Antibiotic Use and Antimicrobial Resistance

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Conflicts/Associations

- Theradoc - Editorial Advisory Board
- Tetraphase - Scientific Advisory Board
- T2 Biosystems - Scientific Advisory Board
- Astra-Zeneca - Consultant
Are antimicrobial usage strategies a high priority in the effort to control resistance?

Yes!

Is Infection Control the Answer?
VA MRSA Initiative

• Universal screening for nasal MRSA colonization on admission, transfer and discharge
• Contact precautions for patients colonized or infected
• Rapid PCR method used; confirmed by culture
• Change to “Positive deviance” culture

Nationwide MRSA Infections at VAs

Nationwide MRSA Infections at VAs

Is Infection Control the Answer?

- Role of patient-to-patient transmission* in acquisition of
  - ESBL- *E. coli* - 13%
  - ESBL- *K. pneumoniae* - 52%
  - Imipenem-resistant *P. aeruginosa* - 11%

*Isolate identical to one from other patient in unit with an overlapping stay

Axiom

No Antibiotics - No Resistance
First clinical use of penicillin: 1942
First clinical use of ampicillin: 1962
First clinical use of cefotaxime: 1979
First clinical use of imipenem: 1985
Osteomyelitis due to penicillinase-producing S. aureus: 1949
Description of TEM penicillinase: 1966
ECMP (SHV-2): 1985
1st clinical carbapenemase from Enterobacteriaceae: 1990
1st carbapenemase from Enterobacteriaceae: 1993
Relation between use and Resistance

*S. pneumoniae*

Use and Resistance do not always follow predictable patterns

<table>
<thead>
<tr>
<th>Pathogen (# tested)</th>
<th>Antibiotic (%S/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Piperacillin-</td>
</tr>
<tr>
<td></td>
<td>tazobactam</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>P. aeruginosa (439)</td>
<td>90.2/9.8</td>
</tr>
<tr>
<td></td>
<td>85.4/7.5</td>
</tr>
<tr>
<td></td>
<td>85.6/9.8</td>
</tr>
<tr>
<td></td>
<td>77/17</td>
</tr>
</tbody>
</table>

*Rhomburg and Jones (2009) DMID 65 (Suppl. 3) 414-26
Use and Resistance do not always follow predictable patterns

• Vancomycin used from 1958 until early 1980 without a hint of resistance
• Resistance rapidly emerged after use of glycopeptides in GI tracts
• Despite initial fears, resistance determinants have remained largely restricted to Enterococcus faecium
• Use-resistance associations more common with cephalosporins than with IV vancomycin
Reduced use of antibiotics will lead to reductions in resistance
Reduced Macrolide Use and Resistance - Finland

Figure 1. Total Consumption of Macrolide Antibiotics by Outpatients in Finland from 1976 through 1995.
Consumption is expressed in terms of defined daily doses per 1000 inhabitants per day.

Figure 2. Frequency of Resistance to Erythromycin among Group A Streptococcal Isolates from Throat-Swab and Pus Samples in Finland in 1990 and in 1992 through 1996.
The data from 1990, obtained from six regional microbiology laboratories, are shown here for comparison; the dashed line indicates that the 1990 data were not included in the statistical analyses reported in the text.

Persistence of Sulfa Resistance


Table 1. Proportions (%) of resistant isolates from each collection (data for 1991 and 1999 taken from Enne et al.2)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>1991 (n = 360)</th>
<th>1999 (n = 359)</th>
<th>2004 (n = 391)</th>
<th>$\chi^2$ for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>46.9</td>
<td>59.9</td>
<td>51.9</td>
<td>NS</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>20.2</td>
<td>15.3</td>
<td>7.9</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>6.7</td>
<td>2.8</td>
<td>0.5</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>8.1</td>
<td>5.6</td>
<td>1.8</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>33.9</td>
<td>34.3</td>
<td>41.2</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Sulphamethazine</td>
<td>39.7</td>
<td>46.0</td>
<td>45.5</td>
<td>NS</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>36.9</td>
<td>40.9</td>
<td>30.7</td>
<td>NS</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>33.3</td>
<td>39.3</td>
<td>35.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.

Agents no longer widely used in human medicine in the UK.

97% reduction in sulfa use in U.K. from 1991-1999

Piperacillin/tazobactam is not appropriate therapy for the treatment of known ESBL infections.

Reprinted from Rice LB. *Pharmacotherapy*. 1999;19:120S-128S.
Evolution and Control of Antibiotic Resistance Among GNR in NY Hospital ICU

- **Ceftazidime-resistant Acinetobacter baumannii (chromosomal)**
  - 1988
  - **Contact Isolation, Patient cohorting, local polymixin**
  - **Elimination of imipenem resistance 1999**

- **Ceftazidime-use**
  - **Imipenem use**
  - **Reduction of Ceftazidime Resistance 44% hospitalwide 87% in ICUs**

- **Ceftazidime-cephamycin-imipenem-resistant Klebsiella pneumoniae (chromosomal and plasmid mediated)**
  - 1995
  - **Class restriction of cephalosporins and cephemycins**

- **Ceftazidime-resistant Klebsiella pneumoniae (plasmid mediated)**
  - 1993
  - **Elimination of imipenem resistance 1999**

- **Imipenem-use**
  - **Contact Isolation, Local polymixin**

- **Imipenem-resistant Pseudomonas aeruginosa (chromosomal)**
  - 1996

- **Ongoing**

Reasons for Resistance Persistence

- Rates of reacquisition (facilitated by ongoing horizontal gene transfer [HGT] and spontaneous mutation events)
- Mutation-based alterations in microbial physiology to reduce the fitness costs of acquired-resistance determinants
- Directional selection of genetically linked traits
- The presence of systems regulating segregational stability of extra-chromosomal elements carrying resistance determinants.

