Relationship Between Antibiotic Consumption and Resistance in European Hospitals

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The World (of Antimicrobial Resistance) According to...

Human Bacterial Pathogens and Their Habitat

- R *Pseudomonas aeruginosa*
- R *Acinetobacter baumannii*
- R *Salm.
- R *Camp.
- R *E. coli*
- R *Strep. pneumoniae*
- R *Haem. influenzae*
- MRSA
- R *S. aureus*

le MONDe de la Résistance Intrinsèque et Acquise aux ANtibiotiques ;-).
Antimicrobial Consumption and Resistance: Examples from ARPAC European Hospitals, 2001

Source: ARPAC, 2004 (http://www.abdn.ac.uk/arpac/)
Usefulness of Antimicrobial Resistance and Antimicrobial Use Data Comparison

High level of resistance
Low antimicrobial use
Possible areas of improvement:
  . infection control
  . identif. of colonized patients upon admission
  . appropriate dosage (low dose)
  . use of other antimicrobials

Low level of resistance
Low antimicrobial use

Low level of resistance
Relatively high antimicrobial use
Possible area of improvement: detection of resistance in the laboratory
Possible explanation: resistant bacteria has not been introduced in setting


Percent Ceftazidime-Resistant/Intermediate Gram-Negative Bacilli and Hospital Ceftazidime Use, Hospital Vega Baja, Spain, 1991-1998

Yearly data

Monthly data (5-month moving average)

Ceftazidime use (DDD/1,000 pt-days)  Ceftazidime-resistant GNB (%)

Examples of Time Series

Crude Death Rates for Infectious Diseases, USA, 1900-1996

Dow Jones Industrial Average


Multivariate Time Series Analysis

- To assess relationships between a target (output) series and one or several explanatory (input) series
- Various types of models: transfer function (TF), polynomial distributed lag (PDL), etc.
- TF models: cross-correlation function (CCF) to identify time lags between series

Sources:
Transfer Function Model for Percent Ceftazidime-Resistant/Intermediate Gram-Negative Bacilli Series (taking into account hospital ceftazidime use)

<table>
<thead>
<tr>
<th>Term</th>
<th>Parameter (SE)</th>
<th>T-ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1.354 (0.760)</td>
<td>1.78</td>
<td>0.078</td>
</tr>
<tr>
<td>AR3</td>
<td>0.352 (0.096)</td>
<td>3.68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AR5</td>
<td>0.265 (0.098)</td>
<td>2.72</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ULAG1</td>
<td>0.420 (0.096)</td>
<td>4.34</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Average delay = 1 month  
+1 DDD/1,000 patient-days = 6.5 days of treatment  
→ +0.42 %R  
e.g. from R = 5% → R = 5.42%

5-Month Moving Average Percent Amikacin-Resistant/Intermediate *P. aeruginosa* and Hospital Antimicrobial Use, Hospital Vega Baja, Spain, 1991-1999

5-Month Moving Average Percent Amikacin-Resistant/Intermediate *P. aeruginosa* and Hospital Antimicrobial Use, Hospital Vega Baja, Spain, 1991-1999

Transfer Function Model for Percent Amikacin-Resistant *Pseudomonas aeruginosa* Series (taking into account aminoglycoside and 3rd-generation cephalosporin use)

<table>
<thead>
<tr>
<th>Term</th>
<th>Order</th>
<th>Parameter (SE)</th>
<th>T-ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0</td>
<td>-20.741 (4.516)</td>
<td>-4.59</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Amikacin</td>
<td>7</td>
<td>0.973 (0.391)</td>
<td>2.49</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7</td>
<td>0.420 (0.153)</td>
<td>2.75</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>3</td>
<td>0.297 (0.112)</td>
<td>2.66</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>6</td>
<td>0.437 (0.110)</td>
<td>3.98</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AR</td>
<td>2</td>
<td>0.295 (0.091)</td>
<td>3.24</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

### Co-Resistances in Amikacin-Resistant/Intermediate and Susceptible *Pseudomonas aeruginosa* Isolates, Hospital Vega Baja, Spain, 1991-1999

