Educational Workshop

EW02: Challenges and change in pneumonia - focus on Streptococcus pneumoniae and community-acquired MRSA

GRACE Workshop

( Genomics to Combat Resistance against Antibiotics in Community-acquired LRTI in Europe)

arranged with ERS (European Respiratory Society)

Convenor: Javier Garau, Barcelona, Spain

Faculty: Ron Dagan (Beer Sheva, IL)  
Ake Ortvist (Stockholm, SE)  
Javier Garau (Barcelona, ES)  
Marc Bonten (Utrecht, NL)  
Jan Kluymans (Breda, NL)  
Robert Masterton (Kilmarnock, UK)
Impact of Pneumococcal Conjugate Vaccines on Pneumonia and LRIs

Challenges and Changes in Pneumonia – Focus on S. pneumoniae and CAS-MRSA
Helsinki, May 16th, 2009

Ron Dagan
The Pediatric Infectious Disease Unit
Soroka University Medical Center
Ben-Gurion University
Beer-Sheva, Israel

Antibiotic consumption
transmission
 carriage
Antibiotic resistance
PCV and pneumonia

Impact of Pneumococcal Conjugate Vaccines on Pneumonia and LRIs

PCV7

Antibiotic resistance

PCV and pneumonia

PCV7
PNEUMONIA: Diagnosis

“Classical” diagnosis is made when fluid accumulation is great enough to allow it to be seen radiographically as a nonlucent or “consolidated” area.

Theoretical Efficacy of PCV7/PCV9 Against CXR-Confirmed (Consolidated) Pneumonia

<table>
<thead>
<tr>
<th>CXR confirmed pneumonia</th>
<th># Cases Preventable</th>
<th>Vaccine Serotype</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal</td>
<td>100</td>
<td>50-70%</td>
<td>50-70%</td>
</tr>
<tr>
<td>PCV7/PCV9 against CXR-confirmed (consolidated) pneumonia: 12.5-34%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Efficacy of Pneumococcal Conjugate Vaccines Against Radiographic Alveolar Pneumonia

<table>
<thead>
<tr>
<th>Site</th>
<th>Schedule</th>
<th>Vaccine</th>
<th>Efficacy * (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (North California)</td>
<td>2, 4, 6, 12-15 mos</td>
<td>PCV7</td>
<td>26% (7, 41)</td>
</tr>
<tr>
<td>South Africa: HIV (-)</td>
<td>6, 10, 14 wks</td>
<td>PCV9</td>
<td>20% (3, 35)</td>
</tr>
<tr>
<td>Gambia</td>
<td>6-51 wks (≥1 dose ≥25d apart)</td>
<td>PCV9</td>
<td>37% (17, 48)</td>
</tr>
</tbody>
</table>

* ITT
Dagan – Conjugate pneumococcal vaccine

**Defining Bacterial Pneumonia**

- Clinical diagnosis
- Chest X-ray obtained
- Any Chest X-ray abnormality
- Lobar consolidation/pleural effusion
- Culture-positive

*BACTERIAL PNEUMONIA*

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**Vaccine probe studies**

Trying to understand pathogenesis, epidemiology and disease burden through unexpected or unpredictable responses to vaccine

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**Effect of PCV9 on Lower Respiratory Morbidity in DCC Attendees (Age Window 15 - 35 m)**

- LR problems (mainly bronchitis/bronchiolitis/cough)
- 23% risk reduction
- \( P = 0.015 \)

![Graph showing 23% risk reduction in lower respiratory morbidity with PCV9 vaccination.](image)
Dagan – Conjugate pneumococcal vaccine

**Outcome measure**

<table>
<thead>
<tr>
<th>Vaccine N=18,433</th>
<th>Placebo N=18,626</th>
<th>Efficacy (95% CI)</th>
<th>P</th>
<th>Incidence in placebo /100,000 pgy</th>
<th>VAR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningococcal (MCXR confirmed)</td>
<td>140</td>
<td>214</td>
<td>28 (2.7, 30)</td>
<td>0.03</td>
<td>40</td>
</tr>
<tr>
<td>Clinical pneumonia (CP)</td>
<td>556</td>
<td>681</td>
<td>17 (7.3, 26)</td>
<td>0.001</td>
<td>1,073</td>
</tr>
</tbody>
</table>

*Vaccine Attributable Reduction

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**Summary of PCV Efficacy (VE) Burden of Pneumonia Prevented in Efficacy Trials in the USA, S. Africa and The Gambia**

<table>
<thead>
<tr>
<th>Country</th>
<th>Efficacy</th>
<th>Variability</th>
<th>Radiologically confirmed pneumonia</th>
<th>All clinically diagnosed LRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>18%</td>
<td>6%</td>
<td>500</td>
<td>1,000</td>
</tr>
<tr>
<td>S. Africa</td>
<td>20%</td>
<td>7%</td>
<td>600</td>
<td>1,200</td>
</tr>
<tr>
<td>The Gambia</td>
<td>37%</td>
<td>7%</td>
<td>700</td>
<td>1,400</td>
</tr>
</tbody>
</table>

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Is Bronchiolitis a Pure Viral Infection?

- Ampicillin vs placebo, no differences in outcome
- Of 165 infants admitted to PICU, in 42% bacteria were found in lower airways:
  - 22% definitely infected
  - 20% possibly infected

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Table 2: Sputum cultures for VE obtained on admission to the PICU from the lower airway in 70 children with severe ETV bronchitis

<table>
<thead>
<tr>
<th>Microbiologic species</th>
<th>9 cultures</th>
<th>11 cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community acquired</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Of which</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Bacteria</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Of which</td>
<td>17</td>
<td>11</td>
</tr>
</tbody>
</table>

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*40% given antibiotics prior to intubation
Dagan – Conjugate pneumococcal vaccine

Respiratory Viruses Identified In Children Hospitalized for Community Acquired Pneumonia In the Absence of PCV

Impact Of PCV On Incidence of Viral-Associated Pneumonia Hospitalization In Children

<table>
<thead>
<tr>
<th>Virus</th>
<th>PCV</th>
<th>Placebo</th>
<th>Efficacy</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A/B</td>
<td>31</td>
<td>56</td>
<td>45</td>
<td>14 to 64</td>
<td>0.01</td>
</tr>
<tr>
<td>PIV 1-3</td>
<td>24</td>
<td>43</td>
<td>44</td>
<td>8 to 66</td>
<td>0.02</td>
</tr>
<tr>
<td>hMPV</td>
<td>26</td>
<td>62</td>
<td>58</td>
<td>34 to 73</td>
<td>0.001</td>
</tr>
<tr>
<td>RSV</td>
<td>90</td>
<td>115</td>
<td>22</td>
<td>3 to 41</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Changes of Admissions for All Cause Pneumonia by December 2004 Compared to Expected Rates (Pre-Vaccination Rates) in the US

Decline 39% (95% CI 22 to 52)

Annual ~3,000 admissions

Annual ~41,000 admissions
Effectiveness Data from PCV7 2+1 Programs

Hospital Admissions for Pneumonia in Children <5 Yrs

Quebec: 2, 4, 12 mos and catch-up <5 yrs

Liguria, Italy (3, 5, 11-12 mos)

12.5% reduction in all-cause pneumonia
75% reduction in SP pneumonia

Changes in Rates of Hospitalizations and Ambulatory Visits for All-cause Pneumonias among Children <2 Yrs, USA, 2004 vs. 1997-9

Hospitalization for all-cause
Ambulatory visit for all-cause

-1.5 vs 0.5 per 1000 Person-Years
-0.3 vs 0.5 per 1000 Person-Years
-6 per 1000
-40.8 per 1000

Data were abstracted from a database with ~10 self-insured employer self-insured employers each year, and includes ~500 million claims.


<table>
<thead>
<tr>
<th>Year</th>
<th>AR (per 1000, adjusted)</th>
<th>ARI (per 1000, adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-99</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>2005</td>
<td>7.0</td>
<td>1.9</td>
</tr>
<tr>
<td>2006</td>
<td>7.6</td>
<td>1.7</td>
</tr>
</tbody>
</table>

8
Improved effectiveness in overall pneumonia/LRI

~12.5-34% reduction in pneumonia

~50% reduction in VT carriage

Continuous combined effectiveness

On going cumulative reduction in VT carriage

Monthly Frequency of Hospital Admissions for Pneumonia in Children <5 Yrs According to Diagnostic Groups

April 1997–March 2006

PCV7 licensed
PCV7 recommended to high-risk
PCV7 in National Immunization Plan

Dagan – Conjugate pneumococcal vaccine

Global Distribution (Proportion) of Serotype Isolates Causing IPD in Children <5 Years of Age

PCV7

Global Distribution (Proportion) of Serotype Isolates Causing IPD in Children <5 Years of Age

PCV10

Global Distribution (Proportion) of Serotype Isolates Causing IPD in Children <5 Years of Age
Dagan – Conjugate pneumococcal vaccine

Global Distribution (Proportion) of Serotype Isolates Causing IPD in Children <5 Years of Age

PCV13

Parapneumonic Empyema Cases in Spain 1998-2006

Parapneumonic Empyema Cases in Spain 1998-2006

- Children <14 yrs admitted to Seville and Malaga Hospitals 1998-2006
- Children <18 yrs of Age Admitted to a Barcelona Hospital 2003-2006
- A total of 208 children were prospectively enrolled; blood and PF samples were collected
- Pneumococci were detected in 90% of blood-positive and 68% of culture-negative samples

Distribution of Serotypes in Pleuropneumonia in Children < 16 Yrs, France, (Dec 2002 to Feb 2004)
Non-culture Surveillance of Pneumococcal Serotypes Causing Empyema in UK Children, Post PCV7 Introduction

All referrals of empyema fluid samples were tested in a Bio-Plex 6. The assay was a multiplex antigen detection assay capable of detecting 14 serotypes/groups (1, 3, 5, 6A, 6B, 7F/A, 8, 9V, 14, 18, 19A, 19F, 23F) + C-polysaccharide. The majority of samples were collected between September 2006 and January 2008 (after PCV7 introduction).

Only 2 were positive by culture.

Serotypes detected:
- 1 (60%)
- 3 (13%)
- 5, 14, 19A (7% each)
- 6A, 6B, 9V, untypable (2% each)
- 19F, 23F (1% each)

Sheppard et al, ISPPD, June 2008, Iceland Abstr P1-092

ORs for NP Carriage of Pneumococcal Serotypes in Children <5Y with Acute Community-Acquired Pneumonia vs. Healthy Controls

ORs adjusted for age, ethnicity, and antibiotic treatment (1m before Cx).

Proportion of all IPD Isolates of Serotype 19A with Intermediate or Full Pen-R and Nonsusceptibility to ≥3 Antibiotic Classes in Children <5 years old, Active Bacterial Core Surveillance Sites, July 1999–June 2004

CDC; Hicks et al, IDSA 2005

serotype 19A

9.1
3
12
Conclusions

- PCV effect on pneumonia is greater than expected
- What was considered as non-pneumococcal pneumonia or non-pneumonia can be also reduced by PCVs
- For maximal effect, widespread vaccination is required, since much of the prevention is based on herd immunity
- Extension of serotype spectrum in PCVs is important especially in prevention of severe complicated pneumonia
Summary

The herd effect of conjugate pneumococcal vaccine on adult lower respiratory tract infections
Å. Örtqvist (Stockholm, SE)

The 7- and 9-valent conjugate pneumococcal vaccines (PCV7 and PCV9) has been shown to be highly efficacious in prevention of invasive pneumococcal disease (IPD), and about 20% effective in prevention of x-ray verified pneumonia in vaccinated children.