Reasons for Resistance Persistence

Why focus on Duration of Therapy?

• Currently recommended lengths of therapy have little scientific basis
• Docs get irritated when their options are limited in the acute setting
• Avoids arcane discussions regarding “antimicrobial spectrum” or “narrowing down”
Narrowing down?

- **Ampicillin spectrum**
  - Gm+ except staph
  - Enterococci
  - Most anaerobes
  - *E. coli* and similar GNRs

- **Imipenem spectrum**
  - Gm+ except staph
  - Most anaerobes
  - *E. coli*
  - *K. pneumoniae*
  - *Enterobacter* spp.
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*

The only truly convincing streamlining is stopping!!!
Shortened durations of therapy will lead to decreased selective pressure and decreased resistance.
Resistance and Duration of Therapy

• Notably, among patients who developed recurrent pulmonary infections, multiresistant pathogens emerged significantly less frequently in those who had received 8 days of antibiotics (42.1% vs 62.3% of recurrent infections; \( P = .04 \)).

• Antimicrobial resistance, or superinfections, or both, developed in 15% (5 of 37) of the patients in the experimental (3-day) versus 35% (14 of 37) of the patients in the standard therapy group (p = 0.017).

Pharmacodynamic Support for Shorter Durations

## Restricted Duration in ICU

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>NNIS</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>% difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 gen ceph</td>
<td>103</td>
<td>85</td>
<td>57</td>
<td>-32</td>
</tr>
<tr>
<td>2 gen ceph</td>
<td>34</td>
<td>81</td>
<td>38</td>
<td>-53</td>
</tr>
<tr>
<td>3 gen ceph</td>
<td>144</td>
<td>238</td>
<td>196</td>
<td>-18</td>
</tr>
<tr>
<td>4 gen ceph</td>
<td>-</td>
<td>195</td>
<td>233</td>
<td>+20</td>
</tr>
<tr>
<td>Total ceph</td>
<td>-</td>
<td>599</td>
<td>526</td>
<td>-12</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>38</td>
<td>244</td>
<td>185</td>
<td>-25</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>206</td>
<td>87</td>
<td>88</td>
<td>+2</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>86</td>
<td>158</td>
<td>136</td>
<td>-14</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>201</td>
<td>98</td>
<td>95</td>
<td>13</td>
</tr>
<tr>
<td>Inhibitor comb</td>
<td>72</td>
<td>83</td>
<td></td>
<td>+6</td>
</tr>
<tr>
<td>Total</td>
<td>1265</td>
<td>1112</td>
<td></td>
<td>-12</td>
</tr>
</tbody>
</table>

Restricted Duration in ICU

Incidence density nosocomial infection in ICU/100 pat-days

### Restricted Duration in ICU

<table>
<thead>
<tr>
<th></th>
<th>% Resistance</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2001-3</td>
<td>2005</td>
<td>Phase 1</td>
<td>Phase 2</td>
</tr>
<tr>
<td><strong>Ceftazr</strong>Pa</td>
<td>30</td>
<td>77</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td><strong>Imipr</strong> Pa</td>
<td>55</td>
<td>76</td>
<td>60</td>
<td>38</td>
</tr>
<tr>
<td><strong>Cipro</strong> Pa</td>
<td>60</td>
<td>69</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td><strong>Ceftazr</strong>Ab</td>
<td>62</td>
<td>94</td>
<td>92</td>
<td>50</td>
</tr>
<tr>
<td><strong>Imipr</strong> Ab</td>
<td>22</td>
<td>72</td>
<td>89</td>
<td>20</td>
</tr>
<tr>
<td><strong>A/Sr</strong> Ab</td>
<td>44</td>
<td>17</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td><strong>Ceftazr</strong> Kp</td>
<td>48</td>
<td>89</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td><strong>Cefep</strong> Kp</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td><strong>Imipr</strong> Kp</td>
<td>0</td>
<td>4</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td><strong>Cipro</strong> Kp</td>
<td>0</td>
<td>82</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td><strong>APACHE</strong></td>
<td></td>
<td></td>
<td>18.6</td>
<td>19.0</td>
</tr>
<tr>
<td><strong>Cr Mort</strong></td>
<td></td>
<td></td>
<td>29% (47/163)</td>
<td>17% (33/197)</td>
</tr>
</tbody>
</table>

Conclusions

• Resistance is related to antimicrobial consumption in ways that are not always predictable
• That reductions in antimicrobial consumption with lead to reductions in resistance is an unproven hypothesis
• That reductions in duration are equivalent to other methods of reducing consumption is an unproven hypothesis
Conclusions

• New antibiotics, if and when available, will likely promote their own resistance
• Infection control measures are difficult to achieve and not consistently effective against all types of resistance
• Despite the lack of conclusive data, reductions in therapy durations remain the safest road to decreased consumption