MRSA nosocomial pneumonia: the latest data from the ZEPHyR trial

Michael S Niederman, MD

Chairman, Department of Medicine
Winthrop-University Hospital
Mineola, NY, USA
Professor of Medicine
Vice-Chairman, Department of Medicine
SUNY at Stony Brook, NY
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Nosocomial Infection in the ICU

  - 51% with infection, 71% on antibiotics
  - 70% in ICU > 7 days with infection, 32% on day 1
  - 64% of infections were respiratory, 70% with infections had positive cultures
  - 62% gram-negative, 47% gram-positive, 19% fungal
  - ICU mortality 25% vs. 11% if infected vs. not (p<0.001)
Resistance as A Risk For Nosocomial Pneumonia Mortality

- 8432 nosocomial pneumonias from 202 German ICU’s 1997-2003
- Multiple logistic regression for mortality risks: medical or surgical ICU, > 1,000 bed hospital, age >65, infection with MRSA or MDR *P. aeruginosa*.
- Is resistance a cause of mortality, a surrogate marker of more severe illness, or a cause of inappropriate or delayed appropriate therapy?

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio for mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical or surgical ICU</td>
<td>1.55 (1.32-1.82)</td>
</tr>
<tr>
<td>Hospital with &gt;1,000 beds</td>
<td>2.14 (1.81-2.56)</td>
</tr>
<tr>
<td>University-affiliated hospital</td>
<td>0.32 (0.25-0.41)</td>
</tr>
<tr>
<td>Age greater than the median value</td>
<td>1.54 (1.31-1.81)</td>
</tr>
<tr>
<td><strong>Causative pathogen</strong></td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>2.39 (1.81-3.12)</td>
</tr>
<tr>
<td>Multidrug-resistant <em>P. aeruginosa</em></td>
<td>3.00 (1.90-4.63)</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>...</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>...</td>
</tr>
<tr>
<td><strong>NOTE.</strong> CI, confidence interval; <em>P. aeruginosa</em>, <em>Pseudomonas aeruginosa</em>; <em>S. aureus</em>, <em>Staphylococcus aureus</em>.</td>
<td></td>
</tr>
<tr>
<td>* Sixty-five years for patients with pneumonia and 63 years for patients with primary BSI.</td>
<td></td>
</tr>
</tbody>
</table>
Attributable mortality of MRSA nosocomial pneumonia: not all appropriate therapy is adequate

- Case-control study of MRSA VAP
  - 75 cases with VAP; 75 controls (23 with VAP)
  - All MRSA treated with vancomycin (n=69) or teicoplanin (n=6)
    - Mortality of MRSA VAP 48% vs 25.3% in controls (p=0.01)
    - Mortality lower with continuous-infusion vancomycin (n=16) vs intermittent: 25% vs 54.7% (p=0.03)
  - VAP with MRSA with OR for mortality of 3.8 (p=0.04)
  - Increased attributable mortality for appropriately treated MRSA VAP vs controls? Need for better treatment
    - Should compare with controls with MSSA VAP or all with VAP

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; OR, odds ratio; VAP, ventilator-associated pneumonia

Impact of MRSA VAP on ICU LOS

- Using a prior study database, compared MRSA VAP to MSSA VAP
  - All dx with bronch and quantitative cults
  - 107 patients who survived ICU. Omit those who died.
    - 69 MSSA
    - 38 MRSA
  - All got appropriate rx within 24 hours of bronch
  - Both groups with similar MV duration prior to VAP, severity scores, gram-neg coinfection, bacteremia, short course rx., superinfection, relapse, MV duration after VAP
- ICU LOS significantly longer for MRSA (33 vs. 22 days, p<0.05)
Even With Appropriate Therapy (Of All Types), MRSA VAP Is Slow To Clinically Resolve

Vancomycin resistance and increased mortality in MRSA HAP

- 163 patients with MRSA HAP, VAP or HCAP
  - 32.3% died within 28 days. All but 11 had initial treatment with vancomycin
  - Mortality risks: older age, higher APACHE II score, diabetes, heart failure, vascular disease, from a nursing home, prior home IV therapy
  - 73% with MIC of ≥1.5 µg/mL
    - OR of death of 3.7 for each increase of 1 µg/mL in vancomycin MIC; OR=2.97 after propensity adjustment
  - 79% vancomycin trough >10 µg/mL, 45% at least 15 µg/mL

