td>
</tr>
<tr>
<td>Telavancin</td>
<td>0.25-1</td>
<td>0</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>0.25-2</td>
<td>15</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.5-4</td>
<td>0</td>
</tr>
</tbody>
</table>

### Daptomycin vs Vancomycin for BSI Due to MRSA with High Vancomycin MICs

- Retrospective, case control
  - MRSA with E-test MICs > 1.5 µg/ml
  - 118 vanco cases, 59 dapto cases
  - Vanco trough target 10-20 µg/ml
  - Dapto dose 6-12 mg/kg per 24h
  - 58/59 dapto-treated subjects switched
  - 91% of whom were on vanco
  - Mean time to switch 5 days (60% "not improving, 48% with positive blood cultures)

* Clin Infect Dis 54:51, 2012

### Clinical Failure

<table>
<thead>
<tr>
<th></th>
<th>Vanco*</th>
<th>Dapto</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical failure</td>
<td>37/118</td>
<td>10/59</td>
<td>0.084</td>
</tr>
<tr>
<td>60-day mortality</td>
<td>24/118</td>
<td>5/59</td>
<td>0.046</td>
</tr>
<tr>
<td>Failure, MIC 1.5</td>
<td>31/102</td>
<td>6/25</td>
<td>0.530</td>
</tr>
<tr>
<td>Failure, MIC 2</td>
<td>6/16</td>
<td>4/34</td>
<td>0.065</td>
</tr>
</tbody>
</table>

* Vanco was an independent predictor of failure by logistic regression with adjusted OR = 3.13 (95% CI 1.00-9.76)

§ Composite endpoint of 60-day mortality, microbiological failure, relapse

* Clin Infect Dis 54:51, 2012
**Daptomycin Beta-Lactam Combination**

- Seven cases of relapse (n=2) and/or persistent bacteremia (7-22d)
  - 1 endocarditis, 1 cSSSI, 5 unknown
- Prior regimens
  - 7 vanco, 5 dapto, 5 dapto+gent
- Dapto 8-10 mg/kg + Naf or Ox 12 g/day
  - Negative BC @ 24-48h
  - 2 relapsed (1 death)
  - 3 rising dapto MIC (MIC > 1 in 2 cases)

*Clin Infect Dis 53:158, 2011*

**Telavancin Salvage Therapy for MRSA Endocarditis**

- MV endocarditis, L4-L5 abscess, vanco MIC = 2 (MBD)\(^1\)
  - Day 3: Daptomycin 4-6 mg/kg/d
  - Day 12: Positive blood culture (vanco MIC = 2, dapto MIC =4)
  - Day 16: switch to linezolid day 16 with culture conversion on day 19; valve repaired day 19 (cultures?)
  - Day 38: Linezolid stopped due to toxicity, switch to telavancin 10 mg/kg
- TCV endocarditis, 8 days of bacteremia on vanco (MIC < 0.5)\(^2\)
  - Negative blood cultures after 1 day of telavancin 10 mg/kg
- Pacemaker infection, vanco MIC = 2 (MBD)\(^3\)
  - Early switch to dapto 8-10 mg/kg, pacer removed day 6
  - Day 10: blood culture sterile for the first time
  - Day 15: blood culture positive (vanco MIC = 4, dapto MIC = 2), epidural abscess found
  - Day 18: dapto stopped, telavancin 10 mg/kg started
  - Day 19: blood culture and intraop laminectomy cultures sterile

Ceftaroline Salvage Therapy
MRSA Bacteremia

- 6 patients, case series, UT San Antonio
  - 3 endocarditis
  - 1 UTI; 1 uveitis, ethmoid osteo; 1 septic thrombophlebitis
- Duration of + BC: 11 + 4 days (2-15 days)
- Vanco MICs (µg/ml): 1.5, 1.5, 2, 2, 2, 4
- Dose 600 mg q8h
- Time to clearance: 48h in 4 cases, 5 d in one
- 1 death (GI bleed)


Ceftaroline Salvage Therapy
MRSA Invasive Disease

- 10 patients, case series, San Diego
  - 5 endocarditis
  - 2 pneumonia (neg BC)
  - 3 bone and joint (1 bacteremia)
- Duration of + BC pre-ceftaroline: 5-19
- Vanco MICs (µg/ml): 0.5 (2); 1(4); 2 (4, 1 by E-test)
- Dose 600 mg q8h
- Time to BC clearance with ceftraoline: 2-7 days
- Cures: 7/10 micro, 6/10 clinical
  - Failures: AICD, PJI, pneumonia (comfort care)

J Infect Chemother July 14, 2012

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 agent(s) has been shown to be superior to vancomycin alone
  - In fact, they have been found to be "not inferior"

Summary

- Source control is key!
- Switch (not add) if vancomycin is not working
  - Linezolid probably the least effective
  - Emergence of resistance and VISA cross-resistance are concerns with daptomycin
  - Telavancin and ceftaroline appear promising
- Areas for future study
  - Vancomycin MICs and what they mean
  - Combination therapies
  - RCT of bacteremia and endocarditis