The Importance of Resistance in Gram Positive Bacteria: Epidemiology of Resistance, Resistance Mechanisms, & Future Implications

John C. Rotschafer, Pharm. D.
Professor
College of Pharmacy
University of Minnesota

Objectives

- Identify current & future antibiotic treatment options for gram positive infections
- Identify underlying mechanisms of antibiotic resistance for Staphylococci, Enterococci, & S. pneumoniae
- Identify two unique molecular features of CA-MRSA
- Identify common clinical features associated with VISA & VRSA infections
- Identify risk groups for CA-MRSA

12 Steps to Prevent Antimicrobial Resistance in Hospitalized Adults

- **PREVENT INFECTION**
  1. Vacinate
  2. Get the catheters out
- **USE ANTIBIOTICS WISELY**
  3. Use local data
  4. Access the experts
- **PREVENT TRANSMISSION**
  5. Isolate the pathogen
  6. Break the chain of contagion
- **DIAGNOSE AND TREAT INFECTION EFFECTIVELY**
  7. Treat infection, not colonization
  8. Know when to say "no" to vanco
  9. Stop treatment when infection is cured or unlikely
- **TREAT INFECTION, NOT CONTAMINATION**
  10. Treat infection, not colonization
- **TREAT INFECTION, NOT COLONIZATION**
  11. Isolate the pathogen
  12. Break the chain of contagion

U.S. Trends in Gram-Positive Resistance

1980 to 2004

- MRSE 80%
- MRSA 55%
- PRSP 35%
- VRE 20%
- VISA
- VRSA

VRE Trends in Study Hospitals

vD. Gamache 2001

Rates of Resistance in Specific Patient Populations

- MRSA: ICU 17.9%, Non-ICU 73.2%
- MRSA: ICU 17.9%, Non-ICU 73.2%
- VRE: ICU 0.7%, Non-ICU 6.6%

* p < 0.05
Nosocomial Bacteremia
Distribution of Pathogens from 49 US Hospitals
n = 10,935

- Coag Neg Staph (32%)
- S aureus (16%)
- Enterococcus (11.1%)
- Candida (8%)
- Viridans streptococci (1.4%)
- All GNR (21.4%)
- Other (10.1%)


VRE vs VSE Bacteremia in Matched Liver Transplant Patients

<table>
<thead>
<tr>
<th></th>
<th>VSE</th>
<th>VRE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>54</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>46</td>
<td>19</td>
<td>0.03</td>
</tr>
<tr>
<td>Males/Females</td>
<td>40/14</td>
<td>31/17</td>
<td>NS</td>
</tr>
<tr>
<td>Mean LOS (d)</td>
<td>43</td>
<td>24</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>EF Occurrence</td>
<td>22</td>
<td>7</td>
<td>0.006</td>
</tr>
<tr>
<td>Recurrent episodes</td>
<td>11</td>
<td>1</td>
<td>0.006</td>
</tr>
<tr>
<td>Autopsy infection</td>
<td>57%</td>
<td>35%</td>
<td>0.04</td>
</tr>
<tr>
<td>Mortality</td>
<td>46%</td>
<td>25%</td>
<td>0.04</td>
</tr>
<tr>
<td>Entero at death</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Enterococcal Antibiotic Resistance

**Enterococci**

- Most beta-lactam antibiotic resistance caused by an alteration in penicillin binding proteins (PBP)
- Small percent (~2%) of enterococci are beta-lactamase producing
- Have enzymes that inactivate aminoglycosides
-ypass the effect of vancomycin

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Enterococcal Glycopeptide Resistance


<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Terminal Peptidoglycan</th>
<th>MIC (mg/L)</th>
<th>Source</th>
<th>Induction</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van A</td>
<td>D-Ala-D-Lact</td>
<td>V=64</td>
<td>Acquired</td>
<td>Inducible</td>
<td>E. faecium</td>
</tr>
<tr>
<td>Van B</td>
<td>D-Ala-D-Lact</td>
<td>V&gt;16</td>
<td>Tn 1546</td>
<td>Inducible</td>
<td>E. faecalis</td>
</tr>
<tr>
<td>Van C</td>
<td>D-Ala-D-Ser</td>
<td>V&lt;2</td>
<td>Tn 1547</td>
<td>Inducible</td>
<td>E. faecium</td>
</tr>
<tr>
<td>Van D</td>
<td>D-Ala-D-Lact</td>
<td>V=16</td>
<td>Intrinsic Constitutive &amp; Inducible</td>
<td>E. faecium</td>
<td></td>
</tr>
<tr>
<td>Van E</td>
<td>D-Ala-D-Ser</td>
<td>V=16</td>
<td>Acquired Inducible</td>
<td>E. faecalis</td>
<td></td>
</tr>
</tbody>
</table>

