Use of surrogate inflammatory markers in the diagnosis & monitoring of patients with severe sepsis

Dr Duncan Wyncoill
Guy’s & St Thomas’ NHS Trust, London

Conflicts of Interest
In the last 3 years I have acted as consultant, or received honoraria/research grants from:
Astellas, Biovo, Covidien, Iskus Health, J&J, Pfizer, Sage & Vygon
Current status

Yes, we do prescribe individually targeted, exclusively formulated medicines - but not for severe sepsis.
Biomarkers in Critical Care

Markers of Inflammation
- C-reactive Protein
- Procalcitonin

Markers of Homeostasis
- Renal: creatinine, urea, electrolytes
- Endocrine: TSH, T3, T4, Cortisol
- Haematology: CD4
- Liver: Albumin

Markers of Cellular Integrity
- Heart: CK-MB, troponin, LDH, BNP
- Liver: AST, ALT, γGT
- Muscle: Myoglobin
- Blood: D-dimer, C3, C4 etc

Markers of Infection
- [TNF, IL-6]
- [Procalcitonin]
- [Protein C]

‘Not much real change in the last decade...’
Molecular medicines & targeted care

Molecular medicine
- Right disease
- Right subtype
- Right drug
- Right patient
- Right dose
- Right duration

Proactive medicine: Disease prediction & prevention
- Less empirical,
  Removal of non-responders
- Risk mitigation
  - Lifestyle
  - Treatment
- Reduce toxicity,
  Improved outcomes
  & Resource utilisation

Diagnostic Proteomics
Discovery Proteomics
Genome-disease correlation

Molecular medicines & targeted care
Definitions of an ‘ideal biomarker’

- Specific
- Sensitive
- Predictive
- Robust
- Bridges preclinical trials
- Non-invasive/accessible/rapid & low cost
‘Types’ of Biomarkers

- Indicator of normal biologic process, pathology, or response to therapeutic intervention

  - Type 0: disease markers - correlate longitudinally with clinical indices

  - Type 1: drug effect markers & correlate with mechanism of action

  - Type 2: used as surrogate end-point; drug efficacy markers & correlate with clinical benefit
What do I want a biomarker to help with?

- **Prognosis & risk?**
  - Low priority

- **Diagnosis in shock (i.e. is it septic shock?)**
  - Possibly

- **Infection in a colonised/inflammatory pt?**
  - Would definitely help in critically ill patients...

- **Tailoring therapy**
  - Monitoring response: could be useful
  - Antibiotic course length: could be very useful
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Biomarkers - a review

- “sepsis” & “biomarker”
- >3,500 references & >180 biomarkers
- Cytokines, chemokines, cell markers, cell receptors, coagulation biomarkers, vascular damage surrogates, vasodilatation, biomarkers of organ dysfunction, acute phase proteins, etc, etc...
- Mainly used for prognosis; very few for diagnosis

Pierrakos C & Vincent JL. Crit Care 2010; 14: R151
Biomarkers - which determine severity of sepsis?

- Single values
- vs. Pneumonia Severity Index
- Overlap +++

**FIGURE 4.** Prognostic assessment in community-acquired pneumonia. Data are compiled from [61, 64, 101]. CRP: C-reactive protein; ADM: adrenomedullin; ANP: atrial natriuretic peptide; PCT: procalcitonin; PSI: pneumonia severity index. (b–d) p=ns; (e–h) p<0.001.

- CRP
- WCC
- VAS
- T°C
- Copeptin
- Pro-ADM
- Pro-ANP
- PCT

Christ-Crain M & Muller B. *Eur Respir J* 2007; 30: 556-73
Observational study of PCT in ICU patients with pneumonia

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Surviving Sepsis

In patients with SEVERE SEPSIS using the ‘Sepsis Resuscitation Bundle’ saves lives

- Measure the **LACTATE** level (ABG)
- Take **CULTURES** before antibiotic administration
  - Aseptic BC technique
- **FLUID CHALLENGE** if hypotensive or lactate > 2mmol/L
- Administer **ANTIBIOTICS** within 1 hour

