Treatment failure in the absence of resistance: a historical perspective and examples

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ESCMID Conference, Freiburg, October 2009
CAUSES OF ANTIBIOTIC FAILURE NOT PRIMARILY RELATED TO RESISTANCE

- Immunedeficiencies and immunocompromised states
- Comorbidities and severity of disease
- Time to treatment
- PK/PD causes
- Duration of antimicrobial therapy
- Inoculum effects
- Tolerance and persistence
- Bacteriostasis vs. bactericidal activity
- Biofilms and sanctuaries
- Antagonism vs. synergy
- Cryptic antibiotic resistance
- Emergence of resistance while on therapy
COMORBIDITIES AND SEVERITY OF DISEASE
### Case Fatality Rate in Patients with Type I Pneumococcal Pneumonia by Severity
(Park, et al., 1928)

<table>
<thead>
<tr>
<th>Condition at baseline</th>
<th>Serum-treated</th>
<th>Standard treatment</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any condition</td>
<td>20% (N=114)</td>
<td>34% (N= 109)</td>
<td>14%</td>
</tr>
<tr>
<td>Good (&gt; 70)</td>
<td>9%</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Fair (50-70)</td>
<td>29%</td>
<td>52%</td>
<td>23%</td>
</tr>
<tr>
<td>Poor (&lt; 50)</td>
<td>64%</td>
<td>100%</td>
<td>36%</td>
</tr>
</tbody>
</table>
### Controlled Clinical Trial: Treatment of Pneumococcal Pneumonia with Sulfapyridine

**Graham, et al. (1939)**

- Hospitalized patients with pneumococcal pneumonia
- Alternate patients
- Control: no specific therapy (20% bacteremic)
- Dagenan (M&B 693) = Sulfapyridine (34% bacteremic)

#### Case Fatality Rate

<table>
<thead>
<tr>
<th></th>
<th>Dagenan (M&amp;B 693)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/50 (6%)</td>
<td></td>
<td>7/30 (23%)</td>
</tr>
<tr>
<td>3/17 (18%) bacteremic</td>
<td></td>
<td>3/6 (50%) bacteremic</td>
</tr>
</tbody>
</table>
PSEUDOMONAS AERUGINOSA BACTERAEMIA: PREDICTORS OF EARLY MORTALITY
MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>5.9</td>
<td>1.1-23</td>
<td>0.012</td>
</tr>
<tr>
<td>Inappropriate Empirical Antibiotic treatment</td>
<td>4.0</td>
<td>1.1-15</td>
<td>0.03</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>3.5</td>
<td>1.1-12</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Pascual V et al, 49th ICAAC, San Francisco 2009
% Failed % Dead Predicted % Deaths

No. enrolled

APACHE II Range

0-4 5-9 10-14 15-19 20-24

24 39 36 36 18

Risk factors for treatment failure in patients with VAP receiving appropriate antibiotic therapy.

- Observational cohort study in an ICU of a University hospital. 90 patients with VAP enrolled

- RESULTS: Mean age was 72 +/- 13 years. 53 of the patients had TF. Transfusions, bacteremia, infection with multidrug-resistant microorganisms, initial bacterial load (CFU/mL), and steroid therapy were similar across the groups.

- Independent predictors for TF:
  - Comorbidity (OR, 4.4; 95% CI, 1.2-16.8; P = .030)
  - VAP-APACHE II scores above 16 (OR, 6.4; 95% CI, 2.1-18.6; P = .001)
  - Daily carbohydrate intake below 190 g/d (OR, 3; 95% CI, 1.1-8.6; P = .038)
  - Lymphocyte number below 1000/mm³ (OR, 4.1; 95% CI, 1.3-12.9; P = .014)

CONCLUSIONS: Patients with comorbidities, who are severely ill and lymphocytopenic at the time of VAP diagnosis, are at high risk for TF.

Gursel G et al, J Crit Care. 2008
Risk factors for treatment failure in patients with VAP receiving appropriate antibiotic therapy.

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Gursel G et al, J Crit Care. 2008
TIME TO TREATMENT
Time to appropriate therapy in ICU and survival

Risk of mortality increase by 12% for each hour of delay in effective therapy

Survival in Bacteremic Pneumococcal Bacteremia Treated with Penicillin or Serum

Austrian and Gold. Ann Int Med 1964
INADEQUATE DEBRIDMENT AND DRAINAGE
• Accepted treatment for patients with solid organ abscesses involves image-guided percutaneous drainage followed by an intensive course of antimicrobial therapy.

