Procalcitonin: What To Do with This Biomarker?

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Objectives

• Understand what Procalcitonin (PCT) is and its clinical role
• Recognize clinical situations where PCT may be useful and how to interpret PCT levels
• Review evidence supporting the use of PCT in decreasing antimicrobial use in lower respiratory tract infections (LRTI) and sepsis
• Recognize the drawbacks of PCT
Antimicrobial Use Isn’t Optimal

- From 30-50% of inpatient antimicrobial use is inappropriate
- Antimicrobial use and misuse is the key driver of drug resistance
- Antimicrobials can be toxic
- Antimicrobial is the key risk factor for *C. difficile* infection

[Get Smart: Know When Antibiotics Work](www.cdc.gov/gets smart)

[Combat Drug Resistance](www.who.int/drug_resistance)
Diagnosis of Bacterial Infection is Difficult

• Sepsis
  – Etiology determined 30-60%
  – Cultures often positive for colonizing organisms

• Pneumonia
  – Etiology determined in only 39-54%
  – Yield of blood cultures 5-10% at best
  – Sputum culture and gram stain
    • 40% can’t produce
    • Yield rapidly drops with antibiotic administration
# Comparison of Clinical Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Specific for Infection</th>
<th>Sensitive to Inflammation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>+</td>
<td>+++</td>
<td>Simple sensitive</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>+</td>
<td>+++</td>
<td>Simple sensitive</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Cytokines</td>
<td>+</td>
<td>+++</td>
<td>Sensitive Rapid induction</td>
<td>Highly variable Short half life (minutes) Expensive</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>++</td>
<td>++</td>
<td>Inexpensive Moderately specific</td>
<td>Moderately specific Slow induction (peak &gt;24h) No correlation with severity</td>
</tr>
<tr>
<td>Procalcitonin (PCT)</td>
<td>++++</td>
<td>+</td>
<td>Quite specific Rapid induction (peak 6-12h) Correlates with severity of illness</td>
<td>Expensive Low sensitivity for localized infection</td>
</tr>
</tbody>
</table>

Procalcitonin Gene (CALC)

**PCT**, procalcitonin; **CT**, calcitonin; **CGRP**, CT gene-related peptide; **ADM**, adrenomedulllin.
Procalcitonin Under Normal Conditions

Physiologic PCT Levels: 46.7 pg/ml (97.5 percentile); median = 12.7 pg/ml*


After P. Linscheid, Endocrinology 2003
The Presence of **Bacterial** Infection Stimulates Procalcitonin Production

- Bacterial infection and cytokines **stimulate production** of PCT in parenchymal tissues
- PCT is **rapidly released** into bloodstream
- Cytokines produced by viral infection inhibit this
Calcitonin: Sources of production in healthy people

Production is Ubiquitous

- Ubiquitous 10-100 fold increase in production
- More widespread than other common cytokines (TNF-α, IL-6)

Müller B. et al., J Clin Endocrin Metab. 2001;86:396-404
Procalcitonin Rises Rapidly

Serial procalcitonin concentrations in plasma of normal subjects injected with endotoxin (4 rig/kg BW) at time zero.

PCT is Modulated by Cytokines and Has Predictable Time Dynamics

- PCT levels rise within 3-6 hours after infectious challenge
  - Peak 6-12 hrs.
  - Half-life ~24hrs

Brunkhorst FM et al., *Intens. Care Med* 1998;24: 888-892
PCT Levels Correlate with Severity of Illness

PCT on the first day of fever among neutropenic patients who presented with infection.

**It Isn’t Affected by Immunosuppression**

Prospective Daily PCT Levels in 39 Patients with Neutropenia who Developed Fever of Unknown Source

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Chemo</td>
<td>0.11</td>
<td>ND - 0.80</td>
</tr>
<tr>
<td>Afebrile Neutropenia</td>
<td>0.20</td>
<td>ND - 0.64</td>
</tr>
<tr>
<td>Fever Day 2</td>
<td>0.45</td>
<td>ND - 129.44</td>
</tr>
</tbody>
</table>

Similar findings with steroid use and organ transplantation

It’s All About the Dynamics

Follow-up of procalcitonin (PCT) over time in patients with bacteremia and with severe sepsis and their response to administration of antimicrobials

