Challenges and Advancements for Treating MRSA Infections in 2012

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What is MRSA?
- *Staphylococcus aureus*
- Acquired “mec” gene in a large genetic element
- Produces altered penicillin binding proteins
  - Not susceptible to beta-lactam antibiotics
  - Limits antibiotic choices
- Worse outcomes, increased LOS, increased costs
- An important healthcare associated pathogen
- An epidemic community pathogen

What MRSA is not
- More virulent than MSSA
- More common than MSSA
- The only important antibiotic resistant pathogen found in healthcare settings

Comparing CA-MRSA and HA-MRSA

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
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<tbody>
<tr>
<td>CA-MRSA</td>
<td>Often susceptible to TMP-SMZ, doxycycline, and clindamycin*&lt;br&gt;USA300, USA400 by PFGE&lt;br&gt;SCCmec type IV encodes meth R</td>
</tr>
<tr>
<td>HA-MRSA</td>
<td>Resistant to more classes of antibiotics. Susceptible to vanco, daptomycin, and linezolid&lt;br&gt;USA100, USA200, and USA800 are most common&lt;br&gt;SCCmec types II-III encode meth R</td>
</tr>
</tbody>
</table>

*Clindamycin resistance is increasing in CA-MRSA in many geographical areas within USA
* PFGE = pulsed field gel electrophoresis
SCCmec = staphylococcal cassette chromosome mec
Enhanced virulence of USA300

- Panton-Valentine Leukocidin (PVL)
- Arginine Catabolic Mobile Element (ACME)
- Enterotoxins K and Q
  - Pyrogenic superantigens
  - Stimulate large numbers of T cells
- Staphylokinase
  - Potent plasminogen activator, dissolves clots
- Chemotaxis inhibiting protein
  - Inhibits recruitment of neutrophils
- Other unknown factors

67 yo admitted for suspected sepsis syndrome

- CC: fevers, night sweats, confusion x 3 days
- HPI:
  - Recent hospital stay for CHF with STEMI, stent LAD
  - Discharged LTCF for rehab 10 days ago
  - IDDM, CAD, CKD (Cr 1.9), HLD, PVD
  - Admitted from LTCF
- ROS: no focal findings of infection, SOB+
- ER → MICU: noted to have BP 85/40, P 120, T 102.7, R 20, Sats 86% RA, new aortic diastolic murmur, bilateral rales throughout, JVD
67 yo with sepsis syndrome

- BC = 2/2 MRSA on admission, vanco MIC 2.0 mg/L
- Repeat BC 72 hrs later, 2/2 GPC
- CXR: pulmonary edema
- TTE: old aortic stenosis, new mod AI and MR, EF 35%, no vegetations seen
- Cr 2.8, troponin elevated
- EKG no change, old AMI

Treatment Outline for the Case
Per IDSA Guidelines

**Uncomplicated Bacteremia**
- 2+ weeks of abx therapy
  - Vancomycin
  - Daptomycin 6 mg/kg

**Complicated Bacteremia**
- 4-6 weeks of abx therapy
  - Vancomycin
  - Daptomycin 6 v. 8-10 mg/kg

- Gentamicin or Rifampin ONLY for PVE
- Additional blood cultures, 2-4 days after initial positive
- ECHO

Vancomycin

- Gold-standard
  - All new agents are non-inferior
- Longevity threatened by resistance
  - Overuse
  - MIC creep

- Must use APPROPRIATELY

Vancomycin MICs and Outcomes

<table>
<thead>
<tr>
<th>Type of in vitro test done matters: MB dilution 1.0 = E test 1.5</th>
</tr>
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<tbody>
<tr>
<td>Soriano A et al. CID 2008;46:193-200</td>
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<tr>
<td>414 episodes of MRSA bacteremia</td>
</tr>
<tr>
<td>Vancomycin troughs &gt; 10 mg/L</td>
</tr>
<tr>
<td>Evaluated mortality v. MIC</td>
</tr>
<tr>
<td>Results:</td>
</tr>
<tr>
<td>- Mortality (odds ratio)</td>
</tr>
<tr>
<td>- MIC = 1 (1)</td>
</tr>
<tr>
<td>- MIC = 1.5 (2.06, p = 0.08)</td>
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<tr>
<td>- MIC = 2 (6.39, p &lt; 0.001)</td>
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<tr>
<td>Relationship of Vanco MIC to Mortality in Patients with MRSA Hospital-Acquired, Ventilator-Associated and Healthcare-Associated Pneumonia</td>
</tr>
<tr>
<td>Results:</td>
</tr>
<tr>
<td>- Odds ratio of death was 2.97 for a 1 mcg/mL increase in vanco MIC</td>
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</table>

