Potential conflict of interest

PS received research support from

- BioMerieux
- Roche Diagnostics
- Thermofisher / BRAHMS
- Abbott
Objectives

- Explain the regulation and kinetics of Procalcitonin and other inflammatory markers during sepsis
- Discuss strength and limitations of traditional parameters and novel markers, such as Procalcitonin in the diagnostic work-up of patients with suspicion of infection
- Detail the importance of early recognition of sepsis and early and adequate treatment (Sepsis bundles)
- Determine how Procalcitonin can be used for monitoring treatment response and antibiotic de-escalation in patients in and outside the ICU
- Describe the concept of Procalcitonin-aided antibiotic stewardship in sepsis in the ICU and respiratory tract infections in the Emergency Department and medical ward
WANTED

Sepsis

The largest KILLER
Of children in the World
Recognition

Initial Resuscitation

Diagnosis Management

Supportive Management

PCT?
Can Procalcitonin help us to improve management of sepsis patients?

1. Does PCT provide prognostic information?

2. Can PCT improve antibiotic decisions?
   - Rule out bacterial infection in low risk patients
   - Monitor patients for early stop of antibiotic therapy

3. Can PCT improve clinical outcomes?
PCT = Patient Care & initial Triage

Patient history:
• 66-years old, male patient
• current smoker,
• 5 day history of cough, yellow sputum production,
• feels feverish

• Do Antibiotics bring a benefit?

• Cultures < 10% positive
• WBC, CRP not specific
• Chest X-ray? CT scan?

This patient has not Sepsis – but still large antibiotic overuse!
PCT = Prognosis & Careful MoniToring

Patient history:
• 55 years old, female,
• never-smoker,
• non-productive cough, chills,
• BP 90/70, HR 115

• Sepsis! Still high mortality!
What are optimal durations of antibiotics?

• Individualized AB treatment vs fixed doses
• Daily reassessment for antibiotic de-escalation
Can Procalcitonin help us to improve management of sepsis patients?

1. Does PCT provide **prognostic information**?

2. Can PCT improve antibiotic decisions?
   - Rule out bacterial infection in low risk patients
   - Monitor patients for early stop of antibiotic therapy

3. Can PCT improve clinical outcomes?
Kinetics of PCT upon Infection

![Graph showing the kinetics of PCT upon infection with markers for TNFa, IL6, PCT, and CRP levels over time.]

- **Endotoxin iv**
- **Fatal Outcome**

adapted from Meisner M, J Lab Med 1999
Harbarth S, AJRCCM 2001
Becker KL, J Clin Endocrinol Metab 2004
Prognostic value of PCT in sepsis
Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOonitoring SEpsis (MOSES) Study

Philipp Schuetz, MD, MPH¹; Robert Birkhahn, MD²; Robert Sherwin, MD³; Alan E. Jones, MD⁴; Adam Singer, MD⁵; Jeffrey A. Kline, MD⁶; Michael S. Runyon, MD, MPH⁶; Wesley H. Self, MD⁷; D. Mark Courtney, MD⁸; Richard M. Nowak, MD⁹; David F. Gaieski, MD¹⁰; Stefan Ebmeyer, MD¹¹; Sascha Johannes, PhD¹¹; Jan C. Wiemer, PhD¹¹; Andrej Schwabe, PhD¹¹; Nathan I. Shapiro, MD, MPH¹²

Demonstrated in the Procalcitonin Monitoring Sepsis Study (MOSES) 858 adult patients with sepsis across 13 US sites

Can Procalcitonin help us to improve management of sepsis patients?

1. Does PCT provide prognostic information?

2. Can PCT improve antibiotic decisions?
   - Rule out bacterial infection in low risk patients
   - Monitor patients for early stop of antibiotic therapy

3. Can PCT improve clinical outcomes?
“Microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out…
In such cases, the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”

Definition of Antimicrobial Stewardship

Co-ordinated interventions designed to optimize the appropriate use of antimicrobials to

• Optimize clinical outcomes of patients with infectious diseases

and

• Minimize unintended consequences of antimicrobial use
Proof-of-Concept RCTs

Respiratory Tract Infection

Standard Group (without PCT-result)

Treatment Based on Standard Guidelines

Randomization

Follow-up After 10-14 Days

PCT Group

Antimicrobial Treatment

Clinical and PCT Control After 6-24h

PCT (ng/ml)

- <0.1 → NO!
- 0.1-0.25 → No
- 0.25-0.5 → Yes
- >0.5 → YES!
Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections (Review)


Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis


Summary

Background In February, 2017, the US Food and Drug Administration approved the blood infection marker procalcitonin for guiding antibiotic therapy in patients with acute respiratory infections. This meta-analysis of patient data from 26 randomised controlled trials was designed to assess safety of procalcitonin-guided treatment in patients with acute respiratory infections from different clinical settings.
990 records identified through database searching of Cochrane Central Register of Controlled Trials, MEDLINE, and Embase

919 records excluded based on review of titles and abstracts

71 articles assessed for eligibility

39 articles excluded
- 1 did not use procalcitonin
- 2 reviews
- 2 paediatric studies
- 2 editorials
- 26 non-randomised trials
- 6 duplicate publications

32 RCTs included in aggregate data analysis (9909 participants)

4 datasets not received
- 2 datasets with no identifiable respiratory infection patients

26 RCTs included in final patient data analysis (6708 participants with acute respiratory infections)

Figure 1: Study selection
RCT = randomised controlled trial.
Better Abx use in Sepsis patients

Figure 3: Antibiotic use
(A) Proportions of patients on antibiotics. (B) Mean duration of antibiotic use.
Procalcitonin-guided Antibiotic Treatment in Patients With Positive Blood Cultures: A Patient-level Meta-analysis of Randomized Trials

Marc A. Meier,1 Angela Branche,2 Olivia L. Neese,1 Yannick Wirz,1 Sebastian Haubitz,1 Lila Bouadma,3 Michel Wolff,3 Charles E. Luyt,4 Jean Chastre,4 Florence Tubach,5 Mirjam Christ-Crain,6 Caspar Corti,7 Jens-Ulrik S. Jensen,8,9 Rodrigo O. Deliberato,10 Kristina B. Kristoffersen,11 Pierre Damas,12 Vandack Nobre,13 Carolina F. Oliveira,14 Yahya Shehabi,15,16 Daiana Stolz,17 Michael Tamm,17 Beat Mueller,1,18 and Philipp Schuetz1,16

1Medical University Department, Kantonsspital Aarau, Switzerland; 2Department of Medicine, University of Rochester, Rochester General Hospital, New York; 3Service de Réanimation Médicale, Université Paris 7-Denis-Diderot, Assistance Publique–Hôpitaux de Paris (AP-HP), 4Service de Réanimation Médicale, Université Paris 6-Pierre-et-Marie-Curie, and 5Département d’Épidémiologie Biostatistique et Recherche Clinique, AP-HP, Hôpitaux Universitaires Paris Nord Val de Seine, France; 6Division of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel, Switzerland; 7Department of Respiratory Medicine, Copenhagen University Hospital Bispebjerg, 6Centre of Excellence for Health, Immunity and Infections, Department of Infectious Diseases and Rheumatology, Finsencentret, Rigshospitalet, University of Copenhagen, and 3Department of Internal Medicine, Respiratory Medicine Section, Copenhagen University Hospital Herlev-Gentofte Hospital, Denmark; 10Critical Care Unit, Hospital Israelita Albert Einstein, São Paulo, Brazil; 11Department of Infectious Diseases, Aarhus University Hospital, Denmark; 12Department of General Intensive Care, University Hospital of Liege, Domaine universitaire de Liege, Belgium; 13Department of Intensive Care, Hospital das Clinicas and 14Department of Internal Medicine, School of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; 15Critical Care and Peri-operative Medicine, Monash Health, and 16School of Clinical Sciences, Faculty of Medicine Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia; and 17Clinic of Pneumology and Pulmonary Cell Research, University Hospital Basel, and 18Faculty of Medicine, University of Basel, Switzerland

**Background.** Whether procalcitonin (PCT)–guided antibiotic management in patients with positive blood cultures is safe remains understudied. We performed a patient-level meta-analysis to investigate effects of PCT-guided antibiotic management in patients with bacteremia.
A

Adjusted OR for 30-day mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.82 (.57, 1.16)</td>
</tr>
<tr>
<td>Gram-positive</td>
<td>0.97 (.60, 1.57)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>0.77 (.43, 1.37)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>0.75 (.43, 1.32)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0.58 (.07, 4.56)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1.40 (.29, 6.86)</td>
</tr>
<tr>
<td>Urogenital infections</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0.67 (.12, 3.72)</td>
</tr>
<tr>
<td>Abdominal infections</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1.00 (.50, 3.00)</td>
</tr>
<tr>
<td></td>
<td>1.56 (.16, 15.46)</td>
</tr>
<tr>
<td></td>
<td>0.36 (.03, 4.54)</td>
</tr>
</tbody>
</table>

