Risk Factors for Antibiotic Resistance
Keith P. Klugman, MD, PhD
Acute Respiratory Infections: The Leading Infectious Cause of Death

*HIV-positive people who have died with tuberculosis have been included among AIDS deaths.

Factors Influencing the Selection of Antibiotic-Resistant Pneumococci

- Age
- Site of specimen
- Hospitalization
  - Antibiotic use
    - National, individual
    - Dose and duration of therapy
    - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine
## Risk Factors for Penicillin-Resistant Pneumococcal Infections

- French retrospective study on 10,350 isolates

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;15 years</td>
<td>2.01</td>
</tr>
<tr>
<td>Isolation from URT</td>
<td>2.36</td>
</tr>
<tr>
<td>Isolation from sinus and middle ear</td>
<td>1.63</td>
</tr>
<tr>
<td>HIV infection</td>
<td>2.01</td>
</tr>
<tr>
<td>$\beta$-lactam Rx in prev. 6 months</td>
<td>1.99</td>
</tr>
<tr>
<td>Nosocomial acquisition</td>
<td>2.12</td>
</tr>
</tbody>
</table>

URT = upper respiratory tract.

Fluoroquinolone Use and PRSP, Canada, 1988-1998

PRSP = penicillin-resistant *Streptococcus pneumoniae*.

Risk Factors for Acquisition of Levofloxacin-Resistant Pneumococci in Hong Kong

- Nosocomial origin – OR 16.2 (95% CI 2.1-122.2)  
  \( P = 0.007 \)
- Exposure to an FQ in past 12 months – OR 10.7 (95% CI 1.6-71.2)  
  \( P = 0.01 \)
- Presence of COPD – OR 10.3 (95% CI 1.6-66.2)  
  \( P = 0.01 \)
- Residence in a nursing home – OR 7.4 (95% CI 1.5-35.1)  
  \( P = 0.01 \)

OR = odds ratio; FQ = fluoroquinolone; COPD = chronic obstructive pulmonary disease.

Residence in a Long-Term Care Facility as a Risk for Fluoroquinolone Resistance, USA

- Patients admitted to hospital with pneumococcal bacteremia from long-term care facilities had higher rates of FQ resistance than did age-matched controls admitted from the community.
- Cipro, levo $\geq 4$, gati $\geq 2$

<table>
<thead>
<tr>
<th>FQ</th>
<th>LTCF % R</th>
<th>Community % R</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cipro</td>
<td>8.7</td>
<td>2.2</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Levo</td>
<td>4.2</td>
<td>0.4</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Gati</td>
<td>3.5</td>
<td>0.3</td>
<td>$&lt;0.01$</td>
</tr>
</tbody>
</table>

FQ Resistance in Kids – A Warning From Africa?


- Ongoing surveillance of blood isolates of the *Pneumococcus* in adults and children in South Africa susceptibility testing was performed through July 2005 on 14,204 isolates. Of these only 14 (0.1%) were FQ-resistant, increasing from 0.05% in 2001 to 0.3% in 2005

- If this were the USA, none would be expected to be from children – 12/14 were children

- All HIV-infected, 9 known to be receiving treatment for tuberculosis and all 12 resistant also to rifampin (12/12 (100%) vs 254/5911 (4%), \(P <0.001\))

- Risk is exposure to hospitals where children are given FQ for multidrug-resistant tuberculosis

Factors Influencing the Selection of Antibiotic-Resistant *Pneumococci*

- Age
- Site of specimen
- Hospitalization
- **Antibiotic use**
  - National, individual
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine
Association of Antibiotic Use With Resistance in the *Pneumococcus*

The log odds of resistance to penicillin among invasive isolates of *Streptococcus pneumoniae* (PNSP; \(\ln(R/[1-R])\)) is regressed against outpatient sales of \(\beta\)-lactam antibiotics in 11 European countries.

DDD = defined daily doses.
Azithromycin Use vs Macrolide Resistance in Portugal

## Differences in Antibiotic Use and Resistance, Germany and France

<table>
<thead>
<tr>
<th>Variable</th>
<th>France</th>
<th>Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin resistance</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td>Macrolide resistance</td>
<td>47</td>
<td>4</td>
</tr>
<tr>
<td>No. office visits for common cold/1000 population</td>
<td>253</td>
<td>19</td>
</tr>
<tr>
<td>No. prescriptions/100 office visits for common cold</td>
<td>48.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Prescriptions for common cold/1000 population*</td>
<td>123</td>
<td>1</td>
</tr>
</tbody>
</table>

*Calculated from figures above.

