Pneumococcal pneumonia

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Nottingham University Hospitals NHS Trust
University of Nottingham
Declarations of interest

• Unrestricted investigator-initiated research funding from Pfizer to Nottingham University Hospitals NHS Trust: pneumonia study. WSL – Chief Investigator.

• Was Member of NICE Pneumonia GDG.

• Developed the CURB65 pneumonia mortality risk score

• Views expressed are my own.
Clinical case

69 year old man
Unwell a few days only.
Fever, cough, green sputum.
Very tried. Loss of appetite.

Hypertension. Fit and well.
Retired – fibre glass factory

Temp 38 °C
Pulse 110/min
BP 110/60
Resp rate 20/min

Hb 120
WCC 12
Platelets 628
CRP 95

Urea 4.0
Creat 63
Infection? Pathogen?
Is this an infection?

What is the pathogen?

Start Smart - Then Focus
Antimicrobial Stewardship Toolkit for English Hospitals
Updated March 2015
British Thoracic Society
National CAP audit (n=24,180)

Mean age 72 years (range: 16 – 108)
Female 53%
Admitted from care facility 15.7%

65 years old
<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>5398</td>
<td>(22.3)</td>
</tr>
<tr>
<td>Chronic Heart Disease</td>
<td>5269</td>
<td>(21.8)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>2940</td>
<td>(12.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2450</td>
<td>(10.1)</td>
</tr>
<tr>
<td>Congestive Cardiac Failure</td>
<td>2002</td>
<td>(8.2)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1772</td>
<td>(7.3)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>1868</td>
<td>(7.7)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>251</td>
<td>(1.0)</td>
</tr>
</tbody>
</table>
### Microbiology of CAP (UK): pre-PCVs

**Pathogen identified** 75%
**Single pathogen** 46%
- **Bacteria** 54%
- **Virus** 23%
- **Atypical pathogen** 22%

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Total (%) (n=267)</th>
<th>Died (%)</th>
<th>Age &lt;75 years (n=155)</th>
<th>Age ≥75 years (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pathogens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>129 (48)</td>
<td>18 (14)</td>
<td>80 (52)</td>
<td>49 (43)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>20 (7)</td>
<td>1 (5)</td>
<td>11 (7)</td>
<td>9 (8)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>5 (2)</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td>4 (4)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>4 (1.5)</td>
<td>2 (50)</td>
<td>2 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>GNEB*</td>
<td>4 (1.4)</td>
<td>1 (25)</td>
<td>3 (1.9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Anaerobes†</td>
<td>3 (1.1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

Lim, Thorax 2001
UK IPD: 2000 to 2013

Waight Lancet ID 2015
NP carriage (<5 yr olds): Southampton

Carriage rate

Vaccine and Non-Vaccine Type Pneumococci (%)

Winter


PCV13

PCV7

Devine, Vaccine 2017
Post-PCV effects on SPn carriage (Sweden)

Vaccination programme 2007: PCV7 → 2010: PCV13
NP samples 2004 (n=260) and 2011–13 (n=2161)
Pneumococcal CAP in adults (UK)

Rodrigo, ERJ 2015
US CDC study. 5 hospitals (2010 – 2012)
2488 of 3634 eligible adults (68%) with CAP

- Viral pathogen only (22%)
- Viral–viral co-detection (2%)
- Bacterial–viral co-detection (3%)
- Bacterial pathogen only (11%)
- Fungal or mycobacterial detection (1%)

Jain NEJM 2015
Pneumococcal serotypes: Canada 2010 - 2013

CAP: 3851 adults - any test done  14% SPn
621 adults – 4 tests done  23% SPn

LeBlanc, Vaccine 2017
CAP microbiology: Spain 2011 - 2014

- Sputum: 10.1%
- Pleural fluid: 1.9%
- Blood: 16.3%
- Binax Now®: 61.4%
- UAD: 59.2%

- Others: 0.5%
- Other virus: 10.5%
- S. aureus: 1.5%
- L. pneumophila: 1.9%
- Influenza virus: 1.7%
- S. pneumoniae: 29.3%
- Negative: 54.5%

N=368
N=1,258
N=685

Menendez Vaccine 2017
Pneumococcal serotypes in Spain 2011 - 2014

CAP 1258 adults
29% SPn (n=368)

Menendez Vaccine 2017
Serotypes in CAP: novel 24-serotype assay. 2015 UK

Sep 2014 to Sep 2015. Adults with CAP n=667.
Of 481 participants (consent + samples) → 40% SPn

80% PPV23

26% PCV13

Eletu, CVI 2017
Daniel et al. Manuscript submitted
Pneumococcal CAP in adults (UK)

