50 years of antibiotic resistance

Gary French
Guy’s & St Thomas’ Hospital & King’s College, London

Antibiotics are different

- The only drugs that are:
  - Not directed against the patient
  - Taken at some time by almost everyone in the West
- Every treatment upsets microbial ecology
  - Alteration in the normal bacterial flora of patient and environment
  - Associated with an inevitable evolutionary change to antibiotic resistance

1940–41


Fleming, Penicillin, 1929

*Streptococcus pneumoniae* is also very sensitive. There were some differences in the blue wild, different strains, but it may be said generally that it is slightly more sensitive than *Staphylococcus*. The pneumococci vary very considerably, a few strains being almost unaffected while others are sensitive to 3 or 4 weeks. Different, however, are those of the brain-negative which tend to withstand conditions more sensitive to ampicillin. Many of the brain-negative are found in the mouth and throat, however, rare sensitivity.

Certain interesting facts emerge from these tables. It is clear that penicillin contains factors which inhibit bacterial growth which is very active towards one strain while not affecting others. The number of the sulphonamide group are extended as an easy method to the sulphonamides.
Some organisms are always sensitive or resistant to a given antibiotic (inherent sensitivity or resistance)
- Syphilis is always sensitive to penicillin
- *P. aeruginosa* is always resistant to ampicillin
- Some sensitive orgs 'acquire' resistance

Antimicrobial resistance is an inevitable evolutionary response to antimicrobial use

Emergence of resistance

Population effect

Emergence of resistance

Population effect
- Antibiotic use kills sensitive members of bacterial population
- More resistant orgs flourish (Within & between species)

Emergence of resistant mutants
- Related to short bacterial generation time

Infectious resistance
- Acquisition of new 'resistance genes' (R-factors) by plasmid or transposon transmission
- 90% Staph aureus now resistant to penicillin
- 60% *E. coli* now resistant to ampicillin
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Prof. Gary French, Kings College, London
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Resistance to penicillin in S. aureus, ampicillin in E.coli

Main mechanisms of antimicrobial resistance
- Enzyme inactivation
- Target site alteration
- Reduced permeability/increased extrusion
  ○ Two or more mechanisms may interact to determine the actual level of resistance

Resistance mechanisms in MRSA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Chromosome</th>
<th>Plasmid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl penicillin</td>
<td>Enzyme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminopenicillins</td>
<td>Enzyme</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Membrane damage</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Membrane damage</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Membrane damage</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>Membrane damage</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Mutations in ribosome</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Mutations in ribosome</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Mutations in ribosome</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td></td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td></td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

Antibiotic ‘pressure’
- Antibiotic use is concentrated in hospitals
- Resistant bacteria proliferate in the hospital environment and treated patients
- Infection with resistant organisms fails to respond to empirical therapy, increasing the time during which cross-infection may occur
- More and more hospital infections become antibiotic resistant

Antibiotic ‘pressure’
- Resistance thus favours hospital infection:
- Hospital infection is resistant infection
- At any given time the common nosocomial pathogens are often resistant to the antibiotics in current use
  ○ S. aureus (MRSA)
  ○ Enterococci (GRE)
  ○ Klebsiella/Enterobacter/Serratia
  ○ Ps. Aeruginosa/Acinetobacter etc.

Which is safer?
Increasing resistance and multi-resistance with time

- **HOSPITAL**
  - Penicillin, methicillin, ciprofloxacin in *S. aureus*
  - Glycopeptides in enterococci
  - Ampicillin, gentamicin, ESBLs in *E. coli*
  - Aminoglycosides in *P. aeruginosa*

- **COMMUNITY**
  - Penicillin etc. in pneumococcus
  - MDR in *Haemophilus*
  - Penicillin, methicillin in *S. aureus*
  - Ampicillin, ESBLs in *E. coli*
  - Ampicillin, ciprofloxacin in salmonellas
  - MDR in *M. tuberculosis*

Increasing resistance and multi-resistance with time

- The gradual worldwide emergence of multidrug and ‘pan-resistance’
- Associated with antimicrobial use & abuse and falling standards of hygienic practice