B

Adjusted difference for antibiotic therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Difference in days (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>-2.86 (-4.88, -0.84)</td>
</tr>
<tr>
<td>Gram-positive</td>
<td>-4.63 (-7.87, -1.39)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>-1.29 (-3.37, 1.80)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>-2.11 (-4.55, .33)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>-4.75 (-7.71, -1.80)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>3.44 (-3.05, 9.94)</td>
</tr>
<tr>
<td>Urogenital infections</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>-4.82 (-8.94, -0.69)</td>
</tr>
<tr>
<td>Abdominal infections</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>-4.21 (-7.98, -0.43)</td>
</tr>
<tr>
<td></td>
<td>0.19 (-9.36, 9.74)</td>
</tr>
<tr>
<td></td>
<td>11.17 (33, 22.01)</td>
</tr>
</tbody>
</table>
PCT algorithm for patients with LRTI in GP / Emergency Department

<table>
<thead>
<tr>
<th>PCT (ug/L)</th>
<th>Bacterial Infection?</th>
<th>Recommendation for antibiotics</th>
<th>Important considerations and overruling criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Very likely</td>
<td>AB YES!</td>
<td>Consider the course of PCT</td>
</tr>
<tr>
<td>1</td>
<td>likely</td>
<td>AB Yes</td>
<td>If antibiotics are initiated:</td>
</tr>
<tr>
<td>0.5</td>
<td>unlikely</td>
<td>AB No</td>
<td>- Repeat PCT on days 3, 5, 7; stop antibiotics using the same cut offs</td>
</tr>
<tr>
<td>0.25</td>
<td>very unlikely</td>
<td>AB NO!</td>
<td>- if peak PCT levels are very high, then stop when 80-90% decrease of peak</td>
</tr>
<tr>
<td>0.1</td>
<td></td>
<td></td>
<td>- If PCT remains high, consider treatment failure</td>
</tr>
<tr>
<td>0.01</td>
<td></td>
<td></td>
<td>If Antibiotics are withheld, control PCT after 6-24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Initial antibiotics can be considered in case of:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Respiratory or hemodynamic instability, severest comorbidities, ICU admission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- PCT &lt; 0.1 ug/L: CAP with PSI IV or CURB &gt;3, COPD with GOLD IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- PCT &lt; 0.25 ug/L: CAP with PSI IV &amp; V or CURB &gt;2, COPD with GOLD III &amp; IV</td>
</tr>
</tbody>
</table>

Schuetz P, CHEST, 2012
PCT = Patient Care & initial Triage

Patient history:
• 66-years old, male patient
• current smoker,
• 5 day history of cough, yellow sputum production,
• feels feverish

• Do Antibiotics bring a benefit?
• Cultures < 10% positive
• WBC, CRP not specific
• Chest X-ray? CT scan?

This patient has not Sepsis – but still large antibiotic overuse!
**Lower antibiotic initiation in low risk patients**

**B. Primary care (n=1008)**

<table>
<thead>
<tr>
<th>Day</th>
<th>Control</th>
<th>PCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>63%</td>
<td>23%</td>
</tr>
<tr>
<td>2</td>
<td>63%</td>
<td>21%</td>
</tr>
<tr>
<td>4</td>
<td>59%</td>
<td>19%</td>
</tr>
<tr>
<td>6</td>
<td>43%</td>
<td>13%</td>
</tr>
<tr>
<td>8</td>
<td>43%</td>
<td>6%</td>
</tr>
<tr>
<td>10</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>12</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>14</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall</th>
<th>Control</th>
<th>PCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.6</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**Mean antibiotic days**

![Graph showing patients on antibiotics over different days and mean antibiotic days]
PCT = Prognosis & Careful Monitoring

Patient history:
- 55 years old, female,
- never-smoker,
- non-productive cough, chills,
- BP 90/70, HR 115

- Sepsis! Still high mortality! What are optimal durations of antibiotics?

