The role of ZmpC in the clinical manifestation of invasive pneumococcal disease

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A mirror between North and South
14-11-2014
Streptococcus pneumoniae
Streptococcus pneumoniae

ACQUISITION

TRANSMISSION

TISSUE INVASION

DISEASE

RECOVERY?

Nasopharyngeal carriage

Meningitis

Bacteremia

Pneumonia

Radboudumc
Streptococcus pneumoniae

Disease

Nasopharyngeal carriage

Meningitis
Pneumonia with bacteremia
Pneumonia
*Streptococcus pneumoniae*

Invasive pneumococcal disease (IPD)
Streptococcus pneumoniae

Invasive pneumococcal disease (IPD)

Annually 1.6 million deaths worldwide
Streptococcus pneumoniae

Serotype – prevention
Streptococcus pneumoniae

Serotype – replacement
Streptococcus pneumoniae

Serotype – clinical image
Streptococcus pneumoniae
Streptococcus pneumoniae

Does clinical diversity among pneumococcal infections originate from the pneumococcal genome?
ZmpC
- Present in part of the pneumococcal population
- Large secreted pneumococcal protein
- Sequence highly conserved
- Activates degradation of extracellular matrix, MMP-9
- Inhibits innate host defense, syndecan-1 ectodomain shedding
- Inhibits neutrophil influx, PSGL-1
- More severe disease in animal studies

**Its role in different aspects of IPD?**
Methods – cohort study

Blood culture + \textit{S.pneumoniae}

Two Dutch hospitals ’01–’13
Serotype (n=549)

- Yellow bars: zmpC -
- Red bars: zmpC +
- Light blue bars: ~4000bp PCR product

The graph shows the distribution of isolates across different serotypes.
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>zmpC+</th>
<th>zmpC−</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>542</td>
<td>112</td>
<td>430</td>
<td>0.649</td>
</tr>
<tr>
<td>Age</td>
<td>68 (55–78)</td>
<td>70 (57–78)</td>
<td>68 (54–78)</td>
<td>0.649</td>
</tr>
<tr>
<td>Males</td>
<td>47.6 (258/542)</td>
<td>39.3 (44/112)</td>
<td>49.8 (214/430)</td>
<td>0.048</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cancer</td>
<td>21.8 (114/522)</td>
<td>18.5 (20/108)</td>
<td>22.7 (94/414)</td>
<td>0.348</td>
</tr>
<tr>
<td>Liver disease</td>
<td>6.9 (36/521)</td>
<td>4.7 (5/107)</td>
<td>7.5 (31/141)</td>
<td>0.395</td>
</tr>
<tr>
<td>Renal disease</td>
<td>6.2 (32/519)</td>
<td>6.5 (7/107)</td>
<td>6.1 (25/142)</td>
<td>0.823</td>
</tr>
<tr>
<td>COPD</td>
<td>21.0 (114/542)</td>
<td>26.8 (30/112)</td>
<td>19.5 (84/430)</td>
<td>0.094</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17.5 (95/542)</td>
<td>12.5 (14/112)</td>
<td>18.8 (81/430)</td>
<td>0.116</td>
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<tr>
<td>Charlson Comorbidity Score</td>
<td>4.4 ± 2.7</td>
<td>4.3 ± 2.4</td>
<td>4.4 ± 2.7</td>
<td>0.079</td>
</tr>
<tr>
<td>Immunocompromising therapy</td>
<td>7.4 (40/538)</td>
<td>8.2 (9/110)</td>
<td>7.2 (31/428)</td>
<td>0.688</td>
</tr>
<tr>
<td>Smoking</td>
<td>62.4 (204/327)</td>
<td>73.2 (52/71)</td>
<td>59.4 (152/256)</td>
<td>0.033</td>
</tr>
<tr>
<td>Treated at hospital A</td>
<td>83.4 (441/529)</td>
<td>88.8 (95/107)</td>
<td>82.0 (346/422)</td>
<td>0.092</td>
</tr>
</tbody>
</table>
Clinical syndrome

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>All</th>
<th>zmpC+</th>
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<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>79.0 (387/490)</td>
<td>85.0 (85/100)</td>
<td>77.4 (302/390)</td>
<td>0.098</td>
</tr>
<tr>
<td>Pleural empyema</td>
<td>7.5  (29/387)</td>
<td>5.9 (5/85)</td>
<td>7.7 (24/302)</td>
<td>0.645</td>
</tr>
<tr>
<td>Meningitis</td>
<td>9.2  (45/490)</td>
<td>8.0 (8/100)</td>
<td>9.5 (37/390)</td>
<td>0.846</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.0  (5/490)</td>
<td>1.0 (1/100)</td>
<td>1.0 (4/390)</td>
<td>1.000</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1.0  (5/490)</td>
<td>2.0 (2/100)</td>
<td>0.8 (3/390)</td>
<td>0.271</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1.0  (5/490)</td>
<td>1.0 (1/100)</td>
<td>1.0 (4/390)</td>
<td>1.000</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0.6  (3/490)</td>
<td>0.0 (0/100)</td>
<td>0.8 (3/390)</td>
<td>1.000</td>
</tr>
<tr>
<td>Unknown focus of infection</td>
<td>8.2  (40/490)</td>
<td>4.0 (4/100)</td>
<td>9.2 (36/390)</td>
<td>0.102</td>
</tr>
<tr>
<td>Not retrieved</td>
<td>9.6  (52/542)</td>
<td>10.7 (12/112)</td>
<td>9.3 (40/430)</td>
<td>0.651</td>
</tr>
</tbody>
</table>
# Severity and course of disease

