Factors in the Selection of Anti-infectives: MICROBIAL RESISTANCE

Therapeutics PHMPR-732
John A. Bosso, Pharm.D.

In what part of the country is antibiotic resistance among bacterial respiratory pathogens the highest?

1. Northeast
2. Southeast
3. Midwest
4. Southwest
5. West Coast

OVERVIEW OF PRESENTATION

- Mechanisms of development of resistance
- Mechanisms of resistance
  - Examples
- Examples of Problem Bacteria; 2006 and beyond
  - Mechanisms, prevalence, susceptibility patterns
  - Respiratory pathogens
  - Gram-positives
  - Gram-negatives

The history of antimicrobials...

2000 BC: Here, eat this root.
1000 AD: Roots are heathen; say this prayer.
1850: Prayers are superstition; take this potion.
1945: Potions are a crock; take this penicillin.
1955:Oops, forget penicillin. Take tetracycline.
1960-2002: 39 or more “oops.”
2001: The bugs have won. Eat this root.
The Evolution of Bacterial Resistance

1. Penicillin-susceptible staphylococci
2. Penicillin-resistant staphylococci
3. Methicillin-resistant staphylococci

History of resistance

<table>
<thead>
<tr>
<th>Year</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>Penicillin</td>
</tr>
<tr>
<td>1943</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>1945</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>1950</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>1952</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>1956</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>1960</td>
<td>Methicillin</td>
</tr>
</tbody>
</table>

Impact of Anti-infective Resistance

- Infections with resistant organisms associated with:
  - Higher rates of hospitalization
  - Greater length of hospital stay
  - Higher rates of illness and death
- Estimated cost of treating associated infections in USA is several billion dollars

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How do bacteria become resistant?

Intrinsic vs. Acquired Resistance
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Intrinsic Resistance
• Lack of drug-susceptible target
  – e.g., resistance of PBPs of enterococci to cephalosporins
• Inherent property of organism preventing abx from reaching target
  – e.g., resistance of Gram-negative organisms to vancomycin due to its inability to penetrate the outer membrane

Acquired Resistance
• Apparent change in genetic information through:
  – Mutation (chromosomal)
  – Expression of latent gene
  – Acquisition of new genetic material
    • Conjugation
    • Transduction
    • Transformation

Exchange of Genetic Information Through Conjugation (± plasmids)

Acquisition of DNA Through Transduction (via bacteriophage)
Mutation
- In general, not a common/frequent mode of resistance evolution
- *Hypermutable* strains
  - Up to 1000X increased spontaneous mutation rate
  - Due to defects in genes involved in DNA repair or error avoidance
- e.g., *P. aeruginosa*

Organisms Known to Exchange Resistance Genes in Nature

Mechanisms of Bacterial Resistance
- Antibacterial Inactivation
- Alteration of Target Site
- Decreased Intracellular concentrations

MECHANISMS OF RESISTANCE
Variations on the Theme(s)
- INACTIVATION
  - overproduction of inactivating enzymes
- ALTERATION OF TARGET
  - overproduction of protein target
- DECREASED PENETRATION
  - active efflux pumps
Expression of Bacterial Resistance

**INDUCTION vs. SELECTION**

e.g.,

**INDUCTION OF GROUP-1 β-LACTAMASE PRODUCTION**

NORMAL (UNINDUCED STATE)

- Regulator Gene
- β-lactamase

INDUCED (TEMPORARY) STATE

- β-lactam antibiotic
- Regulator Gene
- β-lactamase
**Resistance**
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### Induction Potential for AmpC β-lactamases

<table>
<thead>
<tr>
<th>Highest</th>
<th>Carbapenems &amp; cephamycins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aminopenicillins</td>
</tr>
<tr>
<td></td>
<td>Carbenicillin, ticaracillin</td>
</tr>
<tr>
<td></td>
<td>Ureidopenicillins</td>
</tr>
<tr>
<td></td>
<td>Cephalosporins</td>
</tr>
<tr>
<td></td>
<td>Clavulanic Acid</td>
</tr>
<tr>
<td></td>
<td>Cefepime, cefpirome</td>
</tr>
<tr>
<td></td>
<td>Sulfone inhibitors</td>
</tr>
</tbody>
</table>

| Lowest  | Aztreonam                 |

### Normal (Uninduced State)

- **Regulator Gene**
- **β-lactamase**

### Constitutive (Stably Derepressed) State (Via Mutation)

- **Mutation**
- **Regulator Gene**
- **β-lactamase**

### Selection of Resistant Mutants
Selection for Antimicrobial-Resistant Strains

Antibacterial Inactivation

The β-Lactamases

Class A, C, and D β-lactamases: Mode of Action

Classification of β-lactamases

- Two families have evolved over time: the serine β-lactamases (classes A, C, D) and the metallo-β-lactamases (class B)
- Molecular class (primary structure)\(^1\)
  - Classes A - D
- Substrate spectrum & response to inhibitors
  - Bush-Jacoby-Medeiros classification\(^2\)

