Management of severe staphylococcal infections

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BSAC April 7th 2009

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Objectives

- Mortality related to MSSA and MRSA infections
- Glycopeptides for MSSA infections
- Limitations of glycopeptides for MRSA
- Clinical management
- Serious [High mortality and/or complications] MRSA infections and their management: pneumonia (nosocomial/VAP and community PVL) & bacteraemia
Comparison of Mortality Associated with MRSA versus MSSA Bacteremia [Meta-Analysis]

Methicillin Resistance Impact on Mortality in S. aureus VAP

Athanassa et al. Eur Respir J 2008; 31:625-32
Vancomycin Treatment of MSSA

Vanc vs B-lactam for MSSA

- Time-kill assays vancomycin kills *S. aureus* more slowly than beta-lactam antibiotics
- Vancomycin treatment of R-sided endocarditis is assoc with failure in 15% - 33% vs. 5% for nafcillin
- Bacteremia lasts a median of 7-9 days with vancomycin treatment vs. 3-5 days with nafcillin

Outcome of vancomycin treatment in patients with MSSA bacteremia
Kim SH et al AAC2008; 52(1): 192-197

- Retrospective cohort study using a propensity score to adjust for confounding by treatment assignment
  - Mortality V=37% v BL=18% (p<0.02)
  - OR 3.3 (95% 1.2-9.5)
- Matched case control study 1:2 (case:control)
  - V (case) against BL (control) for MSSA-B depending on objective matched score and propensity score
  - Mortality V=37% v BL=11% (p<0.01)

Beta-lactam is inferior to Vancomycin in the treatment of MSSA-B
Vancomycin may be sub-optimal for MSSA infection

Sub-analysis of mortality in staphylococcal bacteraemic pneumonia according to methicillin-resistance and antibiotic treatment

Infection-related mortality (%)

- MRSA: 50
- MSSA: 34
- Vancomycin (8/17): 47
- Cloxacillin (0/10): 0

Vancomycin

- Gold standard for MRSA$^1$
  - Rapid development of penicillin resistance led to increased use of vancomycin
- Less effective than β-lactams against MSSA$^1$
- Moderately bactericidal$^2$
- Susceptibility of *S. aureus* compromised?
  - Resistance
  - MIC creep
  - Tolerance
  - Inadequate dosing

Vancomycin MIC creep detected in single-centre studies

MRSA isolates (n=662) measured in a single US tertiary care institution

Relationship between vancomycin MIC and failure rate for MRSA infection

Comparision of outcomes between high MIC and low (<1.5mg/l) in patients with MRSA bacteraemia Lodise *TP et al AAC 2008; 52(9):3315-3320*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High MIC (n=66%/)</th>
<th>Low MIC (n=26%/)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall failure</td>
<td>24(36.4)</td>
<td>4(15.4)</td>
<td>0.049</td>
</tr>
<tr>
<td>-30d mortality</td>
<td>12(18.2)</td>
<td>3(11.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>-60d recurrence</td>
<td>11(16.7)</td>
<td>1(3.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>LOS after culture (median)</td>
<td>21 (9-43)</td>
<td>10.5(9-16.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Switch to alternative antibiotic</td>
<td>13(19.7)</td>
<td>2(7.7)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Poisson regression V an >1.5  a 2.6 fold increased risk of failure, p = 0.01
## No evidence of vancomycin MIC creep in MRSA over 5 years


<table>
<thead>
<tr>
<th>Year (no.)</th>
<th>% of strains at vancomycin MIC (µg/ml) of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.375</td>
</tr>
<tr>
<td>2002 (342)</td>
<td>2.6</td>
</tr>
<tr>
<td>2003 (365)</td>
<td>1.1</td>
</tr>
<tr>
<td>2004 (347)</td>
<td>2.9</td>
</tr>
<tr>
<td>2005 (380)</td>
<td>2.4</td>
</tr>
<tr>
<td>2006 (366)</td>
<td>1.1</td>
</tr>
</tbody>
</table>