• Size and location of the abscess are critical
PK/PD CONSIDERATIONS
DOSAGE AND DURATION OF TREATMENT
Penicillin in Bacterial Endocarditis

<table>
<thead>
<tr>
<th>No. of patients Relapsed or died</th>
<th>1 million Units a Day for 5 Days</th>
<th>0.5 million Units a Day for 10 Days</th>
<th>0.25 million Units a Day for 20 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>95%</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>123 days</td>
<td></td>
<td>110 days</td>
<td>83 days</td>
</tr>
</tbody>
</table>

RONALD V. CHRISTIE, BMJ 1945
Secretary, Penicillin Clinical Trials Committee.
Patients Treated for 28 Days with Daily Dose of 500,000 Units. (No Patient had Previously Received Penicillin)

<table>
<thead>
<tr>
<th></th>
<th>Before March, 1946</th>
<th>After March, 1946</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Treated</td>
<td>58</td>
<td>71</td>
<td>129</td>
</tr>
<tr>
<td>Died with infection</td>
<td>25</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>Apparently Controlled</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Died with infection Uncontrolled</td>
<td>29</td>
<td>35</td>
<td>64</td>
</tr>
<tr>
<td>Relapsed</td>
<td>43</td>
<td>20</td>
<td>64</td>
</tr>
<tr>
<td>“Cured”</td>
<td>7%</td>
<td>20%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Patients Treated for 4 to 6 Weeks with a Daily Dose of 2,000,000 U

<table>
<thead>
<tr>
<th>No. Treated</th>
<th>Died with infection</th>
<th>Apparently Controlled</th>
<th>Died with infection Uncontrolled</th>
<th>Relapsed</th>
<th>“Cured”</th>
<th>Average Follow-up (Months)</th>
<th>Relapsed or Died Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous treatment with penicillin</td>
<td>18</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>11</td>
<td>0%</td>
</tr>
<tr>
<td>Previously treated with penicillin</td>
<td>13</td>
<td>1</td>
<td>-</td>
<td>4</td>
<td>8</td>
<td>16½</td>
<td>31%</td>
</tr>
</tbody>
</table>

In Streptococcus viridans endocarditis, penicillin G doses should be at least 2,000,000 U/day, for 4 to 6 weeks.

When the organism is resistant to the action of Penicillin or when the cultures are negative, is difficult to estimate the right dose.

Christie R, B Med J 1949
Penicillin doses and duration of treatment in pneumococcal pneumonia. Early studies

- 54 patients. Blood cultures were positive before the first dose in > 50% of the cases.
- In 37 patients treated from the start with penicillin alone, the average total dose was 110,000 units (246 mg) given during an average of 86 h. 7 patients died.
- In 17 other patients to whom the penicillin was given after an apparent failure to respond to sulphonamidine therapy, the average total dose was 728,000 units in 6 and one half days. 3 patients died.

• Bacteremia in surviving patients was rapidly cleared, usually before the second dose of penicillin was given

• Pneumococci were eliminated from the sputum in one half of the patients within 48 h, but in 17% the organisms persisted for more than 5 days
  (Ory EM et al, J Lab Clin Med 1947;31:409-432)
• Bacteremia in surviving patients was rapidly cleared, usually before the second dose of penicillin was given

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  (Ory EM et al, J Lab Clin Med 1947;31:409-432)

• Mortality was 18.5% (10/54)
Aureomycin treatment in pneumococcal pneumonia

- 33 adult patients with pneumococcal pneumonia treated with chlortetraacycline (Aureomycin)
- Aureomycin, 0.5-1 Gm Q4-6h given orally in most cases.
- Most of the patients received less than 20 Gm (range, 5.52-56.5) and were treated for 5 days or less.
- Pneumococci were obtained from the pretreatment blood cultures in 11(33%) patients.
- Auromycin, when given orally proved as effective as penicillin and cleared pneumococci from sputum even more rapidly.
- 2/33(6%) patients died.

Gocke TM et al, Arch Int Med 1949; 84:857-874
Effect of Treatment Duration on PK/PD Indices Correlating with Efficacy of Ceftazidime in Experimental *Klebsiella pneumoniae* Lung Infection

- Treatment duration in the experimental animal setting is relatively short and usually varies from 24 h to 48 h.