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Examples of β-lactamases of Gram-negative Bacteria

<table>
<thead>
<tr>
<th>β-lactamase</th>
<th>Ex</th>
<th>Substrates</th>
<th>CA inh</th>
<th>Med. Clk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad spectrum</td>
<td>TEM-1</td>
<td>older BLs</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>OXA-1</td>
<td>older BLs &amp; meth</td>
<td>?</td>
<td>D</td>
</tr>
<tr>
<td>ESBL</td>
<td>TEM-12</td>
<td>old &amp; new BLs</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>PER-1</td>
<td>old &amp; new BLs</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>CTX-M</td>
<td>old &amp; new BLs</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>OXA-15</td>
<td>old &amp; new BLs</td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td>AmpC</td>
<td>ACC-1</td>
<td>ESBL &amp; cephamycins</td>
<td>0</td>
<td>C</td>
</tr>
<tr>
<td>Carbapenemase</td>
<td>IMP</td>
<td>AmpC &amp; carb’s</td>
<td>0</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>KPC</td>
<td>AmpC &amp; carb’s</td>
<td>++++</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>OXA-23</td>
<td>AmpC &amp; carb’s</td>
<td>+</td>
<td>D</td>
</tr>
</tbody>
</table>


Amp C β-lactamases
(Molecular class C)
- Inducible/selectable resistance
- Chromosomal and plasmid mediated
- Hydrolyze most β-lactams (except carbapenems and cefepime)
- Must be expressed at high levels to confer resistance to 3rd generation cephalosporins
  - High level expression of chromosomal Amp C β-lactamase must generally be induced while high level expression is common for plasmid-mediated
- Originally P. aeruginosa, Acinetobacter, Serratia, Providencia, etc. but now moved (via plasmids) to more common organisms (E. coli and K. pneumoniae)

Bacteria Producing Inducible AmpC β-lactamases
- Serratia marcescens; Providencia retgeri & stuartii; Acinetobacter spp; Citrobacter freundii; Enterobacter aerogenes, cloacae & sakazakii
- Hafnia alvei; Morganella morgani; Aeromonas hydrophila & sobria; Chromobacterium violaceum; Rhodobacter sphaeroides
- Pseudomonas aeruginosa

Extended-Spectrum β-lactamases (ESBL)
[Molecular classes A & D]
- early examples arose from mutation of common β-lactamases (TEM, SHV)
- hydrolyze ceftotaxime, cefazidime & other broad-spectrum cephalosporins and monobactams
- do not hydrolyze carbapenems or cefamycins
- inhibited by clavulanate and tazobactam
- easily transferrable (conjugative plasmids)
- Enterobacteriaceae (K. pneumonia, E. coli)

Overview of Selected β-Lactamase–Producing Pathogens

- **Gram-positive bacteria**
  - Plasmid-mediated
    - *S. aureus*
    - *S. epidermidis*
    - *E. faecalis*
  - Chromosomal
    - *Inducible* Bush group 1 β-lactamases
    - *Constitutive* SPACE organisms

- **Gram-negative bacteria**
  - Plasmid-mediated
    - *Enterobacter spp*
    - *C. freundii*
  - Chromosomal
    - *Inducible* E. coli
    - *Constitutive* K. pneumoniae

Other Inactivating Enzymes

- Adenylation
- Acetylation
- Phosphorylation

Other Inactivating Enzymes

- **Summary of Enterococcal Aminoglycoside-Modifying Enzymes**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Gentamicin</th>
<th>Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-adenylyltransferase (6-AAD)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3'-phosphotransferase (3'-APH)</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>6'-acyetyltransferase (6'-AAC)</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4'-adenylyltransferase (4'-AAD)</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2''-phosphotransferase/6' acetyltransferase (2''-APH/6'-AAC)</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Sites for Aminoglycoside Modification
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Decreased Intracellular Concentrations
Decreased Penetration