APACHE II, Acute Physiology and Chronic Health Evaluation II; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; IV, intravenous

Haque et al. Chest 2010;138:1356-1362
The need to push vancomycin dosing to reduce mortality

- As MRSA MIC values rise, need to push vancomycin dose, due to increased mortality with rising MIC (in bacteraemia)\(^1\)
- IDSA recommendations:
  - Vancomycin trough of 15-20 mg/L for MIC <1 mg/L. Higher MIC needs alternative treatment\(^2\)

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**Table 5.** Factors independently associated with mortality in a logistic regression model of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.02 (1.00–1.04)</td>
<td>.013</td>
</tr>
<tr>
<td>Receipt of corticosteroids</td>
<td>1.85 (1.04–3.29)</td>
<td>.034</td>
</tr>
<tr>
<td>Prognosis of underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rapidly fatal</td>
<td>1.81 (1.06–3.10)</td>
<td>.029</td>
</tr>
<tr>
<td>Ultimately fatal</td>
<td>10.2 (2.85–36.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Source of bacteremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.18 (1.17–4.04)</td>
<td>.014</td>
</tr>
<tr>
<td>High risk</td>
<td>3.60 (1.89–6.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMIC1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>VMIC1.5</td>
<td>2.86 (0.87–9.35)</td>
<td>.08</td>
</tr>
<tr>
<td>VMIC2</td>
<td>6.39 (1.68–24.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NA</td>
<td>3.62 (1.20–10.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shock</td>
<td>7.38 (4.11–13.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

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IDSA, Infectious Diseases Society of America; MIC, minimum inhibitory concentration

Vancomycin nephrotoxicity increases as trough levels are increased

- Retrospective study to relate nephrotoxicity to vancomycin pharmacokinetics
- Included 166 patients: age ≥18 years, non-neutropenic, vancomycin for >48 hours, no vasopressors or contrast dye, baseline Cr <2.0 mg/dL
  - 21 with nephrotoxicity: increase in Cr by 0.5 mg/dL or by >50% (whichever greater)
- In multivariate model, only trough level and ICU residence, but not AUC, correlated with toxicity

AUC, area under the curve; Cr, creatinine; ICU, intensive care unit

Vancomycin : We Can’t Get There From Here

• Monte-Carlo Analysis
  – Probability of AUC/MIC >400 with trough of 15-20 mg/L
  • Nephrotoxicity rises with rising vancomycin doses and worsening baseline renal function
  – Patel et al. CID 2011; 52:969-974
Why Combination Therapy in VAP?

• Combination therapy increases the likelihood of more appropriate empiric therapy in VAP for those with MDR pathogens, but had no impact on mortality, when MDR pathogens were uncommon.

• Empiric addition of an aminoglycoside to a beta-lactam may be better than adding a quinolone

• Not proven to prevent the emergence of resistance during therapy

• May reduce mortality in bacteremic Pseudomonal infection
  – BUT adequate empiric monotherapy not as effective as adequate empiric combination therapy. Chamot E, et al. AAC 2003; 47:2756-64

• Does 1+1=3? Combination therapy may correct for relative mistakes of monotherapy: delay, delay in adding second agent, using less rapidly bactericidal agents
  – Niederman MS. Crit Care Med 2010; 38: 1906-8
Combination Regimens Must Account For Local Microbiology

- 111 patients with HAP
- Most common organisms: *S. aureus*, *Acinetobacter baumannii*, *P. aeruginosa*
- Piperacillin resistance more likely after 10 days
- Amikacin more active vs. gram –negatives than quinolones

Table 4—Adequacy of Various Antibiotic Combinations Against All Gram-Negative Isolates (n = 139)*

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Additional Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>80%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>81%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>82%</td>
</tr>
</tbody>
</table>

*Data are presented as percentage susceptible to at least one antibiotic.
Therapy principles

• Use an empirical therapy regimen that includes agents different from those the patient has recently received\(^1\)

• Maybe reserve quinolones for a second bout of ICU infection, not for the first episode\(^2\)

Should we NOT use quinolones for a first ICU infection?

