Role of PCT in sepsis

Alternative (non cytokine) pathway during sepsis: ‘Hormokine’

- **Bacterial toxins** (gran +/gram-) and cytokines stimulate production of Procalcitonin in all parenchymal cells
- This process can be attenuated or **blocked during viral infection by interferons.**
- PCT is immediately released into the bloodstream
SERIOUS AND GROWING THREAT TO U.S. AND GLOBAL PUBLIC HEALTH

- Antibiotic misuse, inappropriate initiation and prolonged use
- Safety risk to patients due to rise of antibiotic resistance
- 2 million illnesses and ~23,000 deaths per year in U.S.*

*Centers for Disease Control and Prevention (CDC)
DIAGNOSING BACTERIAL INFECTION THAT WILL RESPOND TO ANTIBIOTICS IS DIFFICULT

- Bacterial cultures can take 2-3 days to perform
- May have low sensitivity
- Faster, more accurate indicators of infection needed to make critical antibiotic decisions
50% OF ANTIBIOTICS PRESCRIBED FOR ACUTE RESPIRATORY CONDITIONS ARE UNNECESSARY

Out of 69M people who are given antibiotics for respiratory issues, annually in the U.S.

34.3 Million Get antibiotics unnecessarily

34.6 Million Who need antibiotics get them

Misuse associated with drug toxicity, increased antibiotic resistance, and collateral damage

Increased drug-resistant infections result in:
- More-serious illness or disability
- Higher death rate
- Prolonged recovery
- More-frequent or longer hospitalizations

Two common syndromes: Lower respiratory tract infection and sepsis
Procalcitonin

How can we use this cellular signal of infection in the management of both septic and non-septic patients

Goals

- Provide antibiotic therapy to pts who need it as soon as possible
- Avoid antibiotic prescription to those without infection
- Do both with a strong likelihood of being correct, at least as good as other markers such as WBC, bands, fever, CRP
PCT kinetics provide important information on prognosis of sepsis patients

- PCT levels, can be observed within 3-6 hours after an infection with a peak - up to 1000 ng/ml - after 6-12 hrs. Half-life: ~24hrs
- Specific to bacterial origin of infection and reflects the severity of the infection

Adding PCT results to clinical assessment improves the accuracy of the early clinical diagnosis of sepsis

- PCT levels accurately differentiate sepsis from noninfectious inflammation*
- PCT is the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infection

Sensitivity: 89%
Specificity: 94%
NPV: 90% PPV:94%

PCT PROPERTIES FAVORABLE FOR ANTIBIOTIC DECISION MAKING

*Nosocomial infection resulting from a single contaminated infusion at time 0

Data on file at bioMérieux Inc.
PCT LEVELS CORRELATE WITH DISEASE SEVERITY

Harbath et al. Am J Respir Crit Care Med 2001;164:396-402
Data on file at bioMérieux Inc.
PCT LEVELS HAVE A HIGH NEGATIVE PREDICTIVE VALUE IN LRTI

NPV = probability condition is absent given negative test

<table>
<thead>
<tr>
<th>Endpoint (Prevalence)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed bacterial co-infection (20%)</td>
<td>90%</td>
<td>31%</td>
<td>25%</td>
<td>92%</td>
</tr>
<tr>
<td>Need for antibiotics (24%)</td>
<td>84%</td>
<td>98%</td>
<td>93%</td>
<td>94%</td>
</tr>
</tbody>
</table>

^b Stolz et al. Swiss Med Wkly 2006;136:434-40
Data on file at bioMérieux Inc.
Typical time course of PCT: successful tx

![Graph showing PCT level over time](image)
Effect of Procalcitonin-Based Guidelines vs. Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial

Philipp Schuetz, MD; Mirjam Christ-Crain, MD; Robert Thomann, MD; Claudine Falconnier, MD; Marcel Wolbers, PhD; Isabelle Widmer, MD; Stefanie Neidert, MD; Thomas Fricker, MD; Claudine Blum, MD; Ursula Schild, RN; Katharina Regez, RN; Ronald Schoenenberger, MD; Christoph Henzen, MD; Thomas Bregenzer, MD; Claus Hoess, MD; Martin Krause, MD; Heiner C. Bucher, MD; Werner Zimmerli, MD; Beat Mueller, MD

Overview

- **Unnecessary antibiotic use**
  - Contributes to increasing bacterial resistance
  - Increases medical costs and the risks of drug-related adverse events

- **Lower respiratory tract infections (LTRI)**
  - Most frequent indication for antibiotic prescriptions in the Northwestern hemisphere
  - 75% of patients are treated with antibiotics
  - Predominantly viral origin of infection

- **Procalcitonin (PCT) algorithm**
  - Reduced antibiotic use in patients with LTRIs

Objective

Examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes.

