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

Con

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Copenhagen University Hospital
Conflicts of Interest

NONE
1) Procalcitonin for sepsis diagnosis...

Medicine is a science of uncertainty and an art of probability.

~ William Osler
Procalcitonin: Laboratory Studies – *Discriminating Bacteria from Virus*

**Fig. 3.** Time course of CALC I expression and ProCT secretion. *Ex vivo* differentiated adipocytes were treated with 20 U/ml IL-1β alone or together with 100 U/ml IFNγ. After 2-, 4-, 6-, 8-, 10-, 24-, 48-, or 60-h incubation periods, total RNA was extracted and analyzed for CT mRNA abundance with quantitative real-time PCR and conventional RT-PCR (A). ProCT secretion into culture supernatant was analyzed by chemiluminimetric assay (B). Results are presented as the mean ± SD of two independent experiments.

Linscheid et al. 2003, Endocrinology
Procalcitonin: Observational Studies – Bacteremia

From: Gaïni et al. Crit Care 2007
Procalcitonin – *Sepsis Diagnosis?*

Cut off? Performance?
Severe publication bias detected...

For every 40 patients decrease in study sample, Diagnostic OR increased by 1.8 !!!


Missing studies

Funnel plot. P=0.006.

Actual studies

2) Procalcitonin for antibiotic reduction
Primary care...
Prescribed antibiotics in 25% vs. 97% in favor of the PCT-guided algorithm !!!

Table 2. Summary of Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCT-Guided Therapy Group</th>
<th>Difference (95% CI) Between PCT-Guided and Standard Therapy Groups</th>
<th>Standard Therapy Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary End Points</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with RA, mean (SD)</td>
<td>8.7 (3.9)</td>
<td>0.01 (-0.7 to 0.7)</td>
<td>8.7 (3.8)</td>
</tr>
<tr>
<td>Unadjusted difference in days (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>0.1 (-0.5 to 0.8)</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in days (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intention-to-treat analysis</td>
<td>n=232</td>
<td>n=226</td>
<td></td>
</tr>
<tr>
<td>Days with RA, mean (SD)</td>
<td>8.7 (3.9)</td>
<td>8.6 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Unadjusted difference in days (93% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>0.1 (-0.6 to 0.8)</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in days (93% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>0.2 (-0.4 to 0.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary End Points</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed antibiotics, No. (%)</td>
<td>58 (25)</td>
<td>219 (97)</td>
<td></td>
</tr>
<tr>
<td>Percentage difference (95% CI)</td>
<td></td>
<td>-72 (-78 to -68)</td>
<td></td>
</tr>
<tr>
<td>Adjusted odds ratio (95% CI)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.01 (0.002 to 0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with antibiotics, mean (SD)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>6.2 (2.8)</td>
<td>7.1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in days (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>-1.0 (-1.7 to -0.4)</td>
<td></td>
</tr>
<tr>
<td>Degree of discomfort from infection score at 14 d, mean (SD)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1.9 (2.7)</td>
<td>1.1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in score (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.8 (0.4 to 1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with adverse effects within 14 d, mean (SD)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.3 (4.6)</td>
<td>3.6 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in days (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>-1.1 (-2.1 to -0.1)</td>
<td></td>
</tr>
<tr>
<td>Days of work missed within 14 d, mean (SD)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>4.9 (4.6)</td>
<td>4.8 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Adjusted difference in days (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>0.3 (-0.6 to 1.2)</td>
<td></td>
</tr>
<tr>
<td>Patients with any symptoms of ongoing or relapsing infection at 28 d, No. (%)</td>
<td>68 (30)</td>
<td>67 (30)</td>
<td></td>
</tr>
<tr>
<td>Adjusted odds ratio (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>1.0 (0.7 to 1.5)</td>
<td></td>
</tr>
</tbody>
</table>

Emergency department ...

Schuetz et al. JAMA 2009
## Intensive Care ...

<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>Antibiotic consumption (days)</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>1.22 (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>0.0016</td>
</tr>
</tbody>
</table>

**Mortality (%)**

- **De Jong et al. Lancet ID 2016**

**Figure 4**

Patients receiving antibiotics for days 1–28

**Bouadma et al. Lancet 2010**
So – it’s done-done!

??

???
A few things to consider...

- Regression towards the mean revisited:

ProRATA trial

SAPS trial

Close to 100% receiving antibiotics at baseline

ProHosp trial
**...regression towards the mean...**

<table>
<thead>
<tr>
<th><strong>ProRATA trial SOC:</strong></th>
<th><strong>SAPS trial SOC:</strong></th>
<th><strong>ProHosp trial SOC:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;For patients in the control group, before study onset all investigators received and approved a reminder including recommendations for duration of antimicrobial therapy for the most frequent infections; these were derived from international and local guidelines. However, investigators were free to decide the optimum duration of antibiotic...&quot;</td>
<td>&quot;Antibiotics in the standard-of-care group were stopped according to local or national guidelines and according to the discretion of attending physicians.&quot;</td>
<td>&quot;In the control group, antibiotic use was in accordance with recommendations from up-to-date guidelines...&quot;</td>
</tr>
</tbody>
</table>
...regression towards the mean...

**ProRATA trial**

**PCT group:**

The study protocol advised to **stop the prescribed antibiotics if procalcitonin concentration had decreased by 80% or more of its peak value** (relative stopping threshold), or when **it reached a value of 0.5 μg/L or lower** (absolute stopping threshold).

