Procalcitonin (PCT) For Guiding Antibiotic Therapy In Heart Failure

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Disclosures

Consultant Relationships
• ThermoFisher Scientific
• Roche Diagnostics
Objectives:

Diagnostic Dilemmas in the Management of Dyspneic States Due to Disease Overlap
Procalcitonin (PCT) and its role in the identification and management of serious bacterial infections
PCT guidance for more effective antibiotic stewardship
Additive role of PCT to natriuretic peptides in the differential diagnosis of dyspnea
Significant Overlap in Dyspnea Etiologies (A Clinical Reality)
Due to clinician indecision, over- or under-assuming comorbid disease leads to inappropriate treatment.
Because of Diagnostic Uncertainty Inappropriate Therapy Can Occur Due To Either:

**OVERestimating comorbid states**

- CHF
- COPD
- PNA

**UNDERestimating comorbid states**

- CHF
- COPD
- PNA

OR

“Shoot ‘em all and let God sort ‘em out..’ Uses a rusty version of Occam’s Razor

- Harried ED to Hospitalist handoff
- Gets Abx, Inhalers and Diuretics
- Multiple Consequence

- MD striving to be the purist..
- (Or simply unable to figure out ICD-10)
- Multiple Consequences
Diagnostic Challenges in the Emergency Department

Differentiation between sepsis and non-infectious causes of SIRS is complicated.

The large number of patients presenting to the ER at the same time can limit the ability to obtain comprehensive histories and physical examinations.

Scoring systems and commonly available diagnostic tools provide limited value in determining which patients will have a poor outcome.
Diagnostic Challenges in the Emergency Department

Initial vital signs can be incomplete, an accurate core temperature can be lacking

• Novel medical interventions may block our ability to recognize SIRS criteria e.g.
  ➢ WBC affected by G-CSF use
  ➢ HR affected by betablockers, pacemakers

All these limitations combine can result in the delayed diagnosis of sepsis which in turn delays treatment, increases hospital length-of-stay, increases costs and leads to increased preventable mortality
Procalcitonin (PCT)

Propeptide of the hormonal active calcitonin (116 AA; 12.3 kD)
Specifically induced by bacterial infections
Low levels in viral infections or autoimmune disorders
Procalcitonin – Precursor to Calcitonin

LOW PCT values in the blood of healthy persons: 95% have measurement of 0.1ng/ml or less**

Tissue Expression

Healthy Individuals

Systemic response to bacterial infection

Alternative Processing of PCT during Bacterial Infections

Hormonal Regulation of Calcium Homeostasis

Endocrine

Regulated

Release CT

Calcitonin (CT)

Calcitonin-Related Protein (PCT)

Golgi

Thyroidal C-cell

LPS

IL-1β

TNFα

Calcitonin-Related Protein (PCT)

Differentiated Parenchymal Cell

Constitutive

Release PCT

Alternative synthesis of PCT
Bacterial toxins (gram+/-) and cytokines stimulate production of PCT in all parenchymal tissues
PCT is immediately released into bloodstream
This process can be blocked during viral infections

Adapted from Linscheid P, et al., Endocrinology 2003;144:5578–84.
Clinical symptoms alone are often insufficient for early and accurate diagnosis. PCT levels, can be observed within 3-6 hours after an infectious challenge with a peak—up to 1000ng/mL - after 6-12 hrs. Half-life: ~24hrs. Specific to bacterial origin of infection and reflects the severity of the infection.

Procalcitonin Interpretation

Clinical Condition

- Septic Shock
- Severe Sepsis
- Systemic Infections (Sepsis)
- Local Infections
- Normal Values

PCT (ng/mL)
- 100
- 10
- 5
- 2
- 0.5
- 0.05

PCT thresholds depend on clinical situation of the patient.

Interpretation of PCT levels

PCT values must always be interpreted within the clinical context of each individual patient.

Always pay attention to conditions that may influence the PCT level.

Always think about the dynamic of the disease process (development of PCT levels).