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Staph Stinks
How Rosie survived a life-threatening infection.
### S. aureus Susceptibility to Vancomycin

<table>
<thead>
<tr>
<th>Susceptibility Type</th>
<th>Vancomycin MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive (VSSA)</td>
<td>≤ 4 mg/L</td>
</tr>
<tr>
<td>S. aureus Reduced Susceptibility (SARV or heterovariant)</td>
<td>1-4 mg/L (Still NCCLS Sensitive)</td>
</tr>
<tr>
<td>Intermediate (VISA or GISA)</td>
<td>8-16 mg/L</td>
</tr>
<tr>
<td>Resistant (VRSA)</td>
<td>≥ 32 mg/L</td>
</tr>
</tbody>
</table>

- Lab needs to backup primary testing with 6mg/L vancomycin overnight plate

### Vancomycin Resistant S. aureus (VRSA)

**May be the next modern day plague**


“The emergence of VRSA would represent the most important issue in antibiotic resistance since the dawn of the antibiotic era. A common, virulent, & transmissible bacterial agent with no known effective therapy would set infectious diseases back 60 years.”

### Staphylococcal Resistance

- Virtually all *S. aureus* & *S. epidermidis* are beta-lactamase producers

- Primary mechanism of MRSA or MRSE resistance is an alteration of penicillin binding protein affinity (PBP)

  - MRSA (mecA positive) ~50% hospital & ~20% of community are MRSA PBP 2a or PBP 2’

  - ARV
    - Mechanism not well understood

  - ISA/GISA
Community Acquired Methicillin Resistant S. aureus
Chambers, HF: APUA Newsletter 21(2), 2003

Estimated incidence 5-15% without established risk factors
- Two main clones
  - 1997 North Dakota/Minnesota
  - Los Angeles County

Outbreaks/Risk groups
- Minnesota and North Dakota & elsewhere
- Correctional facilities
- Contact sports
- Native American reservations
- Men having sex with men

Prevalence up to 75% in select groups

Unique features of CMRSA vs nosocomial strains
- Susceptible to antibiotics other than beta-lactams
- CMRSA genotypes different from hospital strains
- Harbor novel methicillin resistance cassette
- Panton Valentine Leukocidin toxin present
- CRMSA occur in patients lacking traditional risk factors

Molecular Biology of CA-MRSA

Staphylococcal Chromosome Cassette
- mec complex & cassette recombinase genes (ccr)
- 5 distinct SCC-mec elements known
- SCC-mec Type IV & V found in CA-MRSA
- Type IV & V causes resistance to beta-lactams

Toxins
- Super antigen enterotoxin H (seh) & enterotoxin O (seo) cause a syndrome similar to toxic shock syndrome
- Panton Valentine Leukocidin (lukS-PV & lukF-PV)
**Community Acquired MRSA**

- Organism genotypically different from hospital MRSA
  - SCC mec Type IV & V
  - PVL Toxin
  - Enterotoxin H, B, & C
- Can spread rapidly causing necrotic hemorrhagic pneumonia
- May be susceptible to a variety of antibiotics
- Likely will be a growing and concerning healthcare problem in United States and elsewhere

**Treatment of CMRSA**

**Stevens, DL: APUA Newsletter 21(2),2003**

- **Soft tissue (Non Toxic)**
  - Linezolid, Vancomycin, Q/D, TMP/SMX, or Tetracycline
- **Pneumonia (Toxic)**
  - Linezolid or Vancomycin
- **Bacteremia (Toxic)**
  - Vancomycin, Q/D, or Linezolid
- **Endocarditis (Toxic)**
  - Vancomycin or Q/D
- **TSS (Toxic)**
  - Linezolid
- **Complicated Skin/Soft Tissue (Toxic)**
  - Vancomycin, Linezolid, or Q/D

**VISA & VRSA Background**

- Develop in hospital background where vancomycin is overused
- Common patient history
  - Host is compromised with multiple medical maladies
  - HD or PD
    - Indwelling catheter
    - Intra-peritoneal sledge with PD
  - Infection with MRSA or Enterococci
  - Extended duration of vancomycin therapy
    - Patients would have met CDC guidelines
- While VISA’s appear independent, VRSA seems to have acquired resistance from enterococci via vanA plasmid
Vancomycin Resistant *S. aureus* (VRSA)

