Antibiotic Resistance:
Epidemiology of Resistance, Resistance Mechanisms, & Future Implications

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Objectives

- Identify current & future antibiotic treatment options for gram positive and gram negative infections
- Identify underlying mechanisms of antibiotic resistance for gram positive and gram negative pathogens
- Identify two unique molecular features of CA-MRSA
- Identify common clinical features associated with VISA & VRSA infections

Current Gram Positive Issues

- **S. aureus**
  4 Methicillin (Oxacillin) resistant (MRSA or ORSA)
  4 Heteroresistant variants (h-VISA)
  4 Vancomycin intermediate (VISA)
  4 Vancomycin resistant (VRSA)
  4 Community acquired
- **Enterococci**
  4 Beta-lactam resistant
  4 Vancomycin resistant
  4 Aminoglycoside resistant
- **Penicillin &/or Macrolide Resistant S. pneumoniae**

Current Gram Negative Issues

- **K. pneumoniae & E. coli**
  4 Extended Spectrum Beta-lactamases (ESBL)
- **Carbapenemases**
  4 K. pneumoniae & P. aeruginosa
- **P. aeruginosa, Acinetobacter spp, & Stenotrophomonas spp** resistant to all commonly tested antibiotics

As Industry Profits Elsewhere, U.S. Lacks Vaccines, Antibiotics

WSJ (November 8, 2005)

- Antibiotics comprise 5/506 (<1%) drugs in development
- Lipitor revenues ($12B) more than entire vaccine market
- U.S. vaccine manufacturers have dropped from 25 thirty years ago down to handful
- Government will not indemnify manufacturers
- Industry cannot recover costs on most biologicals
- BioShield legislation has not been successful at creating an incentive for new antibiotics and biologicals

Colistin

- Colistin identified in 1950 (*B. colistinus*)
  4 Polycationic peptide ring of 8-10 amino acids with substituted 2, 4-diamino-butyric (DAB) acid residues
  4 Fatty acid (FA) side chain attached to peptide ring
    - Colistin A (Polymyxin E1) 6-methyl-octanoic acid
    - Colistin B (Polymyxin E2) 6-methyl-heptanoic acid
  4 Combination of DAB and fatty acid side chain give colistin amphipathic properties
  4 MW 1200
- First clinical use 1959
- Colistin methanesulfonate introduced in 1961

E. Hermsen IDCNA 17: 545-562, 2003
Colistin Housekeeping
- Synonymous terms
  4 Colistin and Polymyxin E
  4 Sulphomethyl, colistimethate, methanesulfonate, & CMS
- Product differences
  4 Colistin sulfate used topically and orally not IV or IM
  4 CMS is the parenteral form of the drug
- Potency differences
  4 Colistin sulfate is 4-8 fold more potent than CMS

Mechanisms of Action of Antibiotics

Mechanisms of Resistance to Antibiotics

Is there a doctor in the house?
- You have an 80 year old patient admitted from a NH with an E. coli UTI and possible bacteremia. Patient was initially started on Ceftriaxone 1Gm Q24H but has not done well. You review the antibiotic susceptibility data:
  - Levofloxacin 1mg/L, Gentamicin 0.5 mg/L, Ceftriaxone 2 mg/L, Imipenem 1 mg/L, & P/T 4mg/L
  - The pathogen is resistant to TMP/SMX, Ampicillin, & 1st generation cephalosporins
- You should???

ESBL Outbreak in NYC Hospital ICU

CLSI (NCCLS) Testing Recommendations for ESBL’s
- Test E. coli & Klebsiella spp where MIC ≥ 2 mg/L for 3rd generation cephalosporin or aztreonam
- Cefpodoxime ≥ 8 mg/L
- Test cefotaxime or ceftazidime alone and in combination with 4 mg/L clavulanate
  4 Look for ≥3 tube dilution change in MIC with clavulanate
- Backup Confirmation Test
  - ESBL E-test strip
  - Disk approximaiton test
Carbapenemase Producing Enterobacteriaceae

- Diverse group of enzymes from Class A, B, & D active against oximinocephalosporins, cephamycins, & carbapenems
  1. 17 IMP (Plasmid mediated carbapenemases Japan 1999’s)
  2. 10 VIM (Italy 1999)
  3. KPC (Plasmid mediated)
- 30 imipenem resistant gram negative rods isolated from 7/16 U.S. rivers 1999-2001
- Enterobacter asburiae producing IMI-1 & IMI-2 carbapenemases
- 4KPC-2 first inducible & plasmid encoded carbapenemase
- Now have a U.S. environment and enterobacteriaceae reservoir
  Emerging Infectious Diseases 11(2) Feb 2005
- Outbreak 2003/2004 in Brooklyn, NY with K. pneumoniae
  JAC 2005