No MIC creep
Holmes RL et al AAC 2008; 52:757-760
Alos JI et al JAC 2008; 63: 773-775
Vancomycin MICs and MRSA Bacteremia

- 414 cases bacteremia

**Mortality**
- Vanco Tx with MIC2=6.39
- Inappropriate Initial Empiric Therapy (IIET)=3.62
- Shock=7.38
- High (incl Pneumo)=3.6 or Intermediate Risk=2.18
- Steroids=1.85
- Ultimately=10.2 or rapidly fatal underlying disease=1.81
- Age=1.02/year

*Soriano, Clin Infect Dis, 2008*
Vancomycin Treatment of MRSA VAP

Rello, CCM 2005;33:1983
Serious MRSA infections

- Pneumonia
  - Nosocomial & VAP
  - Community acquired necrotising pneumonia
- Bacteraemia /endovascular infections
- Soft tissue infection [NOT COVERED]
Mary MacDonald; 64 year old

Admitted for SOB and DOE for the past 4 days. PMH includes heart failure, COPD, and PVD. The patient was reports that he has not taken his frusemide for the past 7 days as he was unable to go to his pharmacy. He was admitted for CHF exacerbation. Prior hospital admission 2m earlier On the third day of his hospitalization, the patient developed respiratory failure and was intubated. 3 days after intubation, the patient developed fevers, an elevated WBC and new CXR infiltrates. Empiric antibiotics were initiated. Tracheal aspirate revealed 4+ MRSA.

What antibiotics would you recommend?
Chemical structures of select antibiotics active against Gram-positive cocci
Antibiotic Choices

• Vancomycin 15 mg/kg IV (trough 15-20mg/l)
• Linezolid 600 mg IV Q12h
• Tigecycline 100 mg IV LD; 50 mg IV Q12h
• Daptomycin 6 mg/kg IV Q24h
• Synercid 7.5 mg/kg IV Q8h
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Reason not to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>None</td>
</tr>
<tr>
<td>Linezolid</td>
<td>None</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Broad agent but would work; equivocal clinical data</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Does not penetrate the lung</td>
</tr>
<tr>
<td>Synercid</td>
<td>Side effects</td>
</tr>
</tbody>
</table>
Clinical Cure Rate in VAP Linezolid Versus Vancomycin

Retrospective analysis of 2 randomized, double-blind studies

VAP, ventilator-associated pneumonia.

Linezolid Survival Benefit?

- **ITT S. aureus (n = 339)**
  - Linezolid (131 alive, 37 dead)
  - Vancomycin (121 alive, 50 dead)
  - \( p = .131 \)

- **ITT MRSA (n = 160)**
  - Linezolid (60 alive, 15 dead)
  - Vancomycin (54 alive, 31 dead)
  - \( p = .025 \)

- The use of subgroup analyses is associated with several difficulties. Post hoc subgroups are not randomized. Nonrandomized data are more likely to reach false-positive conclusions. Randomization controls for unmeasured and unknown factors, as well as for measured factors. While the patient characteristics of the entire population and the MRSA subset appear to be similar, this does not account for other potential unmeasured or unknown factors. The imbalance in treatment groups favoring linezolid therapy in the MRSA subgroup, most notably cardiac disease and diabetes, may influence outcome and survival.

- When the primary end point shows similar efficacy for two drugs but a subgroup analysis shows superiority for one of the drugs, it follows that there also is a subgroup in which the other drug must show an advantage. This translates into higher survival and clinical success rates for therapy with vancomycin compared with linezolid in patients with MSSA. One could question the biological plausibility of this discrepancy, as the in vitro activity of both drugs is similar between MRSA and MSSA.