**MMWR 51(26):565-566, 2002 / ICAAC 2002**

- June 2002, 40 yr Michigan patient with DM, PVD, & CRF had catheter swab + VRSA
  - Patient maintained on HD
  - Chronic foot ulcerations since April 2001 treated with multiple courses of antibiotic including vancomycin
  - April 2002 toe amputated & developed MRSA bacteremia with infected AV HD graft (VM & rifampin plus graft removed)
  - June 2002 temporary HD catheter exit wound infection with MRSA (Vancomycin MIC 1024 mg/L & vanA & mecA positive), VRE, & *K. oxytoca*

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**VRSA Pennsylvania**

**MMWR October 11, 2002**

- Patient admitted to hospital for evaluation & treatment of chronic foot ulcer + osteomyelitis
  - Culture revealed *S. aureus* and susceptibility testing suggested decreased susceptibility to vancomycin
  - E-test MIC = 64 mg/L (CDC MIC = 32 mg/L microdilution)
  - mecA & vanA positive
  - Sensitive to chloramphenicol, linezolid, minocycline, quinupristin/dalfopristin, rifampin, & TMP/SMX

- Resistance likely transferred from enterococci

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**VRSA New York 2004**

**MMWR 53(15):322-324, 2004**

- Urine culture from a LTCF patient grew *S. aureus*
  - Microscan overnight panel Vancomycin MIC = 4 mg/L
  - E-Test Vancomycin MIC > 256 mg/L
  - CDC(NCCLS) Vancomycin MIC = 64 mg/L
  - Routine lab testing may not detect VRSA
    - 24 Hr Vancomycin (6 mg/L) Agar Screening Plate used in conjunction
  - mecA & vanA positive
  - Organism unrelated to 2 previously reported strains
Linezolid Resistance S. aureus

- Resistant enterococci previously reported in clinical trials
- First case of S. aureus developing resistance to linezolid (Tsiodras S, et al. The Lancet 2001;358;207-208)
  - 85 y.o. CAPD pt with MRSA peritonitis (MIC = 2)
  - Linezolid for at least 4 weeks (intolerant to vanco)
  - PD cath not removed - accidental laceration at home
  - Re-hospitalized for recurrent peritonitis - recovered a different MRSA resistant to linezolid (MIC > 32)
- Additional cases of VRE being reported post marketing

Pneumococcal Sentinel Surveillance System
Definition of PCN-R S. pneumoniae

- Sensitive
  - PCN MIC < 0.06 mg/L
- Non-susceptible
  - PCN MIC = 0.12 to 1.0 mg/L
- Resistant
  - PCN MIC > 2.0 mg/L
- NCCLS* may change definition
- Mechanism of resistance is alteration of penicillin binding proteins not beta-lactamase production

Antimicrobial Resistance Trend:
S. pneumoniae, USA, 2002-2004

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>TRUST 6 2002</th>
<th>%R</th>
<th>TRUST 7 2003</th>
<th>%R</th>
<th>TRUST 8 2004</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin*</td>
<td>18.4</td>
<td>17.3</td>
<td>18.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>27.5</td>
<td>27.5</td>
<td>25.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimeth/Sufa</td>
<td>26.0</td>
<td>23.9</td>
<td>21.2</td>
<td></td>
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<td></td>
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<tr>
<td>Ceftriaxone (mean/m)</td>
<td>1.7</td>
<td>1.5</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.9</td>
<td>0.9</td>
<td>1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of institutions</td>
<td>239</td>
<td>227</td>
<td>220</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of isolates</td>
<td>7671</td>
<td>4452</td>
<td>4309</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levo - MIC90 (mg/ml)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
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</tr>
</tbody>
</table>

**S. pneumoniae Antimicrobial Resistance**

**TRUST 8 (2003–2004)**

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Penicillin</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC ≥ 2 µg/mL</td>
<td>National Rate: Penicillin = 18.6% R</td>
<td>National Rate: Azithromycin = 25.4% R</td>
</tr>
</tbody>
</table>

- **4,233 isolates from 220 labs**
- Resistance rates for Michigan and Maine are from TRUST 7 (2002-2003)