In the U.S., PCV7 was introduced in the year 2000 and in children 19-35 months of age a high coverage (>80%), was reached in 2004. Since the introduction in the U.S. there has been a significant lowered incidence of IPD in vaccinated age-groups, but also in non-vaccinated age-groups indicating the presence of herd immunity. In adults this herd effect has been most prominent in persons belonging to the parent- (20-39 years of age) and grand-parent- (> 65 years of age) generations. Since about 80% of all IPD in adults is associated with a community-acquired pneumonia, herd immunity does seem to affect the risk for severe pneumonia in these age groups. A case-control study showing a 80% reduction in the odds of bacteraemic pneumococcal pneumonia among adults with children in the home is also in support of this.

In addition, a U.S.-wide study based on ICD-9 discharge codes found that there was a significant decline of hospital admission of all-cause pneumonia in adults 18-39 years after the introduction of PCV7, and a tendency for a decline also in the elderly. However, these findings could not be confirmed in a more recent study from Washington, USA, where the rates of confirmed pneumonia cases in adults admitted to hospital increased, instead of decreased, when comparing the pre- (1998-2000) and after- (2003-2004) PCV7-periods.

In conclusion, conjugate pneumococcal vaccination of children probably has a herd effect on bacteraemic pneumococcal pneumonia in adults, but, so far, such an effect has not been clearly detected for all-cause pneumonia.
Is there a herd effect of conjugate pneumococcal vaccine on adult LRTI?

Åke Örtqvist, Assoc. Professor
Karolinska Institutet
Head, Dep. of Communicable Diseases Control and Prevention
Stockholm County, Sweden

Pneumococcal disease

- *Streptococcus pneumoniae*
  - major cause of illness and death in adults
- Most common cause of community-acquired pneumonia and meningitis
- Captain of the men of death (Sir William Osler 1849–1919)
  - about 1.6 million fatal cases of pneumococcal disease yearly, mostly in infants and elderly (WHO 2002)

Pneumococci causes most deaths of vaccine-preventable diseases!

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>&lt;5 yrs of age</th>
<th>Adults</th>
<th>Total (2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningococcal</td>
<td>15</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Haemophilus</td>
<td>114</td>
<td>1,912</td>
<td>2,026</td>
</tr>
</tbody>
</table>
Pneumococcal vaccines
1881 - S.pneumoniae isolated
- 1914 - whole-cell vaccine
- 1930-ies - discovery of serotypes
- 1940-ies - 6-valent capsular polysaccharide vaccine
- 1977 - 14-valent vaccine
- 1983 - 23-valent vaccine (PPV23)
- 2000 - 7-valent protein-polysaccharide conjugate vaccine (PCV7)

Why is it of interest if there is an herd effect of conjugate vaccine on adult LRTI?

23-valent pneumococcal polysaccharide vaccine (PPV23)
- Capsular polysaccharide antigen from 23 of 91 pneumococcal serotypes
- Represents about 90% of all serotypes causing invasive pneumococcal disease (IPD)
- About 60-80% protection in adults/elderly against invasive pneumococcal disease (IPD), but
  - No evidence of protection against non-bacteremic pneumonia

(Moberley et al. Cochrane Database of Systematic Reviews 2008, Issue 1)
Conjugate vaccines

- **PCV7**
  - include seven serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F
- **PCV 10 and 13** on the market 2009-2010
  = PCV7
  + types 1, 5, 7F (GSK)
  + types 1, 3, 5, 6A, 7F, 19A (Wyeth)

Conjugate vaccine in adults

- **Immunogenicity**
  - In general, not more immunogenic than PPV, and booster response has not been shown in adults (Abraham-Van Parijs B. Vaccine 2004; 22)
  - One recent study, showed that PCV7 elicited higher antibody levels than PPV23 in adults 70+ (de Roux CID 2008;46)
  - It may also be a question of dose and dosing! A 2-4 times higher dose (1-2ml of PCV7) gave a significant better response, both quantitatively and qualitatively, to 5-6/7 serotypes in adults, 70-79 years of age (Jackson, Vaccine 2007; 25:4029)
- **Efficacy/effectiveness??**
  - studies with PCV13 are on the way

Conjugate vaccines

- Induce a T-cell dependent immune response
  - affects nasopharyngeal carriage, contrary to the 23-valent polysaccharide vaccine
  - basis for an indirect effect, or herd immunity, i.e. protection also of the non-vaccinated population
Herd effect on IPD in adults?

Most experience and data from the US
- ABC – Active Bacterial Core surveillance from the CDC
  - Population 16-20 million
  - Reports up to 2004
    (Whitney, Lexau, Hicks, and MMWR)

Some early reports from Europe

Indirect effects of PCV7 on IPD

ABC surveillance, US

Decline 1999 to 2001
- 8% (-1 to -15)
- 18% (-11 to -24)
- 40% (-29 to -49)

Asterisks * indicate p<0.05 for 2000-2001 vs. 1998-1999.

IPD in “older” adults

ABC surveillance, US

% reductions
1998-1999 to 2002-2003
- 85 years, -28%
- 75-84 y, -35%
- 65-74 y, -29%
- 50-64 y, -17%

PCV7 Licensee: Lexau JAMA 2005; 294
Örtqvist – Herd effect of conjugate pneumococcal vaccine

**Incidence of IPD, by serotype and year**
Data from ABC surveillance, about 20 million inhabitants

**Children aged <5 years (A)**

**Adults aged ≥65 years (B)**

**Herd immunity on IPD in Spain??**
Incidence of IPD by year and serotype among adults in the Barcelona area

**Herd effect on IPD in adults?**
- **Yes**, most likely for vaccine types
- **But**, requires high vaccine coverage in children
- **And**
  - Overall incidence of IPD dependent on many factors, e.g.
    - Normal temporal trends
    - Antibiotic pressure
    - Serotype replacement
Is there a herd effect on pneumonia in adults?

About 80% of IPD is due to bacteremic pneumococcal pneumonia

Temporal trends of bacteremic pneumococcal pneumonia in Pennsylvania, US

- Population based surveillance in 5 counties, 2002-2004
- Adult population about 2.8 million
- Overall rate of bacteremic pneumococcal pneumonia (BPP) declined 9% (95% CI -19, +2, p=0.1)
- Odds of a vaccine type BPP decreased 30% per year, adjusted for seasonal variation (p=0.006)

Metlay Vaccine 2006;24

Adult bacteremic pneumococcal pneumonia in Pennsylvania, US
Herd effects on hospitalisation of pneumonia in adults?
- Nationwide Inpatient Sample in the US
  - Obtain data for about 20% of all hospitalisations in the US
- Interrupted time series analysis with pneumonia (all cause and pneumococcal) as outcome
- The year (2000) when the vaccine was introduced was excluded
- Rates of admission for dehydration assessed for validation

Grijalva, Lancet 2007;369

Herd effects on hospitalisation of pneumonia in adults?
- ICD9 codes for pneumonia, pneumococcal pneumonia
- Regression model accounting for secular trends, possible multiple admission, seasonality
- Estimated
  - the post-PCV7 rate for December 2004, compared to
  - the expected rate, calculated from the model as the projection of pre-PCV7 trends with the assumption that no intervention occurred
- 10 787 865 admissions for all-cause pneumonia
  - 4% of those with diagnoses of pneumococcal pneumonia, whereof one third with concurrent diagnoses of septicemia or bacteremia

Grijalva, Lancet 2007;369

<table>
<thead>
<tr>
<th>Age group</th>
<th>Estimated rate/100,000</th>
<th>Expected rate/100,000</th>
<th>Rate difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39 yy</td>
<td>78</td>
<td>105</td>
<td>-27 (-5 to -45) <em>Decline</em> 26% (4 to 43)</td>
</tr>
<tr>
<td>40-64 yy</td>
<td>328</td>
<td>402</td>
<td>-75 (10 to -142) <em>Decline</em> 19% (-3 to 35)</td>
</tr>
<tr>
<td>≥65 yy</td>
<td>2163</td>
<td>2559</td>
<td>-397 (61 to -774) <em>Decline</em> 15% (-2 to 30)</td>
</tr>
</tbody>
</table>

Grijalva, Lancet 2007;369
Hospitalisation for pneumococcal pneumonia pre- vs post-PCV7

<table>
<thead>
<tr>
<th>Age group</th>
<th>Estimated rate/100,000</th>
<th>Expected rate/100,000</th>
<th>Rate difference (95% CI)</th>
<th>&quot;Decline&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39 yy</td>
<td>2.9</td>
<td>4.2</td>
<td>-1.3 (-0.4 to -2.0)</td>
<td>30% (9 to 47)</td>
</tr>
<tr>
<td>40-64 yy</td>
<td>14.8</td>
<td>16.5</td>
<td>-1.6 (1.0 to -4.6)</td>
<td>11% (-10 to 28)</td>
</tr>
<tr>
<td>≥ 65 yy</td>
<td>59.3</td>
<td>73.9</td>
<td>-14.6 (2.0 to -27.6)</td>
<td>20% (-3 to 37)</td>
</tr>
</tbody>
</table>

Grijalva, Lancet 2007;369

Possible biases in the Grijalva study

- Before and after
  - Temporal changes of pneumococcal epidemiology, influence of viral epidemics
  - Secular trends in admission rates/bed availability
- An "expected rate", based on the before trend, compared with the post-PCV7 rate
- Based on ICD codes
- All-cause pneumonia "dilute" the possible herd effect on pneumococcal pneumonia
- The diagnosis of pneumococcal pneumonia is difficult, not standardised, and very unprecise

Case-control study in South Africa did not indicate presence of a herd effect

- Adult persons living at the same address as children participating in RCT of a PCV9 (reported in NEJM 2003; 349)
- 178 episodes of hospitalisation for pneumonia in 158 adults hospitalised during one year
- No significant difference between adults who lived at the same address as children receiving PCV9 or those receiving placebo
  - Bacteremic pneumococcal pneumonia, 2 vs 2
  - Pneumococcal pneumonia, OR 1.0
  - All-cause pneumonia, OR 1.07

(Albrich, Lancet 2007;370, letter)
Population-based surveillance in Washington state, US

- Group Health members, n= 794,282
- Outpatients and inpatients
- Presumptive pneumonia based on ICD9 codes
- Confirmed pneumonia based on review of chest radiograph reports
- Multivariate Poisson regression analysis, adjusted for month of year, and gender

(Nelson, Vaccine 2008;26)

Population-based surveillance in Washington state, US

Vaccine coverage

- "Before", nearly no doses given
- "During", percentage of children who had received three doses by their first birthday - from 60% late 2001 to 84% mid 2002
- "After", most children vaccinated

(Nelson, Vaccine 2008;26)