- 239 ICU patients with no prior antibiotic exposure

- Multivariate analysis of risks of acquiring MDR pathogens
  - 77 patients with ICU-acquired MDR organisms (50 with ICU infection)
    Multivariate risks for MDR acquisition: fluoroquinolone use (OR=3.3), duration antibiotics (OR=1.1)

- 135 received a quinolone (ofloxacin / ciprofloxacin). Case-control matching for 72 of 135 treated with fluoroquinolones
  - Cases with more ICU-acquired MRSA (26% vs 12%; p=0.028), ICU-acquired ESBL (11% vs 1%; p=0.017)
    Maybe reserve quinolones for a second course of ICU infection

Data taken from reference 1
Broad-spectrum therapy of HAP

Core organisms plus:
- *Pseudomonas aeruginosa*
- Acinetobacter

Aminoglycoside or anti-pseudomonal quinolone (ciprofloxacin, high-dose levofloxacin) plus:
- Anti-pseudomonal penicillin
- Ceftazidime or cefoperazone; cefepime
- Aztreonam
- Imipenem, meropenem
- Beta-lactam / beta-lactamase inhibitor (piperacillin/tazobactam)
- ± linezolid or vancomycin

Consider MRSA

Linezolid vs glycopeptides for nosocomial pneumonia

- Nine trials of linezolid vs glycopeptides with 2329 patients. Included one trial with neutropenic fever
- No advantage of linezolid vs glycopeptides or vancomycin alone for clinical or bacteriological cure, for all enrolled patients or for MRSA alone
- Linezolid has more incidences of thrombocytopenia and gastrointestinal upset than vancomycin
- Both have similar rates of nephrotoxicity, but linezolid has a relative risk $= 0.40$ vs vancomycin ($p=0.13$), 1.04 vs teicoplanin

Kalil et al. Crit Care Med 2010;38:1802-1808
Linezolid vs glycopeptides for MRSA nosocomial pneumonia

Microbiological eradication of MRSA

*Methicillin Resistant Staphylococcus Aureus. Z=0.771; P=0.441. Heterogeneity: Q=5.93; P=0.06; I²=16%*

Figure 3. Linezolid vs. glycopeptides: Methicillin-resistant *Staphylococcus aureus*. MH, Mantel-Haenszel; CI, confidence interval.
Linezolid vs glycopeptides for MRSA nosocomial pneumonia

- Linezolid vs glycopeptides in eight trials with 1641 patients
- Clinical and microbiological success and mortality all equivalent
- Clinical success with documented MRSA (OR=1.23; p=0.09)

Walkey et al. Chest 2011;139:1148-1155
Linezolid efficacy in NP due to known or suspected MRSA (1)

Prospective, randomised, double-blinded

Clinical cure rate (%)

<table>
<thead>
<tr>
<th>ITT</th>
<th>Clinically evaluable patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>53.4% 86/161</td>
<td>52.1% 74/142</td>
</tr>
<tr>
<td>66.4% 71/107</td>
<td>68.1% 62/91</td>
</tr>
</tbody>
</table>

NS, not significant; ITT, intent to treat

Linezolid efficacy in NP due to known or suspected MRSA (2)

Prospective, randomised, double-blinded

\[ \begin{align*}
\text{Clinical cure rate} & \quad \% \\
\text{ITT} & \quad p=\text{NS} \\
\text{Linezolid} & \quad 52.7\% \\
\text{Vancomycin} & \quad 52.2\% \\
\text{Clinically evaluable patients} & \\
\text{Linezolid} & \quad 67.9\% \\
\text{Vancomycin} & \quad 64.9\% \\
\end{align*} \]

Linezolid efficacy in Gram-positive VAP: retrospective analysis from two identical trials

- 1019 patients (524 linezolid, 495 vancomycin). In ITT analysis:
  - 544 VAP
  - 264 Gram-positive VAP
  - 221 *S. aureus* VAP
  - 91 MRSA VAP in ITT (21 with missing data)