PCT Levels Can Be Prognostic

<table>
<thead>
<tr>
<th>PCT Peak Level, ng/ml</th>
<th>30 Day Mortality Rate, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>10.1</td>
<td>--</td>
</tr>
<tr>
<td>1.0-5.0</td>
<td>26.4</td>
<td>.001</td>
</tr>
<tr>
<td>5.0-20.0</td>
<td>37.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>20.0-50.0</td>
<td>46.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>&gt;50.0</td>
<td>47.2</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Mortality Associated with:
- Peak PCT
- Increasing PCT value

Initial PCT level not predictive

Time-course of procalcitonin plasma concentrations (mean, SEM) in 36 cardiac surgery patients. 1=CABG with cardiopulmonary bypass (CPB), 2=CABG without CPB, 3 = Valvular surgery

Procalcitonin plasma concentrations in infection and rejection in liver transplant patients (n = 11, mean and SEM; *p < .05). Day 0 = day the diagnosis was made
Keep In Mind the Confounders

• Physiologic Stress
  – Newborns (<48-72 hours; after 72 interpret levels as usual)
  – Massive stress (severe trauma, surgery, cardiac shock, burns)
    • In absence of infection levels trend down
  – Prolonged, severe cardiogenic shock or organ perfusion abnormalities

• Non-bacterial cytokine activation
  – Some forms of vasculitis and acute graft vs. host disease
  – Malaria and some fungal infections
  – Chronic renal disease (mild increase in baseline)

• Dysregulated PCT production
  – Treatment with agents which stimulate cytokines (OKT3, anti-lymphocyte globulins, alemtuzumab, IL-2, granulocyte transfusion)
  – Paraneoplastic syndromes due to medullary thyroid and small cell lung cancer
Procalcitonin: advantages

• Specific for bacterial infection
• Correlates with severity of disease and mortality
• Rapidly rises declines with control of infection
  – 50% daily decrease associated with control of infection by host immune system/antimicrobials
• PCT is not impaired by neutropenia or other immunocoupresive states

Schuetz P. *BMC Medicine*. 2011;9:107
Is PCT How We Diagnose Bacterial Infection?

• Numerous studies in sepsis
• 4 meta-analyses
  – “PCT markers were particularly good for differentiating bacterial infections from viral infections.”
  – “PCT represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock, difficult diagnoses in critically ill patients.”
  – “We found the diagnostic performance of PCT test for identifying bacteremia in ED patients to be moderate.”
  – “PCT cannot reliably differentiate sepsis from other non-infectious causes of SIRS in critically ill adult patients.”

Why the Conflicting Results?

Meta-Analysis

Randomized Controlled Studies

Meta-Analysis

Observational Studies

Quality of Evidence

Variables
- Gold Standard
- PCT Cut-off
- Assay Used
- Clinical Setting
- Selection Bias
Where is the evidence?

Key: + moderate evidence; ++ good evidence; +++ strong evidence; ? Evidence still undefined

Lower respiratory tract Infection & antimicrobial therapy

• Pneumonia
  – Duration for CAP at least 5 days
  – Duration for HCAP/HAP/VAP 7-15 days
• COPD exacerbation
  – May be caused by viral and/or bacterial infection
  – Duration of antimicrobials not clear
• Acute bronchitis
  – Typically viral and antibiotics not recommended
PCT in LRTI

- Single center, randomized, single-blinded trial of PCT in LRTI
  - PCT guided antibiotic initiation vs. standard care
    - PCT <0.1 μg/L – Abx Strongly discouraged
    - PCT 0.1-0.25 μg/L – Abx discouraged
    - PCT >0.25 μg/L – Abx encouraged
    - PCT >0.5 μg/L – Abx strongly encouraged
    - Antibiotics not started repeat PCT in 6-24 hours
  - Physician over-ruling was allowed
    - Occurred in 17.7%