Bakker-Woudenberg IA et al, AAC 2006
Effect of Treatment Duration on PK/PD Indices Correlating with Efficacy of Ceftazidime in Experimental *Klebsiella pneumoniae* Lung Infection

- Treatment duration in the experimental animal setting is relatively short and usually varies from 24 h to 48 h.
- To explore the correlation between the PK/PD indices for ceftazidime and outcome in relation to the treatment duration and treatment endpoint in an animal model of *Klebsiella pneumoniae* lung infection.

  Bakker-Woudenberg IA et al, AAC 2006
Effect of Treatment Duration on PK/PD Indices Correlating with Therapeutic Efficacy of Ceftazidime in Experimental *Klebsiella pneumoniae* Lung Infection

Relationship between fTMIC or 24-h fAUC/MIC ratio of ceftazidime and outcome in rats with *K. pneumoniae* lung infection. (A and B) decrease in bacterial numbers in the left lung after 48 h of treatment compared to the numbers at the start of treatment (dlog CFU; n = 3 per group); (C and D) 43-day survival of rats after 18 days of treatment (n = 10 per group).

Bakker-Woudenberg IA et al, AAC 2006
• When the treatment duration was extended to a period of 18 days instead of 48 h and animal survival rate instead of microbiological efficacy was taken as the endpoint, the \( fAUC/MIC \) ratio was the PK/PD index that best correlated with therapeutic efficacy.

Bakker-Woudenberg IA et al, AAC 2006
When the treatment duration was extended to a period of 18 days instead of 48 h and animal survival rate instead of microbiological efficacy was taken as the endpoint, the fAUC/MIC ratio was the PK/PD index that best correlated with therapeutic efficacy. The PK/PD index that best correlates with outcome is dependent on the duration of treatment and/or the parameter of outcome.

Bakker-Woudenberg IA et al, AAC 2006
INOCULUM EFFECT
MIC of 4 antibiotics against an endocarditis Staphylococcus aureus strain (TX0117) and 2 ATCC strains (29213 and 25923) at 24 h.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>High inoculum&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intermediate inoculum&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Standard inoculum&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TX0117&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ATCC 29213&lt;sup&gt;e&lt;/sup&gt;</td>
<td>ATCC 25923&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>128</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>16</td>
<td>4</td>
<td>0.25</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>4</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> 5 x 10<sup>7</sup> cfu/mL.
<sup>b</sup> 5 x 10<sup>6</sup> cfu/mL.
<sup>c</sup> 5 x 10<sup>9</sup> cfu/mL.
<sup>d</sup> Isolate recovered from the patient described here (producer of type A β-lactamase).
<sup>e</sup> Weak type A β-lactamase producer.
<sup>f</sup> Non-β-lactamase producer.

A patient with MSSA aortic native valve endocarditis; relapse, involving fever and positive blood culture results while receiving cefazolin.

DNA sequencing of the β-lactamase gene: type A β-lactamase, known to efficiently inactivate cefazolin.

Nannini AC et al, Clin Infect Dis 2003
Inoculum effect with cefazolin in clinical isolates of MSSA. Frequency and possible cause of cefazolin treatment failure.

- 98 MSSA clinical isolates
- 26% produced type A Bla, 15% type B, 46% type C, and none type D and that 13% lacked blaz.
- The cefazolin MIC$_{90}$ was 2 µg/ml for a standard inoculum and 32 µg/ml for a high inoculum.
- At the high inoculum, type A producers displayed higher cefazolin MICs than type B or C producers
- Among isolates from hemodialysis patients with MSSA bacteremia, three from the six patients who experienced cefazolin failure showed a cefazolin inoculum effect, while none from the six patients successfully treated with cefazolin showed an inoculum effect, suggesting an association between these strains and cefazolin failure (P = 0.09 by Fisher's exact test).

Nannini AC et al, AAC 2009
ANTIMICROBIALS-DIFFERENT MODES OF ACTION
Release of bacterial compounds during treatment of GNB infections

- Antibiotic treatment causes up to a 100-fold rises in endotoxin levels in the supernatants of bacterial cultures.

- The release of LPS during therapy is drug and dose dependent.

- Quantitative differences in the release of LPS correlate with antibiotic-initiated Morphological changes in bacteria

- The impact of this release is controversial

Release of LPS from *E. coli* following exposure to various antibacterials.

