-Procalcitonin- the best bacterial sepsis and infection biomarker we have?

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Infectiologist- intensivist

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Overview

1. What is Procalcitonin (PCT)?
2. SMART biomarkers
3. PCT the best biomarker for early detection of sepsis?
4. Can I use it to safely stop antibiotics in ICU patients?
5. How should PCT fit into daily clinical practice?
6. Is it the best bacterial sepsis biomarker?
Structure of PCT (adapted from Le Moullec et al. 1984)

- **PAM** = Peptidyl-amidating mono-oxygenase
- **N-ProCT**
- **Calcitonin**
- **Katacalcin**
- **Cleavage of endopeptidases**
Procalcitonin

- PCT precursor of calcitonin
- PCT $\rightarrow$ calcitonin is produced in C-cells of thyroid gland
- Healthy individuals low levels of PCT
- In post-thyroidectomy levels of PCT > 100 ng/mL in septic patients

Assicot M. Lancet 1993: 34:515-18
When is procalcitonin released?

- Bacterial infection → promotor PCT gene
  - stimulation by lipopolysaccharids
  - stimulation by toxins
  - cytokines IL-6, TNF-α
  - Inhibition by INF-γ (viral)

PCT is immediately released into the bloodstream

A hormone that becomes a cytokine...

**Calcitonin:**
Source of production in healthy people

**PCT:**
Source of Production in Septic Patients

Müller B. et al., JCEM 2001
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SMART biomarker

- Specific and sensitive
- Measurable
- Available & Affordable
- Responsive & Reproducable
- Timely fashion to guide
Sensitivity – Specificity

### Bacterial vs. non-infective causes

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<th>Procalcitonin markers</th>
<th>C-reactive protein markers</th>
</tr>
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<tr>
<td></td>
<td>No. of results</td>
<td>Sensitivity, % (95% CI)</td>
</tr>
<tr>
<td></td>
<td>TP/FN</td>
<td>FP/TN</td>
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<td>3/42</td>
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<td>Suprin et al. [126]</td>
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<td>Ugarte et al. [127]</td>
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<td>Viallon et al. [128]</td>
<td>19/2</td>
<td>2/38</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
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</table>

Measurable

Meisner M., J Lab Med 1999;23:263-72
Available and Affordable

• Discovered in 1980’s → 1993 sepsis biomarker (*Assicot*)
• Measured in serum or plasma

• automated assays →
  – TRACE (time resolved amplified cryptate emission)
  – ELFA (enzyme-linked fluorescent assay)
  – CLIA (chemiluminescent immunoassay)
  – ECLIA (electrochemiluminescent immunoassay)

• several automated platforms
  • *vidas*, Roche, Kryptor, Liaison, Siemens

• Relatively affordable.... Around 12 euro per assay
Responsive

Elevation correlates severity of infection

Responsive in SIRS events

- Peak PCT 32.9 +/- 11 ng/ml in burns (40p) [Carsin]
- Peak PCT 3.4 +/- 1.0 ng/ml with heatstroke (25p) [Nylen]
- Peak PCT 2.0 (0.5-6.8) ng/ml with trauma (21p) [Mimoz]
- Peak PCT 0.38-1.5 ng/ml post-surgery (117p) [Meisner]
Timely fashion to guide

• Starts to rise at 2-4 hours and peaks between 8-24 h

• Halves daily when infection is controlled

• Time to positive result
  – 1-2 days for the blood culture
  – hours for PCR
  – 25 minutes for PCT

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Is PCT the best biomarker to detect sepsis?
Belgian study: start ABX on guidance of single PCT-value at the time of suspicion of infection
  - Encourage abx: PCT > 0.5
  - Discourage abx: PCT < 0.5

No difference in duration

34% of cases PCT was high (>1 µg/L) no infection confirmed

15% of cases PCT was low (0.25 µg/L) with confirmed infection

Layios et al. Crit Care 2012; 40: 2304-09
Sensitivity 0.77

Specificity 0.79
Procalcitonin the best biomarker??