- Decreased penetration through outer wall
  - Defense mechanism of Gram-negative bacteria
  - Antibiotics affected include:
    - β-lactams
    - Quinolones
    - Aminoglycosides
- Biofilms
  - Exopolymer matrix
  - Decreased penetration or antibiotic binding
    - e.g., aminoglycosides

Decreased Antibiotic Penetration

Active Efflux

- Tetracyclines
  - As with *S. aureus*
- Macrolides
  - As with *S. pneumoniae*

Antibiotics Affected by Efflux Pumps in *P. aeruginosa*

<table>
<thead>
<tr>
<th>MexA-MexB-OprM</th>
<th>MexC-MexD-OprJ</th>
<th>MexE-MexF-OprN</th>
<th>MexX-MexY-OprM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>Cefepime</td>
<td>Chloramphenicol</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Carbencillin</td>
<td>Cefuroxime</td>
<td>Ciprofloxacin</td>
<td>Cefepime</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Chloramphenicol</td>
<td>Clavulanic</td>
<td>Cefotaxime</td>
</tr>
<tr>
<td>Cefradine</td>
<td>Ciprofloxacin</td>
<td>Imipenem</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Erythromycin</td>
<td>Levofloxacin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Levofloxacin</td>
<td>Norfloxacin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Clavulanate</td>
<td>Nafcillin</td>
<td>Sulbactam</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Norfloxacin</td>
<td>Trimethoprim</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Tetracycline</td>
<td>Tetracycline</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>Trovafloxacin</td>
<td>Tetracycline</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Tetracycline</td>
<td>Tetracycline</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>Sulbactam</td>
<td>Trimethoprim</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Tetracycline</td>
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<tr>
<td>Trimethoprim</td>
<td>Tetracycline</td>
<td>Tetracycline</td>
<td>Tobramycin</td>
</tr>
</tbody>
</table>

Altered Antibiotic Target Site

- β-lactams
- Quinolones
- Aminoglycosides
- Macrolides
- Tetracyclines
- Rifampin and TMP/SMX
- Glycopeptides

Antibiotic Resistance in *S. pneumoniae*: a case study in altered target sites

<table>
<thead>
<tr>
<th>Antibiotic/Class</th>
<th>Target Altered</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>Penicillin-binding proteins</td>
</tr>
<tr>
<td>Macrolides, lincosamides, streptogramins*</td>
<td>23S ribosomal RNA subunit</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>DNA gyrase</td>
</tr>
<tr>
<td></td>
<td>Topoisomerase IV</td>
</tr>
<tr>
<td>Rifampin</td>
<td>DNA polymerase</td>
</tr>
</tbody>
</table>

*Resistance phenotype MLSB

Multiple resistance mechanisms can be present in the same organism


Mechanisms of Resistance: Disturbing the Normal Flora

- Resistance to colonization by opportunistic organisms: colonization resistance
  - provided by normal flora & various physiologic factors
- Antimicrobial administration may alter this defense system by altering normal flora

Why has resistance become so common?

Resistance: Factors Affecting Emergence and Spread

- Selective pressures
  - Conditions enhancing bacterial ability to develop resistance and proliferate
  - Increased by antibiotic overuse or misuse
- Proliferation of multiply-resistant clones
- Inability to detect emerging phenotypes
- Environmental: antibiotics for non-human use

References:
Factors Increasing Resistance in Hospitals

- greater severity of illness
- immunocompromised patients
- newer devices and procedures
- ↑ introduction of resistant organisms from community
- poor infection control practices
- ↑ antibiotic prophylaxis
- ↑ empiric polymicrobial antibiotic therapy
- high abx use per geographic area per unit time


Evidence that Antibiotic Use Influences Resistance

- Resistance more common in organisms causing hospital-acquired infections
- During outbreaks, patients who have received antibiotics are more likely to become infected
- Changes in antibiotic use lead to changes in resistance
- Areas with the highest antibiotic use have the highest rates of resistance

Evidence that Antibiotic Use Influences Resistance (con’d)

- Increased duration of therapy causes increased likelihood of superinfection or colonization
- Increased dosage causes increased likelihood of superinfection or colonization

Settings for Antibiotic Resistance

- Hospitals
  - tertiary
  - community
- Nursing Homes
- Day Care Centers
- The Community
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Environments that influence the evolution and spread of antimicrobial resistance

What are today’s big resistance problems?