Percentages of Penicillin-Sensitive and Penicillin-Resistant Pneumococci


Model Predicting the Emergence of Dual Resistance in USA

Year

Proportion Resistant

- Penicillin
- Macrolide resistance
- Multiresistance
### Selection of Resistant Pneumococci by High-Dose, Short-Duration Amoxicillin

<table>
<thead>
<tr>
<th>Relative Risk of PRSP in Carriers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose vs low dose</td>
<td>0.78 (0.65-0.95)</td>
</tr>
<tr>
<td>Day 28 vs day 0 high dose</td>
<td>1.22 (1.02-1.48)</td>
</tr>
<tr>
<td>Day 28 vs day 0 low dose</td>
<td>1.60 (1.36-1.89)</td>
</tr>
</tbody>
</table>

Factors Influencing the Selection of Antibiotic-Resistant *Pneumococci*

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, individual
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine
Impact of Fansidar Therapy for Malaria on Cotrimoxazole Resistance in the *Pneumococcus*

Factors Influencing the Selection of Antibiotic-Resistant Pneumococci

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, individual
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- **Day care**
- **Clonal spread**
- HIV
- Mechanisms of resistance
- Conjugate vaccine
Isolation of *S. pneumoniae* 23F, intermediately susceptible to penicillin and resistant to trimethoprim-sulfamethoxazole

## Multivariate Analysis of Risk Factors for Penicillin-Resistant Invasive *S. pneumoniae* Infections (52 Penicillin-Resistant Cases, 280 Control Subjects)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Covariate</th>
<th>Adjusted OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-59 months</td>
<td>Recent day-care attendance</td>
<td>3.79</td>
<td>1.85-7.77</td>
</tr>
<tr>
<td></td>
<td>At least one recent course of antibiotics</td>
<td>3.08</td>
<td>1.28-7.40</td>
</tr>
<tr>
<td></td>
<td>At least one recent ear infection</td>
<td>2.38</td>
<td>1.05-5.42</td>
</tr>
</tbody>
</table>

*Adjusted for age.

Family Transmission of Resistant Strains

In a multivariate model of risk factors for the acquisition of resistant (pen and/or erythro and/or TMP/SMX) pneumococcal carriage in children in Utah, US, the significant risk factors were

—Cephalosporin use in previous 4 months
  OR 2.7  95% CI 1.1-6.6  \( P = 0.035 \)

—Sibling carrying a resistant strain
  OR 7.5  95% CI 0.7-20.7  \( P <0.001 \)

Clonal Spread of *S. pneumoniae* 23F
<table>
<thead>
<tr>
<th>Country</th>
<th>Serotype Isolated</th>
<th>International Clone Number</th>
<th>Subsequent Serotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eg, Spain</td>
<td>23F</td>
<td>-1</td>
<td>-19F</td>
</tr>
</tbody>
</table>

IUMS = International Union of Microbiological Societies.
Linkage Distance

0.0  0.2  0.4  0.6  0.8  1.0

S. Africa\textsuperscript{19A–7}
Poland\textsuperscript{23F–16}
Hungary\textsuperscript{19A–6}
Taiwan\textsuperscript{23F–15}
S. Africa\textsuperscript{6B–8}
S. Africa\textsuperscript{19A–13}
CSR\textsuperscript{19A–11}
England\textsuperscript{14–9}
CSR\textsuperscript{14–10}
Spain\textsuperscript{14–5}
Taiwan\textsuperscript{19F–14}
Tennessee\textsuperscript{23F–4}
Finland\textsuperscript{6B–12}
Spain\textsuperscript{6B–2}
Spain\textsuperscript{9V–3}
Spain\textsuperscript{23F–1}