CON..?  PRO!
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PCT guidance of antibiotics
# Procalcitonin to reduce antibiotic use

<table>
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<tr>
<th>Authors</th>
<th>Study name</th>
<th>Research question</th>
<th>Setting</th>
<th>n</th>
<th>Mortality (n; control versus PCT group)</th>
<th>Overall AB exposure (control versus PCT group)</th>
<th>Relative antibiotic reduction (%)</th>
<th>Ref.</th>
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<td>ProRESP</td>
<td>Reduction of antibiotic prescription for LRTI in the ED?</td>
<td>ED, single center</td>
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<td>55.8</td>
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<td>7.0 vs 3.7†</td>
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<td>Briel et al.</td>
<td>PARTI</td>
<td>Safety and reduction of antibiotic exposure in upper and lower RTI?</td>
<td>Primary care, multicenter</td>
<td>458</td>
<td>1 vs 0</td>
<td>6.8 vs 1.5†</td>
<td>77.9</td>
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<td>Nobre et al.</td>
<td>ProSEP</td>
<td>Reduction of antibiotic exposure in sepsis in the ICU?</td>
<td>ICU, single center</td>
<td>79</td>
<td>8 vs 8</td>
<td>9.5 vs 6†</td>
<td>36.8</td>
<td>[44]</td>
</tr>
<tr>
<td>Schuetz et al.</td>
<td>ProHOSP</td>
<td>Safety and feasibility in LRTI in a multicenter setting?</td>
<td>ED and hospital, multicenter</td>
<td>1359</td>
<td>33 vs 34</td>
<td>8.7 vs 5.7†</td>
<td>34.5</td>
<td>[49]</td>
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<tr>
<td>Stolz et al.</td>
<td>ProVAP</td>
<td>Reduction of antibiotic exposure in VAP in different ICUs?</td>
<td>ICU, multicenter</td>
<td>101</td>
<td>12 vs 8</td>
<td>9.5 vs 13†</td>
<td>27</td>
<td>[62]</td>
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<tr>
<td>Kristoffersen et al.</td>
<td>1-PCT</td>
<td>Reduction of antibiotic exposure for LRTI in Denmark?</td>
<td>ED and hospital, single center</td>
<td>210</td>
<td>1 vs 2</td>
<td>6.8 vs 5.1†</td>
<td>25.0</td>
<td>[52]</td>
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<tr>
<td>Hochreiter et al.</td>
<td>ProSICU</td>
<td>Guiding antibiotic therapy with PCT in a surgical ICU?</td>
<td>Surgical ICU, single center</td>
<td>110</td>
<td>14 vs 15</td>
<td>7.9 vs 5.9†</td>
<td>25.3</td>
<td>[46]</td>
</tr>
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<td>Bouadma et al.</td>
<td>ProRATA</td>
<td>Reduction of antibiotic exposure for sepsis in different French ICUs?</td>
<td>ICU, multicenter</td>
<td>621</td>
<td>64 vs 65§</td>
<td>11.6 vs 14.3§</td>
<td>23</td>
<td>[45]</td>
</tr>
</tbody>
</table>

**Total**                                                                                                      **3691**   **166 vs 159**                     |
Stop Antibiotics on Procalcitonin guidance Study

A prospective randomized multicenter intervention trial

# Methods

<table>
<thead>
<tr>
<th>Inclusion:</th>
<th>Estimated number patients</th>
</tr>
</thead>
</table>
| 1. Admitted to the ICU | **Hypothesis:**  
2. > 18 years | average: 8 days of antibiotics  
3. Antibiotics for (suspected) infection | PCT-guided: 6 days  
| | Reduction: 15% |

<table>
<thead>
<tr>
<th>Exclusion:</th>
<th>Antibiotic reduction:</th>
</tr>
</thead>
</table>
| 1. > 24 hr antibiotics prior to inclusion | **α** 0.05  
2. < 24 hr stay on ICU | **β** 0.1 (power 90%)  
3. Antibiotics as prophylaxis or SDD | 526 patients per arm (=1052)  
4. Immunosuppressed patients |  
1. Transplantation |  
2. HIV+ CD4count < 200k/ml |  
5. Longterm antibiotics neccessary |  
6. Viral infection, Mycobacterial infection |  
| | Non-inferiority +8%  
| | Mortality ~28% (control) vs 30% (PCT)  
| | **β** 0.1 |  
| | 663 patients per group (=1326) |

SAPS-flow

Intention-to-treat
Methods

Stopping advice

“relative”

 Days since randomisation

PCT (µg/L)

>80% decrease

“absolute”

