"Revenge of the Microbes"

Bacterial Resistance
Overview and Implications for Clinical Practice

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Case Study:
F.T. is a 25-year-old male with a 2-months history of cough and increased sputum production. He presents to the outpatient clinic with fever, new chest pain when he coughs, shortness of breath, and blood tinged sputum.

Past Medical History:
F.T. has had asthma since childhood. He also has sickle cell anemia required splenectomy.

Medication History:
1) Salbutamol inhaler 2 puffs qid prn
2) Oxycodone and aspirin 2 tablets PO q6h prn pain
3) Beclomethasone inhaler 2 puffs tid
4) Ciprofloxacin 500mg q8h × 10 d (one month ago)

F.T. was diagnosed with CAP and his Fine PSI score = 3
He was admitted to the internal medicine ward on Levofloxacin 500mg q24h

Sputum culture:
S. pneumoniae

Initial: Levo MIC = 2 µg/ml (parC)
Subsequent: Levo MIC = 16 µg/ml (parC, gyrA)

No improvement. Meningitis on day 4. Died

Why?
**Brief History of Antibiotics**

- 1928- Penicillin discovered by Fleming
- 1932- Sulfonamide antimicrobial activity discovered (Erlich)
- 1935- First unsuccessful attempt to use sulfonamide to treat a case of meningitis
- 1943- Drug companies begin mass production of penicillin
- 1948- Cephalosporins precursor sent to Oxford for synthesis
- 1952- Erythromycin derived from Streptomyces erythreus
- 1956- Vancomycin introduced for penicillin resistant staphylococcus
- 1962- Quinolone antibiotics first discovered
- 1970s- Linezolid discovered but not pursued
- 1980s- Fluorinated quinolones introduced, making them clinically useful
- 2000- Linezolid introduced into clinical practice

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**Emergence of Antibiotic Resistance Bacteria**

<table>
<thead>
<tr>
<th>Year</th>
<th>Hospital-acquired</th>
<th>Community-acquired</th>
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<tbody>
<tr>
<td>1950</td>
<td>S. aureus</td>
<td></td>
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<tr>
<td>1960</td>
<td>E. coli</td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td>K. pneumonia</td>
<td></td>
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<tr>
<td>1980</td>
<td>P. aeruginosa</td>
<td></td>
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<tr>
<td>1990</td>
<td>M. tuberculosis</td>
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*Cohen, Science 1992;257:1050*
Outbreaks of Community-Associated Methicillin-Resistant Staphylococcus aureus Skin Infections — Los Angeles County, California, 2002–2003

During 2002, the Los Angeles County Department of Health Services (LA County DHSS) investigated three consecutive outbreaks of skin infections associated with methicillin-resistant Staphylococcus aureus (MRSA). MRSA infections have occurred in health care settings; however, recent investigations of community-associated MRSA (CA-MRSA) have identified infection in various settings, including correctional facilities, athletic teams, and others (CDC, unpublished data, 2005). This report describes investigations of CA-MRSA in Los Angeles County.

- Overview and history of bacterial resistance
- Assessment of the problem
- Molecular and cellular mechanisms of bacterial resistance
- Acquisition of resistance
- Implications for clinical practice

- Defined as erythromycin-resistant

<table>
<thead>
<tr>
<th>Prevalence Range</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>&lt;10%</td>
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<tr>
<td>10–20%</td>
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<td>20–30%</td>
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<tr>
<td>30–40%</td>
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<tr>
<td>&gt;40%</td>
<td></td>
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<tr>
<td>No data</td>
<td></td>
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</table>

* Defined as erythromycin-resistant
Resistant Pathogens of Concern: Healthcare Facilities

- *Staphylococcus aureus*:
  - oxacillin, clindamycin, vancomycin, linezolid
- *Enterococcus*:
  - penicillin, aminoglycosides, vancomycin, linezolid, quinupristin-dalfopristin
- *Enterobacteriaceae*:
  - ESBL, prodigiosins, carbapenems
- *Candida* spp:
  - fluconazole
- *Mycobacterium tuberculosis*:
  - INH, rifampin