Antibiotic Prescriptions in LRTI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard Care (n=119)</th>
<th>PCT (n=124)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3%</td>
<td>3%</td>
<td>0.95</td>
</tr>
<tr>
<td>Days Admitted (mean)</td>
<td>11.2</td>
<td>10.7</td>
<td>0.89</td>
</tr>
<tr>
<td>Antibiotics Prescribed</td>
<td>83%</td>
<td>44%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antibiotic Use /1000 days</td>
<td>661</td>
<td>332</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ProHOSP Trial

- Multicenter, non-inferiority, randomized trial
  - Adults with LRTI presenting to ED
  - Excluded immunosuppressed, HAP, those with need for prolonged antibiotics
  - PCT levels at admission and if antibiotics started day 3, 5, 7
    - Recommendation to stop based on algorithm
  - Overruling was allowed due to hemodynamic instability, severe disease, + Legionella Ag

ProHOSP Protocol

Procalcitonin (PCT) algorithm for stewardship of antibiotic therapy in patients with LRTI

- < 0.1 µg/l
  - Bacterial etiology very unlikely
  - NO antibiotics!

- 0.1 - 0.25 µg/l
  - Bacterial etiology unlikely
  - no antibiotics

- >0.25 - 0.5 µg/l
  - Bacterial etiology likely
  - Antibiotics yes

- >0.5 µg/l
  - Bacterial etiology very likely
  - Antibiotics YES!

Control PCT after 6-24 hours

Initial antibiotics can be considered in case of:
- Respiratory or hemodynamic instability
- Life-threatening comorbidity
- Need for ICU admission
- PCT < 0.1 µg/l: CAP with PSI V or CURB65 >3, COPD with GOLD IV
- PCT < 0.25 µg/l: CAP with PSI ≥IV or CURB 65>2, COPD with GOLD ≥ III
- Localised infection (abscess, empyema), L.pneumophilia
- Compromised host defense (e.g. immuno-suppression other than corticosteroids)
- Concomitant infection in need of antibiotics

Consider the course of PCT

If antibiotics are initiated:
- Repeated measurement of PCT on days 3, 5, 7
- Stop antibiotics using the same cut offs above
- If initial PCT levels are >5-10 µg/l, then stop when 80-90% decrease of peak PCT
- If initial PCT remains high, consider treatment failure (e.g. resistant strain, empyema, ARDS)
- Outpatients: duration of antibiotics according to the last PCT result:
  - >0.25-0.5 µg/l: 3 days
  - >0.5 - 1.0 µg/l: 5 days
  - >1.0 µg/l: 7 days

Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (N=1359)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final Diagnosis, No (%)</strong></td>
<td></td>
</tr>
<tr>
<td>CAP</td>
<td>925 (68.1)</td>
</tr>
<tr>
<td>Exacerbation of COPD</td>
<td>228 (16.8)</td>
</tr>
<tr>
<td>Acute Bronchitis</td>
<td>151 (11.1)</td>
</tr>
<tr>
<td>Other Diagnosis</td>
<td>55 (4.0)</td>
</tr>
<tr>
<td><strong>Pneumonia Severity Index Class, No (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>90 (9.7)</td>
</tr>
<tr>
<td>Class 2</td>
<td>173 (18.7)</td>
</tr>
<tr>
<td>Class 3</td>
<td>189 (20.4)</td>
</tr>
<tr>
<td>Class 4</td>
<td>349 (37.7)</td>
</tr>
<tr>
<td>Class 5</td>
<td>124 (13.4)</td>
</tr>
<tr>
<td>Hospitalized, No (%)</td>
<td>1257 (92.5)</td>
</tr>
</tbody>
</table>

- Compliance was 90.8% with algorithm
- Most non-compliance was with discontinuation of antimicrobials

Antibiotic Use Outcomes

- Reduction in mean antibiotic exposure (32-65%)
- Reduction in rate of antibiotic prescriptions (8-27%)
- Most change seen in COPD and bronchitis

