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

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Objectives
- Review current & future antibiotic treatment options for gram positive infections
- Review pharmacokinetic and pharmacodynamic properties of newer agents
- Examine optimal treatment strategies including antibiotic selection and dosing of newer antibiotics for gram positive infections
- Discuss the clinician’s role in combating gram positive resistance
  1. Appropriate use of narrow spectrum agents
  2. Targeting antibiotic therapy
  3. Role of pharmacokinetics & pharmacodynamics
  4. Monitoring antibiotic use & duration of therapy

12 Steps to Prevent Antimicrobial Resistance in Hospitalized Adults

PREVENT INFECTION
1. Vaccinate
2. Get the catheters out

DIAGNOSE AND TREAT INFECTION EFFECTIVELY
3. Target the pathogen
4. Access the experts

USE ANTIMICROBIALS WISELY
5. Practice antimicrobial control
6. Use local data
7. Treat infection, not contamination
8. Know when to say “no” to vanco
9. Stop treatment when infection is cured or unlikely

PREVENT TRANSMISSION
11. Isolate the pathogen
12. Break the chain of contagion

U.S. Trends in Gram-Positive Resistance

Percent of Pathogens Resistant to Antibiotics

0 10 20 30 40 50 60 70 80 90 100

MRSE 80%
MRSA 55%
VRE 20%
PRSP 35%
VISA ~5-75% MRSA In Community

VRE Trends in Study Hospitals

V. O. Gamache 2001

Rates of Resistance in Specific Patient Populations

MRSA/MRCNS/VRE/ICU: 0.1% - 95.3% * 17.3% Non-ICU: 28.1% - 73.2% *

* p < 0.05

**Nosocomial Bacteremia**

Distribution of Pathogens from 49 US Hospitals  
**n = 10,935**

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

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**VRE vs VSE Bacteremia in Matched Liver Transplant Patients**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mortality</th>
<th>Mean Hosp Cost (1988)</th>
<th>Per Diem Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSE</td>
<td>17</td>
<td>3 (18%)</td>
<td>$91,833</td>
<td>$5766</td>
</tr>
<tr>
<td>VRE</td>
<td>17</td>
<td>9 (53%)</td>
<td>$190,728</td>
<td>$9435</td>
</tr>
</tbody>
</table>

*P = .0001  
P = .005*

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**Outcomes in VR-**E. faecium** Bacteremia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>VREF</th>
<th>VSEF</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>54</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>46</td>
<td>52</td>
<td>NS</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>46</td>
<td>19</td>
<td>0.03</td>
</tr>
<tr>
<td>EF Occurrence</td>
<td>43</td>
<td>24</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Recurrent episodes</td>
<td>22</td>
<td>7</td>
<td>0.006</td>
</tr>
<tr>
<td>Autopsy infection</td>
<td>11</td>
<td>1</td>
<td>0.006</td>
</tr>
<tr>
<td>Mortality</td>
<td>57%</td>
<td>35%</td>
<td>0.04</td>
</tr>
<tr>
<td>Entero at death</td>
<td>46%</td>
<td>25%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Gram Positive Resistance

Primary mechanism of beta-lactam resistance is an alteration of penicillin binding protein affinity (PBP).
- **MRSA** (mecA positive) ~50% hospital & ~20% of community are MRSA
- **PRSP**
- **Enterococci**
  - Small percent (~2%) of enterococci are beta-lactamase producing
  - Have enzymes that inactivate aminoglycosides
  - Bypass the effect of vancomycin

**ISA/GISA**
- Over production PBP-2 & thickened cell wall

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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>VanA</td>
<td>D-Ala-D-Lact</td>
<td>V&gt;64</td>
<td>Acquired</td>
<td>Inducible</td>
<td><em>E. faecium</em></td>
</tr>
<tr>
<td>VanB</td>
<td>D-Ala-D-Lact</td>
<td>V=4</td>
<td>Acquired</td>
<td>Inducible</td>
<td><em>E. faecalis</em></td>
</tr>
<tr>
<td>VanC</td>
<td>D-Ala-D-Ser</td>
<td>V&gt;2</td>
<td>Tn 1547</td>
<td>Acquired</td>
<td><em>E. faecium</em></td>
</tr>
<tr>
<td>VanD</td>
<td>D-Ala-D-Lact</td>
<td>V=16</td>
<td>Intrinsic</td>
<td>Constitutive &amp; Inducible</td>
<td><em>E. gallinarum</em></td>
</tr>
<tr>
<td>VanE</td>
<td>D-Ala-D-Ser</td>
<td>V=16</td>
<td>Acquired</td>
<td>Constitutive</td>
<td><em>E. faecium</em></td>
</tr>
<tr>
<td>Van G</td>
<td>D-Ala-D-Ser</td>
<td>V=16</td>
<td>Acquired</td>
<td>Inducible</td>
<td><em>E. faecalis</em></td>
</tr>
</tbody>
</table>

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Staph Stinks
How Rosie survived a life-threatening infection.
Community Acquired Methicillin Resistant S. aureus  
Chanbers, 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

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
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.”