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Severity at admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start symptoms (days)</td>
<td>2 (1–4)</td>
<td>2 (1–3)</td>
<td>2 (1–4)</td>
<td>0.433</td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>45.3 (192/424)</td>
<td>48.2 (40/83)</td>
<td>44.6 (152/341)</td>
<td>0.553</td>
</tr>
<tr>
<td>Cough</td>
<td>65.0 (282/434)</td>
<td>75.3 (64/85)</td>
<td>62.5 (218/349)</td>
<td>0.026</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>61.6 (270/438)</td>
<td>76.4 (68/89)</td>
<td>57.9 (202/349)</td>
<td>0.001</td>
</tr>
<tr>
<td>Confusion</td>
<td>27.0 (93/344)</td>
<td>29.3 (17/58)</td>
<td>26.6 (76/286)</td>
<td>0.669</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.6 (37.8–39.3)</td>
<td>38.6 (37.8–39.3)</td>
<td>38.6 (37.8–39.2)</td>
<td>0.949</td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>7.9 (7.1–8.6)</td>
<td>8.2 (7.3–9.1)</td>
<td>7.9 (6.9–8.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Leukocytes (x10^9/L)</td>
<td>15.8 (10.7–21.8)</td>
<td>16.0 (12.0–22.4)</td>
<td>15.7 (10.4–21.7)</td>
<td>0.524</td>
</tr>
<tr>
<td>Proportion neutrophils (%)</td>
<td>89 (84–93)</td>
<td>91 (84–93)</td>
<td>89 (85–92)</td>
<td>0.382</td>
</tr>
<tr>
<td>pH</td>
<td>7.46 (7.41–7.49)</td>
<td>7.45 (7.42–7.48)</td>
<td>7.46 (7.41–7.49)</td>
<td>0.757</td>
</tr>
<tr>
<td>Infiltrate on chest X-ray</td>
<td>79.5 (379/477)</td>
<td>81.8 (81/99)</td>
<td>78.8 (298/378)</td>
<td>0.513</td>
</tr>
<tr>
<td>Pleural effusion on chest X-ray</td>
<td>41.4 (127/307)</td>
<td>48.4 (31/64)</td>
<td>39.5 (96/243)</td>
<td>0.197</td>
</tr>
<tr>
<td><strong>SIRS</strong></td>
<td>89.4 (389/435)</td>
<td>96.6 (84/87)</td>
<td>87.6 (305/348)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Course of hospital stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>23.5 (110/468)</td>
<td>33.3 (32/96)</td>
<td>21.0 (78/372)</td>
<td>0.011</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>9.5 (42/442)</td>
<td>15.1 (13/86)</td>
<td>8.1 (29/356)</td>
<td>0.048</td>
</tr>
<tr>
<td>Hospital stay survivors (days)</td>
<td>10 (6–16)</td>
<td>10 (6–16)</td>
<td>10 (6–16)</td>
<td>0.786</td>
</tr>
<tr>
<td>Death</td>
<td>14.5 (71/491)</td>
<td>14.4 (15/104)</td>
<td>14.5 (56/387)</td>
<td>0.990</td>
</tr>
<tr>
<td>Time to death (days)</td>
<td>5 (1–17)</td>
<td>5 (1–23)</td>
<td>5 (1–17)</td>
<td>0.669</td>
</tr>
</tbody>
</table>
Spread at the risk of...?
Conclusion

The presence of \textit{zmpC} was associated with a more severe clinical manifestation of IPD

Information on pneumococcal genetic background may be useful

- To identify vulnerable individuals
- To predict clinical presentation, severity and course of disease
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\rightarrow \text{Provide additional value to rapid diagnostics}
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The presence of \textit{zmpC} was associated with a more severe clinical manifestation of IPD.

Information on pneumococcal genetic background may be useful:
- To identify vulnerable individuals
- To predict clinical presentation, severity and course of disease

→ Provide rationale for more tailored prevention of IPD
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Information on pneumococcal genetic background may be useful

- To identify vulnerable individuals
- To predict clinical presentation, severity and course of disease

\rightarrow Provide rationale for more tailored prevention of IPD

Is it ZmpC to be targeted?
Why not....?

Start from clinically relevant phenotype
→ explore pneumococcal origin
Why not....?

Start from clinically relevant phenotype
⇒ explore pneumococcal origin

Pre vs post
Why not....?

Start from clinically relevant phenotype
→ explore pneumococcal origin

Pre vs post

Carriage vs IPD
**Why not….?**

Start from clinically relevant phenotype
→ explore pneumococcal origin

- Pre vs post
- Carriage vs IPD
- Survivors vs deaths
Why not....?

Start from clinically relevant phenotype → explore pneumococcal origin

- Pre vs post
- Carriage vs IPD
- Survivors vs deaths
- Susceptible vs resistant
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Thank you for your attention!

Questions?