**SAPS trial**

**PCT group:**

**ProHosp trial**

**PCT group:**
So – what have we learned through these trials?

- If nearly all patients receive antibiotics, it’s easier to arrange some timing of stopping (!!!)

- If there is, in fact, an algorithm for stopping, doctors more often stop, than if there is NOT an algorithm (!!!)

- OK – hardly surprising

- We’re ”on the edge” of Popper’s falsification-criterion”

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Karl Popper

The criterion of the scientific status of a theory is its falsifiability, or refutability, or testability.

-Karl Popper
- Any evidence to support another algorithm may work?

Intensive Care – antibiotics – Strict PCT algorithm vs. Strict CRP algorithm

Active CRP algorithm!

Figure 1. Flowchart for the decision to discontinue antibiotic treatment. PCT = procalcitonin, SOFA = Sequential Organ Failure Assessment, CRP = C-reactive protein.

Intensive Care – antibiotics – Strict PCT algorithm vs. Strict CRP algorithm

- Median antibiotic duration: CRP 6 vs. PCT 7 days, NS.

Figure 3. Cox analysis showing the risk of antibiotic therapy discontinuation in the first episode of infection for the procalcitonin group (dotted line) and C-reactive protein group (continuous line) (hazard ratio, 1.206 [95% CI, 0.774–1.8]; p = 0.13).

Primary Care – CRP guidance – 4000 patients

**Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, factorial, controlled trial**

Paul Little,† ‡ Beth Stuart,† Nick Francis,§ Elaine Douglas,‡ Sarah Hasse Melbye,§ Miriam Santer,‡ Michael Moore,‡ Samuel Godske,§ Artur Nerzeczki,§ Antoni Torres,† Carl Lior,§ Jochen WL Gals,§ Mark Kelly,§ Maciek Godycki-Cwirko,† Adam WA Geraghty,§ Herman Goossens,§

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<table>
<thead>
<tr>
<th>No CRP training</th>
<th>No communication training</th>
<th>Communication training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude percentage</td>
<td>48% (876/1932)</td>
<td>45% (876/1932)</td>
</tr>
<tr>
<td>Basic risk ratio (95% CI)</td>
<td>1.00 (0.48–0.70, p &lt; 0.0001)</td>
<td>1.00 (0.76 (0.63–0.89, p &lt; 0.0001)</td>
</tr>
<tr>
<td>Adjusted risk ratio</td>
<td>0.54 (0.42–0.69, p &lt; 0.0001)</td>
<td>0.69 (0.54–0.87, p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein.

† The basic model adjusted for baseline prescribing and clustering by physician and practice.

‡ The adjusted model additionally controlled for age, smoking, sex, major cardiovascular or respiratory comorbidity, baseline symptoms, crepitation of 100 beats per min, temperature higher than 37.8°C, respiratory rate, blood pressure, physician’s rating of severity, and duration of cough.

Algorithm adherence?

SAPS:
Non-adherence 24 hours: 56% !!!
- more than half of patients in PCT group did not get PCT-guided therapy

48 hours: 47% !!!

ProRATA:
Non-adherence 53% !!! - more than half of patients in PCT group did not get PCT-guided therapy
Algorithm adherence

So:

The method may work in some way

- But we do not know which patients it can be applied to?
- How can it be implemented?
3) Procalcitonin for improved survival
Mortality...

- SAPS – de-escalation of antibiotics

- ProRATA – de-escalation of antibiotics

- PASS – escalation of antibiotics when PCT did not decrease
Mortality...SAPS, ProRATA, PASS – with long term follow-up

Mortality - PCT-guided antibiotics in the intensive care unit
Two questions...

• Why is the direction of the mortality change different between SAPS and ProRATA? (~same algorithm, ~same adherence)

• If we believe the mortality reduction in SAPS, and we believe the explanation (side effects from antibiotics, C. diff, resistant organisms), then why is mortality unchanged in PASS, where antibiotics given were nearly doubled?
Conclusion – CON

• Algorithm adherence is a separate and HUGE problem in PCT-guided trials in the ICU
• This makes implementation meaningless – who and how and when should the algorithms be used???
• Procalcitonin is NOT better than C-reactive protein for sepsis diagnosis
• Procalcitonin can be used to reduce antibiotic overuse in primary care (a lot), in the emergency department (some), in the ICU (a little), but:
  • So can CRP (and probably other ACTIVE algorithms)
  • Procalcitonin cannot, with any of the tested algorithms, cause a reduced mortality in the ICU
In wine there is wisdom, in beer there is Freedom, in water there is bacteria.

Benjamin Franklin

Questions ?
REBUTTAL:

Figure 4.1. Prescribed antimicrobial agents for humans, and for all animal species, including the number of pigs produced, Denmark

Humans: ~50 tonnes
Animals: ~110 tonnes
Total: ~160 tonnes

Tonnes of antibiotics used in Denmark – distribution between animals and humans. DanMAP 2015.

REBUTTAL:

Distribution between primary care and hospitals. DanMAP 2015.
REBUTTAL:
- Total: 160 tonnes (Animals and Humans)
- Primary Care: 45 tonnes
- Hospital: 5 tonnes
- Intensive Care: ½ ton

If we can reduce antibiotics in the ICU by 20% - in Denmark ~ 100 kg, this corresponds to 0.06% - or 1/1600 part of the problem

Procalcitonin-guided algorithms in the intensive care unit can – maybe – reduce the purple part by 20% - if we can reproduce the algorithms.