- Individualized AB treatment vs fixed doses
- Daily reassessment for antibiotic de-escalation
PCT algorithm for patients with Sepsis in the Intensive Care Unit

<table>
<thead>
<tr>
<th>PCT (μg/L)</th>
<th>Bacterial Infection?</th>
<th>Recommendation for antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Very likely</td>
<td>AB YES!</td>
</tr>
<tr>
<td>2</td>
<td>Likely</td>
<td>AB Yes</td>
</tr>
<tr>
<td>1</td>
<td>Unlikely</td>
<td>AB No</td>
</tr>
<tr>
<td>0.5</td>
<td>Very unlikely</td>
<td>AB NO!</td>
</tr>
<tr>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Important considerations:
- Consider the course of PCT
- If antibiotics are initiated:
  - Daily measurement of PCT; discontinue antibiotics when PCT decreases >80% of the peak level or an absolute PCT value <0.5 μg/L is reached.
  - If PCT remains high, consider treatment failure
- If Antibiotics are withheld, observe PCT after 6-24 hours,
  - Close clinical evaluation is recommended

Schuetz P, CHEST, 2012
Similar to high risk patients for PE … don’t waste time!

Patient Admitted to the ICU with Systemic Inflammatory Response Syndrome (SIRS)

- Clinical Evaluation
  - No Life Threatening Disease, Not Immuno-Compromised
  - Life Threatening Disease, High Suspicion of Bacterial Infection
    - Consider Initial Empiric Antibiotic Therapy

- Measurement of Procalcitonin
  - No Identification
  - Identification of Organism
    - Exclusion of Contamination

- Microbiological Workup

Reevaluation of the Clinical Course and Procalcitonin After 6 - 24 h, 48h, 72h

- No Infectious Cause of Fever
  - Stop Antibiotics

- Infection
  - PCT not decreasing
  - Patient Deteriorating
    - Consider Surgery Drainage, Removal of Foreign Body or Obstruction

Schuetz P, Curr Opin Crit Care, 07
Similar to high risk patients for PE … don’t waste time!

- Patient Admitted to the ICU with Systemic Inflammatory Response Syndrome (SIRS)
  - Clinical Evaluation
    - No Life Threatening Disease, Not Immuno-Compromised
    - Life Threatening Disease, High Suspicion of Bacterial Infection
      - Consider Initial Empiric Antibiotic Therapy
  - Measurement of Procalcitonin
    - Evaluation of Procalcitonin Cut off Range
      - <0.25: NO AB!
      - >0.25-0.5: No AB
      - >0.5-1.0: AB Yes
      - >1.0: AB YES!
    - Reevaluation of the Clinical Course and Procalcitonin After 6-24 h, 48h, 72h
  - Microbiological Workup
    - No Identification
    - Identification of Organism
      - Exclusion of Contamination
      - Consider Surgery Drainage, Removal of Foreign Body or Obstruction

Schuetz P, Curr Opin Crit Care, 07
Earlier stop in Sepsis patients

D. ICU patients (n=598)

<table>
<thead>
<tr>
<th>Day</th>
<th>Control (%)</th>
<th>PCT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>98%</td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td>94%</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>88%</td>
<td>63%</td>
</tr>
<tr>
<td>8</td>
<td>69%</td>
<td>48%</td>
</tr>
<tr>
<td>10</td>
<td>59%</td>
<td>41%</td>
</tr>
<tr>
<td>12</td>
<td>50%</td>
<td>34%</td>
</tr>
<tr>
<td>14</td>
<td>42%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Mean antibiotic days:
- Control: 13.7
- PCT: 10.5
Can Procalcitonin help us to improve management of sepsis patients?

1. Does PCT provide prognostic information?

2. Can PCT improve antibiotic decisions?
   - Rule out bacterial infection in low risk patients
   - Monitor patients for early stop of antibiotic therapy

3. Can PCT improve clinical outcomes?
The SAPS Study: Multicenter, ICU, Sepsis

15 hospitals in the Netherlands, n = 1545 patients with presumed or proven infection

Figure 2: Kaplan-Meier plot for probability of survival from random assignment to day 365, in the modified intention-to-treat population