Resistant Pathogens of Concern in the Community

- *Staphylococcus aureus* methicillin
- *Pneumococci* penicillin/cephalosporins, erythromycin, quinolones
- *Group A streptococci* macrolides/ketolides
- *Mycobacterium tuberculosis* INH, rifampin
- *Neisseria gonorrhoeae* penicillin, quinolones
- *Plasmodium falciparum* multiple drugs including chloroquine
**Consequences of antimicrobial resistance**

- Compromised therapy of human infections
- Serious complications for elderly and children
- Increased length of therapy and more doctor visits
- Prolonged hospital stay and significant increase of treatment cost

"Bacterial resistance is a major threat to public health"

**Overview and history of bacterial resistance**

- Assessment of the problem
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**The four main mechanisms of antibacterial action**

- Bypass (TMP / SMX)
- Efflux (macrolides, quinolones)
- Decreased permeability (TMP / SMX)
- Target site modification (intra- or extracellular; β-lactams, macrolides, quinolones, glycopeptides)
- Enzymic degradation (intra- or extracellular; β-lactams, aminoglycosides)
- Decreased permeability (β-lactams, aminoglycosides)
- Target site modification (macrolides, quinolones)
- Bypass (macrolides, quinolones)

**Major mechanisms of antimicrobial resistance**

- Bacterial resistance is a major threat to public health
Penicillin inactivation by \( \beta \) lactamase production by \( H. \) influenzae

S. pneumoniae resistance to \( \beta \)-lactams by target alterations

Active efflux of antibiotics

Mechanisms of Resistance to Fluoroquinolones

- Efflux pump is a less potent and less common cause of resistance
- Mutation of bacterial genes for binding sites causes resistance
  - gyrA, parC, (parE, gyrB)
- Efflux pump
  - Pmr A
- DNA
- Cell wall
Vancomycin Resistance

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Types of resistance

* Intrinsic
  - Spontaneous mutation in chromosomal DNA
  - Accumulation of several point mutations
  - An evolutionary process occurring only under selective antibiotic pressure
  - Shared by all members of a genus

* Acquired
  - Maintained on horizontal mobile element plasmids, phages, integrons and transposons
  - Resistance genes can be transferred among bacteria
  - Can be integrated into the bacterial chromosome or can be maintained in an extra-chromosomal state

Mechanisms of acquiring resistance

a) Conjugation:
  - Direct cell to cell contact for transfer of extra-chromosomal DNA
  - (the most important transfer mechanism)

b) Transduction:
  - Transfer mediated by bacteriophages

c) Transformation:
  - Uptake of naked DNA by the cell
Multi-resistance

Multi-resistance to different antibiotics generally results from a combination of different independent mechanisms of resistance.

- *P. aeruginosa* is a type of multi-resistant bacteria. It is resistant to β-lactams, including third-generation cephalosporins, quinolones, chloramphenicol, and cyclines. (natural resistance)
- Methicillin-resistant strains have become resistant to most antibiotics and with a high frequency of high resistance. (acquired)

Cross-resistance

Cross-resistance Occurs generally in antibiotics of the same family.

- Cross-resistance between penicillins, more widely between all the β-lactams including cephalosporins.

Reasons for bacterial resistance:

- Uncontrolled, improper and indiscriminate use of antibiotics for therapy and prophylaxis
- Observation: increase in antibiotic resistance parallels in antibiotic use in humans
- Poor hand hygiene and failure of infection control measures
- Excessive use of cleaners, detergents and other antibacterials
- Antibiotics in livestock, other animals, birds and agriculture

Reasons for antibiotic resistance

Improper use of antibiotics due to:
- poor patient compliance
- inadequate lengths of therapy
- unnecessary use
- lack of activity
- insufficient doses
- low penetration to body sites
Combating bacterial resistance:

* Clinical Measures:   Education and training

* Epidemiological:  Surveillance

* Experimental: Technical development

* legislative regulations

Strategies for Antimicrobial Use and Monitoring in ICU

- Formulary restriction
- Approval policies
  - Mandatory consult
  - ID approval
- Antimicrobial support (surveillance) team
- Antimicrobial cycling
- Programmed termination

Rice LB. Cleve Clin J Med 2003; 79:3-800

The greatest possibility of evil in self-medication is the use of too small doses so that instead of clearing up infection, the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to other until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save.

Sir Alexander Fleming