Population-based surveillance in Washington state, US

Confirmed hospitalised pneumonia

<table>
<thead>
<tr>
<th>Age group</th>
<th>Rate &quot;Before&quot; per 1000 py*</th>
<th>Rate &quot;After&quot; per 1000 py*</th>
<th>After relative to Before Adjusted IRR** (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-64 yy</td>
<td>0.8</td>
<td>1.0</td>
<td>1.17 (1.04 to 1.33)</td>
<td>0.01</td>
</tr>
<tr>
<td>65-74 yy</td>
<td>4.9</td>
<td>6.4</td>
<td>1.30 (1.12 to 1.50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥ 75 yy</td>
<td>15.3</td>
<td>20.0</td>
<td>1.47 (1.35 to 1.59)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* person-years
** Incidence Rate Ratios

(Nelson, Vaccine 2008;26)
Population-based surveillance in Washington state, US

• Similar results in analyses of
  – presumptive rates as confirmed rates
  – subgroup analysis by smoking status and pneumococcal immunization status

• Conclusion
  – No reduction of pneumonia in adults after general introduction of PCV7 in children

(Nelson, Vaccine 2008;26)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Rate “Before” per 1000 py*</th>
<th>Rate “After” per 1000 py*</th>
<th>After relative to Before Adjusted IRR** (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-64 yy</td>
<td>4.1</td>
<td>4.3</td>
<td>1.07 (1.01 to 1.13)</td>
<td>0.03</td>
</tr>
<tr>
<td>65-74 yy</td>
<td>12.3</td>
<td>12.0</td>
<td>0.97 (0.88 to 1.08)</td>
<td>0.95</td>
</tr>
<tr>
<td>≥ 75 yy</td>
<td>21.7</td>
<td>21.9</td>
<td>1.01 (0.94 to 1.08)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

* person-years
** Incidence Rate Ratios

(Nelson, Vaccine 2008;26)

Conclusion

Is there a herd effect of conjugate pneumococcal vaccine on adult LRTI?

• No,
  – at least not convincingly shown as yet
  – but, there is probably a reduction of vaccine-type bacteremic pneumococcal pneumonia
Garau – Treatment of pneumococcal lung disease

Antibiotic choices and controversies in the treatment of pneumococcal lung disease

Javier Garau, MD, PhD
Department of Medicine
Hospital Universitari Mutua de Terrassa
Universitat de Barcelona
GRACE EW, ECCMID Helsinki, May 2009

OUTLINE

• Historical perspective
• Drugs active in the treatment of pneumococcal pneumonia
• Monotherapy vs. Combination
• Conclusions

Natural History of CAP

• “Recovery followed the crisis, an abrupt decrease in temperature over 12 hours, accompanied by passage from a condition of extreme distress and anxiety to one of comparative comfort and occurred in a large proportion of cases. A fatal outcome was noted in 20-35%. Worse prognosis was evident in drunkards and the elderly, with fatality increasing to 50-65% in the elderly in those in their 6th and 7th decades”

Sir William Osler, 1894, who succumbed to Haemophilus influenzae pneumonia in 1919
Garau – Treatment of pneumococcal lung disease

Survival in Bacteremic Pneumococcal Bacteremia Treated with Penicillin or Serum
Austrian and Gold (1964)

Mortality in patients with Type 1 pneumococcal pneumonia by severity of disease

<table>
<thead>
<tr>
<th>Severity</th>
<th>Serum therapy</th>
<th>Standard Treatment</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any condition</td>
<td>20% (n=114) 34% (n=119)</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>9% 13%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>29% 52%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>64% 100%</td>
<td>36%</td>
<td></td>
</tr>
</tbody>
</table>

Park et al. 1928
(Adapted from Mary Singer, Clinical Trial Design for Community-Acquired Pneumonia; Public Workshop: January 17-18, 2008, Presentation by FDA/IDSA/CFP Workshop)
Garau – Treatment of pneumococcal lung disease

**BACTEREMIC PNEUMOCOCCAL PNEUMONIA**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HCAP N=25 (10)</th>
<th>CAP N=107 (76)</th>
<th>HAP N=9 (6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male(%)</td>
<td>14 (56%)</td>
<td>74 (69%)</td>
<td>4 (44%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Age in years, mean, (SD)</td>
<td>75 (12)</td>
<td>57 (20)</td>
<td>66.8 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson score, (SD)</td>
<td>1.86 (1.1)</td>
<td>1.47 (1.3)</td>
<td>2.35 (1.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Shock</td>
<td>2 (8%)</td>
<td>11 (10.5%)</td>
<td>2 (22%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Coma</td>
<td>2 (8%)</td>
<td>10 (9.5%)</td>
<td>1 (11.1%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Penicillin susceptibility</td>
<td>19 (76%)</td>
<td>88 (85%)</td>
<td>6 (67%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Pitt score, (SD)</td>
<td>1.45 (2.1)</td>
<td>0.9 (1.8)</td>
<td>0.6 (1.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Length of stay, days, (SD)*</td>
<td>12 (3)</td>
<td>7 (10)</td>
<td>17.5 (33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>8 (32%)</td>
<td>19 (17.5%)</td>
<td>3 (33.3%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Deaths in the first 72 hours</td>
<td>7/8 (87.5%)</td>
<td>5/10 (50%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Calbo E et al, submitted

**MORTALITY. MULTIVARIATE ANALYSIS**

- In the multivariate analysis:
  - **Severity of disease** *(OR=1.2; CI95% 1.06-1.5, p=0.007)*
  - **HAP** *(OR=3.9 CI95% 1.2-13, p=0.02)*
  - **HCAP** *(OR=5.6; CI95% 1.9-16.6, p=0.001)*

were independent predictive factors for increased mortality.

*measured using Pitt score

**OUTLINE**

- Historical perspective
- Drugs active in the treatment of pneumococcal pneumonia
- Monotherapy vs. Combination
- Conclusions
Garau – Treatment of pneumococcal lung disease

Community-acquired Respiratory Tract Infections caused by Streptococcus pneumoniae
Therapeutic options

- Cloramphenicol
- Tetracyclines
- Cotrimoxazol
- Macrolides/azalides
- β-lactams
- Fluoroquinolones

MACROLIDES

<table>
<thead>
<tr>
<th>Country</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>90.8</td>
<td>2.6</td>
<td>6.6</td>
</tr>
<tr>
<td>Belgium</td>
<td>89.4</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>93.2</td>
<td>4.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Croatia</td>
<td>69.7</td>
<td>0.6</td>
<td>19.3</td>
</tr>
<tr>
<td>Cyprus</td>
<td>81.9</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>59.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Denmark*</td>
<td>75.0</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Finland*</td>
<td>63.8</td>
<td>0.3</td>
<td>35.9</td>
</tr>
<tr>
<td>France*</td>
<td>86.3</td>
<td>0.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Germany*</td>
<td>65.0</td>
<td>0.7</td>
<td>18.8</td>
</tr>
<tr>
<td>Ireland*</td>
<td>90.2</td>
<td>0.0</td>
<td>9.8</td>
</tr>
<tr>
<td>Italy*</td>
<td>64.5</td>
<td>0.0</td>
<td>35.5</td>
</tr>
<tr>
<td>Malta*</td>
<td>81.7</td>
<td>0.6</td>
<td>16.7</td>
</tr>
<tr>
<td>The Netherlands*</td>
<td>91.7</td>
<td>0.9</td>
<td>7.4</td>
</tr>
<tr>
<td>Norway*</td>
<td>89.8</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Portugal</td>
<td>76.0</td>
<td>0.0</td>
<td>21.4</td>
</tr>
<tr>
<td>Romania</td>
<td>75.0</td>
<td>0.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Slovenia*</td>
<td>87.2</td>
<td>0.5</td>
<td>12.7</td>
</tr>
<tr>
<td>Spain</td>
<td>81.5</td>
<td>1.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Sweden</td>
<td>60.0</td>
<td>0.0</td>
<td>39.0</td>
</tr>
<tr>
<td>Switzerland</td>
<td>60.0</td>
<td>0.0</td>
<td>39.0</td>
</tr>
<tr>
<td>United Kingdom*</td>
<td>88.5</td>
<td>0.1</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Susceptibility results for S. pneumoniae isolates in European Countries
Erythromycin, 2006 (*) and 2007

www.EARSs.org
Garau – Treatment of pneumococcal lung disease

- Resistance to macrolides in the pneumococcus is generally by virtue of an efflux pump (mefA or mefE gene) or the presence of a ribosomal methylase (ermB or, rarely, the ermA gene)
- Also, exposure of the pneumococcus to macrolides can lead to the spontaneous generation of resistant mutants in vivo and in vitro; mutations in the 23S rRNA and ribosomal proteins L4 and L22 have been described.

Emergence of Macrolide-Resistant S. pneumoniae in vivo (during therapy)

1. JMS Dixon. The Lancet 1967
- 62 y. o. man. Lung cancer. Pneumonia treated with erythromycin first, lincomycin afterwards. Same serotype recovered from empyema, now R to ERY (MIC, 100 µg/ml) and Unicromyc.

2. D Musher et al. NEJM 2002
- 28 y. o. man. Previously healthy. Pneumonia treated with IV azithromycin. Initial improvement. On day 4, sudden worsening, increasing infiltrates, pleural effusion.
- Second isolate (sputum and pleural fluid) identical genotype; R to ERY/CLA, MICs, 2-4 µg/ml; Mutation: ribosomal protein L22.

- 46 y. o. man. Alcohol abuser. Bacteremic pneumonia treated with CEFURO, then erythromycin. Recurrence of fever; endocarditis and epidural abscess.
- Second isolate (blood culture) identical genotype; R to ERY/CLA > 128 µg/ml; Mutation: 23S rRNA A2058G (4/4 alleles)

4. Perez-Trallero E et al. EID 2003
- 71 y. o. man. COPD. Pneumonia treated with IV LEVO, then clarithromycin, on and off for 25 days. AECB, pleural effusion. Vancomycin.
- 5th isolate (pleural fluid) with identical genotype. R to ERY/CLARI > 128 µg/ml; Mutation: 23S rRNA A2058G (4/4 alleles)

Emergence of macrolide resistance during therapy of pneumococcal pneumonia

- 28-year old male (previously healthy)
- 5-day history of cough/dyspnea; hypotension; hypothermia; rales; WBC 14,000 mm³ (28% bands); RUL and RML infiltrates. Sputum: abundant GP diplococci
- S. pneumoniae cultured from sputum; (-) blood cultures

- Empirical therapy with 500 mg azithromycin i.v.
- Condition improved rapidly; 4th day of treatment sudden deterioration; pneumococci isolated from BAL and pleural fluid. Ceftriaxone+vancomycin given but patient died

- Initial isolate fully susceptible to Pen and macrolides
- Later isolate susceptible to penicillin, clindamycin but AZI/ERY/CLA QUIN/DAL resistant (MICs 2–4 µg/ml)
- Not erm or mef; Mutation of the gene of ribosomal protein L22
  Musher D et al. NEJM 2002;
In Vivo Emergence of High-Level Macrolide Resistance in Streptococcus pneumoniae following a Single Dose of Azithromycin

Nasopharyngeal carriage of serial serotype 22F pneumococcal isolates in a 2.5-month-old indigenous infant. The 22F isolate developed resistance to azithromycin while identical BOX typing patterns and multilocus sequence types. The mefA/E and ermB genes and mutations in the ribosomal protein L4 and L22 genes were not found in the isolates; however, the previously described 23S rRNA A2059G mutation was detected in the posttreatment isolate. 'remaining sensitive to penicillin, tetracycline, chloramphenicol, and cotrimoxazole after the infant received a single dose of azithromycin (250 mg) as routine prophylaxis following a trachoma contact.