The IDSA Big Six

<table>
<thead>
<tr>
<th>Organism</th>
<th>Why:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii</td>
<td>Problematic, MDR, nosocomial and comm-unity-acquired pathogens of increasing incidence</td>
</tr>
<tr>
<td>E. coli &amp; Klebsiella spp</td>
<td>Common Gram-negative pathogens causing life-threatening diseases; increasing resistance</td>
</tr>
<tr>
<td>Vancomycin-resistant E. faecium</td>
<td>Common cause of BSI, IE, CAR, meningitis &amp; IAI with few therapeutic options</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Causes a variety of severe infections with increasing incidence in ICUs; wide-based resistance</td>
</tr>
<tr>
<td>MRSA</td>
<td>Increasing incidence in hospital- and community-acquired cases with fewer therapeutic options</td>
</tr>
</tbody>
</table>

Talbot et al. CID 2006;42:657-68.

Worldwide Resistance to Selected Antimicrobials

United States/North America

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Resistance %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>52.7%</td>
</tr>
<tr>
<td>P. aeruginosa/cefepime</td>
<td>2.8%</td>
</tr>
<tr>
<td>E. coli/PIP-TAZ</td>
<td>10.3%</td>
</tr>
<tr>
<td>VRE</td>
<td>4.4%</td>
</tr>
<tr>
<td>ESBL (K pneumoniae)</td>
<td>17.3%</td>
</tr>
<tr>
<td>S. pneumoniae/penicillin</td>
<td>40.3%</td>
</tr>
</tbody>
</table>

Europe

<table>
<thead>
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<tr>
<td>S. pneumoniae/penicillin</td>
<td>40.3%</td>
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Asia Pacific

<table>
<thead>
<tr>
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<th>Resistance %</th>
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<tbody>
<tr>
<td>MRSA</td>
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<td>E. coli/PIP-TAZ</td>
<td>10.3%</td>
</tr>
<tr>
<td>VRE</td>
<td>4.4%</td>
</tr>
<tr>
<td>ESBL (K pneumoniae)</td>
<td>24.6%</td>
</tr>
<tr>
<td>S. pneumoniae/penicillin</td>
<td>60.5%</td>
</tr>
</tbody>
</table>

Latin America

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Resistance %</th>
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<tr>
<td>MRSA</td>
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Community-Acquired Infections

- URI (H. influenzae, M. catarrhalis)
- N. gonorrhoeae
- E. coli
- S. pneumoniae
- Enteric pathogens
  - Shigella, Salmonella, Campylobacter
- M. tuberculosis
- CAMRSA

Resistance in Respiratory Pathogens
(common community pathogens)

- *Streptococcus pneumoniae*
  - Resistance to β-lactam antibiotics due to altered penicillin-binding proteins (PBPs)
  - Multidrug resistance due to various mechanisms
  - Macrolide resistance due to altered ribosomes and increased efflux
  - Tetracycline resistance due to presence of tetM gene

- *Haemophilus influenzae*
  - Resistance to ampicillin and amoxicillin due to β-lactamase production
  - Resistance to β-lactam antibiotics due to alteration of PBPs (rare)

- *Moraxella catarrhalis*
  - Resistance to ampicillin and amoxicillin due to β-lactamase production
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Multidrug-Resistant S. pneumoniae

<table>
<thead>
<tr>
<th>Year-Month</th>
<th>% Resistant S. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-1998</td>
<td>6.2</td>
</tr>
<tr>
<td>1999-2000</td>
<td>11.0</td>
</tr>
<tr>
<td>2000-2001</td>
<td>12.2</td>
</tr>
<tr>
<td>2001-2002</td>
<td>13.5</td>
</tr>
</tbody>
</table>

*92.4% were R to PEN-AZI-SXT

PRSP*: Reduced Susceptibilities to β-Lactams and Macrolides: TRUST 10 (2006), N=426