# ProHOSP: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (n=688)</th>
<th>PCT (n=671)</th>
<th>Statistical Analysis [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic Prescription Rate</td>
<td>603 (87.7%)</td>
<td>506 (75.4%)</td>
<td>-34.8% (-40.3% to -28.7%)</td>
</tr>
<tr>
<td>Mean Antibiotic Exposure (days)</td>
<td>8.7</td>
<td>5.7</td>
<td>-12.2% (-16.3% to -8.1%)</td>
</tr>
<tr>
<td>Antibiotic Adverse Event Rate</td>
<td>193 (28.1%)</td>
<td>133 (19.9%)</td>
<td>-8.2% (-12.7% to -3.7%)</td>
</tr>
<tr>
<td>30 day Adverse Outcomes</td>
<td>130 (18.9%)</td>
<td>103 (15.4%)</td>
<td>-3.5% (-7.6% to 0.4%)</td>
</tr>
<tr>
<td>Mortality - ITT</td>
<td>34 (5.1%)</td>
<td>33 (4.8%)</td>
<td>Absolute difference: 0.3% (-2.1 to 2.5)</td>
</tr>
<tr>
<td>Mortality - PP</td>
<td>29 (4.6%)</td>
<td>31 (4.8%)</td>
<td>Absolute difference: -0.2% (-2.6 to 2)</td>
</tr>
</tbody>
</table>

Adverse Outcome = death, ICU admission, recurrence, disease-specific complications

**OR of Combined Adverse Outcome = 0.76 (95% CI, 0.57-1.01), p=0.64**
Community-acquired Pneumonia

- Hospitalized CAP
  - N=302
  - Randomized PCT or usual care
  - Median duration therapy 5 vs. 12 days (P<0.001)
  - No difference in complications or clinical outcomes

COPD Exacerbation

• Single-center, randomized trial PCT guided Tx of patients with COPD exacerbation in ED
  – Enrolled 208 with >70% GOLD stage III-IV
  – PCT <0.1 μg/L – Abx discouraged
  – PCT 0.1-0.25 μg/L – Base abx on stability
  – PCT >0.25 μg/L – Abx encouraged

• Abx use 40% PCT vs. 72% control (p<0.0001)

• No difference clinical success, mortality, LOS, ICU stay, exacerbation rate or hospitalization rate at 6 months

PCT Guided Therapy

Change in FEV1 in Patients not Treated with Antibiotics

![Graph A](image1.png)

- Standard-therapy
- Procalcitonin-group

p=0.297

Change in FEV1 in Patients Treated with Antibiotics

![Graph B](image2.png)

- Procalcitonin-group
- Standard-therapy

p=0.017

• Prospective, randomized trial of LRTI comparing PCT management vs. control in adults
  – 8 studies – COPD, CAP, VAP, U/LRTI (2), LRTI (3)
  – Enrolled 3431 patients
  – All used similar algorithms, cutoffs, and assay
  – Analyzed mortality, ICU admission, length of stay, antibiotic prescription, and duration of use

Comparison of all-cause mortality between PCT-guided antibiotics and control group

Comparison of ICU admission between PCT-guided antibiotics and control group

Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR [95% CI]</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>I-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>0.998 (0.977 - 1.018)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>ICU admissions</td>
<td>0.785 (0.57 - 1.076)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Antibiotic prescriptions</td>
<td>0.69 (0.55 - 0.88)</td>
<td>-</td>
<td>96.9%</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>-</td>
<td>-0.35 (-.077 – 0.06)</td>
<td>95.0%</td>
</tr>
<tr>
<td>Duration of Antibiotic Use</td>
<td>-</td>
<td>-1.27 (-1.86 - -0.68)</td>
<td>98.2%</td>
</tr>
</tbody>
</table>

• Conclusions
  – PCT use is safe and unlikely to result in patient harm
  – PCT decreases antibiotic use but that effect varies significantly based on underlying patient population and disease

LRTI algorithm: **Initial PCT**

<table>
<thead>
<tr>
<th>PCT Value</th>
<th>Antibiotic Use Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1 μg/L</td>
<td>Strongly Discouraged</td>
</tr>
<tr>
<td>0.1 - 0.24 μg/L</td>
<td>Discouraged</td>
</tr>
<tr>
<td>≥ 0.25 - 0.5 μg/L</td>
<td>Encouraged</td>
</tr>
<tr>
<td>&gt;0.5 μg/L</td>
<td>Strongly Encouraged</td>
</tr>
</tbody>
</table>