Always follow the Trust antibiotic guideline & Infection team advice
Prescribe 1st dose as once only & inform nurse for urgent admin
Document the antibiotic indication & the review/stop date
Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle

Russell R. Miller III\textsuperscript{1,2}, Li Dong\textsuperscript{3}, Nancy C. Nelson\textsuperscript{3}, Samuel M. Brown\textsuperscript{1,2}, Kathryn G. Kuttler\textsuperscript{3,4}, Daniel R. Probst\textsuperscript{3}, Todd L. Allen\textsuperscript{3}, and Terry P. Clemmer\textsuperscript{1,2}; for the Intermountain Healthcare Intensive Medicine Clinical Program

![Graph showing mortality and total bundle compliance over years.](image-url)
Most patients with severe sepsis score ≥2 SIRS:
- Tachycardia
- Fever or hypothermia
- Tachypnoea
- Abnormal WBC or ↑CRP

Is there a good explanation other than infection?

Assess for organ dysfunction:
- Hypotension
- Lactate > 2mmol/l
- Oliguria < 0.5ml/kg/hr
- Acute confusion
- CXR infiltrates + hypoxia
- Low platelets/abn clotting

Can’t exclude infection

Yes, now what?

How do I tell?

My patient is unwell
Could they have severe sepsis?
Procalcitonin as a diagnostic marker for sepsis: a systematic review & meta-analysis

‘PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients...

BUT

...it cannot be recommended as a single definitive test’
Biomarker combinations to diagnose infection: a prospective study

- 151 Adults with 2 SIRS, admitted to medical emergency dept
  - 96 bacterial
  - 16 viral
  - 5 parasitic
- Linear model

Kofoed K et al. Crit Care 2007; 11: R38
Prospective, multicenter derivation of a biomarker panel to assess risk of OD, shock & death in severe sepsis patients

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Case example

- 78 year old lady admitted to ICU with infected leg ulcers, AKI & GI bleed.

- Transfused, fluids vasopressors & antibiotics

10 days into ICU admission

- New fever, moderate PS ventilation (40% oxygen), moderate yellow secretions, pulse 109/min SR, BP 134/48, WCC 20, CRP 68

- CXR: bilateral infiltrates
Case example

More tests? or more antibiotics now? or wait?
Case example

More tests? or more antibiotics now? or wait?

- What if her CRP was 90 the day previously?
Case example

More tests? or more antibiotics now? or wait?

- What if her CRP was 90 the day previously?
- What if her CRP was 40 the day previously?

(i.e. dynamic changes...)
Case example

More tests? or more antibiotics now? or wait?

- What if her CRP was 90 the day previously?
- What if her CRP was 40 the day previously?
  (i.e. dynamic changes...)
- Would measuring her PCT help?
Daily monitoring of biomarkers of sepsis in complicated ICU patients: can it support treatment decisions?

Iapichino G et al. *Minerva Anesthesiol* 2010; 76: 814-23
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CRP as a marker of VAP resolution

Fast response

Slow response

No response

Biphasic response

CRP as a marker of VAP resolution

<table>
<thead>
<tr>
<th></th>
<th>Fast response</th>
<th>Slow response</th>
<th>No response</th>
<th>Biphasic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>10</td>
<td>20</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>
### PCT kinetics

<table>
<thead>
<tr>
<th>Procalcitonin changes at various time points in patients with bacterial sepsis according to the outcome</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT at D1 ((n = 180; 129 S, 51 NS)^a)</td>
<td>21.7 (52.0)</td>
<td>43.0 (107.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>PCT at D2 ((n = 163; 117 S, 46 NS)^a)</td>
<td>25.7 (41.5)</td>
<td>43.9 (76.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>ΔPCT D1–D2</td>
<td>+1.8 (35.9)</td>
<td>+4.8 (44.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>PCT at D3 ((n = 164; 117 S, 47 NS)^a)</td>
<td>21.3 (41.0)</td>
<td>40.8 (85.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>ΔPCT D2–D3</td>
<td>-4.5 (24.0)</td>
<td>+5.4 (52.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PCT at D4 ((n = 121; 80 S, 41 NS)^a)</td>
<td>14.0 (29.1)</td>
<td>34.9 (66.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔPCT D1–D4</td>
<td>-3.2 (38.8)</td>
<td>-14.1 (97.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>ΔPCT D3–D4</td>
<td>-5.9 (14.8)</td>
<td>-13.1 (28.2)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