Evelien de Jong, Lancet Inf Disease 2016
Use of PCT to guide antibiotic decisions results in a significant reduction in mortality.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=3372)</th>
<th>Procalcitonin group (n=3336)</th>
<th>Adjusted OR (95% CI)*, p value</th>
<th>P_interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>336 (10%)</td>
<td>286 (9%)</td>
<td>0.83 (0.7 to 0.99), p=0.037</td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>841 (25%)</td>
<td>768 (23%)</td>
<td>0.90 (0.80 to 1.01), p=0.068</td>
<td></td>
</tr>
<tr>
<td>Length of ICU stay, days</td>
<td>13.3 (16.0)</td>
<td>13.7 (17.2)</td>
<td>0.39 (-0.81 to 1.58), p=0.524</td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>13.7 (20.6)</td>
<td>13.4 (18.4)</td>
<td>-0.19 (-0.96 to 0.58), p=0.626</td>
<td></td>
</tr>
<tr>
<td>Antibiotic-related side-effects</td>
<td>336/1521 (22%)</td>
<td>247/1513 (16%)</td>
<td>0.68 (0.57 to 0.82), p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Setting-specific outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care</td>
<td>501</td>
<td>507</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1 (&lt;1%)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>164 (33%)</td>
<td>159 (31%)</td>
<td>0.96 (0.73 to 1.25), p=0.751</td>
<td>0.715</td>
</tr>
<tr>
<td>Days with restricted activities</td>
<td>8.9 (4.2)</td>
<td>8.9 (4.1)</td>
<td>0.07 (-0.44 to 0.59), p=0.777</td>
<td></td>
</tr>
<tr>
<td>Antibiotic-related side-effects</td>
<td>128/498 (26%)</td>
<td>102/506 (20%)</td>
<td>0.65 (0.46 to 0.91), p=0.012</td>
<td>0.596</td>
</tr>
<tr>
<td>Emergency department</td>
<td>1638</td>
<td>1615</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>62 (4%)</td>
<td>57 (4%)</td>
<td>0.91 (0.63 to 1.33), p=0.635</td>
<td>0.546</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>292 (18%)</td>
<td>259 (16%)</td>
<td>0.87 (0.72 to 1.05), p=0.141</td>
<td>0.807</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>8.2 (10.5)</td>
<td>8.1 (7.5)</td>
<td>-0.14 (-0.73 to 0.44), p=0.631</td>
<td>0.684</td>
</tr>
<tr>
<td>Antibiotic-related side-effects</td>
<td>208/1023 (20%)</td>
<td>145/1007 (14%)</td>
<td>0.66 (0.52 to 0.83), p=0.001</td>
<td>0.596</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>1233</td>
<td>1214</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>273 (22%)</td>
<td>229 (19%)</td>
<td>0.84 (0.69 to 1.02), p=0.081</td>
<td>0.619</td>
</tr>
<tr>
<td>Length of ICU stay, days</td>
<td>14.8 (16.2)</td>
<td>15.3 (17.5)</td>
<td>0.56 (0.82 to 1.93), p=0.427</td>
<td>0.849</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>26.3 (26.9)</td>
<td>25.8 (23.9)</td>
<td>-0.33 (-2.28 to 1.62), p=0.739</td>
<td>0.641</td>
</tr>
</tbody>
</table>
Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials


Abstract

Background: The clinical utility of serum procalcitonin levels in guiding antibiotic treatment decisions in patients...
<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Country</th>
<th>Setting, type of trial</th>
<th>Patients included</th>
<th>Follow-up</th>
<th>Clinical diagnosis</th>
<th>Type of procalcitonin algorithm, procalcitonin cutoffs used (µg/L)</th>
<th>Compliance with the PCT protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane (2013) [7]</td>
<td>France</td>
<td>ICU, multicenter</td>
<td>62</td>
<td>Hospital stay</td>
<td>Severe sepsis without overt source of infection and negative blood culture</td>
<td>Initiation and duration; R against AB: &lt; 0.5 (&lt; 0.25); R for AB: &gt; 0.5 (&gt; 5.0)</td>
<td>63% adherence</td>
</tr>
<tr>
<td>Bloos (2016) [8]</td>
<td>Germany</td>
<td>ICU, multicenter</td>
<td>1089</td>
<td>3 months</td>
<td>Severe sepsis or septic shock (SIRS and documented infection + criteria for severe sepsis/septic shock)</td>
<td>Discontinuation at days 4, 7, and 10; R against AB: &lt; 1.0 or &gt; 50% drop over previous value</td>
<td>49.6% adherence</td>
</tr>
<tr>
<td>Bouadma (2010) [9]</td>
<td>France</td>
<td>ICU, multicenter</td>
<td>621</td>
<td>2 months</td>
<td>Critically ill patients with assumed/proven bacterial infection</td>
<td>Initiation and duration; R against AB: &lt; 0.5 (&lt; 0.25); R for AB: &gt; 0.5 (&gt; 1.0)</td>
<td>47% adherence</td>
</tr>
<tr>
<td>De Jong (2016) [10]</td>
<td>The Netherlands</td>
<td>ICU, multicenter</td>
<td>1546</td>
<td>1 year</td>
<td>Critically ill patients with assumed infection</td>
<td>Duration; R against AB: &lt; 0.5 or &gt; 80% drop over peak value</td>
<td>44% adherence</td>
</tr>
<tr>
<td>Deliberato (2013) [11]</td>
<td>Brazil</td>
<td>ICU, single center</td>
<td>81</td>
<td>ICU discharge or 14 days postrandomization</td>
<td>Sepsis patients with microbiologically confirmed bacterial infection</td>
<td>Duration; R against AB: &lt; 0.5 or &gt; 90% drop over peak value</td>
<td>47.6% adherence</td>
</tr>
<tr>
<td>Hochreiter (2009) [14]</td>
<td>Germany</td>
<td>Surgical ICU, single center</td>
<td>110</td>
<td>Hospital stay</td>
<td>Sepsis (SIRS and documented infection)</td>
<td>Duration; R against AB: &lt; 1.0 or &gt; 65% drop over 3 days</td>
<td>not reported</td>
</tr>
<tr>
<td>Layios (2012) [15]</td>
<td>Belgium</td>
<td>ICU, single center</td>
<td>379</td>
<td>1 month</td>
<td>Critically ill patients with assumed infection</td>
<td>Initiation; R against AB: &lt; 0.5 (&lt; 0.25); R for AB: &gt; 0.5 (&gt; 1.0)</td>
<td>46.3% adherence</td>
</tr>
<tr>
<td>Nobre (2008) [17]</td>
<td>Switzerland</td>
<td>ICU, single center</td>
<td>79</td>
<td>1 month</td>
<td>Severe sepsis or septic shock</td>
<td>Duration; R against AB: &lt; 0.5 (&lt; 0.25) or &gt; 80% drop over peak value; R for AB: &gt; 0.5 (&gt; 1.0)</td>
<td>81% adherence</td>
</tr>
<tr>
<td>Oliveira (2013) [16]</td>
<td>Brazil</td>
<td>ICU, multicenter</td>
<td>94</td>
<td>28 days or hospital discharge</td>
<td>Severe sepsis or septic shock (SOFA score &gt; 10 and/or bacteremia)</td>
<td>Discontinuation; Initial &lt; 1.0: R against AB: 0.1 at day 4; Initial &gt; 1.0: R against: &gt; 90% drop over peak value</td>
<td>87.8% adherence</td>
</tr>
<tr>
<td>Schroeder (2009) [13]</td>
<td>Germany</td>
<td>Surgical ICU, single center</td>
<td>27</td>
<td>Hospital stay</td>
<td>Severe sepsis following abdominal surgery (SIRS and documented infection + criteria for severe sepsis/septic shock)</td>
<td>Duration; R against AB: &lt; 1.0 or &gt; 65% drop over 3 days</td>
<td>not reported</td>
</tr>
<tr>
<td>Shehabi (2014) [1]</td>
<td>Australia</td>
<td>ICU, multicenter</td>
<td>394</td>
<td>3 months</td>
<td>Sepsis (SIRS and documented infection)</td>
<td>Duration; R against AB: &lt; 0.25 (&lt; 0.1) or &gt; 90% drop over peak value</td>
<td>97% adherence</td>
</tr>
</tbody>
</table>

AB: antibiotic, ICU: intensive care unit, PCT: procalcitonin, R: recommendation, SIRS: systemic inflammation response system, SOFA: Sequential Organ Failure Assessment

* Cutoffs are listed as recommendation (strong recommendation)
Fig. 2 Forest plot showing 30-day mortality. Association of procalcitonin (PCT)-guided antibiotic stewardship and mortality in predefined subgroups. CI confidence interval, CNS central nervous system, SOFA Sequential Organ Failure Assessment
Blood test reduces mortality and shortens antibiotic use among adults with chest infection

Published on 16 January 2018

It may be feasible to use procalcitonin blood levels to guide antibiotic treatment for adults in hospital with a suspected chest infection. By measuring procalcitonin, an indicator of bacterial infection, clinicians could review their diagnosis earlier.

This reduced antibiotic exposure by 2.5 days with fewer adverse effects and also less mortality. About 14 extra people in every 1,000 who had their management guided by the blood test would be expected to survive the first month, compared with those receiving standard care without this test.

Antibiotics are commonly prescribed pre-emptively for a suspected respiratory infection and may be continued longer than necessary. As blood procalcitonin levels increase in response to bacterial infection, procalcitonin may have potential to guide starting or stopping antibiotics.