- Consider alternative diagnosis
- Repeat PCT in 6-12 hours if antibiotics not begun and no clinical improvement
- If clinically unstable, immunosuppressed or high risk consider overruling (PSI Class IV-V, CURB>2, GOLD III or IV)

Repeat every 2-3 days to consider early antibiotic cessation

*See Algorithm 2*
LRTI algorithm: Follow Up PCT

**PCT Value**
- <0.1 μg/L or drop by >90%
  - Cessation Strongly Encouraged
  - Consider continuing if clinically unstable
- 0.1 - 0.24 μg/L or drop by >80%
  - Cessation Encouraged
- ≥0.25 - 0.5 μg/L
  - Cessation Discouraged
- >0.5 μg/L
  - Cessation Strongly Discouraged

**Antibiotic Use Recommendation**
- If PCT rising or not adequately decreasing consider possible treatment failure and evaluate for need for expanding antibiotic coverage or further diagnostic evaluation.
PCT In the Real World

Antibiotic Treatment in CAP Patients from ProHOSP Study and Post-Study Survey Patients

- Post-study surveillance of PCT and antibiotic use
  - Single center from ProHOSP study
  - Compared study and post-study use
  - Patients sicker and more immunocompromised (N=302)

The Sepsis Dilemma

- Early treatment decreases mortality
- Non-specific criteria
- Cultures take time
- Overuse of antibiotics leads to toxicity, super infection, and resistance
- A way to decide who to treat and for how long is needed
PCT for Sepsis Diagnosis

• Data worth evaluating
  – Can assist in the diagnosis of sepsis (or other bacterial infection)

• Decisions regarding antimicrobial therapy should NOT be based solely on PCT serum concentrations
  – PCT should be placed into the clinical context of each patient scenario considering the site of possible infection, the likelihood of bacterial infection, the severity of illness, and any other pertinent clinical data
PRORATA Trial

• Multicenter (7), randomized, open-label
  – Goal: assess safety and effectiveness of PCT guided therapy in sepsis
    • Primary endpoints – 28 and 60-day mortality, days without antibiotics at 28 days
  – Patients admitted to ICU with suspected bacterial infection not on abx or less than 24 hours (N=630)
    • Excluded: Kids, BMTx or neutropenia, infections requiring long duration of abx therapy (e.g. endocarditis), low chance survival
  – Randomized to PCT guided therapy or usual care

PRORATA algorithm

Guidelines for starting of antibiotics*

- Concentration < 0.25 μg/L
  - Antibiotics **strongly** discouraged

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

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

- 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

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

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

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

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

PRORATA: results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCT (n=307)</th>
<th>Control (n=314)</th>
<th>Absolute difference, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 day mortality</td>
<td>65 (21.2%)</td>
<td>64 (20.4%)</td>
<td>0.8% (-4.6% to 6.2%)</td>
</tr>
<tr>
<td>60 day mortality</td>
<td>92 (30%)</td>
<td>82 (26.1%)</td>
<td>3.8% (-2.1% to 9.7%)</td>
</tr>
<tr>
<td>#days without abx</td>
<td>14.3 (9.1%)</td>
<td>11.6 (8.2%)</td>
<td>2.7 (1.4 to 4.1)</td>
</tr>
<tr>
<td>DOT/1000 pt days</td>
<td>653</td>
<td>812</td>
<td>-159 (-185 to -131)</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>15.9 (16.1)</td>
<td>14.4 (14.1)</td>
<td>1.5 (-0.9 to 3.9)</td>
</tr>
</tbody>
</table>

- Adherence lower than respiratory trials
- Despite this antimicrobial use decreased with no difference in mortality
- Mortality higher in PCT group at day 60
  - Related to underlying disease and not infection

• Meta-analysis of 5 RCT (N=947)
  – Adult critically ill treated using PCT vs standard care