Relationship between fluoroquinolone use & changes in susceptibility to fluoroquinolones

- Observed changes in 11 pathogens at 10 U.S. teaching hospitals 1991-2000
- Data demonstrated significant decreases in fluoroquinolone susceptibility for P. aeruginosa (25.1%), P. mirabilis (11.9%), E. coli (6.8%), & S. aureus (26.8%)
- Change in fluoroquinolone susceptibility linked to increase in fluoroquinolone use

Antimicrobial Susceptibility for P. aeruginosa USA 2002-2005

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<tbody>
<tr>
<td>Ceftazidime</td>
<td>79.7</td>
<td>80.6</td>
<td>73.1</td>
<td>83.2</td>
<td>86.0</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>NT</td>
<td>79.5</td>
<td>76.9</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Gentamicin</td>
<td>76.7</td>
<td>72.3</td>
<td>72.4</td>
<td>82.7</td>
<td>86.4</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>85.8</td>
<td>87.0</td>
<td>81.8</td>
<td>87.1</td>
<td>89.8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>81.9</td>
<td>78.8</td>
<td>81.3</td>
<td>84.5</td>
<td>85.2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>67.4</td>
<td>68.8</td>
<td>63.5</td>
<td>67.2</td>
<td>70.4</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>67.7</td>
<td>65.3</td>
<td>60.6</td>
<td>65.9</td>
<td>69.1</td>
</tr>
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<tbody>
<tr>
<td>998 (36)</td>
<td>862 (36)</td>
<td>888 (36)</td>
<td>549</td>
<td>1219</td>
<td></td>
</tr>
</tbody>
</table>

- No antimicrobial demonstrated > 90% Susceptibility for 2005

The Changing Face of S. aureus: The 1940’s to Present
S. aureus

- Penicillin sensitive
- Penicillin resistant
- Methicillin (Oxacillin) resistant (MRSA or ORSA)
  - Traditional hospital acquired (HA-MRSA)
- Vancomycin intermediate (VISA)
- Vancomycin resistant (VRSA)
- Heterovariants (h-VISA)
- Agr II status (+ dysfunctional)
- Community acquired (CA-MRSA)
- Tolerance
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 (PBP)

RSA (mecA positive) ~60% hospital & ~60% of community are MRSA

BP 2a or PBP 2'

eteroressistant (h-VISA)

VISA & VRSA Background

- Develop in hospital background where vancomycin is overused
- Common patient history
  - Host is compromised with multiple medical maladies
  - HD or PD
  - 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

Community Acquired MRSA

- Organism genotypically different from hospital MRSA
  - SCC mec Type IV & V
  - PVL Toxin
  - Enterotoxin H, B, & C
- Most often presents as a skin infection
- Can cause necrotic hemorrhagic pneumonia
- May be susceptible to a variety of antibiotics
- A growing and concerning healthcare problem in United States and elsewhere

Characteristics of Staphylococcal Cassette Chromosome mec (SCCmec) Types I-V

<table>
<thead>
<tr>
<th>SCCmec Type</th>
<th>SCCmec Size (kb)</th>
<th>Other antibiotic-resistant elements (gene) on SCCmec</th>
<th>Organism site (hospital or community)</th>
<th>Presence of Panton-Valentine Leukocidin in S. aureus isolates carrying the specified SCCmec type</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>34</td>
<td>S. aureus isolates: PUB100, PUB110, Tn501</td>
<td>Hospital</td>
<td>Intrequent</td>
</tr>
<tr>
<td>II</td>
<td>33</td>
<td>PUB110 (aadD + tetr,D, VISA/VRSA)</td>
<td>Hospital</td>
<td>Intrequent</td>
</tr>
<tr>
<td>III</td>
<td>47</td>
<td>PUB110, PUB100, Tn501, T1001 (ortR) HVR92</td>
<td>Hospital</td>
<td>Intrequent</td>
</tr>
<tr>
<td>IV</td>
<td>25–34</td>
<td>Community isolates: hVISA</td>
<td>Community</td>
<td>Frequent</td>
</tr>
<tr>
<td>V</td>
<td>28</td>
<td>Community isolates: VRSA</td>
<td>Community</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

In general, ~5% of staphylococci that carry SCCmec types I-III also carry the PVL gene; with some exceptions, ~80% of all staphylococci that carry SCCmec type IV carry the PVL gene.

Characteristic to resist vancomycin, ampicillin, clindamycin, and erythromycin.

