Antimicrobial Stewardship: Building the Case

David Paterson
Overview

• Why is Antimicrobial Stewardship important?

• A personal experience of Antimicrobial Stewardship
MRSA
Consequences - MRSA

• Still a problem in hospitalised patients

• *Staphylococcus aureus* is carried by 30-40% of all Australians

• Infections due to community-acquired *Staphylococcus aureus* are now MRSA in 10-50% of cases depending on the geographic setting

• More resistant, more severe!
Vancomycin Resistant Enterococci

- Developed in late 1980s in ICUs and haemodialysis units in USA
- Risks included use of vancomycin and antibiotics with anti-anaerobic activity
- Untreatable till the late 1990s
- Sporadic outbreaks in Australian hospitals
VRE Consequences

• Hospitalised patients in Australia increasingly face the risk of being colonised with an organism resistant to one of our most useful antibiotics, vancomycin

• In some Australian institutions, more VRE bloodstream infections are seen than MRSA

• An escalation of our “nuclear arms race” against bacteria
Clostridium difficile associated diarrhoea

- Pittsburgh: tripling of cases of hospital-acquired *C. difficile*
  - 40 colectomies in one year (toxic megacolon)
  - 15% of all patients with CDAD died

- Epidemic strain (027) in North America and Europe
Consequences – 027 C. difficile

- Epidemics of potentially fatal gastrointestinal illness in compromised and elderly patients

- Virtually always ANTIBIOTIC ASSOCIATED
Coloured transmission electron micrograph of *Pseudomonas aeruginosa*
New antibiotics active against Gram negative bacilli
# Australia – *E. coli* susceptibility

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>%S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>99+%</td>
</tr>
<tr>
<td>Cefotaxime (ESBL producers)</td>
<td>90+%</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>99+%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>90% (“Quinolone resistance”)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>99+%</td>
</tr>
<tr>
<td>Pip-tazobactam</td>
<td>99%</td>
</tr>
</tbody>
</table>
## Susceptibility of *E. coli* - CHINA

<table>
<thead>
<tr>
<th></th>
<th>%S 2002</th>
<th>%S 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amp/sulbactam</td>
<td>43%</td>
<td>19%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>94%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Cefotaxime</strong></td>
<td>82%</td>
<td>44%</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>92%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td>57%</td>
<td>30%</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>Imipenem</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>Pip-tazo</td>
<td>96%</td>
<td>93%</td>
</tr>
</tbody>
</table>
Why the differences?

• In most hospitals, 3rd generation cephalosporins have been restricted since outbreaks of ESBL producers in the mid 1990s

• Quinolone use by General Practitioners requires the approval/authority of the government on a patient by patient basis
Consequences: Carbapenem Resistance

• Carbapenems are our “end of the road” antibiotic

• Carbapenem resistant Acinetobacter and Klebsiella easily become endemic in ICUs

• The potential is **untreatable** infections
Sir Ganga Ram Hospital,
New Delhi 2010 Antibiogram

• ICU Respiratory tract Gram negatives:

  % S to
  meropenem

  *E. coli*  87%
  *Klebsiella*  53%
  *P. aeruginosa*  23%
  *Acinetobacter*  2%
Conclusions – Australian issues

• Community-acquired MRSA (widespread)
• Hospital entrenched VRE (yes) and hypervirulent C. difficile (not yet)

• Community-acquired ESBLs (sporadically, but increasing markedly)
• Carbapenem resistant Acinetobacter (outbreaks)
• Carbapenem resistant Klebsiella (sporadically, with the “wolf at our door”)
Pittsburgh protocol

• Outside of the ICU, the following antibiotics needed prior approval:
  – Aztreonam, cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, daptomycin, ertapenem, gatifloxacin, gentamicin, imipenem, levofloxacin, linezolid, meropenem, moxifloxacin, piperacillin/tazobactam, ticarcillin/clavulanate
Pittsburgh C. difficile

- Case-control study of risk factors for hospital-acquired C. difficile
- Three antibiotics were independently associated with C. difficile
  - Clindamycin
  - Ceftriaxone
  - Levofloxacin

Muto et al ICHE 2005;26:273-280
Combined DDD’s of Levofloxacin, Clindamycin and Ceftriaxone
## Ciprofloxacin

<table>
<thead>
<tr>
<th>Year</th>
<th>DDDs/100 patient days</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>1.9</td>
</tr>
<tr>
<td>2002</td>
<td>2.2</td>
</tr>
<tr>
<td>2003</td>
<td>1.7</td>
</tr>
<tr>
<td>2004</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Effects of restricting drugs associated with hospital-acquired *C. difficile*

<table>
<thead>
<tr>
<th>Year</th>
<th>Hospital-acquired Cdiff per 1000 discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>2.7</td>
</tr>
<tr>
<td>2000/2001</td>
<td>6.8</td>
</tr>
<tr>
<td>2003</td>
<td>5.2</td>
</tr>
<tr>
<td>2004</td>
<td>4.6</td>
</tr>
</tbody>
</table>
The Big Picture – Antibiotic Expenditure Reduced by 13% ($384,776)
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>01/01</th>
<th>07/03</th>
<th>07/04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>76%</td>
<td>81%</td>
<td>83%</td>
</tr>
<tr>
<td>Pip/tazo</td>
<td>74%</td>
<td>77%</td>
<td>81%</td>
</tr>
<tr>
<td>Ciproflx.</td>
<td>62%</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>Levoflox.</td>
<td>48%</td>
<td>59%</td>
<td>62%</td>
</tr>
</tbody>
</table>

*Pseudomonas susceptibilities*
Clinical Outcomes –
Gram negative Bacteremia

Baseline  |  Current  
---|---
106/519   |  134/657  
24%       |  24%      
p>0.20

Outcome is mortality at 28 days after onset of bacteremia
Conclusions

• Antibiotic resistance and *Clostridium difficile* are multifactorial problems
  – Infection control
  – Antibiotic use

• Introduction of an ASP can lead to:
  – 10-15% reduction in acquisition costs
  – Improvement of susceptibilities
  – Reduction in *C. difficile*
  – No deterioration in clinical outcome