Antibiotic Utilization

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference days, Random, 95% CI</th>
<th>Mean Difference days, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouadma 2010</td>
<td>10.3</td>
<td>7.7</td>
<td>307</td>
<td>13.3</td>
<td>7.6</td>
<td>314</td>
<td>9.0%</td>
<td>-3.00 [-4.20, -1.80]</td>
<td></td>
</tr>
<tr>
<td>Hochreiter 2009</td>
<td>5.9</td>
<td>1.7</td>
<td>57</td>
<td>7.9</td>
<td>0.5</td>
<td>53</td>
<td>61.5%</td>
<td>-2.00 [-2.46, -1.54]</td>
<td></td>
</tr>
<tr>
<td>Nobre 2008</td>
<td>8.6</td>
<td>6</td>
<td>39</td>
<td>10.5</td>
<td>5.7</td>
<td>40</td>
<td>2.0%</td>
<td>-1.90 [-4.48, 0.68]</td>
<td></td>
</tr>
<tr>
<td>Schroeder 2009</td>
<td>6.1</td>
<td>1.1</td>
<td>14</td>
<td>8.3</td>
<td>0.7</td>
<td>13</td>
<td>27.5%</td>
<td>-2.20 [-2.89, -1.51]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>417</td>
<td>420</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>-2.14 [-2.51, -1.78]</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Hospital Mortality

**Other Endpoints (# of trials) | Relative Risk (95% CI)**
---|---
28-day Mortality (5) | 0.98 (0.75-1.29)
Recurrent/Relapsed Infection (2) | 1.26 (0.68-2.35)

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**Cost analysis**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost/Day</th>
<th>PCT Therapy Cost*</th>
<th>Standard Therapy Cost**</th>
<th>Incremental Costs***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>51.44</td>
<td>605.16</td>
<td>411.52</td>
<td>193.64</td>
</tr>
<tr>
<td>Average</td>
<td>383.57</td>
<td>2597.94</td>
<td>3068.56</td>
<td>-470.62</td>
</tr>
<tr>
<td>Expensive</td>
<td>715.69</td>
<td>4590.66</td>
<td>5725.52</td>
<td>-1134.86</td>
</tr>
</tbody>
</table>

*Note: All costs in Canadian dollars

Cheap=ceftriaxone  Average=average between cheap & expensive  PCT cost: Can$49.42/tes t
Expensive=meropenem, ciprofloxacin, linezolid  *PCT costs = 6 days abx therapy + 6 days PCT
**Standard therapy based on 8 days abx  ***Incremental=PCT cost-standard therapy cost

**Sepsis algorithm: Initial PCT**

<table>
<thead>
<tr>
<th>PCT Value</th>
<th>Antibiotic Use Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.25 μg/L</td>
<td>Strongly Discouraged</td>
</tr>
<tr>
<td>0.25 - 0.49 μg/L</td>
<td>Discouraged</td>
</tr>
<tr>
<td>≥0.5 - 1.0 μg/L</td>
<td>Encouraged</td>
</tr>
<tr>
<td>&gt;1.0 μg/L</td>
<td>Strongly Encouraged</td>
</tr>
</tbody>
</table>

- **Strongly consider antibiotic initiation in all patients with suspicion of infection**
- **See Algorithm 4**

- Consider alternative diagnosis
- Repeat PCT in 6-12 hours if antibiotics not begun
- If clinically unstable, immunosuppressed or high risk consider overruling
- Repeat daily for 3 days to consider early antibiotic discontinuation
Sepsis algorithm: Follow up PCT

**PCT Value**
- **<0.25 μg/L**
  - Cessation Strongly Encouraged
  - Consider continuation if clinically unstable
- **0.25 – 0.49 μg/L or drop by >80%**
  - Cessation Encouraged
- **≥ 0.5 μg/L and decreased by <80%**
  - Cessation Discouraged
- **≥0.5 μg/L and rising or not decreasing**
  - Cessation Strongly Discouraged

**Antibiotic Use Recommendation**
- A PCT value which is rising or not declining at least 10% per day is a poor prognostic indicator and suggests infection is not controlled
- Consider expanding antibiotic coverage or further diagnostic evaluation
Mortality Rate in Procalcitonin (PCT) and Control Groups