Study Design

- Multicenter, noninferiority, randomized controlled trial

- **Patients**
  - Randomized to administration of antibiotics based on PCT algorithm
  - Cutoff ranges for initiating or stopping antibiotics (PCT group) or standard guidelines (control)
  - Serum PCT was measured locally

- **Main Outcome Measures**
  - Composite adverse outcomes of death, intensive care unit admission, disease-specific complications, or recurrent infection within 30 days
  - Antibiotic exposure and adverse effects from antibiotics

Flow Diagram of Patients in Trial

1381 Randomized

687 Randomized to Receive Antibiotics Based on PCT Algorithm
- 16 Withdrew Informed Consent
- 1 Lost to Follow-up
- 34 Died
- 636 Completed 30-d Interview
- 671 Included in Primary Analysis
  - 16 Excluded (Withdrew Informed Consent)

694 Randomized to Receive Antibiotics Based on Standard Guidelines
- 6 Withdrew Informed Consent
- 0 Lost to Follow-up
- 33 Died
- 655 Completed 30-d Interview
- 688 Included in Primary Analysis
  - 6 Excluded (Withdrew Informed Consent)

Results

- No difference: death, intensive care unit admission, disease-specific complications, or recurrent infection within 30 days
SIMILAR RATES OF MORTALITY IN LRTI PATIENT-LEVEL META-ANALYSIS

Data on file at bioMérieux.
Antibiotic Exposure in Patients Receiving Antibiotic Therapy

All Patients (n = 1359)

<table>
<thead>
<tr>
<th>Time After Study Inclusion, d</th>
<th>PCT</th>
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<tr>
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<td>603</td>
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<td>1</td>
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<td>72</td>
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<tr>
<td>&gt;13</td>
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Community-acquired Pneumonia (n = 925)

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<td>&gt;13</td>
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<td>91</td>
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</tbody>
</table>

Antibiotic Exposure in Patients Receiving Antibiotic Therapy

Exacerbation of COPD (n = 228)

Acute Bronchitis (n = 151)

No. of Patients

<table>
<thead>
<tr>
<th>Time After Study Inclusion, d</th>
<th>PCT</th>
<th>Control</th>
</tr>
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<tbody>
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<tr>
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<td>4</td>
<td>5</td>
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<td>&gt;13</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Antibiotic Exposure in Patients Receiving Antibiotic Therapy

PCT: Procalcitoin
COPD: Chronic Obstructive Pulmonary Disease

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!

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**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 CURB65 >2, COPD with GOLD > III
- Localised infection (abscess, empyema), L. pneumophila
- Compromised host defense (e.g. immuno-suppression other than corticosteroids)
- Concomitant infection in need of antibiotics

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**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

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Conclusions

An algorithm with PCT cutoff ranges was noninferior to clinical guidelines in terms of adverse outcomes death, intensive care unit admission, disease-specific complications, or recurrent infection within 30 days

- Reduced antibiotic exposure
- Reduced associated adverse effects

In countries with higher antibiotic prescription rates PCT guidance may have clinical and public health implications
A GLOBAL PUBLIC HEALTH EMERGENCY

HIGH-LEVEL MEETING ON ANTIMICROBIAL RESISTANCE
21 SEPTEMBER 2016, UN HEADQUARTERS, NEW YORK

TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
FINAL REPORT AND RECOMMENDATIONS

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015
Additional Results

- Predictive value of baseline PCT to determine + culture (blood, urine, respiratory)
  - Positive vs. Negative culture
    - 9.8ng/mL [1.7-41.3] vs. 3.3ng/mL[0.6-15.8] p<0.001
    - 61% of cultures were positive

- Predictive value of baseline PCT to determine sepsis severity
  - Septic shock vs. Sepsis
    - 13.6ng/mL [2.7-55.2] vs. 3.6[0.5-15.6], p<0.001
Additional Results

Baseline PCT was similar in survivors and non-survivors however there was a significantly faster decline overtime in the serial PCT levels in survivors.

Baseline cut off of $\leq 3$ng/mL excluded positive blood culture with a sensitivity of 90% (95% CI, 82-89) and a NPV of 96% (95% CI, 93-99).

Baseline cut off of $\leq 0.1$ng/mL excluded positive culture in the first 72h with a sensitivity of 100% and NPV of 100%.

Adapted from Shehabi Y et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or sepsis. Amer J Resp Crit Care Med 2014 Nov 15;190(10):1102-10
Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients

Philipp Schuetz¹, Paula Maurer², Vikas Punjabi³, Ami Desai³, Devendra N Amin²† and Eric Gluck³†
Figure 1. Mortality and PCT kinetic of 72 hours

$\text{Mortality\%}$

$\text{PCT decrease >75\%}$ $\text{PCT decrease 50-75\%}$ $\text{PCT decrease <50\%}$

$p < 0.01$
Case 1

- 78 y/o female found unresponsive at home by family. Noted to be in respiratory distress. Intubated in the ED for apnea. Prior h/o DM, HTN, UTI, AV block, pacemaker, and AKA. In ED WBC 14.6 with 31 bands, AG 14, BUN 53, PCT 2.7. Patient had been receiving TPN via porto-cath at home.
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![Graph showing WBC, PCT, Bands, Tmax over days](image-url)
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Porto-cath removed and Antibiotics changed.
Case 2

68 y/o male with h/o CHF, COPD, CAD previously hospitalized two months ago for exacerbation of COPD. Presents with difficulty breathing, SOB. No chest pain, but has cough with clear to yellow sputum. ABG in ED 7.11/76/91 BNP 1301 Trop < .03 WBC 18,000, 0 Bands.
Case 2

- 68 y/o male with h/o CHF, COPD, CAD previously hospitalized two months ago for exacerbation of COPD. Presents with difficulty breathing, SOB. No chest pain, but has cough with clear to yellow sputum. ABG in ED 7.11/76/91 BNP 1301 Trop < .03 WBC 18,000, 0 Bands.
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