Evans ME et al, JID 1993;167:185-9
Meliodosis, a model

- Severe melioidosis is a life-threatening systemic infection caused by the gram-negative bacterium *Burkholderia pseudomallei*.
- In-hospital mortality in severe disease remains 40%–45%, despite the introduction of ceftazidime-containing therapeutic regimens.

Simpson AJ et al, JID 2000
Meliodosis, a model

- Imipenem kill *B. pseudomallei* more rapidly in vitro than do the third-generation cephalosporins such as ceftazidime.
- Imipenem binds preferentially to PBP-2, whereas ceftazidime is a PBP-3–specific agent. PBP-2–specific agents cause spheroplast formation and rapid cell death in vitro, with release of minimal amounts of free endotoxin. PBP-3–specific agents, in contrast, generate long filamentous forms that are capable of releasing large amounts of unbound endotoxin.

Simpson AJ et al, JID 2000
Figure 1: Plasma endotoxin levels over the first 6 h after the initial dose of imipenem ($n = 34$) or ceftazidime ($n = 34$) in patients with acute septicemic melioidosis. Results are presented as median values with 25%–75% interquartile ranges.

* $P < 0.05$

Simpson AJ et al, JID 2000;181: 1014-19
• No overall difference in mortality was observed (35% in both groups [95% confidence interval, 20%–50%]).

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• Differential antibiotic-induced endotoxin release is demonstrable in severe melioidosis.

Simpson AJ et al, JID 2000
• No overall difference in mortality was observed (35% in both groups [95% confidence interval, 20%–50%]).

• Differential antibiotic-induced endotoxin release is demonstrable in severe melioidosis.

• These differences in endotoxin release did not appear to have a significant impact on survival in this group of patients.

Simpson AJ et al, JID 2000
LEVO vs. CRO in Severe Pneumococcal Pneumonia

TNFα, IL 1β and IL 8 Concentrations Over Time

Levo vs. CRO treatment showed a significant difference in TNFα concentration (p = 0.014) but not in IL 1β and IL 8 concentrations.

Calbo E et al, AAC 2008
OTHER VITAL SIGNS OVER TIME

- Basal Oxygen Saturation
- Heart Rate
- Respiratory Rate

**p-values:**
- Heart Rate: p=0.034
- Respiratory Rate: p=0.029
- p=0.2

**Pharmaceuticals:**
- Levofloxacin
- Ceftriaxone
LEVO VS. CRO IN SEVERE PNEUMOCOCCAL PNEUMONIA

- LEVO treated patients showed an earlier clinical recovery phase (expressed as a faster recovery of O$_2$ saturation, a slower cardiac rate, and a trend to an earlier defervescence) in parallel with a faster fall in TNF levels.

Calbo E et al, AAC 2008
LEVO VS. CRO IN SEVERE PNEUMOCOCCAL PNEUMONIA

• LEVO treated patients showed an earlier clinical recovery phase (expressed as a faster recovery of O$_2$ saturation, a slower cardiac rate, and a trend to an earlier defervescence) in parallel with a faster fall in TNF levels.

• However, no differences in mortality were found.

Calbo E et al, AAC 2008
Drawbacks of bactericidal antibiotics

- Release of cell wall products
  - Liberación de productos de la pared que > producción de citoquinas en LCR
- Liberation of exotoxin A in *Streptococcus pyogenes* en presencia de penicilina
- Liberation of endotoxin in BGN por ceftazidime
- Liberation of Shiga toxin in *E. coli* by trimethoprim
- ...
ANTAGONISTIC COMBINATIONS
The classical Lepper and Dowling study.
Clear clinical antagonism with the combination of penicillin and aureomycin in pneumococcal meningitis.

Penicillin G Na: 1 million U/2 h
Tetracycline: 500 mg/6h
• Penicillin is bactericidal while the combination can paradoxically impair killing (in vitro, the addition of an inhibitor of protein synthesis limits the bactericidal activity of an cell wall active agent)
• Penicillin is bactericidal while the combination can paradoxically impair killing (in vitro, the addition of an inhibitor of protein synthesis limits the bactericidal activity of an cell wall active agent)

• In another classical study in children with meningitis, those treated with ampicillin alone had a mortality rate of 4.3%, compared to a mortality rate of 10.5% in the ampicillin + chloramphenicol + streptomycin treated group (Mathies AW et al, AAC 1967)
RIFAMPIN AND STAPHYLOCOCCUS AUREUS ENDOCARDITIS