![Graph showing incidence rate per 100,000 population by year for Pneumococcal CAP, PCV13 CAP, PCV7 CAP, Additional PCV13 CAP, and Other CAP and untyped pneumococcal CAP.](image)

- **2008/9**:
  - Pneumococcal CAP: 35
  - PCV13 CAP: 10
  - PCV7 CAP: 12
  - Additional PCV13 CAP: 5
  - Other CAP and untyped pneumococcal CAP: 2

- **2012/13**:
  - Pneumococcal CAP: 25
  - PCV13 CAP: 9
  - PCV7 CAP: 11
  - Additional PCV13 CAP: 4
  - Other CAP and untyped pneumococcal CAP: 3

- **2014/15**:
  - Pneumococcal CAP: 20
  - PCV13 CAP: 8
  - PCV7 CAP: 10
  - Additional PCV13 CAP: 3
  - Other CAP and untyped pneumococcal CAP: 2

Rodrigo, ERJ 2015
Pneumococcal CAP in adults (UK)

The graph illustrates the incidence rate per 100,000 population over years 2008/9 to 2014/15. The graph shows the decline in pneumococcal CAP after the introduction of PCV13 in 2012/13. The incidence rate for PCV13 CAP decreases significantly, while the rate for non-PCV13 CAP remains relatively stable. The serotype 3 is shown with an arrow indicating a potential increase in incidence in 2014/15.

Rodrigo, ERJ 2015, Daniel, submitted
UK population projections

People aged 85 and over:
- mid-2016: 1.6 million
- mid-2041: 3.2 million

Source: ONS
## Serotypes in CAP: novel 24-valent assay. 2015 UK

<table>
<thead>
<tr>
<th>Severity (CURB65 score)</th>
<th>All CAP n=481</th>
<th>SPn CAP n=196</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>48%</td>
<td>46%</td>
</tr>
<tr>
<td>Moderate</td>
<td>29%</td>
<td>27%</td>
</tr>
<tr>
<td>High</td>
<td>22%</td>
<td>27%</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All CAP</th>
<th>SPn CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS (days)</td>
<td>7 (4 – 11)</td>
<td>7 (4 -10)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>30-d mortality</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Daniel et al. Manuscript submitted.
Treatment of pneumococcal infection

Pneumococcal bacteraemia – all age-groups (US)

Before penicillin (1929 – 1935)

After penicillin (1967 – 1970)
(1952 – 1962)

Watson, CID 1993
Resistance: *Streptococcus pneumoniae* (US)

IPD surveillance (US)

Tomczyk, CID 2016
**Resistance: ***Streptococcus pneumoniae* (UK)

Proportions with triple resistance: IPD (blood, CSF), PHE 2005–2014 (n = 13,551)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Total</th>
<th>Triple resistance</th>
<th>% Triple resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>15A</td>
<td>330</td>
<td>104</td>
<td>31.5</td>
</tr>
<tr>
<td>6B</td>
<td>420</td>
<td>51</td>
<td>12.1</td>
</tr>
<tr>
<td>19F</td>
<td>401</td>
<td>45</td>
<td>11.2</td>
</tr>
<tr>
<td>19A</td>
<td>987</td>
<td>83</td>
<td>8.4</td>
</tr>
<tr>
<td>23F</td>
<td>360</td>
<td>15</td>
<td>4.2</td>
</tr>
<tr>
<td>24F</td>
<td>124</td>
<td>5</td>
<td>4.0</td>
</tr>
<tr>
<td>9V</td>
<td>562</td>
<td>19</td>
<td>3.4</td>
</tr>
</tbody>
</table>

*X = not in PCV13*
NICE Pneumonia Guideline Dec 2014

Low severity CAP → single antibiotic

Moderate-High severity CAP → dual antibiotics
(macrolide + beta-lactam)