- The results support the conclusion that the efficacy of linezolid and vancomycin are similar in patients with NP. Post hoc subgroup analyses can raise hypotheses that require confirmation in other studies before general acceptance. Meanwhile, clinicians should exercise care in drawing conclusions based on subgroup analyses alone.

Nosocomial pneumonia with suspected or proven MRSA (ZEPHYR)  
NCT00084266 (ClinicalTrials.gov)

• Recruiting September 2008
• Treatment, double blind, RCT
• Primary end-point is clinical efficacy
• Secondary endpoint is bacteriological efficacy
Early microbiological response to linezolid versus vancomycin in VAP due to MRSA
Wunderink R et al Chest on line August 21, 2008

• Prospective, open labelled, multi-center trial compared the early microbiological efficacy of linezolid with that of vancomycin in patients with BAL proven MRSA VAP
• Primary outcome was microbiological response based on second BAL performed 72-96h post treatment
• Secondary outcome was healthcare resource utilisation
• Low patient numbers- target enrolment of 300 patients not achieved due to requirement of 2 BAL’s
### Linezolid bacteriological response and resource use in MRSA VAP

<table>
<thead>
<tr>
<th></th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>P value</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>20</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients analysed</td>
<td>23</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cured %</strong></td>
<td>13 (56.5%)</td>
<td>9 (47.4%)</td>
<td>0.757</td>
<td>-21.1,39.4</td>
</tr>
<tr>
<td>Failed%</td>
<td>10 (43.5%)</td>
<td>10 (52.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ICU stay</td>
<td>12.2</td>
<td>16.2</td>
<td>ns</td>
<td>-4d</td>
</tr>
<tr>
<td>Ventilation (mean,days)</td>
<td>10.4</td>
<td>14.3</td>
<td>ns</td>
<td>-3.9d</td>
</tr>
<tr>
<td>Hospitalisation (mean,days)</td>
<td>18.8</td>
<td>20.1</td>
<td>ns</td>
<td>-1.3d</td>
</tr>
</tbody>
</table>

*Trends towards better outcomes; other factors other then bacterial clearance may impact on possibly better outcomes*
# LINEZOLID V BETA-LACTAM OR GLYCOPEPTIDE

## Pneumonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cepeda (2004)</td>
<td>1.04 (0.22-5.01)</td>
</tr>
<tr>
<td>Kaplan (2003)</td>
<td>0.30 (0.01-8.33)</td>
</tr>
<tr>
<td>Rubinstein (2001)</td>
<td>0.92 (0.51-1.67)</td>
</tr>
<tr>
<td>San Pedro (2002)</td>
<td>0.89 (0.30-2.60)</td>
</tr>
<tr>
<td>Stevens (2002)</td>
<td>1.00 (0.18-5.63)</td>
</tr>
<tr>
<td>Wilcox (2004)</td>
<td>1.33 (0.28-6.33)</td>
</tr>
<tr>
<td>Wunderink (2003)</td>
<td>1.14 (0.73-1.79)</td>
</tr>
<tr>
<td><strong>Total (fixed-effects model)</strong></td>
<td><strong>1.03 (0.75-1.42)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity $\chi^2 = 1.03$, df=6 (p=0.98), $P=0\%$

Test for overall effect $Z = 0.20$ (p = 0.84)

Favours comparator Favours linezolid

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Falagas et al. Lancet ID Jan 2008
MRSA nosocomial pneumonia: Linezolid > vancomycin?