CDC 2005:40(15 February)

CA-MRSA vs HA-MRSA

CA-MRSA vs HA-MRSA

<table>
<thead>
<tr>
<th>Toxin Gene</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVL</td>
<td>77%</td>
<td>4%</td>
</tr>
<tr>
<td>sea</td>
<td>58%</td>
<td>4%</td>
</tr>
<tr>
<td>seb</td>
<td>23%</td>
<td>4%</td>
</tr>
<tr>
<td>sec</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>sek</td>
<td>65%</td>
<td>0%</td>
</tr>
<tr>
<td>seh</td>
<td>62%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Naimi, TS et al JAMA 290:2976-2984, 2003

Prevalence of MRSA among 422 ED Patients with SSTI

<table>
<thead>
<tr>
<th></th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7/13 (54%)</td>
<td>11/28 (39%)</td>
</tr>
<tr>
<td></td>
<td>24/47 (51%)</td>
<td>25/42 (60%)</td>
</tr>
<tr>
<td></td>
<td>18/30 (60%)</td>
<td>23/32 (72%)</td>
</tr>
<tr>
<td>MSSA 17%</td>
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</table>


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

CA-MRSA Risk Factors

- Skin on skin exposure
  - Athletes
  - Prisoners
  - Sexual activity
- Close living quarters
  - Prisons
  - Reservations
  - Military Bases
  - Locker rooms
  - Nursing Home
  - Day Care
  - Shelters
- Sharing towels, razors, athletic equipment, etc
- Compromised skin integrity
- Lesion looks like a “spider bite”
- Areas where CA-MRSA endemic

Treatment CA-MRSA

- Local Therapy
  - Hot packs, rest, and elevation
  - Incision & drainage
- Antibiotics
  - Non-MRSA
  - CA-MRSA
- Infection Control
  - Handwashing
  - Education
    - Sharing personal items
    - Personal hygiene
  - Asymptomatic colonizers
  - Contaminated equipment (1:10 bleach solution)

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 - 2002-2005

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>TRUST 6 2002</th>
<th>TRUST 7 2003</th>
<th>TRUST 8 2004</th>
<th>TRUST 9 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>18.4%</td>
<td>17.3%</td>
<td>18.6%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>27.5%</td>
<td>27.5%</td>
<td>25.0%</td>
<td>28.8%</td>
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<tr>
<td>Trimeth/Sulfamycin</td>
<td>26.0%</td>
<td>23.9%</td>
<td>21.2%</td>
<td>20.3%</td>
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<tr>
<td>Ceftriaxone*</td>
<td>1.7%</td>
<td>1.5%</td>
<td>1.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>No. of institutions</td>
<td>239</td>
<td>227</td>
<td>220</td>
<td>184</td>
</tr>
<tr>
<td>No. of isolates</td>
<td>7671</td>
<td>4452</td>
<td>4309</td>
<td>4958</td>
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</tbody>
</table>


## Enterococcal Glycopeptide Resistance


<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Terminal Peptidoglycan</th>
<th>MIC (µg/L)</th>
<th>Source</th>
<th>Induction</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van A</td>
<td>D-Ala-D-Lac V≥64</td>
<td>T≥16</td>
<td>Acquired</td>
<td>Inducible</td>
<td>E. faecium</td>
</tr>
<tr>
<td>Van B</td>
<td>D-Ala-D-Lac V≥24</td>
<td>Tn 1546</td>
<td>Acquired</td>
<td>Inducible</td>
<td>E. faecalis</td>
</tr>
<tr>
<td>Van C</td>
<td>D-Ala-D-Ser V≥2</td>
<td>Tn 1547</td>
<td>Intrinsic</td>
<td>Constitutive &amp; Inducible</td>
<td>E. gallinarum</td>
</tr>
<tr>
<td>Van D</td>
<td>D-Ala-D-Lact V≥16</td>
<td>T≥2</td>
<td>Intrinsic</td>
<td>Constitutive</td>
<td>E. faecium</td>
</tr>
<tr>
<td>Van E</td>
<td>D-Ala-D-Ser V≥16</td>
<td>Acquired</td>
<td>Inducible</td>
<td>E. faecalis</td>
<td></td>
</tr>
<tr>
<td>Van G</td>
<td>D-Ala-D-Ser V≥16</td>
<td>Acquired</td>
<td>Inducible</td>
<td>E. faecalis</td>
<td></td>
</tr>
</tbody>
</table>

## Conclusions

- Need more novel antimicrobials & vaccines
- Support national and international surveillance efforts
- Promote appropriate use of antibiotics in humans & for agricultural use
- Need better real time diagnostics
- Clinical application of pharmacodynamic concepts when dosing antimicrobials

## Conclusions

- Promote appropriate use of infection control measures & vaccination programs
- Develop programs to monitor antibiotic use throughout our society
- Ongoing education and awareness by public & professionals
- In the meantime, patients will die from resistant pathogens for which we have no viable therapy