BTS National CAP Audit dataset

Priya D, Thorax 2016
Antibiotic therapy: Systematic Review

Lee, JAMA 2016

### Table

<table>
<thead>
<tr>
<th>Source</th>
<th>Outcome</th>
<th>β-Lactam Plus Macrolide or Fluoroquinolone Monotherapy</th>
<th>β-Lactam Monotherapy</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. (%) Who Died</td>
<td>No. of Patients</td>
<td>No. (%) Who Died</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason et al, 1999</td>
<td>30-d Mortality</td>
<td>544</td>
<td>46 (8.4)</td>
<td>3430</td>
</tr>
<tr>
<td>Houck et al, 2001</td>
<td>30-d Mortality</td>
<td>312</td>
<td>26 (8.3)</td>
<td>1740</td>
</tr>
<tr>
<td>García-Vázquez et al, 2005</td>
<td>In-hospital mortality</td>
<td>918</td>
<td>63 (6.9)</td>
<td>270</td>
</tr>
<tr>
<td>Paul et al, 2007</td>
<td>30-d Mortality</td>
<td>282</td>
<td>21 (7.4)</td>
<td>169</td>
</tr>
<tr>
<td>Brezler et al, 2008</td>
<td>30-d Mortality</td>
<td>5963</td>
<td>338 (5.7)</td>
<td>4463</td>
</tr>
<tr>
<td>Blasi et al, 2008</td>
<td>End of therapy mortality</td>
<td>320</td>
<td>19 (5.7)</td>
<td>452</td>
</tr>
<tr>
<td>Tessmer et al, 2009</td>
<td>30-d Mortality</td>
<td>946</td>
<td>42 (4.4)</td>
<td>908</td>
</tr>
<tr>
<td>Rodrigo et al, 2013</td>
<td>30-d In-hospital mortality</td>
<td>3239</td>
<td>745 (23.0)</td>
<td>2001</td>
</tr>
<tr>
<td>Garin et al, 2014</td>
<td>30-d Mortality</td>
<td>289</td>
<td>10 (3.4)</td>
<td>291</td>
</tr>
<tr>
<td>Postma et al, 2015</td>
<td>30-d Mortality</td>
<td>566</td>
<td>NR</td>
<td>506</td>
</tr>
</tbody>
</table>

**Diagram:**

- Mortality < 5%
- Combination better
- Monotherapy better

Lee, JAMA 2016
Pneumococcal seasonality: RSV, Flu

>16,000 pneumococcal hospitalisations in children.
RSV increases pneumococcal virulence

A

Adherence

B

Cilary dyskinesis

Smith, AJRCCM 2014
Viral pathogens in CAP

Overall: 24.5% viral pathogens

Odds of IP/30-day mortality:

Any viral infection
OR 1.3 (95% CI 0.8 – 2.16)

Dual viral-bacterial infection
OR 2.1 (95% CI 1.32–3.31)
Engineered liposomes sequester bacterial exotoxins and protect from severe invasive infections in mice

Brian D Henry\textsuperscript{1,2,10}, Daniel R Neill\textsuperscript{3,10}, Katrin Anne Becker\textsuperscript{1,10}, Suzanna Gore\textsuperscript{3}, Laura Bricio-Moreno\textsuperscript{3}, Regan Ziobro\textsuperscript{1,2}, Michael J Edwards\textsuperscript{2}, Kathrin Mühlemann\textsuperscript{4,9}, Jörg Steinmann\textsuperscript{5}, Burkhard Kleuser\textsuperscript{6}, Lukasz Japtok\textsuperscript{6}, Miriam Luginbühl\textsuperscript{7}, Heidi Wolfmeier\textsuperscript{7}, André Scherag\textsuperscript{8}, Erich Gulbins\textsuperscript{1,2,11}, Aras Kadioglu\textsuperscript{3,11}, Annette Draeger\textsuperscript{7,11} & Eduard B Babychuk\textsuperscript{7,11}

Pneumolysin as a potential therapeutic target in severe pneumococcal disease

Ronald Anderson\textsuperscript{a,\ast}, Charles Feldman\textsuperscript{b}
Alternatives to antibiotics—a pipeline portfolio review

Antibodies
Probiotics
Lysins
Bacteriophages
Immune stimulation
Peptides

as of January–March, 2015

C difficile
P aeruginosa
S aureus
Urinary tract infection
Research investments for UK infectious disease research 1997–2013
A systematic analysis of awards to UK institutions

Log-transformed UK research investment by UK mortality

Head, J Infect (in press)
Global Burden of Disease 2015 study
Lower Respiratory Tract Infections in 195 countries

- 5\textsuperscript{th} leading cause of death (of 249 causes)
- 1\textsuperscript{st} leading infectious cause of death
  
  All ages 37 per 100,000 2.74 million
  <5 year olds 105 per 100,000 0.71 million
  >70 year olds 1.27 million

- 2\textsuperscript{nd} leading cause of DALYs after IHD

<table>
<thead>
<tr>
<th>Mortality per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 yrs old</td>
</tr>
<tr>
<td>China</td>
</tr>
<tr>
<td>USA</td>
</tr>
<tr>
<td>Japan</td>
</tr>
</tbody>
</table>

Lancet ID, 2017
LRI mortality in <5-year olds

Western sub-Saharan Africa

Western Europe

Attributable fraction: LRI mortality

Lancet ID, 2017
Summary: Pneumococcal pneumonia

• **Despite vaccines**, burden of disease remains HIGH
• Global inequalities
• Dynamic epidemiology - vaccine & antibiotic pressures
• Diagnosis remains a challenge

• **Despite antibiotics**, significant morbidity and mortality
• Viral interactions
• New treatments needed
• Appropriate research investment

Avoid over-confidence, combat nihilism