Ponder: the Vanco MIC creep

**TABLE 1. Number of S. aureus isolates tested for susceptibility from 2000 to 2004 and vancomycin MICs**

<table>
<thead>
<tr>
<th>No. (%) of strains with vancomycin MICs</th>
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<td>*P &lt; 0.01 compared to the percentage of S. aureus strains with a MIC of 1 mcg/ml in 2000</td>
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<table>
<thead>
<tr>
<th>Publications over time from multiple locations: RESULTS VARY</th>
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<tr>
<td>Some with NO MIC creep</td>
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</table>

<table>
<thead>
<tr>
<th>6,003 isolates from Los Angeles hospitals from 2000-2004</th>
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<tr>
<td>Wang G et al. J Clin Microbial 44: 3883-6</td>
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</table>

Dose Optimization with Vanco

- Dose for bacteremia (actual BW)
  - Load = 25 mg/kg x 1
  - Maintenance = 15-20 mg/kg IV q 8-12 h
  - AUC/MIC ≥ 400 (target for predicting positive clinical outcomes)
    - If MIC = 1 mg/L, need minimum trough of 15 mg/L
    - If MIC ≥ 2 mg/L, unachievable
    - Troughs < 10 mg/L associated with resistance
- Better outcomes with higher troughs?  More toxicity with higher troughs?
Nephrotoxicity with High Troughs

- Retrospective studies:
  - Three-fold increase in nephrotoxicity with troughs > 15 mg/L
    - Bosso JA et al. AAC 2011 Dec;55(12):5475-9

- Observational Studies:
  - 4.5% Developed nephrotoxicity

Daptomycin

- FDA approved for SSTI and BSI, including right-sided endocarditis
- Cidal

Daptomycin Efficacy with Elevated Vancomycin MIC

- Daptomycin MOA:
  - If cell wall is thickened (VISA), will daptomycin work?

Higher Dose Daptomycin for MRSA

- J Antimicrob Agents 36;459:2010
- Retrospective review 55 MRSA bacteremias
- Tolerance equal

<table>
<thead>
<tr>
<th>Dose</th>
<th>Micro cure %</th>
<th>Clinical cure %</th>
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<tbody>
<tr>
<td>5 mg/kg</td>
<td>68%</td>
<td>73%</td>
</tr>
<tr>
<td>8 mg/kg</td>
<td>93%</td>
<td>94%</td>
</tr>
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Daptomycin Versus Vancomycin for Bloodstream Infections Due to Methicillin-Resistant Staphylococcus aureus With a High Vancomycin Minimum Inhibitory Concentration: A Case-Control Study

Findings to note:
- 91% of Dapto patients had been switched from Vancomycin
  - No improvement or worsening
  - 48% still had positive blood cultures
- Patients with initial Vancomycin levels < 15 mg/L had poorer prognosis
- Independent predictors of failure:
  - Renal failure
  - Vancomycin therapy
Effect of Daptomycin With and Without Concurrent Statin Therapy on Creatine Phosphokinase (CPK) Values


512 patients were included in the study. The overall incidence of CPK elevation in the study population was 8.4% and was not statistically different among the 3 groups (dapto alone, dapto + statin ongoing, dapto+statin held). Only baseline CPK elevation was found to be associated with increased odds of developing CPK elevation (p = 0.0005), those with a baseline CPK of >200 had 15 fold higher odds of CPK elevation.

Safety Issues with Daptomycin

- Rhabdomyolysis
- Weekly CPKs?
- Eosinophilic pneumonia
- Accumulation in obesity?

Will Vancomycin Remain First Choice for MRSA Bacteremia?