Levofoxacin Resistance in Common Gram Negatives 2003 - 2004
TSN Data

<table>
<thead>
<tr>
<th>Organism</th>
<th>Total#</th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. cloacae</td>
<td>37,332</td>
<td>87.4</td>
<td>2.0</td>
<td>10.6</td>
</tr>
<tr>
<td>E. coli</td>
<td>506,525</td>
<td>88.5</td>
<td>0.3</td>
<td>11.3</td>
</tr>
<tr>
<td>K. pneumo</td>
<td>109,903</td>
<td>92.6</td>
<td>1.3</td>
<td>6.1</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>69,906</td>
<td>78.4</td>
<td>3.3</td>
<td>18.3</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>134,635</td>
<td>62.6</td>
<td>5.9</td>
<td>31.6</td>
</tr>
</tbody>
</table>

Recent (2001-2003) Outbreaks of Community-Acquired MRSA Infections - USA

Minnesota – Native American Children
Nebraska – Native American Children
San Francisco – MSM
Los Angeles – MSM; Prison Inmates (>900 cases)
Boston – MSM

MMWR 52(8), 2003
CA-MRSA Infections Among Competitive Sports Participants: 2000-2003

- Outbreaks of SSTI due to CA-MRSA reported from Colorado, Indiana, Pennsylvania, Los Angeles County between 2000 & 2003
- Sports involved included fencing, wrestling, and football

MMWR 52:793, 2003

Community-Associated and Health Care-Associated Methicillin-Resistant Staphylococcus aureus Cases, by Infection Type

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Community-Associated (n=131)</th>
<th>Health Care Associated (n=937)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin/soft tissue</td>
<td>98 (75)</td>
<td>343 (37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Otitis media</td>
<td>9 (7)</td>
<td>11 (1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory tract‡</td>
<td>8 (6)</td>
<td>249 (22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bloodstream†</td>
<td>8 (6)</td>
<td>103 (9)</td>
<td>.87</td>
</tr>
<tr>
<td>Urinary tract‡</td>
<td>1 (1)</td>
<td>185 (20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other‡</td>
<td>10 (8)</td>
<td>110 (12)</td>
<td>.21</td>
</tr>
</tbody>
</table>

*Excludes isolates from 1 type of infection, only 1 was selected for inclusion in the table. The hierarchy for choosing the type of infection for patients with multiple infections was: bacteremia, bone, pleural fluid, peritoneal fluid, joint, surgical specimen, patient, eye, ear, sputum, urine, and skin.
†Refers to the statistical probability that the type of infection among community-associated cases differed from the percentage among health care-associated cases (α = .05).
‡Among health care-associated isolates, some respiratory tract isolates were obtained from endotracheal tubes, and some urinary tract isolates were obtained from Foley catheters.
§Included bone, peritoneal fluid, joint, surgical specimen, and perineal wound.

Naimi TS et al. JAMA 2003;290:2976.

Hospital-Acquired Infections

- **Gram-negative organisms**
  - Enterobacteriaceae
  - *P. aeruginosa*
  - *Acinetobacter* spp.
  - *B. fragilis*

Antimicrobial Resistance among Pathogens Causing Hospital-onset Infections

- 3rd generation cephalosporin-resistant *Klebsiella pneumoniae*
- Fluoroquinolone-resistant *Pseudomonas aeruginosa*

Hospital-Acquired Infections

- **Gram-positive Organisms**
  - Methicillin-resistant *Staphylococcus aureus*
  - Methicillin-resistant *Staphylococcus epidermidis*
  - Enterococci

Antimicrobial Resistance Among Pathogens Causing Hospital-onset Infections

- Methicillin (oxacillin)-resistant *Staphylococcus aureus*
- Vancomycin-resistant enterococci

**Gram-Negative Surveillance**

<table>
<thead>
<tr>
<th>Organism</th>
<th>TRUST 7 2005</th>
<th>TRUST 8 2004</th>
<th>TRUST 9 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>1303</td>
<td>75.4</td>
<td>83.2</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>276</td>
<td>82.3</td>
<td>82.7</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>549</td>
<td>64.3</td>
<td>65.9</td>
</tr>
</tbody>
</table>

**Antimicrobial % Susceptibility:**

- *P. aeruginosa*, 2003-2005

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>TRUST 7 2003</th>
<th>TRUST 8 2004</th>
<th>TRUST 9 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cefazolin</em></td>
<td>90.9</td>
<td>82.3</td>
<td>83.2</td>
</tr>
<tr>
<td>Cefepime</td>
<td>79.5</td>
<td>76.2</td>
<td>81.8</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>72.3</td>
<td>82.3</td>
<td>82.7</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>67.0</td>
<td>81.9</td>
<td>87.1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>78.3</td>
<td>80.5</td>
<td>84.5</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>68.8</td>
<td>64.3</td>
<td>67.2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>65.3</td>
<td>60.9</td>
<td>65.9</td>
</tr>
</tbody>
</table>

% Susceptible for *P. aeruginosa*:

- Ceftazidime: 90.9%
- Cefepime: 79.5%
- Gentamicin: 72.3%
- Pip/Tazo: 67.0%
- Ciprofloxacin: 68.8%
- Levofloxacin: 65.3%

In vitro activity does not necessarily correlate with clinical results.