- Bacteriological eradication: MRSA VAP 60.5% (linezolid) vs 22.9% (vancomycin) (p=0.001)

- Survival in MRSA subset: 84.1% linezolid vs 61.7% vancomycin (p=0.02)

- VAP survival predictors: linezolid therapy (OR=1.6), APACHE ≤20, age <65 years, absence of renal and cardiac co-morbidities, single-lobe pneumonia

- OR survival for linezolid: 2.6 in Gram-positive VAP, 4.6 in MRSA VAP. OR=20.0 for clinical cure with MRSA VAP

ITT, intent-to-treat; SA, *S. aureus* 

Secondary benefits of linezolid in VAP therapy

- Prospective, randomised, open-label comparison of linezolid (n=30) with vancomycin (n=20) in MRSA VAP confirmed by BAL and with follow-up BAL 72-96 hours later
- 23 patients treated with linezolid and 19 patients treated with vancomycin with confirmed MRSA and also a repeat BAL
- Microbiological cure (linezolid vs vancomycin): 56.5% vs 47.4% (not significant). All patients with linezolid microbiological failures survived, 50% of patients with vancomycin microbiological failures survived
- Trends for linezolid: higher clinical cure (66.7% vs 52.9%), survival (86.7% vs 70%), shorter-duration MV, duration ICU stay and hospitalisation

BAL, bronchoalveolar lavage; MV, mechanical ventilation

![Figure 2: Health resource outcomes at end of the study after LZD and VAN therapy in mITT patients with MRSA VAP. Data are reported as the duration (days) of mechanical ventilation, hospitalization, and ICU stay.](image-url)
Linezolid concentrations in serum and ELF of critically ill VAP patients

- 16 critically ill VAP patients studied at steady state
  - All with late-onset VAP
  - 12 with organisms: 3 MRSA, 1 MSSA, 8 enteric Gram-negatives
- Serum and ELF concentrations after 2 days of therapy
- Blood at 10, 20, 30, 45 minutes and 1, 2, 4, 8, 12 hours after infusion
- BAL 1 and 12 hours after infusion
- Similar levels in serum and ELF
  - Range of peak penetration: 34-188%
  - Range of trough penetration: 28-220%

ELF, epithelial lining fluid

Linezolid vs vancomycin in bacteriologically documented MRSA nosocomial pneumonia (1)

- Published in *Clin Infect Dis* 2012
- Phase IV, randomised, double-blind, multicentre study. Non-inferiority trial with a nested superiority hypothesis
- 154 centres, 1225 patients: 448 enrolled with proven MRSA (mITT group), 348 at EOS (PP group)
- Treatment 7-14 days, EOT within 5 days of completing treatment, EOS within 7-30 days

EOS, end of study; EOT, end of treatment; mITT, modified intent-to-treat; PP, per protocol

Wunderink et al. Clin Infect Dis 2012; Epub 12 Jan
Study design

- Linezolid IV 600 mg q12h
- Vancomycin IV 15 mg/kg q12h

- 7-14 days
- Within 5 days of EOT
- 7-30 days after EOT

- 1:1 randomisation

- Vancomycin dose adjusted by unblinded pharmacist based on renal function and trough concentration

- Initial cefepime or other Gram-negative coverage (not MRSA-active) required

Adapted from Wunderink et al. Clin Infect Dis 2012; Epub 12 Jan
Linezolid vs vancomycin in bacteriologically documented MRSA nosocomial pneumonia (2)

- **Primary end point:** clinical outcome at EOS in PP group\(^1\)
- **Secondary end points:** clinical outcome at EOT in PP group; clinical outcome at EOS and EOT in mITT group, microbiological outcome at EOS and EOT in PP and mITT groups, and patient survival\(^1\)
- Included HCAP, but \(\sim70\%\) on MV, 5-10\% bacteraemia\(^1\)
- Vancomycin dosed per renal function, aimed at 15 mg/kg twice a day\(^1\)
  - Mean trough 12-16 µg/mL (days 3-9)
  - Only 10\% of patients treated with vancomycin had vancomycin MIC >1.0 µg/mL\(^2\)