- Anti-\textit{S. aureus} drugs vary
- Not due to chance
- Biological explanation
- Consistent with other studies
- Vancomycin dose correct (continuous infusion but no improvement in survival and increased potential for nephrotoxicity with concomitant agents)
ALGORITHM FOR SUSPECTED STAPHYLOCOCCAL PNEUMONIA

Kollef, Rubenstein & Nathwani CID 2008; 46 Suppl 3
MRSA Infections by Organ System and Setting

Results From a Prospective Cohort Study of Patients With MRSA Infections Identified in 12 Minnesota Laboratories, January 1 Through December 31, 2000

Health Care–Associated MRSA

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>20%</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>9%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>22%</td>
</tr>
<tr>
<td>Otitis media externa</td>
<td>1%</td>
</tr>
<tr>
<td>Skin soft tissue</td>
<td>36%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
</tr>
</tbody>
</table>

Community–Acquired MRSA

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>1%</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>4%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6%</td>
</tr>
<tr>
<td>Otitis media externa</td>
<td>7%</td>
</tr>
<tr>
<td>Skin soft tissue</td>
<td>74%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
</tr>
</tbody>
</table>

Management of patient with suspected staphylococcal pneumonia in the healthcare setting

- CAP hospitalised—treat with local hospital severe CAP regimen—cefotaxime/co-amoxiclav and clarithromycin
- Clinical suspicion of PVL—S. aureus pneumonia
  - Pneumococcal urinary Ag flu serology ± NPA—exclude other causes of symptoms as appropriate—vasculitis/PE
  - Admit to ICU
  - Obtain cultures: (masks to be worn if exposed to respiratory secretions)
    - Bronchoalveolar lavage Immediate
    - Protected specimen brush Gram
    - Tracheal aspirate or sputum Stain
  - Start empiric antibiotics covering for MRSA—Linezolid 600mg bd +clindamycin 1.2g qds and if very unwell/features of TSS add IVIG 2g/kg
  - Continue empiric antibiotic therapy for 48–72h or until cultures results are finalized—if sensitive to clindamycin and D-test negative continue with clindamycin
  - No improvement in symptoms
    - Increasing failure to ventilate
      - Exclude complicating issues (e.g. abscess, empyema) and non-infectious issues
      - Consider 2nd dose of IVIG
      - Re-evaluate for infection with antibiotic-resistant pathogen not covered by initial antimicrobial regimen

Bacteraemia

Nosocomial
- Most common pathogen—Staph epi
- 2nd Staph aureus—20% of nosocomial bacteremias
- Risk factors—IV catheters, severe pneumonia, surgical wound, foreign body, dialysis

Community acquired
- More likely to have IVDU, epidural abscess
- Australia 2005 49% of staph bacteraemias community onset, 12% of these MRSA
S. aureus BSI is a Serious Infection

724 Patients at DUMC

Overall 12-week mortality: 24%
Metastatic infectious complication: 34%
IE: 12.2%
Relapse: 10%

Fowler et al. Arch Intern Med 2003
Complications

- Endocarditis
- Vertebral osteomyelitis/discitis
- Septic arthritis
- Splenic abscess
- Mycotic aneurysms
- Meningitis
- Tissue abscess
# Independent Predictors of Complicated SAB

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive f/u blood culture</td>
<td>5.6</td>
</tr>
<tr>
<td>Community-onset</td>
<td>3.1</td>
</tr>
<tr>
<td>Persistent fever @ 72h</td>
<td>2.2</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Fowler, Arch Intern Med 163:2066, 2003*
Principles of treatment

- Remove focus-<18% treatment success if focus remains
- Drain fluid collections
- Replace/remove prosthetic device if possible
- High risk of endocarditis-need echo
  - TTE for line infections with no embolic stigmata???, TEE for all others vs TOE for all
- Vertebral osteo/deep soft tissue abscess often overlooked-may require imaging
TTE vs TOE

- Catheter associated Staph bacteraemia-estimated probability of endocarditis 3-4% here TTE is cost effective
- Unexplained bacteraemia-estimated risk of endocarditis 4-50% but for S.aureus probably exceeds 25% here TOE is cost effective

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
Treatment Summary

- Simple bacteremia—focus removed, neg echo, normal heart valves, repeat cultures at 3 days negative—14 days
- Complicated-positive blood cultures at 3 days, continued fevers-consider imaging for osteo/soft tissue focus—treat for 3-4 weeks
- Endocarditis—treat for 4-6 weeks
- Osteo/abscess—drain focus treat for 4-8 weeks
Bacteriostatic or bactericidal agents?