Clinical outcomes for cases and controls

<table>
<thead>
<tr>
<th>Characteristic or outcome</th>
<th>Value for group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Total no. of subjects</td>
<td>42</td>
<td>22</td>
</tr>
<tr>
<td>Median length of bacteremia</td>
<td>5.2 (1–26)</td>
<td>2.1 (1–8)</td>
</tr>
<tr>
<td>[days (range)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requirement of hemodialysis</td>
<td>8 (19)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>[no. (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve surgery [no. (%)]</td>
<td>9 (21)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Relapse [no. (%)]</td>
<td>9 (21)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Median length of stay [days]</td>
<td>21.3 (2–66)</td>
<td>14.7 (4–62)</td>
</tr>
<tr>
<td>(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival [no. (%)]</td>
<td>33 (79)</td>
<td>40 (95)</td>
</tr>
</tbody>
</table>

All cases of native valve S. aureus IE confirmed by modified Duke criteria in a large urban hospital, 2004-2005

A retrospective cohort analysis was used to assess the impact of the addition of rifampin to standard therapy

Riedel DJ et al, AAC 2008A
THE ORGANISM
- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Escherichia coli*
- ...
Pneumococcal Serotypes and Mortality following Invasive Pneumococcal Disease: A Population-Based Cohort Study

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Patients</th>
<th>Deaths (%)</th>
<th>Crude OR</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>57</td>
<td>28 (46)</td>
<td>10.98</td>
<td>6.30 (3.60-11.04)</td>
</tr>
<tr>
<td>11A</td>
<td>227</td>
<td>96 (42)</td>
<td>9.60</td>
<td>5.00 (4.38-6.20)</td>
</tr>
<tr>
<td>35F</td>
<td>83</td>
<td>34 (41)</td>
<td>9.09</td>
<td>5.64 (3.50-9.09)</td>
</tr>
<tr>
<td>16F</td>
<td>137</td>
<td>48 (35)</td>
<td>7.06</td>
<td>4.39 (2.95-6.51)</td>
</tr>
<tr>
<td>19F</td>
<td>389</td>
<td>136 (35)</td>
<td>7.04</td>
<td>4.30 (3.29-6.60)</td>
</tr>
<tr>
<td>3</td>
<td>916</td>
<td>295 (32)</td>
<td>6.22</td>
<td>4.09 (3.31-5.06)</td>
</tr>
<tr>
<td>10A</td>
<td>111</td>
<td>35 (32)</td>
<td>6.03</td>
<td>4.03 (2.62-6.34)</td>
</tr>
<tr>
<td>Other</td>
<td>451</td>
<td>115 (25)</td>
<td>4.48</td>
<td>3.04 (2.33-3.98)</td>
</tr>
<tr>
<td>19A</td>
<td>316</td>
<td>86 (27)</td>
<td>4.90</td>
<td>2.69 (2.15-3.30)</td>
</tr>
<tr>
<td>9N</td>
<td>449</td>
<td>110 (24)</td>
<td>4.25</td>
<td>2.75 (2.11-3.61)</td>
</tr>
<tr>
<td>23A</td>
<td>86</td>
<td>22 (26)</td>
<td>4.50</td>
<td>2.75 (1.64-4.62)</td>
</tr>
<tr>
<td>6B</td>
<td>397</td>
<td>103 (26)</td>
<td>4.59</td>
<td>2.74 (1.30-6.63)</td>
</tr>
<tr>
<td>6A</td>
<td>407</td>
<td>104 (26)</td>
<td>4.49</td>
<td>2.70 (2.05-3.57)</td>
</tr>
<tr>
<td>23F</td>
<td>530</td>
<td>130 (25)</td>
<td>4.26</td>
<td>2.63 (2.04-3.40)</td>
</tr>
<tr>
<td>18C</td>
<td>238</td>
<td>44 (18)</td>
<td>2.97</td>
<td>2.35 (1.62-3.42)</td>
</tr>
<tr>
<td>24F</td>
<td>146</td>
<td>32 (22)</td>
<td>3.61</td>
<td>2.25 (1.48-3.30)</td>
</tr>
<tr>
<td>14</td>
<td>1339</td>
<td>272 (20)</td>
<td>3.34</td>
<td>2.15 (1.75-2.66)</td>
</tr>
<tr>
<td>12F</td>
<td>759</td>
<td>127 (17)</td>
<td>2.63</td>
<td>1.96 (1.51-2.48)</td>
</tr>
<tr>
<td>20</td>
<td>254</td>
<td>49 (19)</td>
<td>3.13</td>
<td>1.91 (1.34-2.73)</td>
</tr>
<tr>
<td>9V</td>
<td>888</td>
<td>140 (17)</td>
<td>2.64</td>
<td>1.84 (1.45-2.34)</td>
</tr>
<tr>
<td>22F</td>
<td>371</td>
<td>67 (18)</td>
<td>2.39</td>
<td>1.82 (1.33-2.50)</td>
</tr>
<tr>
<td>38</td>
<td>140</td>
<td>25 (19)</td>
<td>2.99</td>
<td>1.81 (1.14-2.86)</td>
</tr>
<tr>
<td>4</td>
<td>1586</td>
<td>212 (14)</td>
<td>2.41</td>
<td>1.60 (1.29-1.88)</td>
</tr>
<tr>
<td>5</td>
<td>254</td>
<td>30 (12)</td>
<td>1.75</td>
<td>1.51 (0.99-2.30)</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
<td>104 (13)</td>
<td>2.04</td>
<td>1.51 (1.16-1.96)</td>
</tr>
<tr>
<td>33F</td>
<td>185</td>
<td>25 (15)</td>
<td>2.34</td>
<td>1.45 (0.92-2.31)</td>
</tr>
<tr>
<td>7F</td>
<td>1129</td>
<td>118 (10)</td>
<td>1.53</td>
<td>1.23 (0.96-1.58)</td>
</tr>
<tr>
<td>1 (ref)</td>
<td>2551</td>
<td>181 (7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Multivariate logistic regression analysis of serotype-specific 30-d mortality associated with IPD in bacteremia patients aged 5 y or older (n = 15,029). OR estimates adjusted for age (in years), sex, time at diagnosis (in decades), alcoholism-related conditions, and low, medium, or high comorbidity score estimated by the Charlson index.