β-Lactamase–resistant
*A baumannii*

- A metallo-β-lactamase (IMP-2) was identified in *A baumannii* strain AC-54/97
  - Allelic determinant (blaIMP-2) is integron-borne
  - The gene cassette confers β-lactam resistance
  - Variants of this resistance determinant exist in nature and can be acquired by clinically relevant species

Plasmid-Mediated Fluoroquinolone Resistance

- Fluoroquinolone resistance results from plasmid-carrying qnr gene
  - 110 ciprofloxacin-resistant *K pneumoniae* and *E coli* were screened in the United States:
    - qnr detected in *K pneumoniae* B72 (11.1%)
    - Not found in any *E coli* (38 tested)
- Strain relatedness
  - 4 strains carried original plasmid pMG252
  - Five carried new plasmids encoded for FOX-5 β-lactamase (AmpC-type)
  - Two strains produced SHV-7 ESBL
- *E coli* isolates from Shanghai carrying qnr exhibit fluoroquinolone resistance

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>K. pneumoniae</th>
<th>A. baumannii</th>
<th><em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Amp/Sul</td>
<td>28</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>18</td>
<td>67</td>
<td>24</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>20</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cefepime</td>
<td>15</td>
<td>64</td>
<td>37</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>23</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>24</td>
<td>58</td>
<td>29</td>
</tr>
</tbody>
</table>

*Source: 2005 annual antibiogram data; non-urine only

**Resistance at MUSC 2005** (% resistant)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>K. pneumoniae</th>
<th>A. baumannii</th>
<th><em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Amp/Sul</td>
<td>28</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>18</td>
<td>67</td>
<td>24</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>20</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cefepime</td>
<td>15</td>
<td>64</td>
<td>37</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>23</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>24</td>
<td>58</td>
<td>29</td>
</tr>
</tbody>
</table>

*Source: 2005 annual antibiogram data; non-urine only

**Pseudomonas aeruginosa %S vs. Time**

- Cellsphere
- Ciprofloxacin
- Imipenem
- Pip/Tazo
- Tobramycin

John A. Bosso, Pharm.D.
RESISTANCE
John A. Bosso, Pharm.D.
Geographic Variation in Resistance

- **USA**
  - *S. pneumoniae*
  - *H. influenzae*
- **Worldwide**
  - *M. tuberculosis*
  - *S. pneumoniae*
  - ß-lactamase producers
    - e.g., ESBLs, Carbapenemases, IRBLs

**S. pneumoniae Antimicrobial Resistance**

TRUST 10 (2006)

- **Penicillin Resistance**
  - National Rate: Penicillin = 14.1% R
- **Azithromycin Resistance**
  - National Rate: Azithromycin = 30.8% R

Viruses & Fungi

- Resistance may be intrinsic or acquired
- Mechanisms typically involve:
  - Altered target site
  - Decreased cell penetration (esp. fungi)
  - Selection of less susceptible species
    - e.g., with non-albicans Candida

Antifungal Resistance

- Basic Mechanisms
  - Altered target site
  - Increased drug efflux
  - Decreased drug influx
  - Mutation

3,014 isolates from 137 labs.

In vitro data does not necessarily correlate with clinical results.