- Bactericidal activity is important for serious infections
  - e.g. IE\textsuperscript{1,2}
- Penicillins: first bactericidal agents – bactericidal activity considered a significant advance
- Rapid development of penicillin resistance
  - Led to increased use of bacteriostatic agents or agents with low bactericidal activity (vancomycin)\textsuperscript{3}
- Potential advantages of bactericidal agents:\textsuperscript{4}
  - Rapid reduction of bacterial load
  - Decreased risk of resistance
  - Improved clinical outcomes

**In vitro** bactericidal activity against MRSA in simulated endocardial vegetations

Time–kill assays performed at simulated human doses*

- Daptomycin achieved 99.9% kill after 13.2 hours of incubation

*Simulated doses were 6 mg/kg for daptomycin, 1 g q12h for vancomycin and 600 mg q12h for linezolid
High-inoculum MRSA was used to simulate vegetative conditions

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Reason not to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>None</td>
</tr>
<tr>
<td>Linezolid</td>
<td>None; limited data for endocarditis/bacteraemia &amp; no license</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Does not concentrate in blood; limited clinical data</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>None</td>
</tr>
<tr>
<td>Synercid</td>
<td>Side effects; limited data for endocarditis</td>
</tr>
</tbody>
</table>
SAB/SAIE trial: primary endpoint – success at Test of Cure

Modified intent-to-treat (mITT)
- Daptomycin: 44.2% (53/120)
- Comparator: 41.7% (48/115)

Per protocol (PP)
- Daptomycin: 54.4% (43/79)
- Comparator: 53.3% (32/60)

Difference in success rates (95% CI): 1.1% (-15.6, 17.8)*

SAB/SAIE trial: MRSA and MSSA success at Test of Cure – pathogen specific therapy (mITT)

What is the drug of choice for the treatment of MRSA bacteremia?

MRSA bacteremia complicated

No

Vancomycin MIC $\leq 1 \mu g/ml$

IV Vancomycin trough $> 10-15 mg/L$

Yes

Vancomycin MIC $> 1$ or $> 1.5 \mu g/ml$

Van trough $15-20 mg/l$
What is the drug of choice for the treatment of MRSA bacteremia?

+ASHP Guidelines Am J Health System Pharm 2009; 66:82-98
@ Perlroth J et al Arch Intern Med 2008; 805-819 (Systematic review)

MRSA bacteremia complicated

Yes, IE

No, other

Use loading dose 25-30mg/L in sick patients

Vanco MIC ≤ 1mg/l

IV Vancomycin 15-20mg/l trough

Vanco MIC > 1 or > 1.5 mg/l

Continue van with high trough levels 15-20mg/l+ or Daptomycin 6-10mg/kg od start initially or if slow response (DN & ++ )

No evidence
For adding low dose gentamicin or rifampicin
Vancomycin is obsolete for treating MRSA infections?

<table>
<thead>
<tr>
<th>Agreement with statement</th>
<th>Evidence base</th>
<th>Expert Panel (n = 11)</th>
<th>IDSA members (n = 744)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accept completely</td>
<td>0%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Accept with some reservation</td>
<td>36%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Accept with major reservations</td>
<td>36%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Reject with reservations</td>
<td>18%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Reject completely</td>
<td>9%</td>
<td>45%</td>
<td></td>
</tr>
</tbody>
</table>

Kollef et al, CID 2008; 47(Suppl2):355-397
Guidelines (2008) for the prophylaxis and treatment of MRSA infections in the UK


JAC 2009; doi:10.1093

MRSA pneumonia glycopeptide or linezolid
MRSA bacteraemia glycopeptide or linezolid (2w)
Complicated MRSA bacteraemia glycopeptide or daptomycin