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCT Algorithm</th>
<th>No PCT Algorithm</th>
<th>Fixed, Peto OR (95% CI)</th>
<th>Peto Fixed OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>Weight, %</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>-------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Primary care trials</strong></td>
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<tr>
<td>Briell et al.14 2008</td>
<td>0</td>
<td>232</td>
<td>0</td>
<td>226</td>
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<tr>
<td>Burkhardt et al.21 2010</td>
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<td>275</td>
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<tr>
<td><strong>Subtotal</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Total No. of events</td>
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<td>507</td>
<td>0</td>
<td>507</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td>Test for overall effect: z = 1.01; P = .31</td>
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<tr>
<td><strong>Emergency department trials</strong></td>
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<tr>
<td>Christ-Crain et al.22 2004</td>
<td>4</td>
<td>124</td>
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<td>119</td>
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<td>Christ-Crain et al.23 2006</td>
<td>18</td>
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<td>Stolz et al.24 2007</td>
<td>5</td>
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<tr>
<td>Kristoffersen et al.25 2009</td>
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<td>Schuetz et al.15 2009</td>
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<td>Long et al.26 2009</td>
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<td>0</td>
<td>64</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
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<tr>
<td>Total No. of events</td>
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<td>67</td>
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<tr>
<td>Heterogeneity: χ² = 1.54; P = .82; I² = 0%</td>
<td>Test for overall effect: z = 0.71; P = .70</td>
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<td><strong>Intensive care unit trials</strong></td>
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<td>Svoboda et al.27 2007</td>
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<td>Nobre et al.28 2008</td>
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<td>Hochreiter et al.29 2009</td>
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<td>Schroeder et al.30 2009</td>
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<td>Bousadma et al.27 2010</td>
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<td>307</td>
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<td>314</td>
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<tr>
<td><strong>Subtotal</strong></td>
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<tr>
<td><strong>Total</strong></td>
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</tr>
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<td>Total No. of events</td>
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<td>Test for subgroup differences: χ² = 1.01; P = .60; I² = 0%</td>
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</tr>
</tbody>
</table>

Procalcitonin and Survival Study Group (PASS)

- Multicenter RCT of 1200 critically ill patients
- Randomized to:
  1. Standard of care for treatment of infection
  2. Procalcitonin group – daily procalcitonin
     1. If $\geq 1$ ng/mL or not decreasing by 10%/day, then:
        - Mandatory escalation of antimicrobial coverage AND intensified diagnostic procedures (cultures, imaging, etc)
        - Antibiotics dependant on if previously on abx (broad spectrum +/- vancomycin or fluconazole)

PASS: Results

• Outcomes: PCT vs. Standard Care
  – 28-day mortality – 31.5% vs. 32% (ARR 0.6%, 95% CI - 4.7% to 5.9%)
  – ICU length of stay – 6 vs. 5 days (p=0.004)
  – Duration of mechanical ventilation increased in PCT group 4.9% (95% CI: 3-6.7%)
  – Days of renal dysfunction increased 5% (95% CI:3-6.9%)
  – Increased use of broad spectrum antibiotics, combination therapy, cultures, and imaging in PCT group

• Conclusion – No difference mortality, but increased morbidity with this PCT management strategy

Why?

• Different cut off (1.0 ng/mL)
  – Not as sensitive
  – Too high to reliably detect candidemia

• Routine escalation of therapy and diagnostics
  – Low resistance rates in Denmark
  – Driven only by PCT not clinical indicators

• “… only diagnostic procedures and high exposure to broad-spectrum antimicrobials can be the explanation (for harm)”
Antibiotic Treatment and All-Cause Mortality Within 90d for Patients with Acute Heart Failure

- 1600 Patients presenting to ED with dyspnea
- PCT levels measured but treating clinicians blinded to results

Conclusions

• PCT is the most specific biomarker and has a number of advantages over previous markers

• It isn’t perfect
  – Interpret in the clinical context of the patient
  – Serial measurements are preferred and provide more useful information
  – Consider the dynamics of the disease
  – Be aware of conditions which may affect PCT levels

• Good clinical judgment should always be applied (Don’t treat or not treat a number)
Final Thoughts

• Use depends on the clinical scenario
  – Low-acuity infections (COPD exacerbation, chronic bronchitis)
    • Helpful with initiation
  – Higher-acuity infections (pneumonia)
    • Improves determination of when to stop therapy
  – Sepsis
    • Most helpful when a clear source is not present (or source is pulmonary)