Clones of Penicillin-Resistant *Pneumococci* in the US

<table>
<thead>
<tr>
<th>Clone</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain^{23F-1} – 14,19</td>
<td>127/328</td>
<td>38.7%</td>
</tr>
<tr>
<td>Spain^{9V-3} – 14,19</td>
<td>40/328</td>
<td>12.2%</td>
</tr>
<tr>
<td>Eight other clones</td>
<td>112/328</td>
<td>34.1%</td>
</tr>
<tr>
<td>The above ten clones</td>
<td>279/328</td>
<td>85.0%</td>
</tr>
</tbody>
</table>

## Clonality of Highly Penicillin-Resistant *Pneumococci* in the US

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spain</strong>$^{23F-1}$</td>
<td>123/672</td>
<td>18.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Spain</strong>$^{9V-3}$</td>
<td>96/672</td>
<td>14.3%</td>
<td></td>
</tr>
<tr>
<td>PFGE type 3</td>
<td>65/672</td>
<td>9.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Spain</strong>$^{6B-2}$</td>
<td>44/672</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>PFGE type 5</td>
<td>42/672</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Tennessee</strong>$^{23F-4}$</td>
<td>33/672</td>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>PFGE types 7-10</td>
<td>95/672</td>
<td>14.1%</td>
<td></td>
</tr>
<tr>
<td><strong>Taiwan</strong>$^{19F-14}$</td>
<td>11/672</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>PFGE types 12,13</td>
<td>15/672</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>12 clones</td>
<td>524/672</td>
<td>78.0%</td>
<td></td>
</tr>
</tbody>
</table>

PFGE = pulsed-field gel electrophoresis.

Clones of Penicillin-Resistant *Pneumococci* in the US

<table>
<thead>
<tr>
<th>Clone Description</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain(^{23F-1} - 19)</td>
<td>23/144</td>
<td>16%</td>
</tr>
<tr>
<td>Spain(^{6B-2})</td>
<td>4/144</td>
<td>3%</td>
</tr>
<tr>
<td>Spain(^{9V-3} - 9A,14)</td>
<td>40/144</td>
<td>28%</td>
</tr>
<tr>
<td>Tennessee(^{23F-4})</td>
<td>19/144</td>
<td>13%</td>
</tr>
<tr>
<td>England(^{14-9})</td>
<td>31/144</td>
<td>22%</td>
</tr>
<tr>
<td>Three other clones</td>
<td>17/144</td>
<td>12%</td>
</tr>
<tr>
<td>The above eight clones</td>
<td>134/144</td>
<td>93%</td>
</tr>
</tbody>
</table>

Increase in FQ Resistance in the *Pneumococcus* in Hong Kong

- Two studies of sequential clinical isolates from 6 hospitals in Hong Kong – 1998 and 2000
- Levo MIC $\geq 4 \ \mu g/mL$ – $\Uparrow$ from 5.5% to 13.3%
- In penicillin-resistant strains – $\Uparrow$ 9.2% to 27.3%
- Risk factors were
  - Patients $\geq 65$ y – 17.1% vs 9.1% (18-64 y) ($P < 0.001$)
  - Adults with COPD – 24.6% vs 9.3% ($P = 0.01$)
- All FQ-resistant strains are a clone of Spain$^{23F}$-1 resistant to penicillin (MIC 2-4 $\mu g/mL$) and cefotaxime (MIC 1-4 $\mu g/mL$)

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- Day care
- Clonal spread
- **HIV**
- Mechanisms of resistance
- Conjugate vaccine
Impact of HIV on Penicillin Resistance in the *Pneumococcus*

<table>
<thead>
<tr>
<th>Age</th>
<th>HIV+</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>19/100 (19%)</td>
<td>11/259 (4%)</td>
</tr>
<tr>
<td>Children</td>
<td>24/45 (53%)</td>
<td>16/53 (30%)</td>
</tr>
</tbody>
</table>

Emerging Problem

- Cotrimoxazole-resistant (and multiply-resistant) pneumococcal infections are more common in HIV-infected children and adults on prophylaxis with the drug

Gender as a Risk Factor for Antibiotic Resistance: Independent Risk Factors in a Multivariate Model for Pneumococcal Bacteremia in Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric serotype</td>
<td>1.59</td>
<td>1.18-2.15</td>
</tr>
<tr>
<td><strong>Penicillin resistance</strong></td>
<td>1.65</td>
<td>1.06-2.59</td>
</tr>
<tr>
<td>HIV seropositive</td>
<td>1.85</td>
<td>1.26-2.71</td>
</tr>
<tr>
<td>Ages 18-39 vs ≥40 years</td>
<td>1.72</td>
<td>1.25-2.36</td>
</tr>
</tbody>
</table>