Vancomycin Resistant S. aureus (VRSA)

VISA & VRSA Background
- Develop in hospital background where vancomycin is overused
- Common patient history
  1. Host is compromised with multiple medical maladies
  2. HD or PD
     - Indwelling catheter
     - Intra-peritoneal sledge with PD
  3. Infection with MRSA or Enterococci
  4. 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)

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
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 & van A positive
- Sensitive to chloramphenicol, linezolid, minocycline, quinupristin/dalfopristin, rifampin, & TMP/SMX
- Resistance likely transferred from enterococci

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

*National Committee for Clinical Laboratory Standards
**Comparison of Antimicrobial Resistance of S. pneumoniae, USA, 2001-2003**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>TRUST 5 2001</th>
<th>TRUST 6 2002</th>
<th>TRUST 7 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin (MIC ≥ 2mg/L)</td>
<td>16.9%</td>
<td>18.4%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>27.5%</td>
<td>27.5%</td>
<td>27.6%</td>
</tr>
<tr>
<td>Trimeth/ Sulfamethoxazole</td>
<td>28.1%</td>
<td>26.0%</td>
<td>24.1%</td>
</tr>
<tr>
<td>Ceftriaxone (nonmening)</td>
<td>1.6%</td>
<td>1.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.78%</td>
<td>0.89%</td>
<td>0.96%</td>
</tr>
</tbody>
</table>

No. of institutions: 240, 239, 226
No. of isolates: 6362, 7671, 4456
Levo - MIC: 90, 1.0, 1.0

NCCLS broth microdilution - centralized lab, Focus Technologies


Data on file, Ortho-McNeil Pharmaceutical, Inc.

4,377 isolates, 226 labs.

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**S. pneumoniae Antimicrobial Resistance TRUST 7 (2002-2003)**

**Newer & Investigational Therapy for Gram Positives**

- Levofloxacin, Moxifloxacin, & Gatifloxacin
- Quinupristin/Dalfopristin (Synercid®-Aventis)
- Linezolid (Zyvox®-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 (RP 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

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**Mechanisms of Resistance**

- **ALTERED PERMEABILITY ON UPTAKE**
- **ALTERED CELLULAR TARGETS**
- **DRUG-MODIFYING ENZYMES**

- Ribosome Modification (quinupristin)
- Cytoplasmic membrane
- Active Efflux (dalfopristin)
- Porin Channels
- Cell Wall
- Periplasmic space
- Quinupristin hydrolase
- Dalfopristin acetylase

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**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

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**Linezolid Adverse Events**

- Linezolid is well-tolerated in adults treated with 600 mg BID for up to 28 days
- Most common drug-related AEs were diarrhea (4%), nausea (3%), and headache (2%)
- Changes in platelet counts and hemoglobin were mild and transient; monitor CBC in patients at risk or with long-term therapy (suppression of bone marrow)
- Linezolid is a mild, reversible inhibitor of MAOI — effects not anticipated to be similar to classic MAOI — events reported rarely

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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

With permission: Kollef M, et al., manuscript submitted September 02.
**Myelosuppression: CUP (n=828)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Total (n%)</th>
<th>&lt;14 days (n%)</th>
<th>14-28 days (n%)</th>
<th>&gt;28 days (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>62 (7.2)</td>
<td>12 (1.4)</td>
<td>26 (3.1)</td>
<td>24 (2.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>35 (4.2)</td>
<td>3 (0.4)</td>
<td>8 (1.0)</td>
<td>24 (2.9)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>18 (2.2)</td>
<td>1 (0.12)</td>
<td>5 (0.6)</td>
<td>12 (1.5)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>2 (0.2)</td>
<td>0</td>
<td>2 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>All hematological</td>
<td>177 (14.1)</td>
<td>16 (1.9)</td>
<td>41 (4.9)</td>
<td>60 (7.2)</td>
</tr>
</tbody>
</table>

- Total hematological events <14 days = 16 (1.9%); >14 days = 101 (12.2%).
- Patients treated <28 days = 289; 14-28 = 301; >14 days = 238.

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**Linezolid (vs Vancomycin) Does Not Increase the Risk of Thrombocytopenia**

Nasraway, SA et al. CID 37:1609-1616, 2003

- 686 patients (1030 enrolled) with nosocomial pneumonia treated with vancomycin or linezolid for ≥ 5 days

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5 days</td>
<td>414</td>
<td>448</td>
</tr>
<tr>
<td>≥ 14 days</td>
<td>89</td>
<td>102</td>
</tr>
</tbody>
</table>

- New onset thrombocytopenia (<150x10^9/L) 19/295 (6.4%) linezolid pts & 22/285 (7.7%) vancomycin patients
- Severe thrombocytopenia (<50x10^9/L) present in one patient in each group
- No statistical difference between linezolid & vancomycin

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**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
Telithromycin (Ketek®)

- Inhibits protein synthesis
  - Attacks 50S ribosome by binding to both domains II & V vs domain V for macrolides
  - Greater affinity for Domain V

- Bacterial resistance
  - Not affected by ermB or ermTR
    - Requires monomethylation of 23S ribosome for macrolide
    - Requires dimethylation of 23S ribosome for ketolide
  - Not affected by efflux (mefE or mefA)

Telithromycin (Ketek®)

- Perspective
  - New & somewhat novel compound expanded spectrum against resistant respiratory pathogens
  - Not clearly positioned in current CAP guidelines
  - May serve as fluoroquinolone alternative
  - Concern for H. influenzae activity
  - Concern for Drug-Drug interactions
  - Isolates already exist with elevated MIC’s
  - Only available orally
  - Cost

Tigecycline
Available ?2006

- Appears to be a bacteriostatic agent exhibiting concentration independent killing
- Available parenterally 100mg LD and 50mg BID
- Likely used for S/ST, 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
Daptomycin (Cidecin)
Cubist Pharmaceuticals Formerly an Eli Lilly Drug

- 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-90 < 0.5 mg/L for MSSA, MRSA, MRSE, & MSSE
- Enterococcus & Strept
- New dosage regimen 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

Conclusions

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