<table>
<thead>
<tr>
<th>Date</th>
<th>SeroType</th>
<th>AZI MIC</th>
<th>BOX type</th>
<th>MLST</th>
<th>ermB</th>
<th>mefA/E</th>
<th>23S rRNA</th>
<th>L4</th>
<th>L22</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Dec 2001</td>
<td>22F</td>
<td>4</td>
<td>A</td>
<td>698</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>G</td>
<td>Neg</td>
</tr>
<tr>
<td>3 Jan 2002</td>
<td>22F</td>
<td>&gt; 256</td>
<td>A</td>
<td>698</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>G</td>
<td>ND</td>
</tr>
<tr>
<td>29 Jan 2002</td>
<td>22F</td>
<td>&gt; 256</td>
<td>A</td>
<td>698</td>
<td>Neg</td>
<td>Neg</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>


Risk factors for macrolide resistance in patients with pneumococcal infections

- Age <5 or >65 years
- Recent hospitalisation
- Day care centre attendance
- Presence of multiresistant pneumococci (serotypes 6A, 6B, 14, 15A, 19A, 19F, 23F, and 23A)
- Recent macrolide use
- Clonal dissemination of multiresistant strains

MACROLIDE-RESISTANT PNEUMOCOCCI SUMMARY

- Increasing worldwide; associated with penicillin-resistance
- Failures in the animal model and increasing number of documented failures of macrolides in the treatment of ERSP infection (pneumonia, AOM). Two recent studies indicate that in vitro R, any level, is a predictor of failure.
- Emergence of resistance while on therapy

The prevalence of R will dictate the need to reassess current recommendations for the treatment of CAP.
**B-LACTAMS**

- B-lactam resistance in pneumococci is due to genetic alteration of the PBPs; main mechanism: import of foreign DNA from other streptococci by transformation.
- The best PK/PD parameter that predicts eradication (and clinical response):
  \[
  T > \text{MIC}
  \]

---

**Streptococcus pneumoniae:** proportion of invasive isolates non-susceptible to penicillin in 2006.

* These countries did not report data or reported less than 10 isolates.

---

**PENICILLIN**

FDA new susceptibility breakpoints for pneumonia caused by *Streptococcus pneumoniae*:

<table>
<thead>
<tr>
<th>susceptible CI</th>
<th>intermediate CI</th>
<th>resistant CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06 - 1.0</td>
<td>1.02 - 2</td>
<td>&gt; 2</td>
</tr>
</tbody>
</table>

The susceptible breakpoint for meningitis caused by *S. pneumoniae* remains unchanged (0.06 mg/mL).
Garau – Treatment of pneumococcal lung disease

### Changing epidemiology of antimicrobial-resistant Streptococcus pneumoniae in the United States, 2004-2005

<table>
<thead>
<tr>
<th>antimicrobial agent</th>
<th>MIC breakpoints (μg/ml)</th>
<th>No of isolates with MIC, n (%)</th>
<th>MIC ≤0.5, n (%)</th>
<th>MIC &gt;0.5, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>penicillin</td>
<td>≤0.06</td>
<td>902/1169 (77.2)</td>
<td>790/1169 (67.2)</td>
<td>212/1169 (18)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>≤0.06</td>
<td>1024/1169 (88)</td>
<td>947/1169 (81)</td>
<td>77/1169 (6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>≤0.25</td>
<td>791/1169 (68)</td>
<td>381/1169 (33)</td>
<td>200/1169 (17)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>erythromycin</td>
<td>≤1</td>
<td>230/1169 (19.9)</td>
<td>204/1169 (17.6)</td>
<td>26/1169 (2)</td>
<td>.03</td>
</tr>
<tr>
<td>tetracycline</td>
<td>≤0.03</td>
<td>767/1169 (65.7)</td>
<td>225/1169 (19.3)</td>
<td>117/1169 (10.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>≤0.03</td>
<td>511/1169 (43.8)</td>
<td>30/1169 (2.6)</td>
<td>82/1169 (7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>≤1</td>
<td>202/1169 (17)</td>
<td>118/1169 (10.2)</td>
<td>84/1169 (7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>rifampin</td>
<td>≤0.125</td>
<td>2/1169 (0.2)</td>
<td>2/1169 (0.2)</td>
<td>1167/1169 (100)</td>
<td></td>
</tr>
<tr>
<td>minocycline</td>
<td>≤0.03</td>
<td>817/1169 (69.9)</td>
<td>201/1169 (17.2)</td>
<td>168/1169 (14.3)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

From the 1999–2000 to the 2004–2005, the prevalence of isolates with penicillin R increased from 12.7% to 17.9%, penicillin G MIC ≥0.5 increased from 21.5% to 14.6%, and prevalence of isolates R to erythromycin increased from 25.7% to 29.1%.


### EUCAST breakpoints (2006)

**Streptococcus pneumoniae breakpoints (S≤R>)**

- **Cefotaxime, Ceftriaxone, 0.5/2**
  - $S \leq 0.5$
  - $R > 2$

### Emergent Streptococcus pneumoniae serotype 19A in the United States, 2005

- The incidence of IPD due to serotype 19A increased from 0.8 to 2.5 cases per 100,000 population between 1998 and 2005 ($P = .03$), whereas the overall incidence of IPD decreased from 24.4 to 13.8 cases per 100,000 population ($P = .05$).
- Simultaneously, the incidence of IPD due to penicillin-resistant 19A isolates increased from 6.7% to 35% ($P < .0001$).
- Of 151 penicillin-resistant 19A isolates, 111 (73.5%) belonged to the rapidly emerging clonal complex 320, which is related to multidrug-resistant Taiwan(19F)-14. The remaining penicillin-resistant strains were highly related to other clones of PCV7 serotypes or to isolates within major 19A clonal complex 199 (CC199). In 1999, only CC199 and 3 minor clones were apparent among serotype 19A isolates. During 2005, 11 multiple-locus clonal sets were detected, including capsular switching variants of a serotype 4 clone.

Moore MR et al, JID 2008
Garau – Treatment of pneumococcal lung disease

Percentage of S. pneumoniae resistant in vitro to commonly prescribed antibacterials

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>MIC&lt;sub&gt;50-90&lt;/sub&gt; mg/L</th>
<th>T&gt;MIC (%)</th>
<th>Break point PK/PD (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>2 MU every 6h</td>
<td>2-4</td>
<td>50-43</td>
<td>4</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1 g every 6h</td>
<td>2-4</td>
<td>71-54</td>
<td>2</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>750 mg every 8h</td>
<td>8-16</td>
<td>36-0</td>
<td>4</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1 g every 8h</td>
<td>1-2</td>
<td>63-52</td>
<td>2</td>
</tr>
<tr>
<td>Ceftiraxone</td>
<td>1 g every 24h</td>
<td>1-2</td>
<td>76-48</td>
<td>2</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1 g every 8h</td>
<td>2</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1 g every 12h</td>
<td>2-4</td>
<td>75-70</td>
<td>1</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.5 g every 8h</td>
<td>2</td>
<td>70-64</td>
<td>1</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1 g every 24h</td>
<td>2</td>
<td>20-24</td>
<td>2</td>
</tr>
</tbody>
</table>

T>MIC of 10 B-lactam antibiotics against Streptococcus pneumoniae Pen R (MIC > 1 mg/L)

Adapted from MR Jacobs, 2002

Analysis of 30-Day Mortality in 429 Episodes* of Nonmeningeal Systemic Pneumococcal Infections According to Treatment Group and MICs of Ceftriaxone/Cefotaxime and Penicillins

<table>
<thead>
<tr>
<th>% of Deaths/End of Follow-Up of Patients Who Died/Treatment Group</th>
<th>Ceftriaxone/Cefotaxime (n = 195)</th>
<th>Amoxicillin/Ampicillin (n = 115)</th>
<th>Others&lt;sup&gt;†&lt;/sup&gt; (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone/Cefotaxime MIC &lt; 4 μg/mL</td>
<td>16/15 (106)</td>
<td>11/12 (105)</td>
<td>4/2 (10)</td>
</tr>
<tr>
<td>4 &lt; MIC &lt; 8 μg/mL</td>
<td>14/22 (101)</td>
<td>8/21 (90)</td>
<td>4/2 (10)</td>
</tr>
<tr>
<td>8 &lt; MIC &lt; 16 μg/mL</td>
<td>13/17 (104)</td>
<td>13/17 (104)</td>
<td>4/2 (10)</td>
</tr>
<tr>
<td>16 &lt; MIC &lt; 32 μg/mL</td>
<td>10/13 (77)</td>
<td>7/12 (60)</td>
<td>3/3 (23)</td>
</tr>
<tr>
<td>Penicillin MIC &lt; 0.1 μg/mL</td>
<td>10/13 (77)</td>
<td>7/12 (60)</td>
<td>3/3 (23)</td>
</tr>
<tr>
<td>0.1 &lt; MIC &lt; 0.2 μg/mL</td>
<td>10/13 (77)</td>
<td>7/12 (60)</td>
<td>3/3 (23)</td>
</tr>
</tbody>
</table>

<sup>*</sup> Of 522 episodes, 93 with nosocomial or polymicrobial infection were excluded.

<sup>†</sup> Penicillins denote intravenous penicillin or intravenous ampicillin.

<sup>‡</sup> Treatment group "Others" includes combinations of a cephalosporin plus a macrolide (n = 31), a macrolide (n = 31), a macrolide (n = 31), and imipenem (n = 21).

No single strain had a ceftriaxone/cefotaxime MIC > 2 μg/mL.

ORAL CEPHALOSPORINS

• Among the oral cephalosporins, cefuroxime and cefpodoxime have the greatest activity against penicillin susceptible S. pneumoniae, but have MICs that are 1–4 dilutions higher than amoxicillin against nonsusceptible strains. The oral cephalosporins cefixime, cefaclor, ceftibuten, and loracarbef are not recommended because of the decreased activity of these agents against nonsusceptible pneumococci.