This NIHR-funded review adds 18 trials to the growing body of evidence indicating that procalcitonin may help refine the use of antibiotics in select patient groups.

Expert commentary

Most people would expect a procalcitonin-based algorithm to reduce antimicrobial prescribing and side-effects. However, the reduced mortality when used in respiratory tract infections is more surprising. The authors suggest:

- low procalcitonin might prompt clinicians to seek an alternative cause of their symptoms (such as heart failure or pulmonary embolism),
- lack of reduction in procalcitonin levels might identify earlier non-responders to empirical treatments, or
- the reduction in side-effects and antibiotic exposure is related to better outcomes

Reducing antimicrobial prescriptions to limit bacterial resistance is challenged by clinicians concerned about “withholding” antibiotics. This study reassures us that this strategy is safe and better.

Dr Helena Parsons, Clinical Lead for Microbiology, Sheffield Teaching Hospitals NHS Foundation Trust
Procalcitonin: A new biomarker for the cardiologist

Due to its high accuracy for the diagnosis of bacterial infections, the inflammatory biomarker procalcitonin (PCT) is increasingly being used in patients with suspected infection. In patients with infections of the respiratory tract, it allows rapid rule out of bacterial etiology and facilitates decisions pertaining to antibiotic management. A growing body of evidence also supports PCT testing in patients with cardiovascular disorders including, but not limited to, those with shortness of breath, possible heart failure, suspected endocarditis, and acute coronary syndromes. In these clinical situations, PCT may provide diagnostic information on the likelihood of an infectious cause in cardiovascular patients presenting with acute symptoms such as dyspnea. It may also have a prognostic value that correlates with clinical outcome and can potentially guide drug therapy. This narrative review summarizes current concepts and evidence from the published literature on the strengths and limitations of PCT as a biomarker, with a focus on patients with a variety of cardiovascular disorders.
Exclusion of lower respiratory tract infection by procalcitonin-monitoring improves outcomes of patients with congestive heart failure: Results from a randomized trial

Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: Results from the randomized ProHOSP trial

Philipp Schuetz a, Alexander Kutz a,*, Eva Grohund a, Sebastian Haubitz a, Desirée Demann a, Alaadin Vogeli a, Fabienne Hitz a, Mirjam Christ-Crain b, Robert Thomann b, Claudine Falconnier b, Claus Hoess a, Christoph Henzen a, Robert J. Marlowe c, Werner Zimmerli c, Beat Mueller c, for the ProHOSP Study Group

a University Department of Medicine, Kantonsspital Aarau, Switzerland
b Department of Internal Medicine, Division of Infectiology, Diabetes and Clinical Nutrition, University-Hospital Basel, Switzerland
c Basel University Medical Clinic Lindau, Switzerland
d Department of Internal Medicine, Kantonsspital Münsterlingen, Switzerland
e Department of Internal Medicine, Kantonsspital Lucerne, Switzerland
f Spencer-Dasgupta Corporation, Jersey City, NJ, USA

Time to the first adverse outcome ↑↑↑↑

Adverse Outcome ↓↓↓↓
Why is PCT not used more widely?
PCT has pitfalls …

- **Cut-off range depends on clinical setting**
  - PCT does not replace the doctor („pretest-probability“!)

- **False positives & negative values occur**
  - **pos**: Surgery, cardiac shock, „cytokine storm“,…
  - **neg**: early, localised, subacute…

- „Single“ PCT measurement is of limited value
  - Course & prognosis of disease?
  - Withhold antibiotic therapy?

- **PCT cannot identify the bug**
  - Should be use in addition to microbiology!

Christ-Crain M, Muller B, Swiss Med Wkly 05; 135: 451-60
Caveats ... only use high sensitive PCT assays
Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection


ABSTRACT

BACKGROUND
The effect of procalcitonin-guided use of antibiotics on treatment for suspected lower respiratory tract infection is unclear.

METHODS
In 14 U.S. hospitals with high adherence to quality measures for the treatment of pneumonia, we provided guidance for clinicians about national clinical practice recommendations for the treatment of lower respiratory tract infections and the interpretation of procalcitonin levels. We then measured the impact of the intervention on the duration of antibiotic therapy.
Cost effectiveness in the ICU setting?