- Schentag, et al Buffalo, data not published
- 5-center prospective comparison of daptomycin alone v. vancomycin alone for SAB (pneumonia excl)
- 124 patients studied to date (Aug 2011)
- Mean duration BC+ 5.8 d vanco vs 4.2 d daptomycin
- Persistent BC+ @ 7 d 16% vs 0%
- Mortality 34% vs 12%

Persistent Bacteremia: IDSA

- Defn = 7 d positive cultures after source control while on vanco therapy with target trough goals of 15-20 achieved and MIC <1.5
- Daptomycin 8-10 mg/kg/d ± 2nd agent (BIII)
  - Gentamicin
  - Rifampin
  - Bactrim
  - Cefaroline
  - Linezolid

Daptomycin Antibiotic Combinations for S aureus Infections

Reviews: Nadrah - Chemother Research Practice 2011 and Steed AAC Dec 2010

- Dapto + gentamicin – synergy in vitro
- Dapto + rifampin – suggestion efficacy for foreign body infections
- Dapto + Bactrim – synergy 40% isolates in vitro
- Dapto + beta-lactam

Use of Anitaphylococcal β-Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to Methicillin-Resistant Staphylococcus aureus: Role of Enhanced Daptomycin Binding

- Therapy in 7 patients with refractory MRSA bacteremia

We used daptomycin plus antimicrobials (β-lactams) in 7 patients with refractory MRSA bacteremia. In vitro studies showed enhanced daptomycin bactericidal activity, increased membrane daptomycin binding, and decrease in positive surface charge induced by β-lactams against daptomycin non-susceptible MRSA. Addition of β-lactams to daptomycin may be of benefit in refractory MRSA bacteremia. (Although the official designation is “daptomycin resistance,” we will use the term “daptomycin intolerance” in this paper for facility of presentation.)
Bactrim v. Vancomycin for MRSA Bacteremia
Goldberg J Antimicrob Chemother Aug 2010

- Retrospective, matched Bactrim (n = 38) v. Vanco (n = 76) for MRSA bacteremia
  - Well matched for ABE, age, severity illness
- Results
  - 30 d mortality 34% v. 40%, (OR 0.76, CI 0.34-1.7)
  - Relapse 2.6% v. 11.8%
  - Persistence (>14 d) not different
  - Toxicity same, renal dysfn, 28% vs 27%

37 yo obese woman with asthma and increasing SOB

- CC: Fever, sore throat, cough, SOB x 4 d
- HPI:
  - Dec 22, seen in ER for worsening asthma. CXR no acute infiltrate. Sats 93% RA after bronchodilator. Seen out on inhalers. Dx: viral illness
  - Dec 25, returns to ER with respiratory failure, intubated soon after arrival
- PMHx:
  - Episodic health care, primarily ER visits for asthma
  - Morbid obesity, BMI = 44, DM, HTN, HLD
  - Recent intertriginous cellulitis, treated levofloxacin

37 yo woman respiratory failure – cont’d

- BAL reveals influenza, H1N1 and 4+ MRSA
- Blood cultures x 2 = MRSA, vanco MIC 1.0 mg/L

- Course:
  - Treated oseltamivir plus vancomycin
  - 3 wks ICU, 5 wk hospital stay
  - Discharged to SNF

Treatment Recommendations
Per IDSA Guidelines

- Vancomycin (A II)
  - 15–20 mg/kg q 8-12h, goal trough 15 – 20 mg/L
- Linezolid (A II)
  - 600 mg IV/PO q 12 h
- Clindamycin (B II)
  - 600 mg IV/PO q 8 h
Pneumonia: Vanco v. Linezolid

- Efficacy
- Safety
- CA-MRSA v. HA-MRSA

Role of Newer Agents for MRSA Pneumonia

Ceftaroline

- FDA approved for CAP and cSSTI
- High affinity for PBP2a
- Cidal
- 600 mg IV q 12 h
- Growing database for off-label use

Important to note little anaerobic activity, and no Pseudomonal or “SPICE” activity

Telavancin (Vibativ)

Lipoglycopeptide (Telavancin, Oritavancin, Dalbavancin)

Vancomycin Core

Lipophilic tail

Hydrophilic side group

\[ \text{Vancomycin Core} \]

Oxacillin

PBP

Transpeptidation

\[ \times \]

Telavancin

Lipoglycopeptide

Hydrophilic side group

Oxacillin

PBP2a

Transpeptidation

meCA gene

meCA gene

meCA gene

meCA gene

meCA gene

meCA gene
Telavancin (Vibativ)

- Lipoglycopeptide approved Fall 2009
  - Adult, complicated skin and skin structure infections (cSSSI)
- Mechanism of action
  - Inhibits cell wall synthesis
  - Disrupts cell membrane barrier
- Spectrum of activity
  - Highly active against MSSA and MRSA
  - Dose 10 mg/kg IV q 24 h