Reference group: patients with IPD caused by serotype 1 in each group. ORs calculated for serotypes with ≥ 50 IPD cases
BIOFILM FORMATION
Crystalline material that blocked a patient’s catheter after just 4 days.

The large coffin-shaped crystals were shown by X-ray microanalysis to be a form of magnesium ammonium phosphate (struvite), and the microcrystalline aggregates were shown to be calcium phosphate (apatite).

A four-membered bacterial community was isolated from this crystalline biofilm composed of *E. coli*, *P. aeruginosa*, *E. faecalis*, and *P. mirabilis*.

**Stickler, DJ et al,**
- Foreign body
- Dead bone tissue (sequestrum)
- Diabetic foot

SANTUARIES

- Brain (cerebral abscess)
- Subarachnoidal space (meningitis)
- The eye
- ...

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TOLERANCE AND PERSISTENCE
Vancomycin-tolerant *S. aureus*

- In the original paper describing β-lactam tolerance in *S. aureus*, most strains also showed cross-tolerance to vancomycin¹.

- Vancomycin tolerance is more common in MRSA than MSSA and in isolates from endocarditis².

- Part of the intermediate glycopeptide-resistance seen in GISA may be due to tolerance³.

- Several small series and case studies report poor clinical response to vancomycin in bacteraemia/endocarditis caused by vancomycin-tolerant *S. aureus* and the need for additional agents for a bactericidal effect⁴–⁷.

Vancomycin therapy for methicillin-resistant Staphylococcus aureus.

- Fifteen of 19 episodes of serious methicillin-resistant S. aureus infection responded to vancomycin.
- Tolerance (a MBC/MIC ratio of at least 32) correlated with therapeutic failure (\( p = 0.04 \))

Sorrell TC et al, Ann Int Med 1992
PERSISTENT INFECTIONS

- *Salmonella* spp
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
EMERGENCE OF RESISTANCE WHILE ON THERAPY
Clinical implications of macrolide resistance

28-yr old male
- previously healthy
- *S. pneumoniae* pneumonia

Initial isolate fully susceptible to penicillin and macrolides
- Later isolate susceptible to penicillin, but macrolide resistant (MICs 2–4 μg/ml)
- Mutation of the gene for ribosomal protein L22

Characteristics of S. pneumoniae isolated before (b), during (d), or after (a) therapy with levofloxacin from 4 patients with CAP
OTHER EXAMPLES

- *Pseudomonas aeruginosa*
- *Mycobacterium tuberculosis*
- Other bacteria and viruses (HIV, the paradigm)