Cost: around 24 USD per measurement

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Procalcitonin-Guided Therapy Costs (Can$)</th>
<th>Standard Therapy Costs (Can$)</th>
<th>Incremental Costs (Can$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>2597.94</td>
<td>3068.56</td>
<td>-470.62</td>
</tr>
<tr>
<td>Cheap</td>
<td>605.16</td>
<td>411.52</td>
<td>193.64</td>
</tr>
<tr>
<td>Expensive</td>
<td>4590.66</td>
<td>5725.52</td>
<td>-1134.86</td>
</tr>
</tbody>
</table>

Heyland KH et al, CCM 2011
Procalcitonin: What is the Evidence?

**Observational studies**
- ++ Bacteremia
- + Endocarditis
- ? Pancreatitis
- ? Abdominal infections
- ++ Blood stream infections
- ++ Pyelonephritis
  - Urinary tract infection
- + Neutropenia
- + Arthritis
- + Postoperative fever

**Intervention studies**
- Meningitis
- Upper respiratory tract infection
- Pneumonia
- COPD exacerbation
- Acute Bronchitis
- Severe Sepsis
  - Septic Shock
- Post-operative infections
Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis

Preeti Malik, Urvish Patel, Deep Mehta, Nidhi Patel, Raveena Kelkar, Muhammad Akrmah, Janice L Gabrilove, Henry Sacks

Abstract

Objective To evaluate association between biomarkers and outcomes in COVID-19 hospitalised patients. COVID-19 pandemic has been a challenge. Biomarkers have always played an important role in clinical decision making in various infectious diseases. It is crucial to assess the role of biomarkers in evaluating severity of disease and appropriate allocation of resources.

Design and setting Systematic review and meta-analysis. English full text observational studies describing the laboratory findings and outcomes of COVID-19 hospitalised patients were identified searching PubMed, Web of Science, Scopus,

Summary box

What is already known about this subject?

- COVID-19 is rapidly spreading global pandemic with increased burden on healthcare. Few observational studies have described association between different biomarkers with severe outcomes.
- Laboratory biomarkers are less expensive, faster and easier to obtain and preferred modality to monitor and predict outcomes and prognosis of disease.
Patient with moderate illness outside ICU
(Defined by setting specific scores, e.g. qSOFA, MEDS, NEWS)

**Initial clinical assessment** (Including microbiology)

**Bacterial infection uncertain**

**Bacterial infection highly suspected**

**PCT result (μg/L)**

**Probability of bacterial infection based on PCT level?**

**Overall interpretation**

**Antibiotic management**

**Recommendations for follow-up of patients**

* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis)

**Figure 2:** PCT use in patients with moderate illness outside the ICU.
**Patient with moderate illness outside ICU**
*Defined by setting specific scores, e.g. qSOFA, MEDS, NEWS*

- **Initial clinical assessment** (Including microbiology)
  - **Bacterial infection uncertain**
    - **PCT result (μg/L)**
      - <0.25: Low probability
      - ≥0.25: High probability
  - **Bacterial infection likely**
  - **Bacterial infection possible**
  - **Bacterial infection highly likely**

- **Overall interpretation**
  - **Bacterial infection unlikely**
  - **Bacterial infection likely**
  - **Bacterial infection possible**
  - **Bacterial infection highly likely**

- **Antibiotic management**

- **Recommendations for follow-up of patients**

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**Figure 2**: PCT use in patients with moderate illness outside the ICU.
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    - High probability
  - **Overall interpretation**
    - Bacterial infection unlikely
    - Bacterial infection likely

- **Bacterial infection highly suspected**
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    - <0.25
    - ≥0.25
  - **Probability of bacterial infection based on PCT level?**
    - Low probability
    - High probability
  - **Overall interpretation**
    - Bacterial infection possible
    - Bacterial infection highly likely

**Antibiotic management**

- Use empiric Abx based on clinical judgement, consider other diagnostic tests
- Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.25 μg/L or drop by 80%
- Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.25 μg/L or drop by 80%

**Recommendations for follow-up of patients**

- Use repeated PCT test within 6–24 h to early stop Abx to if PCT still <0.25 μg/L
- Consider 2nd PCT test within 24 h to stop Abx if PCT still <0.25 μg/L
- Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.25 μg/L or drop by 80%

* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis)

**Figure 2:** PCT use in patients with moderate illness outside the ICU.
PCT-guided Antibiotic Therapy

1. Evaluate
PCT-guided Antibiotic Therapy

1. Evaluate
2. Monitor

- Peak 12-24 hours
- PCT rises 3-6 hours after bacterial infection
- Approx. 24 hour half life
- Effective treatment
- Inadequate infection control
PCT-guided Antibiotic Therapy

1. Evaluate
2. Monitor
3. Discontinue