Suitable b-lactam agents for the treatment of hospitalized patients with pneumonia when Streptococcus pneumoniae infection is suspected

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/Interval</th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>2 g (3.2 mL) iv Q4h</td>
<td>&lt;8 μg/ml</td>
<td>=8 μg/ml</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2 g iv Q6h</td>
<td>&lt;8 μg/ml</td>
<td>=8 μg/ml</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g iv Q6h h</td>
<td>&lt;8 μg/ml</td>
<td>=8 μg/ml</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1 g iv or im Q12 h</td>
<td>&lt;8 μg/ml</td>
<td>=8 μg/ml</td>
</tr>
</tbody>
</table>

Adapted from LR Peterson, CID 2006,42:224-233
Antimicrobial drug kinetics are taken from PDR, 59th Edition, 2005

New Beta-lactams active against MDR Streptococcus pneumoniae

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Range</th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline</td>
<td>&lt;0.008</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Faropenem</td>
<td>0.06-0.25</td>
<td>0.12</td>
<td>0.25</td>
</tr>
<tr>
<td>Tomopenem</td>
<td>0.03-0.25</td>
<td>0.06</td>
<td>0.15</td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>0.5-8</td>
<td>2</td>
<td>4-8</td>
</tr>
<tr>
<td>Cefalosporin</td>
<td>0.5-8</td>
<td>0.5-1</td>
<td>0.5-8</td>
</tr>
</tbody>
</table>

*Kosowska K et al, AAC 2005
**Ge Y et al, 42th ICAAC, Chicago, 2007
¶Koga T et al, AAC 2005
¥ McGee L et al, 42th ICAAC, Chicago 2007
§Critchley IA et al, AAC 2008 (against 19A strain R to Amox-MIC, 8)
Garau – Treatment of pneumococcal lung disease

The activity of ceftaroline was evaluated against highly cefotaxime-resistant isolates of pneumococci from the Active Bacterial Core surveillance program of the Centers for Disease Control and Prevention and against laboratory-derived cephalosporin-resistant mutants of *S. pneumoniae*.

McGee L et al, AAC 2009

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (μg/mL)</th>
<th>Range</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime</td>
<td>4–216</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.5–16</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2–16</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>0.125–2</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.25–&gt;8</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.12–2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

McGee L et al, AAC 2009

**FLUOROQUINOLONES**

Prevalence of First-Step Mutants among Levofloxacin-Susceptible Invasive Isolates of *Streptococcus pneumoniae* in the US

TABLE 1. Levofloxacin MIC distribution of the ABCS collection by year

<table>
<thead>
<tr>
<th>Yr</th>
<th>No. (%)* of isolates with LFX-MIC (mg/liter) ≤C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>1998</td>
<td>272 (7.8)</td>
</tr>
<tr>
<td>1999</td>
<td>685 (17.0)</td>
</tr>
<tr>
<td>2000</td>
<td>363 (9.1)</td>
</tr>
<tr>
<td>2001</td>
<td>397 (11.2)</td>
</tr>
<tr>
<td>2002</td>
<td>521 (16.1)</td>
</tr>
<tr>
<td>2003</td>
<td>531 (16.4)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are cumulative percentages.

Among those with a levofloxacin MIC of 2 mg/liter, 16.2% of isolates recovered from nursing home residents and 6.4% from non-nursing home residents had first-step mutations.

Platts-MExtended AAC 2006;50:1541-63
Garau – Treatment of pneumococcal lung disease

EMERGENCE OF FQ-RESISTANT PNEUMOCOCCI IN ADULTS DURING OR AFTER THERAPY FOR CAP

• Ability of pneumococcus to give rise to in vivo mutants resistant to fluoroquinolones

• It has occurred during or after therapy in:
  - Immunocompromised; probably, at a greater risk (lack of immune response to reduce colonization, length of carriage, and density of organisms)
  - Patients with structural lung disease
  - Previously healthy adults

It may be prudent not to use FQ monotherapy when the patient has a history of FQ therapy in the past 4 months

In patients with documented pneumococcal infection caused by strains with LEVO MIC > 2 µg/ml, FQs should be avoided in cases of severe disease, or used in combination

Anderson KB et al. CID 2003;307:376
De la Campa A et al. AAC 2003;47;1419
Davidson R et al. NEJM 2002;346;750

OUTLINE

• Historical perspective
• Drugs active in the treatment of pneumococcal pneumonia
• Monotherapy vs. Combination
• Conclusions
Garau – Treatment of pneumococcal lung disease

Monotherapy vs. Combination Therapy in CAP

Retrospective study of 27,330 community-dwelling, immunocompetent Medicare patients (age > 65 years) with pneumonia who were hospitalized in 1998–1999 and 2000–2001. Associations between initial antimicrobial regimens and risk-adjusted mortality were assessed, accounting for differences in patient characteristics, comorbidities, illness severity, geographic location, and processes of care.

Bratzler DW et al, Clin Infect Dis 2008;47:S193-201

Adjusted ORs (AORs) for 30-day mortality, according to initial antibiotic treatment and discharge time frame.

<table>
<thead>
<tr>
<th>Initial antibiotic regimen</th>
<th>July-December discharge</th>
<th>October-January discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>AORs (95% CI)</td>
<td>AORs (95% CI)</td>
<td>AORs (95% CI)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1.1 (0.9-1.3)</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1.3 (1.1-1.6)</td>
<td>1.2 (1.0-1.4)</td>
</tr>
<tr>
<td>Other</td>
<td>1.0 (0.8-1.2)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
</tbody>
</table>

Data are for the combined 1998–1999 and 2000–2001 cohorts (n = 27,730). Adjusted for age, sex, neoplastic disease, cardiovascular disease, altered mental status, RR > 30 breaths/min, systolic BP < 90 mm Hg, pulse > 125 beats/min, T < 35C or > 40C, BUN > 111 mmol/L, Na+ < 130 mEq/L, arterial pH < 7.35, PaO2 < 60 mm Hg, pleural effusion, admission to the ICU within 24 h after hospital arrival, geographic region, and administration of antibiotic treatment within 4 h after hospital arrival.

Bratzler DW et al, Clin Infect Dis 2008;47:S193-201

Adjusted ORs (AORs) for 30-day mortality, according to initial antibiotic treatment and pneumonia severity index (PSI) risk class.

<table>
<thead>
<tr>
<th>PSI risk class</th>
<th>Initial antibiotic regimen</th>
<th>AORs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Penicillin</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime</td>
<td>1.3 (1.1-1.6)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1.1 (0.9-1.3)</td>
</tr>
</tbody>
</table>

Data are for the combined 1998–1999 and 2000–2001 cohorts (n = 27,730). ORs are adjusted for admission to the intensive care unit within 24 h after hospital arrival, antibiotic treatment administered within 4 h after hospital arrival, geographic region.

Bratzler DW et al, Clin Infect Dis 2008;47:S193-201
Garau – Treatment of pneumococcal lung disease

- Initial antimicrobial treatment with the combination of a second- or third-generation cephalosporin and a macrolide or initial treatment with a fluoroquinolone was associated with a reduced 30-day mortality rate, compared with treatment with third-generation cephalosporin monotherapy, among non-intensive care unit patients.

- Controversy continues to exist about the use of nonexperimental cohort studies to demonstrate associations between processes of care, such as antibiotic selection, and patient outcomes.

COMBINATION THERAPY VERSUS MONOTHERAPY IN PATIENTS WITH PNEUMOCOCCAL BACTEREMIA

844 consecutive patients enrolled

Excluded: No antibiotic therapy (43)
- No antibiotic therapy on day 2 (30)
- Delayed antibiotic therapy (> 24h) (23)
- Inconsistent regimen (86)
- Different therapy on Day 1 and Day 2 (70)

Included: 592 patients

- All patients (> 15 yr) with documented pneumococcal bacteremia
- 21 hospitals in 10 countries
- Patients monitored for at least 14 days after first positive blood culture or longer if they remained hospitalized

MORTALITY ACCORDING TO SEVERITY OF ILLNESS AND THERAPY RECEIVED

Global mortality by Day 14: 139/844 (16.55%)

14-day mortality in non critically ill: 65/498 (13%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n</th>
<th>14-day mortality</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>202</td>
<td>10.4%</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>390</td>
<td>11.3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

14-day in critically ill: 48/94 (51%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n</th>
<th>14-day mortality</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>47</td>
<td>23.4%</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>47</td>
<td>55.3%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Garau – Treatment of pneumococcal lung disease

### COMBINATION THERAPY VERSUS MONOTHERAPY IN PATIENTS WITH PNEUMOCOCCAL BACTEREMIA

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lactam/Macrolide</td>
<td>14</td>
</tr>
<tr>
<td>Vancomycin/B-lactam</td>
<td>32</td>
</tr>
<tr>
<td>B-lactam/Aminoglycoside</td>
<td>7</td>
</tr>
<tr>
<td>Vancomycin/FQ</td>
<td>4</td>
</tr>
<tr>
<td>B-lactam/Other</td>
<td>4</td>
</tr>
<tr>
<td>B-lactam/Clamphenicol</td>
<td>2</td>
</tr>
<tr>
<td>B-lactam/Trimethoprim</td>
<td>1</td>
</tr>
<tr>
<td>Clindamycin/FQ</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lactam</td>
<td>43</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1</td>
</tr>
</tbody>
</table>

LM Baddour, et al, Am J Respir Crit Care Med 2004

### DEMOGRAPHICS OF THE TWO STUDY GROUPS OF SEVERE ILL PATIENTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Combination n = 47</th>
<th>Monotherapy n = 47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 yr</td>
<td>20.0%</td>
<td>16.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>8.5%</td>
<td>10.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Underlying chronic disease</td>
<td>48.8%</td>
<td>34.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>47.8%</td>
<td>32.6%</td>
<td>NS</td>
</tr>
<tr>
<td>HIV</td>
<td>11.4%</td>
<td>37.0%</td>
<td>0.01</td>
</tr>
<tr>
<td>Neutropenic</td>
<td>19.9%</td>
<td>11.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Asplenia</td>
<td>2.1%</td>
<td>2.1%</td>
<td>NS</td>
</tr>
<tr>
<td>COPD</td>
<td>20.0%</td>
<td>11.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Pneumocillin susceptibility</td>
<td>12.8%</td>
<td>12.8%</td>
<td>NS</td>
</tr>
<tr>
<td>High level resistance</td>
<td>7.8%</td>
<td>51.1%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>76.7%</td>
<td>51.1%</td>
<td>0.01</td>
</tr>
<tr>
<td>APACHE score, mean ± SD</td>
<td>19 ± 1.1</td>
<td>19 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Pneumonia score ± SE</td>
<td>6.6 ± 0.3</td>
<td>6.3 ± 0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

LM Baddour, et al, Am J Respir Crit Care Med 2004

### LOGISTIC REGRESSION MODELS ASSESSING COMBINATION THERAPY

<table>
<thead>
<tr>
<th>Survival</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for HIV status†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>3.2</td>
<td>1.7</td>
<td>0.028</td>
<td>1.1-9.2</td>
</tr>
<tr>
<td>HIV</td>
<td>0.69</td>
<td>0.06</td>
<td>0.000</td>
<td>0.02-0.3</td>
</tr>
<tr>
<td>Adjusted for MV†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>2.9</td>
<td>1.5</td>
<td>0.04</td>
<td>1.1-7.7</td>
</tr>
<tr>
<td>MV</td>
<td>8.1</td>
<td>4.2</td>
<td>0.0001</td>
<td>3.0-2.2</td>
</tr>
</tbody>
</table>

The end point was survival at day 14
† Combination therapy had a significant positive association with survival even when adjusted for HIV status or for MV

LM Baddour, et al, Am J Respir Crit Care Med 2004
Limitations of the study

- Non-randomized, controlled study
- 252/844 (30%) excluded without clear reasons for non-inclusion
- Monotherapy group not well defined
- Optimal duration of combination not defined (35% of patients had antibiotic therapy changed by Day 5)
- Unable to delineate the basis for the superiority of the combination regimen
- Unable to determine which specific components of the combination would be most effective (nonmacrolide combinations also successful)

Are combinations superior to monotherapy in bacteraemic pneumococcal CAP?