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**Yearly vancomycin usage (Kg)**
USA, France, Italy, Germany, UK, Netherlands

**MRSA Hospital Prevalence Rates in Europe, 2001-2005**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>8%</td>
<td>13%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Belgium</td>
<td>22%</td>
<td>31%</td>
<td>0.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Cyprus</td>
<td>n/a</td>
<td>56%</td>
<td>n/a</td>
<td>1.0%</td>
</tr>
<tr>
<td>France</td>
<td>33%</td>
<td>27%</td>
<td>n/a</td>
<td>1%</td>
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<tr>
<td>Germany</td>
<td>18%</td>
<td>21%</td>
<td>Netherlands</td>
<td>0.5%</td>
</tr>
<tr>
<td>Greece</td>
<td>39%</td>
<td>42%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>42%</td>
<td>42%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>41%</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>32%</td>
<td>47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>n/a</td>
<td>61%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>23%</td>
<td>27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>45%</td>
<td>44%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*% of SA isolates that are MRSA.*

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Impact of Antibiotic Resistance

- When adjusted for other risks:
  - Mortality rates, likelihood of hospitalization and length of hospital stay, are generally at least twice as great for patients infected with resistant bacteria as for those infected with susceptible strains of the same species.

Meta-analyses show that MRSA infections have worse outcomes than MSSA

- MRSA bacteraemias had twice the mortality of those with MSSA
  - (OR, 1.93; 95% CI, 1.54–2.42)
- MRSA surgical site infections had significantly greater 90 day mortality, length of hospitalization and hospital charges.

Inadequate Antimicrobial Therapy Associated With Higher Mortality

The crisis in antibiotic resistance


Concern over lack of antibiotics

- Infectious Diseases Society of America 2004. BAD BUGS, NO DRUGS: As Antibiotic Discovery Stagnates … A Public Health Crisis Brews

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Prevention and control of MDR infections: Two main elements

- The control of antimicrobial use (ANTIBIOTIC STEWARDSHIP)
  - Appropriate, prompt therapy based on surveillance, combined with step-down
  - Reduction/elimination of all unnecessary antibiotic usage
- The control of hospital cross-infection

Antibiotics are different

- The only drugs that are:
  - Not directed against the patient
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- Every treatment upsets microbial ecology
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  - Associated with an inevitable evolutionary change to antibiotic resistance

Antibiotic use & resistance

- "Consensus rarely exists on topics in infectious disease. Yet, authors of virtually all of the papers reviewed here [68 references] agree on the need for careful, discriminating use of antibiotics as being the keystone of our attempts to control resistant bacteria in the hospital"

Value antibiotics

- Standing Medical Advisory Committee of the Department of Health (SMAC) ‘The path of least resistance’ 1997:
  - ‘prescription of an antibiotic should be seen as a serious step, similar to the prescription of steroids or any other potentially hazardous medicament’
  - ‘we should regard antimicrobial agents as a valuable and non-renewable resource, to be treasured and protected in their own, and everyone else’s, interest’


<table>
<thead>
<tr>
<th>April-March</th>
<th>MRSA Bacteraemia Episodes</th>
<th>Rate per 10,000 OBDs</th>
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<tbody>
<tr>
<td>2001-2</td>
<td>7291</td>
<td>1.71</td>
</tr>
<tr>
<td>2002-3</td>
<td>7426</td>
<td>1.78</td>
</tr>
<tr>
<td>2003-4</td>
<td>7700</td>
<td>1.83</td>
</tr>
<tr>
<td>2004-5</td>
<td>7233</td>
<td>1.76</td>
</tr>
<tr>
<td>2005-6</td>
<td>7096</td>
<td>1.78</td>
</tr>
<tr>
<td>2006-7</td>
<td>6383</td>
<td>1.67</td>
</tr>
<tr>
<td>2007-8</td>
<td>4448</td>
<td>1.16</td>
</tr>
<tr>
<td>Fall since 2003</td>
<td>2978</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>- 40.1%</td>
<td>- 34.8%</td>
</tr>
</tbody>
</table>

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