Antifungal Resistance

- Polyenes (amphotericin B)
  - MOA: targets plasma membrane ergosterol forming a channel resulting in disruption of the protein gradient
  - MOR: alteration of lipid composition of plasma membrane (decreased ergosterol content) leading to lower affinity for AmB binding

- Azoles
  - MOA: ergosterol biosynthesis inhibition
    - Bind lanosterol demethylase
  - MOR:
    - Increased efflux
      - Candida drug resistance gene (CDR) overexpression
    - Decreased influx
      - Change in sterol composition of plasma membrane leading to decreased drug uptake

Fluconazole Susceptibility over 12 years: 1992-2003

<table>
<thead>
<tr>
<th>Species (N)</th>
<th>Category*</th>
<th>1992</th>
<th>1995</th>
<th>1997</th>
<th>1999</th>
<th>2001</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans (4518)</td>
<td>S (≤8 μg/ml)</td>
<td>100</td>
<td>89</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>S-DD (16-32 μg/ml)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>R (≥64 μg/ml)</td>
<td>0</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C. glabrata (1228)</td>
<td>S</td>
<td>15</td>
<td>49</td>
<td>46</td>
<td>84</td>
<td>64</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>S-DD</td>
<td>67</td>
<td>36</td>
<td>46</td>
<td>12</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>18</td>
<td>15</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>C. parapsilosis (956)</td>
<td>S</td>
<td>98</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>S-DD</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

M. Pfaffer, personal communication
Antifungal Resistance

• 5-Fluorocytosine
  – MOA: disrupts protein synthesis
  – MOR:
    • Mutation leading to decreased activity of cytosine permease or deaminase uptake or transformation to active form intracellularly
    • Loss of activity of uracil phosphoribosyltransferase leading to decreased 5-FC conversion to active form

• Glucan Synthesis Inhibitors
  – Echinocandins
    • MOA: inhibit synthesis of 1,3 β-D-glucan, a component of the fungal cell wall
    • MOR: mutation leading to alteration of the β-glucan synthase

Sensitivity (IC₅₀) of Glucan Synthesis Enzyme Complex of Selected Candida Species to Inhibition by Caspofungin

<table>
<thead>
<tr>
<th>Species</th>
<th>IC₅₀ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>0.5 – 1.3</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>0.3 – 4.0</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>0.5 – 3.1</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>200 – 400</td>
</tr>
<tr>
<td>C. kruzei</td>
<td>11 – 206</td>
</tr>
<tr>
<td>C. guillermondii</td>
<td>9.9 – 32</td>
</tr>
</tbody>
</table>

Candidemia: Sensitivity of Bloodstream Isolates

- SENTRY Antifungal Surveillance Program
  - 2,047 bloodstream isolates
  - Collected during 1997–2000
  - United States, Canada, Latin America, and Europe

<table>
<thead>
<tr>
<th>Species</th>
<th>Frequency of Species Isolation,%</th>
<th>Fluconazole Antifungal Activity</th>
<th>Resistance, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>64</td>
<td>0.5</td>
<td>1–2</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>15</td>
<td>2–4</td>
<td>0</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>10</td>
<td>1–2</td>
<td>1–4</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>16</td>
<td>16–32</td>
<td>25–37</td>
</tr>
<tr>
<td>C. kruzei</td>
<td>2</td>
<td>64</td>
<td>80–91</td>
</tr>
</tbody>
</table>

*MIC₅₀ limits: U.S. NCCLS Breakpoints M07-A (fluconazole).
A local pediatrician calls your pharmacy seeking advise on empiric therapy for a 2 year old with acute otitis media. She was successfully treated one month ago for the same condition with amoxicillin. The child is in day care and has two siblings at home, both under the age of 6 years.

- What risk factors does the child have for infection with a penicillin/amoxicillin-resistant bacteria?
- Which antibiotic should you recommend?

**Effect on Morbidity & Mortality**

“...for both nosocomial and community-acquired infections, the mortality, the likelihood of hospitalization, and the length of hospital stay were usually twice as great for patients infected with drug-resistant strains....”

Holmberg et al. Rev Infect Dis 1987;9:1065-78

**Good Websites for Resistance Info**

- **Comprehensive sites**
  - Bugs & Drugs on the Web
    [http://www.antibioticresistance.org.uk](http://www.antibioticresistance.org.uk)
  - Alliance for the Prudent Use of Antibiotics
    [http://www.tufts.edu/med/apua/index.html](http://www.tufts.edu/med/apua/index.html)
  - Canadian Committee on Antibiotic Resistance
    [http://www.cear-ccra.com](http://www.cear-ccra.com)
- **Prevention in Institutions**
  - CDC
    [http://www.cdc.gov/drugresistance/healthcare/default.htm](http://www.cdc.gov/drugresistance/healthcare/default.htm)
  - Association for Professionals in Infection Control & Epidemiology
    [http://www.apic.org](http://www.apic.org)