- Pintado et al, 43rd ICAAC, Washington, 2004
  Ceftriaxone monotherapy = lowest case fatality rate (20 vs. 24%; p>0.3)
- Dwyer et al, Eur J Clin Microbiol Infect Dis 2006
  - Risk of death monotherapy similar to the combination
  - No differences in mortality
- Ochoa et al, Unpublished.
  - Monotherapy has the lowest mortality rate

ADDITION OF A MACROLIDE TO A B-LACTAM IN BACTEREMIC PNEUMOCOCCAL PNEUMONIA

- Analysis of a prospective, observational, multicenter study carried out in 5 countries between 1993 and 1995 that included 460 patients with bacteremic pneumococcal disease
- The 370 patients with pneumonia were included in the analysis

Table 2. Multivariate analysis of factors with possible independent importance for the risk of death in 3-40 patients with bacteraemic pneumococcal pneumonia

<table>
<thead>
<tr>
<th>Factor</th>
<th>p-value*</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>0.020</td>
<td>2.57</td>
<td>1.18-5.86</td>
</tr>
<tr>
<td>Nursing home residence</td>
<td>0.104</td>
<td>2.53</td>
<td>0.76/7.55</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>0.141</td>
<td>1.89</td>
<td>0.79/4.40</td>
</tr>
<tr>
<td>≥2 lung lobes affected</td>
<td>0.045</td>
<td>2.17</td>
<td>1.01/4.67</td>
</tr>
<tr>
<td>APS 5–9</td>
<td>0.096</td>
<td>2.94</td>
<td>0.89/27.4</td>
</tr>
<tr>
<td>APS 8–14</td>
<td>0.007</td>
<td>8.26</td>
<td>2.13/34.8</td>
</tr>
<tr>
<td>APS 14–17</td>
<td>0.0004</td>
<td>23.8</td>
<td>4.77/180.3</td>
</tr>
<tr>
<td>APS ≥18</td>
<td>&lt;0.0001</td>
<td>53.8</td>
<td>11.8/395.0</td>
</tr>
<tr>
<td>Addition of a macrolide</td>
<td>0.844</td>
<td>1.09</td>
<td>0.41/2.70</td>
</tr>
</tbody>
</table>


MOTIV SUDY: Once daily sequential intravenous/oral (IV/PO) moxifloxacin vs. IV ceftriaxone plus twice daily IV/PO levofloxacin in the treatment of severe CAP requiring hospitalisation.

- **Patients and Methods**: Prospective, randomized, multicenter, multinational, third-party blind, double-dummy trial comparing the efficacy and safety of IV/PO MXF 400 mg OD for 7-14 days, to IV CTX 2 g OD plus IV LFX 500 mg BID, for 7-14 days (LFX dose adjusted for renal function).

- **Patients were stratified to either Pneumonia Severity Index (PSI) Class III (≤50% of population) or Classes IV-V. The primary endpoint was clinical cure at test of cure (4-14 days after final dose).**


---

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- **Patients were stratified to either Pneumonia Severity Index (PSI) Class III (≤50% of population) or Classes IV-V. The primary endpoint was clinical cure at test of cure (4-14 days after final dose).**

Garau – Treatment of pneumococcal lung disease

**Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic (Valid PP analysis)</th>
<th>Moxifloxacin N=291</th>
<th>Ceftriaxone + levofloxacin N=278</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean±SD</td>
<td>66.0±16.2</td>
<td>64.8±16.7</td>
</tr>
<tr>
<td>PSI distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>122 42 111 40</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>138 47 134 48</td>
<td></td>
</tr>
<tr>
<td>Class V</td>
<td>31 11 33 12</td>
<td></td>
</tr>
<tr>
<td>PO2 (mmHg)</td>
<td>60.5</td>
<td>59.5</td>
</tr>
<tr>
<td>% on IV therapy for ≥5 days</td>
<td>64.4</td>
<td>66.9</td>
</tr>
</tbody>
</table>

**Patient characteristics (2)**

<table>
<thead>
<tr>
<th>Characteristic (Valid PP analysis)</th>
<th>Moxifloxacin N=291</th>
<th>Ceftriaxone + levofloxacin N=278</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>25 9</td>
<td>30 11</td>
</tr>
<tr>
<td>Ventilated at inclusion</td>
<td>13 5</td>
<td>14 5</td>
</tr>
</tbody>
</table>

**Overall clinical success rates at test of cure**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Moxifloxacin</th>
<th>Comparator</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically valid population</td>
<td>253 (85.9%)</td>
<td>250 (89.9%)</td>
<td>-9.1% to 2.2%</td>
</tr>
<tr>
<td>PSI III</td>
<td>110 (62.2%)</td>
<td>103 (56.4%)</td>
<td>-11.4% to 1.9%</td>
</tr>
<tr>
<td>PSI IV</td>
<td>121 (71.7%)</td>
<td>114 (65.6%)</td>
<td>-7.5% to 1.4%</td>
</tr>
<tr>
<td>PSI V</td>
<td>34 (61.3%)</td>
<td>28 (52.6%)</td>
<td>-4.9% to 21.1%</td>
</tr>
<tr>
<td>PSI V/IV</td>
<td>145 (83.6%)</td>
<td>132 (75.6%)</td>
<td>-8.9% to 5.1%</td>
</tr>
<tr>
<td>Microbiologically documented population</td>
<td>114 (89.8%)</td>
<td>110 (89.4%)</td>
<td>-6.2% to 8.3%</td>
</tr>
<tr>
<td>Microbiologically valid population</td>
<td>46 (91.9%)</td>
<td>46 (91.9%)</td>
<td>-19.4% to 11.8%</td>
</tr>
<tr>
<td>Pneumonia due to intracellular organisms</td>
<td>39 (96.2%)</td>
<td>39 (96.2%)</td>
<td>-2.8% to 4.1%</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td>69 (79.5%)</td>
<td>74 (85.5%)</td>
<td>-11.1% to 10.1%</td>
</tr>
<tr>
<td>Positive culture with S. pneumonia b</td>
<td>27 (93.5%)</td>
<td>26 (93.6%)</td>
<td>-0.5% to 12.0%</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>15 (75.0%)</td>
<td>16 (75.0%)</td>
<td>-6.3% to 24.8%</td>
</tr>
</tbody>
</table>

b Positive culture or urine antigen.

c Clinical success was obtained in the 1/1 (100%) moxifloxacin- and 2/2 (100%) comparator treated patients who had S. pneumoniae isolates that were non-susceptible to penicillin (MIC>1mg/L).
CONCLUSIONS

- Some non-comparative studies suggest that the initial use of a macrolide in combination with a β-lactam is associated with lower mortality (Mufson et al. 1999; Martinez et al. 2003)
- A recent prospective, non-comparative, non-randomized, multinational study has found an association of dual therapy (any combination) with lower mortality (Baldour et al. 2004)
- No satisfactory explanation for these results is apparent
- We and others have not been able to confirm these associations in our cohorts of adults with well documented bacteremic pneumococcal pneumonia, treated with a 3rd Gen Ceph and compared to its combination with a macrolide (Pintado et al; Garau et al)
- The MOTIV study, the only double blind, randomized, supports our findings
- A recent retrospective cohort study showed that β-lactam plus macrolide was associated with a better outcome than the group treated with a β-lactam plus fluoroquinolone

Future studies should be comparative, randomized, double blind, and adjusted for all known risk factors for increased mortality

Potential benefits of combination therapy with a macrolide

- of pro-inflammatory cytokines
  - Ability to interfere with quorum sensing mechanisms (P aeruginosa)
  - Inhibition of pneumolysin production in pneumococci
  - Cover for atypical pathogens
- Unrecognized polymicrobial infection
- Additional cover for drug-resistant infections
- Synergy between these two classes of agents
- Secondary anti-inflammatory/immunomodulatory properties directed at both the host and the microbial pathogen
  - Down regulation

- Pneumolysin, a toxin produced by all clinically-relevant strains of S. pneumoniae, possesses both cytotoxic and pro-inflammatory properties and is a major virulence determinant of the pneumococcus
- Excessive levels of pneumolysin in the airways results in damage to vascular endothelium as a consequence of the cytolytic actions of the toxin
- This favours extrapulmonary dissemination and poorly controlled influx of neutrophils into the lungs and development of a potentially harmful, hyperacute inflammatory response
Garau – Treatment of pneumococcal lung disease

Inhibition of the production of pneumolysin by clarithromycin in pneumococci

- Clarithromycin causes a dose-related inhibition of production of this toxin by all susceptible strains, maximal at concentrations of 0.05-0.1 mg/L
- Also inhibits pneumolysin production by macrolide-resistant strains carrying either the erm gene, as well as those expressing the mef efflux pump genes

Anderson R et al, JAC 2007;59:224-229

OTHER STUDIES SUPPORTING THESE FINDINGS

- Exposure of a highly macrolide resistant strain of S. pneumoniae to ERY in tissue culture medium was accompanied by a striking decrease in the production of pneumolysin.
  Lagrou K et al, JAC 2000;46:717-23
- Both azitromycin and clarithromycin inhibit the production of pneumolysin in vitro by macrolide-resistant strains, while the administration of these agents to mice prolongs survival following experimental infection with macrolide-resistant pneumococci in the setting of decreased activity of pneumolysin in the lungs.

ADDING A MACROLIDE

- Potential antagonism
- Toxicity
- Negative ecological impact
- Cost
Community-acquired MRSA: the epidemiology and clinical impact on the lung

Marc Bonten, University Medical Center Utrecht

Contents

• Carriage and infection
• Population structure
• Virulence factors
• Antibiotic resistance – MRSA
• Consequences of MRSA
• Changing epidemiology of MRSA
Carriage and sites of infection

Bonten – CA-MRSA
Bonten – CA-MRSA

Possible sites of infection

Population structure

Natural population dynamics and expansion of pathogenic clones of Staphylococcus aureus

829 S. aureus isolates from different origine
High-throughput AFLP analysis
Principal Component Analysis
Virulence factors

*Staphylococcus aureus*

Panton-Valentine Leukocidin Causes Necrotizing Pneumonia

Here we show that PVL is sufficient to cause pneumonia and that the expression of this leukocidin induces global changes in transcriptional levels of genes encoding secreted and cell wall-anchored staphylococcal proteins, including the lung inflammatory factor staphylococcal protein A (SpA).
Bonten – CA-MRSA

Antibiotic resistance in *S. aureus*

- Penicillin, 1950
- Methicillin (= all β-lactam antibiotics), 1961
- Tetracycline, Co-trimoxazol, rifampin, clindamycin, macrolides, quinolones
- Vancomycin, intermediate-R, 2000
- Vancomycin, high-level-R, 2002
- Linezolid, Daptomycin

**The *Staphylococcus aureus* “superbug”**

**Different SCCmec types**

<table>
<thead>
<tr>
<th>SCCmec Type</th>
<th>Size (kb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>34</td>
</tr>
<tr>
<td>Type II</td>
<td>52</td>
</tr>
<tr>
<td>Type III</td>
<td>56</td>
</tr>
<tr>
<td>Type IV</td>
<td>20-24</td>
</tr>
</tbody>
</table>

SCCmec type IV different **ccrA/B** types!
Bonten – CA-MRSA

Global prevalence of MRSA (% of S. aureus bacteremia)

Genetic background of MRSA
Bonten – CA-MRSA

MRSA and attributable mortality

Comparison of mortality associated with MRSA and MSSA bacteremia: a meta-analysis

- Cohort studies reporting mortality rates of patients with MRSA and MSSA infections
- Period: published between 1980-2001
- 31 studies: 2603 MSSA, 1360 MRSA
- Period of patient inclusion: 1975-1999
- Significant heterogeneity
- 77% of the studies: no effects of MRSA on mortality
- Pooled OR: 1.93 (1.54-2.42)

Risk of death from MRSA bacteremia: A meta-analysis.