 Days since randomisation

<0.5 µg/L

Outcome

1. No differences in “baseline characteristics”

2. Less DOT’s en DDD’s in PCT-guidance group, lower mortality

<table>
<thead>
<tr>
<th></th>
<th>Procalcitonin-guided group (n=761)</th>
<th>Standard-of-care group (n=785)</th>
<th>Between-group absolute difference in means (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic consumption (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily defined doses in first 28 days</td>
<td>7.5 (4.0 to 12.8)</td>
<td>9.3 (5.0 to 16.5)</td>
<td>2.69 (1.26 to 4.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>5.0 (3.0 to 9.0)</td>
<td>7.0 (4.0 to 11.0)</td>
<td>2.22 (0.65 to 1.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antibiotic-free days in first 28 days</td>
<td>7.0 (0.0 to 14.5)</td>
<td>5.0 (0 to 13.0)</td>
<td>1.31 (0.52 to 2.09)</td>
<td>0.0015</td>
</tr>
<tr>
<td><strong>Mortality (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>149 (19.5%)</td>
<td>196 (25.0%)</td>
<td>5.4% (1.2 to 9.5)</td>
<td>0.0122</td>
</tr>
<tr>
<td>1-year mortality</td>
<td>265 (34.8%)</td>
<td>321 (40.9%)</td>
<td>6.1% (1.2 to 10.9)</td>
<td>0.0158</td>
</tr>
</tbody>
</table>
Outcome

Hazard ratio standard-of-care group
1.26, 95% CI 1.07–1.49 (p=0.0060)

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>50</th>
<th>100</th>
<th>150</th>
<th>200</th>
<th>250</th>
<th>300</th>
<th>350</th>
<th>400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procalcitonin-guided</td>
<td>761</td>
<td>554</td>
<td>525</td>
<td>503</td>
<td>496</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard-of-care group</td>
<td>785</td>
<td>512</td>
<td>490</td>
<td>473</td>
<td>464</td>
<td></td>
<td></td>
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</tbody>
</table>

### Outcome

<table>
<thead>
<tr>
<th>Costs</th>
<th>PCT</th>
<th>Control</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cumulative costs of antibiotics</td>
<td>€150,082</td>
<td>€181,263</td>
<td>NA</td>
<td>0.0006</td>
</tr>
<tr>
<td>Median cumulative costs antibiotics per patient</td>
<td>€107 (51 to 229)</td>
<td>€129 (66 to 273)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On the intensive care unit</td>
<td>8.5 (5.0 to 17.0)</td>
<td>9.0 (4.0 to 17.0)</td>
<td>-0.21 (-0.92 to 1.60)</td>
<td>0.56</td>
</tr>
<tr>
<td>In hospital</td>
<td>22.0 (13.0 to 39.3)</td>
<td>22.0 (12.0 to 40.0)</td>
<td>0.39 (-2.69 to 3.46)</td>
<td>0.77</td>
</tr>
<tr>
<td>Reinfection</td>
<td>38 (5.0)</td>
<td>23 (2.9)</td>
<td>-2.1% (-4.1 to -0.1)</td>
<td>0.0492</td>
</tr>
<tr>
<td>Repeated course of antibiotics</td>
<td>175 (23.0)</td>
<td>173 (22.0)</td>
<td>-1.0% (-5.1 to 3.2)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Outcome

Discussion – mortality

• timely recognition of an alternative diagnosis?
• adjustment of antibiotics?
• a lower toxicity of antibiotics?

Affordable

- Reduction €34 per patient (antibiotics)
- Mean of 7 PCT measurements/patients
- Outweighs the costs if PCT = €4,-

Considerable fraction of patients did not complete the protocol (29% vs 41%)

Conclusion

• SAPS-study showed a reduction in antibiotic treatment duration and consumption with the addition of a PCT-guided algorithm to aid clinical judgment

• This was achieved in already low background consumption of antibiotics without an increase in mortality
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6. Summary
How should PCT fit into daily ICU practice?

• It is a useful tool but should fit into the arsenal of rational antimicrobial stewardship.
  
  – *Biomarkers are not intended to replace your thinking, but to supplement your thinking*

• If it doesn’t have the opportunity to change your therapy, don’t order it

• Rational PCT use can save antibiotic use and money, and potentially impact on morbidity, (maybe even) mortality and antimicrobial resistance.
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Summary Slide

• Can I use PCT to start abx in the ICU?
  NO, but NO single biomarker can

• Does it reflect adequacy of abx?
  YES

• Can I use it to safely stop antibiotics in ICU patients?
  YES (well, as supplement to rational thinking)

• Is it the best biomarker for bacterial sepsis we have so far?
  YES!
Thank you for your attention

SAPS Steering committee
E. de Jong
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