<table>
<thead>
<tr>
<th>Co-resistance</th>
<th>Amikacin-R/I no. (%)</th>
<th>Amikacin-S no. (%)</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin-R/I</td>
<td>78 (97.5)</td>
<td>177 (17.5)</td>
<td>128.0</td>
<td>&lt;0.0000001</td>
</tr>
<tr>
<td>Cefotaxime-R/I</td>
<td>73 (91.3)</td>
<td>840 (83.0)</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Ceftriaxone-R/I*</td>
<td>40 (81.6)</td>
<td>361 (74.7)</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Tobramycin-R/I</td>
<td>34 (42.5)</td>
<td>18 (1.8)</td>
<td>14.8</td>
<td>&lt;0.0000001</td>
</tr>
<tr>
<td>Ceftazidime-R/I</td>
<td>15 (18.8)</td>
<td>37 (3.7)</td>
<td>4.6</td>
<td>&lt;0.0000001</td>
</tr>
</tbody>
</table>

* only 55.3% of isolates were tested for susceptibility to ceftriaxone

%MRSA and Monthly Use of Macrolides, Third-Generation Cephalosporins and Fluoroquinolones, Aberdeen Royal Infirmary, 01/1996-12/2001

<table>
<thead>
<tr>
<th>Explaining variable for monthly %MRSA</th>
<th>Lag (months)</th>
<th>Estimated coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>%MRSA</td>
<td>1</td>
<td>0.420</td>
</tr>
<tr>
<td>Macrolide use</td>
<td>1,2,3</td>
<td>0.165</td>
</tr>
<tr>
<td>Third-generation cephalosporin use</td>
<td>4,5,6,7</td>
<td>0.290</td>
</tr>
<tr>
<td>Fluoroquinolone use</td>
<td>4,5</td>
<td>0.255</td>
</tr>
<tr>
<td>Constant</td>
<td>-</td>
<td>- 36.7</td>
</tr>
</tbody>
</table>

$R^2=0.902$

5-Month Moving Average Percent Imipenem-Resistant/Intermediate *P. aeruginosa* and Hospital Imipenem Use, Hospital Vega Baja, Spain, 1991-1999

Average delay = 1 month
1 DDD/1,000 pat-days $\rightarrow +0.40$ %R

%Carbapenem-Resistant *Pseudomonas aeruginosa* and Carbapenem Use in 4 Hospitals, 1996-2003

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Location</th>
<th>Data Source</th>
<th>Average Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univ. Hospital, Ulm (D)</td>
<td>Germany</td>
<td>Lepper et al. AAC 2002:46:2920-5.</td>
<td>0-1 month</td>
</tr>
<tr>
<td>Univ. Hospital, Antwerp (B)</td>
<td>Belgium</td>
<td>Goossens H, et al. Unpublished data.</td>
<td>0-2 months</td>
</tr>
<tr>
<td>Univ. Hospital, Utah (USA)</td>
<td>USA</td>
<td>Samore MH, et al. Unpublished data.</td>
<td>0-1 month</td>
</tr>
<tr>
<td>Centre Hosp. Mulhouse (F)</td>
<td>France</td>
<td>Aujoulat O, Delarbre JM. ViResiST.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
ACR Chart

Source: Muller A, et al. (available free-of-charge, September 2005)
Effects of reduction of quinolone use on antibiotic susceptibility in *P. aeruginosa*, Pittsburgh (PA), 2001-2004

Effect of Restricting Fluoroquinolones, ICU, Saint-Etienne (F), 2000-2002

Antibiotic Rotation and Development of Gram-Negative Antibiotic Resistance, Surgical ICU, Utrecht (NL), 2001-2002

Proportion of patients treated (%)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>2001-02</th>
<th>2002-03</th>
<th>2003-04</th>
<th>2004-05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>40</td>
<td>0</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>0</td>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>55</td>
</tr>
</tbody>
</table>

Effect of Cycle Length

10 day cycles
90 day cycles
360 day cycles

Fraction Resistant

Time (days)

Areas for Future Research

- Adequation between studies at patient level and time series analyses?
- Are these relationships found in every hospital?
- More on the effect of interventions aiming at rationalizing antimicrobial prescriptions
- Short cycling vs. optimal mixing of prescriptions
- MRSA vs. antimicrobial consumption
- Outbreaks vs. endemic situations
- Interaction between infection control and antimicrobial consumption
### Pan-Resistant Gram-Negative Bacilli

**ICU, Henry Dunant Hosp., Athens, Greece, 2001-2004**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior colistin use (days)</td>
<td>0</td>
<td>23</td>
<td>11</td>
</tr>
</tbody>
</table>

**Legend:**
- Carbapenem-R, colistin-S only
- Gram-neg. bact.
- 3rd-gen. cephs-R
- Gram-neg. bact.

**Hosp. Clinico San Carlos, Madrid, 08/2003-08/2004:**
>20 pts with carbapenem-R, colistin-R *P. aeruginosa*
It’s a numbers game!

Illustration: Prittie EJ.