Figure 1. The relationship between length of hospital stay and in-hospital mortality rates for groups of patients with either methicillin-resistant Staphylococcus aureus (MRSA) or meticillin-susceptible S. aureus (MSSA). The size of each group is represented by the corresponding size of the squares (17, 21, 31, 31, 31, 18, 78, 268, and 136 patients, respectively). Data points in squares are derived from Huxley et al for patients with hospital-acquired MRSA.
Bonten – CA-MRSA

Attributable mortality due to MRSA in case-control studies with matching on length of stay before infection

  - pair-wise matching (n=38) on sex, age, no of comorbidities, underlying disease, LOS
  - mortality rates 34% vs 34% (OR=1, CI=0.4-2.5)
  - pair-wise matching (n=163) on underlying disease, prognosis of underlying dis, LOS
  - mortality rates 20% vs 11%
  - stepwise conditional regression analysis: OR mortality 1.74, CI 0.79-3.78

The impact of methicillin resistance in S. aureus bacteremia on patient outcomes: Mortality, length of stay, and hospital discharges.
S. Cosgrove et al. ICHE 2005; 26: 166-174

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MRSA</th>
<th>MSSA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>22 (22.9%)</td>
<td>50 (19.8%)</td>
<td>.53</td>
</tr>
<tr>
<td>Median LOS after SAB (IQR)</td>
<td>9 (5-14)</td>
<td>7 (5-12)</td>
<td>.045</td>
</tr>
<tr>
<td>Median hospital charge after SAB</td>
<td>$26,424</td>
<td>$19,212</td>
<td>.008</td>
</tr>
<tr>
<td>Median hospital costs after SAB</td>
<td>$14,655</td>
<td>$10,655</td>
<td>.008</td>
</tr>
</tbody>
</table>

The case of MRSA in Oxford, UK
Impact of Methicillin Resistance on Outcome of Staphylococcus aureus Ventilator-associated Pneumonia

John Coburn, Charles Bond, Robert Fagan, Michael Weil, Jean-Louis Trouiller, Claude Cohen, and John Claxton, for the PRISMA Trial Group

Am J Respir Crit Care Med Vol 170, pp 765-792, 2004

We analyzed a retrospective cohort of 97 patients with methicillin-susceptible and 74 patients with methicillin-resistant Staphylococcus aureus ventilator-associated pneumonia (VAP). Initial empiric antibiotic therapy was appropriate for every patient.

<table>
<thead>
<tr>
<th>Table 4: Univariate and Multivariate Logistic Regression Analysis of Factors Associated With 28-day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Lung injury score ≥2</td>
</tr>
<tr>
<td>Acute respiratory distress index ≥12</td>
</tr>
<tr>
<td>Nasopharyngeal MRSA</td>
</tr>
<tr>
<td>Extrapulmonary MRSA</td>
</tr>
<tr>
<td>TF-100K score ≥10.0</td>
</tr>
<tr>
<td>Extrapulmonary infections</td>
</tr>
<tr>
<td>Pneumonia before initiation of mechanical ventilation</td>
</tr>
<tr>
<td>Age of patient at admission</td>
</tr>
<tr>
<td>Acute respiratory distress index</td>
</tr>
<tr>
<td>Multivariate Model:</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* Mortality rate of all patients in the VAP cohort with MRSA.

Treatment of nosocomial pneumonia caused by MRSA
Linezolid vs Vancomycin
Analysis of Two Double-Blind Studies of Patients With Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia

Richard C. Woodcock, MD, FCCP, Joseph Rea, MD, PhD
Sue K. Gurney, MD, FCCP, Rodney V. Cross-Delbeco, MD, and
Maria M. Kelly, MD, FCCP

(AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE 2003, 168:1749–1757)

Design: Retrospective analysis of data from two prospective, randomized, double-blind studies. Patients received intravenous linezolid or vancomycin and were followed for 28 days, with assessment of clinical cure and rate of mortality.

Results: A total of 2,296 patients with confirmed MRSA pneumonia were enrolled in the study. The results showed that linezolid was as effective as vancomycin in terms of clinical cure and mortality rate. However, linezolid had a lower rate of side effects compared to vancomycin.

The changing epidemiology of MRSA

[Diagram showing trends in MRSA infections over time]

[Graph comparing treatment outcomes for linezolid and vancomycin]

Conclusion: Linezolid appears to be a safe and effective treatment option for MRSA pneumonia, especially in cases where vancomycin is contraindicated due to side effects.
Bonten – CA-MRSA

Definitions of CA-MRSA

- **Epidemiological:**
  - Cultured <72 hours of hospital admission
  - No hospitalization in previous period (6 mo - 3 yrs)

- **Molecular epidemiological:**
  - Presence of SCCmecA type IV (or V)
  - Not phylogenetically related to previously known HA-MRSA clonal lineages

Comparison of MRSA by Origin

<table>
<thead>
<tr>
<th></th>
<th>Nosocomial</th>
<th>Community-acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Hospital risk factors</td>
<td>Usually immunocompetent</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Invasive devices</td>
<td>Contact-related (e.g., sports, jail/prison, MSM, military, kids)</td>
</tr>
<tr>
<td>Antibiorgram</td>
<td>Multi-resistant</td>
<td>Primarily β-lactam resistant</td>
</tr>
<tr>
<td>Clinical Sites</td>
<td>Wounds &amp; blood</td>
<td>Skin &amp; soft tissue</td>
</tr>
<tr>
<td>Virulence</td>
<td>Variable</td>
<td>Prosperity for virulence</td>
</tr>
<tr>
<td>Genetic Basis</td>
<td>SCCmec I-III</td>
<td>SCCmec IV</td>
</tr>
</tbody>
</table>
Bonten – CA-MRSA

Abscess Characterized by a Prominent Inflammatory Reaction (A) and Cutaneous Necrosis (B)


Bonten – CA-MRSA

Initial reported clusters of CA-MRSA
Bonten – CA-MRSA

Pigs as a source of MRSA

Genetic background of pig-associated MRSA

Conclusions 1

- *S. aureus* is both a commensal bacterium as a feared pathogen
- Carriage is associated with infection
- Eradication of carriage probably protects against infection (relevant for post-surgical infections!)
- *S. aureus* has a clonal population structure, with all lineages being capable to cause severe infections
- MRSA has become the paradigm of an antibiotic-resistant nosocomial pathogen
- Uncertain if (and if yes to what extent) MRSA increases patient mortality
- Linezolid is, at least, equally effective as vancomycin for nosocomial VAP caused by MRSA
Conclusions 2

• The epidemiology of MRSA is (rapidly) changing
• Global emergence of MRSA characterized by relatively new SCCmec types and enriched occurrence of PVL-gene
• Unrelated to nosocomial populations of MRSA
• Dissemination in the community
• Predominantly skin and soft tissue infections
• Sporadically severe pulmonary infections (association with influenza)
• High susceptibility for other classes of antibiotics
• There probably is a large reservoir of specific MRSA among animals in Europe
• Their role for human disease is yet unknown
Kluytmans – Diagnosis of CA-MRSA

Detection of MRSA

Jan Kluytmans
VUmc University Medical Center, Amsterdam
Amphia Hospital, Breda
The Netherlands

Question 1

MRSA infections can be diagnosed using clinical signs and symptoms only?

- yes
- no

Question 2

How many people in the community carry MRSA?

- approximately 30%
- approximately 5%
- approximately 1-2%
- less than 1%
Question 3

Carriers can be detected using routine cultures (based on clinical indications)

yes
no

Question 4

Control of transmission of MRSA can be based on taking transmission based precautions for patients with signs and symptoms of infection

yes
no

Question 5

Molecular detection of MRSA is possible using the mec-A gene as a target

yes
no
Question 6

Reliable detection of MRSA can be achieved within two hours

- yes
- no

Question 7

Chromogenic agar plates are the most cost-effective method to detect MRSA

- yes
- no

Question 9

Established reservoirs of MRSA in the community include

- MSM
- soccer players
- pig farmers
- children attending day care centers
Kluytmans – Diagnosis of CA-MRSA

**MRSA infection**

S. aureus infections mainly include:
- SSTI (boils, impetigo, cellulitis)
- osteomyelitis
- pneumonia
- endocarditis

**MSSA <> MRSA**

MSSA infections are not different from MRSA infections considering the clinical presentation. Laboratory diagnosis is essential for detection of MRSA.

**S. aureus**

Staphyle = bunch of grapes
kokkos = round structure
aureus = golden
Carriage of S. aureus

- 30% of the population carries S. aureus
- carriage is asymptomatic
- MRSA carriage in the community is rare
  - USA: 1.5%
  - Netherlands: < 0.1% (pig farmers >30%)
Kluymans – Diagnosis of CA-MRSA

15% detected by clinical cultures

85% not detected by clinical cultures

---

**Special Report**

**SIHA Guidelines for Preventing Nosocomial Transmission of Multidrug-Resistant Strains of Staphylococcus aureus and Enterococcus**

Carolee A. Mast, MD; Michael W. Brueggemann; John R. Weinstein, MD; William E. Sobsey, MD; John M. Tenover, MD; Kerry M. Force, MD; MSc

---

**CONCLUSION:** Active surveillance cultures are essential to identify the reservoir for spread of MRSA and VRE infections and make control possible using the CDC’s long-recommended contact precautions (*Infect Control Hosp Epidemiol* 2003;24:562-586).
Kluytmans – Diagnosis of CA-MRSA

HOW?