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- **Mechanisms of resistance**
- Conjugate vaccine
Amino Acid Substitutions in Sensitive and Resistant DHFRs

<table>
<thead>
<tr>
<th></th>
<th>14</th>
<th>20</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>74</th>
<th>77</th>
<th>78</th>
<th>81</th>
<th>91</th>
<th>92</th>
<th>94</th>
<th>100</th>
<th>111</th>
<th>135</th>
<th>147</th>
<th>149</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCLS</td>
<td>E</td>
<td>E</td>
<td>K</td>
<td>I</td>
<td>P</td>
<td>I</td>
<td>V</td>
<td>A</td>
<td>Q</td>
<td>Q</td>
<td>D</td>
<td>A</td>
<td>E</td>
<td>I</td>
<td>P</td>
<td>L</td>
<td>F</td>
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<tr>
<td>69419</td>
<td>E</td>
<td>E</td>
<td>K</td>
<td>I</td>
<td>P</td>
<td>I</td>
<td>V</td>
<td>A</td>
<td>Q</td>
<td>Q</td>
<td>D</td>
<td>A</td>
<td>E</td>
<td>I</td>
<td>P</td>
<td>L</td>
<td>F</td>
</tr>
<tr>
<td>SENSITIVE</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
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<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>RESISTANT</td>
<td>Q</td>
<td>Q</td>
<td>S</td>
<td>S</td>
<td>L</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>A</td>
<td>A</td>
<td>D</td>
<td>L</td>
<td>S</td>
<td>F</td>
<td>F</td>
<td>S</td>
<td>T</td>
</tr>
</tbody>
</table>

Single-base mutation conferring resistance suggests rapid selection

DHFR = dihydrofolate reductase.

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- HIV
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- **Conjugate vaccine**
### Impact of 9-Valent Conjugate Vaccine on Carriage of Antibiotic-Resistant *Pneumococci*

<table>
<thead>
<tr>
<th>Antibiotic Resistance</th>
<th>Vaccines (%) (n = 130)</th>
<th>Controls (%) (n = 145)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>27 (21)</td>
<td>60 (41)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2 (2)</td>
<td>5 (3)</td>
<td>—</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>14 (11)</td>
<td>13 (9)</td>
<td>—</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>8 (6)</td>
<td>6 (4)</td>
<td>—</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>7 (5)</td>
<td>4 (3)</td>
<td>—</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>—</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>30 (23)</td>
<td>51 (35)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Any of the above</td>
<td>59 (45)</td>
<td>90 (62)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cases in Control Group</th>
<th>Cases in Vaccine Group</th>
<th>Vaccine Efficacy (VE)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>21</td>
<td>7</td>
<td>67</td>
<td>19-88</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>32</td>
<td>14</td>
<td>56</td>
<td>16-78</td>
</tr>
<tr>
<td>Any</td>
<td>39</td>
<td>17</td>
<td>56</td>
<td>21-77</td>
</tr>
</tbody>
</table>

In the cotrimoxazole group, 29 and 13 are HIV+ (VE 55%).

Children <2 Years of Age

Incidence (cases per 100,000)


Penicillin-susceptible disease

Penicillin-non-susceptible disease

Vaccine introduced

>2 Years of Age

Antibiotic Resistance Remains Common in URT Isolates in the Vaccine Era

- Rates of resistance in NP carriage studies in Boston show evidence of replacement, but also no reduction in antimicrobial resistance associated mainly with serotypes 19A and 19F¹
- In Alaska, NP surveillance reveals reduced COT resistance associated with little selective pressure, but no drop in pen resistance associated with increased resistance in 19F²
- In Kentucky, although pneumococci decreased in MEF, antibiotic resistance did not³

Day Care in Portugal

Serotypes Not Represented in PCV7 (N = 4112)

Future Prospects

- Strategies to reduce antimicrobial use in order to decrease resistance are complicated by multiple resistance.

- Pneumococcal conjugate vaccines have been shown to interrupt the transmission of multiply-resistant strains that belong to vaccine serotypes, but resistance is emerging in nonvaccine types.