Response rate in different populations in ZEPHYR study

Patients with EOS outcome of ‘indeterminate’ were excluded from efficacy analysis.
CI, confidence interval

Wunderink et al. Clin Infect Dis 2012; Epub 12 Jan
Microbiological response at EOT in PP group

Adapted from Wunderink et al. Clin Infect Dis 2012; Epub 12 Jan
Clinical success rates in the PP population at EOS by patient subgroup

Patients with EOS outcome of ‘indeterminate’ were excluded from efficacy analysis

Adapted from Wunderink et al. Clin Infect Dis 2012; Epub 12 Jan
Median vancomycin trough plasma levels and relation to outcomes (mITT at EOS)

Clinical

Microbiological

Niederman et al. Am J Respir Crit Care Med 2011;183:A3932
Clinical and microbiological response by vancomycin trough concentrations at days 3, 6 and 9 (mITT at EOS)
Mortality in ITT population at 60 days (15.7%) in linezolid arm
Mortality in ITT population at 60 days (17.0%) in vancomycin arm
Mortality data from Wunderink et al. Chest 2003

Figure 2. Kaplan-Meier survival curves for uncensored data.
Safety and renal impairment in relation to vancomycin trough levels¹

- Renal impairment: rise in Cr of 0.5 mg/dL if normal or >50% increase if abnormal¹
- Renal failure / impairment / azotemia in 7.3% (vancomycin) and 3.7% (linezolid) of patients²
- Comparable adverse events in both groups²
  - Thrombocytopenia: 8/597 linezolid-treated patients; 13/587 vancomycin-treated patients

Two main risk factors for MRSA (≥5 days in hospital + prior antibiotics)?
Or one risk factor and positive tracheal aspirate for Gram + cocci

Yes
↓
Empirical therapy for MRSA

No
↓
Vancomycin / teicoplanin

MSSA
↓
Oxacillin (if not allergic to penicillin)

Yes
↓
Renal impairment or aminoglycoside use, or age >65 years

Yes
↓
Linezolid

No
↓
Culture / response

MSSA
↓
Culture negative: stop treatment

MRSA
↓
Discontinue vancomycin and use linezolid

Clinical response
↓
Yes
Continue

If vancomycin
→ switch to linezolid

If linezolid
→ add rifampicin

Conclusions about MRSA VAP

- VAP is a serious illness with attributable mortality, especially if inappropriate antibiotic therapy is given, and cannot be eliminated even with prevention.

- MRSA VAP has attributable mortality
  - With rising MIC levels for vancomycin, it is essential to optimise drug dosing, although even this may not lead to good outcomes if the vancomycin MIC is >1 mg/L
  - Aggressive dosing may promote nephrotoxicity

- Combination therapy is needed to optimise therapy of Gram-negatives in VAP, and usually requires a beta-lactam with an aminoglycoside (which may be more nephrotoxic if used with vancomycin)

- Linezolid may offer advantages over optimally dosed vancomycin for proven MRSA VAP

- The results of the ZEPHYR study showed that clinical response was significantly higher with linezolid than with vancomycin when both therapeutics were used to treat MRSA nosocomial pneumonia.
Clinical Implications of CA-MRSA CAP

- Incidence is unknown
- Is a distinct illness
  - Severe, necrotizing
  - USA 300 strain
  - PVL toxin leads to necrotizing infection
- Optimal therapy uncertain
  - After influenza or viral illness
  - ? Use antibiotics that inhibit protein synthesis (add clindamycin to vancomycin or use linezolid alone) to counteract toxin production
- Micek et al. : Chest 2005; 128:2732
Clinical Implications of CA-MRSA CAP

- 4 Cases of PVL-producing MRSA:
  - 3 post-influenza CAP
  - 1 VAP (post pancreatitis). Nasal colonization on ICU admit
    - All with positive respiratory secretions, 3 with + BC’s
  - All initially inappropriate Rx, then vancomycin
    - 3 failures (2 persistent bacteremia after 48 h vancomycin)
      - RX: 2 linezolid (and rifampin), 1 clindamycin added and all recovered

- WILL THIS BECOME THE NEW NOSOCOMIAL STRAIN???

- Micek et al. : Chest 2005; 128:2732