The predictive value of serum biomarkers in the assessment and management of paediatric febrile neutropaenia
# Faculty Disclosure

<table>
<thead>
<tr>
<th></th>
<th>No, nothing to disclose</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Yes, please specify:</th>
</tr>
</thead>
</table>
Background

• Febrile Neutropaenia (FN) is the second most common reason for presentation to hospital

• Typical paediatric FN episode different to typical adult FN episode:
  – 33-50% upper respiratory tract infections
  – Higher rate of fever of unknown origin
  – Lower mortality (0.2 – 3%)

• Risk stratification rules are not universal in paediatrics
Aims

• Build on two preceding reviews (2012, 2013) to:

1. Evaluate the sensitivity and specificity of biomarkers at predicting adverse outcomes

2. Evaluate the predictive role of biomarkers in guiding management decisions for cessation or early de-escalation of treatment
Results

- April 2016
- Overall quality of studies good
- 7676 episodes from 4508 patients from 11 countries evaluating 30 biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>2012 review</th>
<th>2013 review</th>
<th>2017 review</th>
<th>Total studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Reactive Protein (CRP)</td>
<td>20</td>
<td>9</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Procalcitonin (PCT)</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Interleukin 6 (IL-6)</td>
<td>10</td>
<td>2</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Interleukin 8 (IL-8)</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
</tbody>
</table>
Biomarkers to predict outcome subgroup

CRP by outcome group

Cross-Hairs plot of CRP to detect adverse outcome
red cross = bacteraemia
blue cross = Clinical bacterial infection
light green cross = Serious bacterial infections
dark green cross = severe sepsis
Length of cross = 95% confidence interval of study specificity and sensitivity.
Small black circle = pooled sensitivity and specificity.
Black ellipse = 95% confidence region of pooled sensitivity and specificity

Pooled sensitivity 45% (95% CI 15-75%)
Pooled specificity 65% (95% CI 30-85%)
Biomarker predictive ability at different thresholds

Cross-Hairs ROC plot showing relationship of sensitivity and specificity of PCT at different cut off levels. Crosses = individual studies; centre of cross = predictive value, length of cross = CIs within the study. Small circle = pooled predictive value of marker, solid ellipse 95% confidence region, dashed ellipse 95% prediction region. ROC curve = average pooled data in population, distance of cross from ROC curve = variance from average.

Pooled sensitivity 80% (95% CI 50-90%)
Pooled specificity 60% (95% CI 25-85%)

Pooled sensitivity 70% (95% CI 45-85%)
Pooled specificity 70% (95% CI 55-85%)

Pooled sensitivity 30% (95% CI 15-30%)
Pooled specificity 80% (95% CI 65-90%)
Serial Biomarkers

• 10 studies in updated review (6 in previous)

• Meta-analyses not possible

• CRP values more discriminatory after 2 days than at admission

• Serial PCT more discriminatory over time (rises and falls)

• IL-6 and IL-8; no benefit in serial testing
Conclusions

• No recommendations for single point use of biomarkers to guide de-escalation or cessation treatment

• Serial biomarkers have promising predictive ability

• Bacteraemia and severe sepsis can be reliably predicted by CRP, PCT, IL-6 and IL-8

• The ideal threshold cut-off biomarker; PCT value of 0.5ng/ml may be most useful
Acknowledgements

Dr Bob Phillips