S, survivors; NS, nonsurvivors; PCT, procalcitonin; D1, day sepsis is diagnosed; ΔPCT D1–D2, procalcitonin decrease between day 2 and day 1 after the onset of sepsis, and so forth. aMissing data are due to insufficient serum samples or death of patients within the 1-day, 2-day or 3-day period following the onset of sepsis.
What do I want a biomarker to help with?

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  - Low priority

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  - Possibly

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The PRORATA Trial

Guidelines for starting of antibiotics*

1. Concentration <0.25 μg/L
   - Antibiotics strongly discouraged

2. Concentration ≥0.25 and <0.5 μg/L
   - Antibiotics discouraged

3. Concentration ≥0.5 and <1 μg/L
   - Antibiotics encouraged

4. Concentration ≥1 μg/L
   - Antibiotics strongly encouraged

*If blood sample taken for calculation of procalcitonin concentration at early stage of episode, obtain a second procalcitonin concentration 6–12 h later.

Guidelines for continuing or stopping of antibiotics

1. Concentration <0.25 μg/L
   - Stopping of antibiotics strongly encouraged

2. Decrease by ≥80% from peak concentration, or concentration ≥0.25 and <0.5 μg/L
   - Stopping of antibiotics encouraged

3. Decrease by <80% from peak concentration, and concentration ≥0.5 μg/L
   - Continuing of antibiotics encouraged

4. Increase of concentration compared with peak concentration and concentration ≥0.5 μg/L
   - Changing of antibiotics strongly encouraged

Bouadma L et al. Lancet 2010; 375: 463-74
The PRORATA Trial

1315 patients with suspected infection assessed for eligibility

685 not enrolled
- 158 expected stay in ICU <3 days
- 138 SAPS II >65
- 104 received antibiotics for >24 h before assessment
- 99 long-term antibiotic treatment needed
- 63 logistical reasons
- 46 do-not-resuscitate orders
- 31 neutropenic
- 15 no medical insurance
- 12 previously enrolled in other studies
- 10 refused consent
- 4 younger than 18 years
- 5 other reasons

630 enrolled and randomly assigned to a treatment group

311 assigned to procalcitonin group
- 4 excluded
  4 withdrew consent

307 included in the analysis (1 lost to follow-up on day 15)

319 assigned to control group
- 5 excluded
  4 withdrew consent
  1 randomised twice

314 included in the analysis (1 lost to follow-up on day 22)
The PRORATA Trial

**Figure 3:** Kaplan-Meier estimates of the probability of survival

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Procalcitonin group (Number at risk)</th>
<th>Control group (Number at risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>307</td>
<td>314</td>
</tr>
<tr>
<td>10</td>
<td>273</td>
<td>284</td>
</tr>
<tr>
<td>20</td>
<td>255</td>
<td>264</td>
</tr>
<tr>
<td>30</td>
<td>235</td>
<td>249</td>
</tr>
<tr>
<td>40</td>
<td>225</td>
<td>240</td>
</tr>
<tr>
<td>50</td>
<td>219</td>
<td>234</td>
</tr>
<tr>
<td>60</td>
<td>215</td>
<td>231</td>
</tr>
</tbody>
</table>

HR 0.96 (90% CI 0.84–1.09)
The PRORATA Trial

Figure 4: Patients receiving antibiotics for days 1–28

23% fewer AB’s in PCT group

Bouadma L et al. Lancet 2010; 375: 463-74
PCT Guided Antibiotics

Similar survival, but increased & more prolonged organ failure

- The biomarker & antibiotic protocol are ‘linked’
- Both have to be optimally defined

Conclusions

- Need to be much clearer about what question we want a biomarker to answer
- Biomarkers to help recognise those with severe sepsis
  - PCT might be able to help
  - Might a ‘panel’ be better?
- Biomarkers might help in early recognition of treatment failure or inadequacy