Sampling sites

Throat Swabs Are Necessary to Reliable Detect Carriers of *Staphylococcus aureus*

The nose is the most important screening site of colonization with *Staphylococcus aureus*. We assessed 2000 individuals for *S. aureus* carriage with nares of both nostrils and throat. A total of 15% of nares were nasal carriers, but only 4.5% of the throat. Tympanic membrane significantly decreases the sensitivity of detection among carriers by 25%.
Broth enrichment

Without a broth enrichment

Cookson et al, Lancet 1987, 34% false-negative
van Ogtrop, AAC 1995, 45% false negative (broth enrichment only: 3% false-negative)

Takes more time but increases the yield

Principles for detection of MRSA

MRSA = S. aureus with the mecA gene
Correct detection means:
Correct identification of S. aureus
Correct detection of methicillin resistance or the molecular mechanism
mecA-gene codes for PBP-2a
Variable expression
MICs can be below the breakpoint
Cefoxitin vs oxacillin
S. aureus identification
Latex agglutination
Fast but needs confirmation

Detection of resistance

Detection of resistance
Detection of resistance

Detection of PBP-2a
Latex agglutination (20 minutes)
Fast and reliable

Detection of resistance

PCR for mecA gene
Gold standard (1-2 hours)

Time to result

Day 0: sampling and inoculation
Day 1: direct plating can produce results using rapid tests and if enough growth and no contamination
Day 2: First day BE-subculture can produce results
Theoretically 1-3 days
Real life often 4-5 days before final result
Molecular detection of MRSA

- meca gene and S. aureus specific target
- MecA gene is found in other staphylococci
- Samples with MSSA and MRSE

SCC-mec and orfX

<table>
<thead>
<tr>
<th>MRSE type</th>
<th>SCC-mec</th>
<th>S. aureus chromosome</th>
<th>Amplification product size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>+</td>
<td>mec618</td>
<td>176</td>
</tr>
<tr>
<td>ii</td>
<td>+</td>
<td>mec619</td>
<td>278</td>
</tr>
<tr>
<td>iii</td>
<td>+</td>
<td>mec262</td>
<td>223</td>
</tr>
<tr>
<td>iv</td>
<td>+</td>
<td>mec514</td>
<td>215</td>
</tr>
<tr>
<td>v</td>
<td>+</td>
<td>mec515</td>
<td>196</td>
</tr>
<tr>
<td>vi</td>
<td>+</td>
<td>mec512</td>
<td>914</td>
</tr>
</tbody>
</table>
Kluytmans – Diagnosis of CA-MRSA

Chromogenic agar plates

Combination:
Chromogenic indicator for S. aureus
Antibiotics that inhibit MSSA

Rapid screening of MRSA with chromogenic agar and PCR: prospective experimental cohort study

MWM Wassenberg, JAJW Kluytmans, ATA Box, GA de Wit, AGM Buiting, SFT Thijssen, A Troelstra, CMJE Vandenbroucke-Grauls, CE Visser, A Voss, PP Wolffs, MWH Wulf, AA v Zwet, M v Rijen, MJM Bonten
Kluytmans – Diagnosis of CA-MRSA

Design

12 Dutch hospitals
admission screening of high risk patients
end of pre-emptive isolation if tested negative
BD-PCR and chromogenic agar-plate

PCR results

Sens: 85.2%
Spec: 96.5%
PPV: 44.2%
NPV: 99.5%

Chromogenic agar: results

Sens: 85.7%
Spec: 96.6%
PPV: 46.2%
NPV: 99.5%
Kluuytmans – Diagnosis of CA-MRSA

Results

time until discontinuation of isolation
  conventional culture: 85.2 hours
  chromogenic plate: 30.0 hours
  PCR: 19.7 hours

PCR reduced the number of isolation days by 60%
  chromogenic agar plates, 47% reduction

results

Costs

  PCR per test:  €52.70
  Chromogenic agar:  €2.05

Costs to prevent one isolation day

  PCR:  €92.25
  Chromogenic agar:  €8.28

Potential for more speed
Conclusions

- Microbiological diagnostics are essential to control MRSA in individual patients.
- Culture with broth enrichment is currently the gold standard but takes 3-5 days.

Conclusions

- PCR can detect MRSA within two hours but in real life time to result is longer (and are relatively expensive).
- Chromogenic agar plates perform equivalent to MRSA, are much cheaper and take 18-24 hours from inoculation.
Management including empirical and definitive antibiotic therapy of MRSA pneumonia

Dr Robert G Masterton
NHS Ayrshire & Arran
UK

Question 1

- Staphylococcus aureus is the commonest gram positive organism causing nosocomial pneumonia in the ICU.
  - True
  - False
  - Do not know

How big is the problem?

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>36%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>10%</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>7%</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>6%</td>
</tr>
<tr>
<td>H. influenza</td>
<td>2%</td>
</tr>
<tr>
<td>C. albicans</td>
<td>2%</td>
</tr>
<tr>
<td>Other pathogens</td>
<td>2%</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>2%</td>
</tr>
</tbody>
</table>

Pathogens Most Frequently Associated With Nosocomial Pneumonia in the ICU

Relative risks of MRSA pneumonia?

- MRSA is more likely to be associated with death than MSSA in pneumonia.
  - True
  - False
  - Do not know

Mortality in Staphylococcus aureus VAP: a systematic review.

- Eight articles were included.
- Crude in-hospital mortality higher in MRSA patients.
- Crude intensive care unit mortality higher in MRSA patients.
- 3 studies adjusted for potential confounding factors, including adequacy of empirical treatment and severity of illness, demonstrated no difference in in-hospital mortality.
- Conclusions:
  - Limited evidence suggests methicillin resistance associated with death among persons acquiring Staphylococcus aureus VAP
  - Even more limited data with adjustment for risk factors suggests association not causal.

Relative risks of MRSA pneumonia?

- MRSA pneumonia is more costly to treat than MSSA disease.
  - True
  - False
  - Do not know
The Costs of MRSA Pneumonia

- MRSA patients excess:
  - MV days = 4.4 (95% confidence interval 0.6–8.2)
  - inpatient days length of stay = 3.8 (95% confidence interval -0.5 to +8.0)
  - ICU days = 5.3 (95% confidence interval 1.0–9.7)

- Excess costs US $7731 (95% confidence interval – US $8393 to +US $23,856)

CAMSRA v. MRSA

<table>
<thead>
<tr>
<th>Drug</th>
<th>CAMSRA</th>
<th>MRSA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>6.4</td>
<td>5.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>8.6</td>
<td>10.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>7.1</td>
<td>9.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Quinupristin</td>
<td>8.4</td>
<td>10.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>7.3</td>
<td>8.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Ceftobiprole</td>
<td>13.0</td>
<td>12.4</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Severe MRSA Pneumonia

Treatment Options

- Vancomycin
- Teicoplanin
- Linezolid
- Quinupristin/dalfopristin
- Daptomycin
- Tigecycline
- Ceftobiprole
What choice?

- How many of the above list of antibiotics cannot be recommended for the treatment of MRSA pneumonia?
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7

What is your first choice?

- Which of the list of antibiotics is your first choice for the treatment of severe MRSA pneumonia?
  1. Vancomycin
  2. Teicoplanin
  3. Linezolid
  4. Quinupristin/dalfopristin
  5. Other

MSSA Bacteremic Pneumonia: Hospital Mortality

Does vancomycin MIC relate to outcome?

- For MIC values below the breakpoint for susceptibility the vancomycin MIC does not affect outcome.
  - True
  - False
  - Do not know

Vancomycin Treatment Failures and MIC

The numbers on the plot are the % failure rates.

Vancomycin as the gold standard for MRSA Pneumonia

- Poor lung penetration
  - 15 mg/kg aiming for a trough level of 15-20 microgram/mL
  - from 8-16 mcg/mL to 4-

- No good randomized controlled trials but rather expert opinion.
- Vancomycin creep
Masterton – Management of MRSA pneumonia

### Vancomycin Creep

<table>
<thead>
<tr>
<th>Year</th>
<th>MIC ≥1.6 µg/mL (%)</th>
<th>MBC ≥1.6 µg/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>36%</td>
<td></td>
</tr>
</tbody>
</table>

MIC = minimum inhibitory concentration; MBC = minimum bactericidal concentration.


### Which glycopeptide for MRSA pneumonia?

- Teicoplanin has better clinical outcomes than vancomycin for mortality, morbidity and cost in the management of MRSA pneumonia?
  - True
  - False
  - Do not know

### Vancomycin & Teicoplanin Comparison

- Clinical comparisons
  - Very few head to head trials
  - Broadly comparable in outcomes

- Soft factors
  - Higher bacteraemia relapse rates with teicoplanin
  - Higher super-infection with teicoplanin
  - Vancomycin has lower incidence of in-treatment resistance development
  - Vancomycin better range of staphylococcal cover

O'Hare et al. JAC: 1992; 30, 753-768.
Cepeda et al. JAC: 2003; 52, 533-534.
Masterton – Management of MRSA pneumonia

**Cost Effectiveness Comparison**

- Cost in Euros of acquisition, administration and monitoring
  - Teicoplanin 647.62 ± 572.75
  - Vancomycin 378.11 ± 225.90

- Total hospital costs in Euros
  - Teicoplanin 4,432.04 ± 3,383.46
  - Vancomycin 4,364.44 ± 2,734.24

- No differences in clinical or economic outcomes.


**PK/PD for Vancomycin in MRSA pneumonia**

- Increasing the dose of vancomycin to improve the trough level will improve clinical outcomes in MRSA pneumonia?
  - True
  - False
  - Do not know

**Vancomycin for MRSA Pneumonia**

![Clinical Response Bar Chart]

Increasing Vancomycin Trough Levels and End of Treatment Response

MIC = minimum inhibitory concentration.
Target trough = 15 to 20 microg/mL.
Infection-related mortality = 24% vs 10%; P = .16) compared with the low-MIC group.
Hidayat Arch Int Med. 2006;166:2138-2144.

Linezolid versus Vancomycin

- Linezolid is clinically superior to Vancomycin in the treatment of MRSA pneumonia?
  - True
  - False
  - Do not know

Linezolid versus Vancomycin in MRSA pneumonia

- Retrospective analysis of two randomized, double-blind studies in Gram-positive, ventilator-associated pneumonia
- Logistic regression showed linezolid as independent predictor of clinical cure
  - Odds ratio 1.8 for all patients,
  - Odds ratio 2.4 for Gram-positive VAP,
  - Odds ratio 20.0 for MRSA VAP
- Logistic regression showed linezolid as independent predictor of survival
  - Odds ratio 1.8 for all patients,
  - Odds ratio 2.6 for Gram-positive VAP,
  - Odds ratio 4.6 for MRSA VAP.

**Linezolid versus Vancomycin in MRSA pneumonia**

- Retrospective analysis of two randomized, double-blind studies in Gram-positive, nosocomial pneumonia.
- Kaplan-Meier survival rates for linezolid vs vancomycin were 80.0% vs 63.5% for MRSA (p = 0.03).
- Logistic regression confirmed survival difference favouring linezolid remained significant after adjusting for baseline variables (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.0 to 4.8; p = 0.05).
- Clinical cure rates for linezolid vs vancomycin were 59.0% vs 35.5% for the MRSA (p < 0.01).
- Logistic regression confirmed difference favouring linezolid remained significant after adjusting for baseline variables (OR, 3.3; 95% CI, 1.3 to 8.3; p = 0.01).


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**Linezolid versus Vancomycin**

- Linezolid is superior to Vancomycin in the cost effectiveness of the treatment of MRSA pneumonia?
  - True
  - False
  - Do not know

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**Linezolid versus Vancomycin in MRSA pneumonia**

- Decision-analytic model using clinical trial data examined costs and outcomes of linezolid or vancomycin in hospitalized patients with suspected MRSA pneumonia.
- Model found higher clinical cure (+8.7%) and survival (+13.2%) for linezolid compared with vancomycin.
- Incremental cost against linezolid of Euro 420 per treatment episode.
- Concluded that on the cost-benefit profile linezolid is a cost-effective alternative to vancomycin for MRSA pneumonia.

Conclusion

- MRSA pneumonia is a significant cause of morbidity and mortality in hospital patients
- Vancomycin should no longer be viewed as the gold standard for the management of severe MRSA pneumonia
- New and better treatments are needed that are proven in clinical and cost effectiveness
  - New antibiotics
  - Combination treatments