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Telavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Slowly cidal</td>
<td>Rapidly cidal</td>
</tr>
<tr>
<td>Spectrum</td>
<td>Staphylococcus with MIC &lt; 2, Strep, E. faecalis, Some E. faecium</td>
<td>+ hVISA, VISA, VRSA*, Enterococcus (non-VanA)</td>
</tr>
<tr>
<td>Dosing</td>
<td>Varies</td>
<td>10 mg/kg IV q 24 h</td>
</tr>
<tr>
<td>Clearance</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td>ADR</td>
<td>&gt; N/V, taste disturbances, foamy urine, nephrotoxicity</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Yes</td>
<td>NO!!!!</td>
</tr>
</tbody>
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Osteomyelitis case

65 yo DM male with back pain

- Poorly controlled IDDM, last HgbA1C = 12.3
  - CKD with last Cr 2.1
- Developed “spider bite” and see in ER
- I&D of soft tissue abscess performed. Given empiric clindamycin PO for 7 days. No culture sent.
- 3 wks later develops lower back pain
- Seen ER 3 times and given NSAID and muscle relaxants

DM with back pain – cont’d

- Back pain gradually worse over 3 months
- Noticed night sweats and weight loss
- Lab done in ER
  - WBC 13K, ESR > 100
- Routine spine films done, followed by MRI
  - “diskitis” L3-4 with no epidural extension
- Blood cultures x 3 = no growth
- CT guided aspirate of spine → MRSA, vanco MIC 1.0 mg/L, clindamycin resistant
Osteomyelitis Treatment
*Per IDSA Guidelines*

- Vancomycin (BII)
- Daptomycin (BII)
- Linezolid (BII)
- Clindamycin (BIII)
- Role of Rifampin

Vancomycin vs. Daptomycin vs. Linezolid

*Which is best?*

- Comparative trials?
- Efficacy rates?
- Long-term safety!
  - Vanco = nephrotox, ototox, BM suppression
  - Daptomycin = CPK, eos pna
  - LZD = BM suppression, optic neuritis, D-D interactions

Rifampin & MRSA Osteomyelitis

- Mixed results
- Data supportive with prosthetic joints

Management of recurrent MRSA SSTIs

- Education on personal hygiene and wound care for all patients (cover wound, clean hands, do not share personal items, clean environment, inform your provider)
- Treatment of MRSA colonization is not routinely recommended.
- Efficacy of methods to reduce recurrence of MRSA and transmission by decolonizing have not been adequately established.
Web-based Evidence on MRSA

- Washington State Antibiotic Resistant Network guidelines for SSTI MRSA. http://www.doh.wa.gov/topics/antibiotics/providers.htm#mrsa
- CDC personal prevention of MRSA SSTI. http://www.cdc.gov/mrsa/prevent/personal.html

Decolonization

- It may be reasonable to consider decolonization for:
  - Patients with recurrent MRSA despite appropriate therapy.
  - MRSA infections with ongoing transmission in a closed cohort.
- Optimal regimens not established:
  - Nasal mupirocin, skin antiseptic, oral antimicrobials (usually rifampin with Bactrim, doxycycline or with minocycline)

Clinical Microbiology and Infection, Volume 16 Number 5, May 2010
E. S. Yang, J. Tan, S. Eells, G. Rieg, G. Tagudar and L. G. Miller

Eradication of nasal carriage

- Efficacy in preventing re-infection or transmission in the outpatient setting not documented, and is NOT routinely recommended
- Generally reserved for outbreaks
- Issues:
  - Re-colonization
  - Emergence of resistance
  - Side effects
  - Cost-effectiveness

Treatment of MRSA Infections

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children: Executive Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>% resistant</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>5-10%</td>
<td>Static, US data lacking</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>5-10%</td>
<td>Inferior to vancomycin in 1 study; few data</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>40%</td>
<td>Cross-resistance w/ macrolide</td>
</tr>
<tr>
<td>FQ</td>
<td>50%</td>
<td>Resistance on therapy</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Rare</td>
<td>Static, $$$, ADR</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>?</td>
<td>Cidal, $$$, few data</td>
</tr>
<tr>
<td>Ceftraroline</td>
<td>?</td>
<td>Cidal, $$, few data</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Rare</td>
<td>Static, $$$, nausea, IV</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Rare</td>
<td>Slowly cidal, cheap, resistance growing</td>
</tr>
</tbody>
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