**Newer & Investigational Therapy for Gram Positives**

- Levofloxacin, Moxifloxacin, Gemifloxacin & Gatifloxacin
- Quinupristin/Dalfopristin (Synercid®-Aventis)
- Linezolid (ZyvoxTM-Pharmacia)
- Daptomycin (Cidecin®-Cubist)
- Oritavancin (LY333328-Intermune)
- Telithromycin-(Ketek® Aventis)
- Dalbavancin –(Versicor)
- Glycyclines (GAR 973 –Tigecycline, Wyeth -Ayerst)

**Quinupristin/Dalfopristin (Synercid®)**

**Streptogramin Overview:**
- Q/D (RF 59500) in 30:70 (w/w) ratio
  - work in synergy at the ribosome to inhibit protein synthesis
- Bactericidal (pathogen dependent)
- FDA Approved Indications
  - VRE- E. faecium only
  - Complicated Skin Infections-MSSA (not MRSA) S. pyogenes
- ADR’s may limit use
- Subject to drug-drug interactions
**Linezolid - Zyvox®**
- Oxazolidinone class antibiotic
- Inhibits protein synthesis
- Oral and IV dosage forms
- Metabolized by chemical oxidation
  - Does not inhibit Cytochrome P450 system
  - Mild, reversible inhibitor of MOA
  - Potential interaction with adrenergic, dopaminergic, and serotonergic agents or tyramine-containing food (ephedrine, SSRI’s, pseudoephedrine, dextromethorphan, & dopamine)
  - Agents could increase BP or serotonin syndrome
  - Not significant clinically to date

**Linezolid Indications**
- FDA Clinical Indications
  - Uncomplicated Skin & Soft Tissue
  - Complicated Skin & Soft Tissue (MSSA & MRSA)
  - Community Acquired Pneumonia
  - Nosocomial Pneumonia (MSSA & MRSA)
  - VRE infections, including bacteremia

Superior results for linezolid vs vancomycin in ventilator-associated pneumonia (VAP)

Subgroup from 2 double-blind, randomized controlled trials in nosocomial pneumonia, n=544 patients with VAP

Clinical cure (%): Superior results for linezolid vs vancomycin in ventilator-associated pneumonia (VAP)

With permission: Kollef M, et al., manuscript submitted September 02.
Ketolides

Telithromycin (Ketek®) Aventis
- Clarithromycin derivative (HMR 3647)
- Effective against macrolide resistant streptococci (erm or mef) & staphylococci (erm)
  - PCN-S, PCN-R & Macrolide-R S. pneumoniae
  - S. pyogenes
  - H. influenzae
  - M. catarrhalis
  - B. pertussis
  - Atypical Respiratory Pathogens
- Usual dose 800 (2-400mg) QD

14 Member Macrolide Structure Macrolides vs. Ketolides

Telithromycin
- Carbamate Extension
- Increased potency via domain II
- Acid Stability
- Sugar
- Cladinose

Telithromycin
- Keto Group
- Acid stability
- Lack of induction of MLSβ resistance

Daptomycin (Cidecin)
- Lipopeptide antibiotic
  - MOA: disrupts cell membrane amino acid transport
  - Concentration-dependent killing
  - $T_{1/2} = 8$ h
  - Protein binding 93%
  - Broad spectrum gram-positive activity
    - MIC ≤ 0.5 mg/L, for MSSA, MRSA, MRSE, & MSSE
    - Enterococcus & Strept
  - New dosage regimens likely 4-6 mg/Kg intravenously QD
LY333328- Oritavancin

- Glycopeptide similar to vancomycin
- Activate against a wide variety of gram-positives, including MRSA & VRE
- Bactericidal, conc-dependent killing
- Long PAE
- Non-renal elimination
- Protein binding (high ~80%)
- Drug very difficult to assay
- Long terminal $T_{1/2}$ (5-7 days)
- Commercial product will be intravenous

Tigecycline
Available ?2006

- Appears to be a bacteriostatic agent exhibiting concentration independent killing
- Available parenterally 100mg LD and 50mg BID
- Likely used for S/S/T, IA, HAP, and CAP
- Good gram negative action (No P aeruginosa or Proteus)
- Good gram positive, anaerobic, and atypical coverage
- Stable 6-8 hrs room temperature, 24 hrs refrigerated
- Cannot mix in Dextrose solution
- Color change from orange to green/black
- Half-life 36hrs

Conclusions

4 Number of new compounds have been introduced & more coming that will address issues with resistant gram positive bacteria
4 Clinicians can help in the education of other healthcare providers regarding appropriate use and dosing of these new & older agents
4 Remember that with every antibiotic prescription you are conducting your own experiment in Darwinian theory