Remember that for localized infections a sensitive assay must be used and low cut-offs must be applied.
Possible PCT False Positives and False Negatives

Elevated PCT in absence of Bacterial Etiology

- 24-48hrs s/p major trauma, surgery, and burns
- Severe organ perfusion anomalies
- Newborns under 72 hrs of age

Molecular treatment with:
- OKT3 antibodies
- Interleukins
- TNF-α

Medullary C-cell, small cell lung carcinoma or bronchial carcinoid.

Low PCT in presence of Bacterial Etiology

- Early in the course of infection
- Sub acute Endocarditis
- Localized infections

What are the unmet needs in the CHF space?

Need for rapid assessment of patients with suspected pneumonia so that antibiotics can be initiated as quickly as possible
Diagnosis of pneumonia difficult in patients with pre-existing lung disease
Detecting superimposed pneumonia on top of acute heart failure challenging
Until recently, biomarkers have not been extensively studied for their ability to identify pneumonia in the setting of AHF
Heart Failure with Comorbid Infection

Heart failure + pneumonia is present ~10-15% of time

Heart failure + any infection may occur in up to 20% of hospitalized HF patients.

Hospital mortality may be up to 20% (vs 5%) in HF patients with untreated infections
Pneumonia Is a Frequent & Complicating Factor in Heart Failure Admissions Portending Higher Mortality Risk

<table>
<thead>
<tr>
<th>Factor</th>
<th>Frequency (%)</th>
<th>In-hospital mortality OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia/ACS</td>
<td>14.7</td>
<td>1.20 (1.03–1.40)</td>
<td>0.02</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>13.5</td>
<td>0.85 (0.71–1.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>Nonadherence to diet</td>
<td>5.2</td>
<td>0.69 (0.48–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>10.7</td>
<td>0.74 (0.55–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nonadherence to medication</td>
<td>8.9</td>
<td>0.88 (0.67–1.17)</td>
<td>0.39</td>
</tr>
<tr>
<td>Pneumonia/respiratory process</td>
<td>15.3</td>
<td>1.60 (1.38–1.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>6.8</td>
<td>1.48 (1.23–1.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>12.7</td>
<td>1.15 (0.97–1.36)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

BACH Trial: Physician Indecision About Pneumonia Diagnosis is Improved When PCT Added

Maisel Eur J HF 2012
BACH Trial: Antibiotic Treatment Discordant with PCT Levels Was Associated with Death

Maisel Eur J HF 2012
BACH Trial: Combination of BNP and PCT can be used to Diagnose Dyspneic Patients

Maisel Eur J HF 2012
ProHOSP Trial 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

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>33 (4.8%)</td>
<td>34 (5.1%)</td>
<td>Absolute difference: 0.3% (-2.1 to 2.5)</td>
</tr>
<tr>
<td>Mortality - PP</td>
<td>31 (4.8%)</td>
<td>29 (4.6%)</td>
<td>Absolute difference: -0.2% (-2.6 to 2)</td>
</tr>
</tbody>
</table>

Adverse Outcome = death, ICU admission, recurrence, disease-specific complications
ITT = intention to treat; PP = per protocol

OR of Combined Adverse Outcome = 0.76 (95% CI, 0.57-1.01), p=0.64
Pro-HOSP: HF Substudy

N=223 with a history of heart failure

PCT-guided antibiotic therapy resulted in decreased antibiotic exposure

• For both low and high initial PCT levels

Improved 30-d outcomes in low PCT group randomized to PCT-guided vs standard therapy

• → Consistent with BACH findings

Adverse outcomes among pts with low initial PCT (<0.25ug/L)

Antibiotics may be harmful in HF without bacterial infection

Interpretation of PCT levels in pts with heart failure and respiratory symptoms

Serial PCT Levels
+ abx – q2 days, same cutpoints or >80% drop
No abx – repeat after 6-24h

Summary of evidence for using PCT for diagnosis and antibiotic stewardship

Sager et al. BMC Med 2017
Procalcitonin in Heart Failure

Baseline and serial levels predict long-term mortality in AHF

Decreased antibiotic exposure when used to guide therapy

IMPACT-EU: prospective study of PCT-guided care of 792 pts presenting to the ED with dyspnea, currently enrolling
Thank You!

Questions? Comments?

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