Procalcitonin and Other Biomarkers

Update in Hospital Medicine Course (Sept 30, 2020)

Chanu Rhee, MD, MPH

Associate Hospital Epidemiologist
Infectious Diseases and Critical Care Medicine
Brigham and Women’s Hospital
Assistant Professor, Harvard Medical School

Disclosures

- Royalties
  - UpToDate (Procalcitonin chapter)

- Grant Funding (related to sepsis and COVID-19 epidemiology)
  - Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality

- Committee Membership
  - IDSA Sepsis Task Force
  - ACEP Sepsis Guidelines Panel
  - CMS Sepsis Outcome Measure Technical Advisory Group

No financial conflicts
Outline

- Procalcitonin
  - Biology and Kinetics
  - False Positives and Negatives
  - Diagnostic Accuracy
  - Guiding Antibiotic Therapy for Respiratory Infections
  - Guiding Antibiotic Therapy for Sepsis / ICU Patients
  - Prognosis
  - Considerations in Immunocompromised Patients
  - Utility in COVID-19

- C-Reactive Protein and Other Biomarkers

Rationale for Procalcitonin and Infection Biomarkers

- Up to 50% of antibiotics given in the hospital are unnecessary\(^1\)
  - Given for non-infectious syndromes, colonizers or contaminants, or longer than recommended durations\(^2\)

- Antibiotic overuse fuels antibiotic resistance, *C. difficile*, and toxicity

- Stewardship efforts impeded by imperfect diagnostic tools
  - Clinicians reluctant to withhold antibiotics if infection possible
    - *Even compelled by quality measures (e.g., SEP-1)*
  - Subsequent antibiotic de-escalation challenging since >40% of septic patients never have a pathogen identified\(^3\)

1. Fridkin, MMWR 2014
2. Hecker, Arch Intern Med 2003
3. Phua, Crit Care 2013
A Constant Tug of War

Rapid Administration of Antibiotics for Potentially Infected / Septic Patients to Improve Individual Patient Outcomes

Better Diagnostic Biomarkers of Infection Are Needed

Judicious Antibiotic Prescribing to Reduce the Global Threat of Antimicrobial Resistance

Is Procalcitonin the Holy Grail?

But it can still be useful… if used (and interpreted) properly!!!
Procalcitonin Biology

- Calcitonin precursor hormone produced by thyroid C-cells
- Normally undetectable in healthy states
- Production upregulated in neuroendocrine cells (lungs, GI tract, elsewhere) in response to inflammatory stimulus, particularly of bacterial origin
  - Triggers include endotoxin, cytokines (TNF-alpha, IL-1, IL-6)
- In contrast, production downregulated with interferon-gamma (stimulated by viral infections)
  - More specific for bacterial infection than other inflammatory markers (CRP, ESR, WBC)

Procalcitonin Kinetics

- Rises within 2-4 hours after stimulus, peaking within 24 hours
  - Most infected patients will express PCT by time of presentation
- Intensity of stimulus affects rise in PCT
  - Prognostic value
  - Chosen cut-off affects sensitivity/specificity
  - Very useful at the “extremes”; mild elevations harder to interpret
- Half-life of ~24 hours – levels decline rapidly with control of infection or resolution of inflammation (~50% decline every 1-2 days)
  - Role for helping when to stop antibiotics
- Lab turn-around time ~20 minutes (if in-house)
PCT: Faster Rise and Fall vs CRP

- **U.S. FDA Approved Indications**
  - Aid in diagnosing sepsis (2006)
  - Serial monitoring in sepsis for 28-day mortality prognosis (2016)
  - Antibiotic Stewardship Tool (2017)
    - Respiratory Infections: Guide antibiotic initiation AND discontinuation
    - Sepsis: Guide antibiotic discontinuation
## Interpreting Procalcitonin Levels

<table>
<thead>
<tr>
<th>PCT Level (ng/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.25</td>
<td>Bacterial pneumonia unlikely</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Systemic infection (sepsis) is not likely. Local bacterial infection is possible (and likely if bacterial pneumonia suspected)</td>
</tr>
</tbody>
</table>
## Interpreting Procalcitonin Levels

<table>
<thead>
<tr>
<th>PCT Level (ng/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.25</td>
<td>Bacterial pneumonia unlikely</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Systemic infection (sepsis) is not likely. Local bacterial infection is possible (and likely if bacterial pneumonia suspected)</td>
</tr>
<tr>
<td>≥0.5 and &lt;2</td>
<td>Systemic infection (sepsis) is possible, but other conditions are known to induce PCT as well</td>
</tr>
<tr>
<td>≥2 and &lt;10</td>
<td>Systemic infection (sepsis) is likely, unless other causes are known</td>
</tr>
<tr>
<td>≥10</td>
<td>Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock</td>
</tr>
</tbody>
</table>
## Interpreting Procalcitonin Levels

<table>
<thead>
<tr>
<th>PCT Level (ng/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.25</td>
<td>Bacterial pneumonia unlikely</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Systemic infection (sepsis) is not likely. Local bacterial infection is possible (and likely if bacterial pneumonia suspected)</td>
</tr>
<tr>
<td>≥0.5 and &lt;2</td>
<td>Systemic infection (sepsis) is possible, but other conditions are known to induce PCT as well</td>
</tr>
<tr>
<td>≥2 and &lt;10</td>
<td>Systemic infection (sepsis) is likely, unless other causes are known</td>
</tr>
<tr>
<td>≥10</td>
<td>Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock</td>
</tr>
</tbody>
</table>

## Procalcitonin False Positives

- **Major stressors causing systemic inflammation**
  - Burns
  - Severe trauma
  - Major surgery
  - Pancreatitis
  - Aspiration pneumonitis
  - Shock (any type)
  - Bowel ischemia
  - Intracerebral hemorrhage

- **Non-bacterial infections:**
  - Malaria
  - Certain fungal infections

- **Chronic Kidney Disease** (if not yet on HD)

- **Neonates** (first ~3 days of life)

- **Oncology-specific conditions:**
  - Medullary thyroid cancers
  - Neuroendocrine cancers
  - Agents that stimulate cytokines (e.g., antilymphocyte / anti-thymocyte globulin, WBC transfusions, alemtuzumab, anti-CD3 antibodies)
  - Acute graft-versus-host disease
**Procalcitonin False Negatives**

- **PCT drawn too early in the course of illness**
  - Most PCT algorithms recommend repeat PCT within 6-24 hours if patient requires hospitalization

- **Localized or compartmentalized infections**
  - Local cellulitis
  - Contained abscess
  - Empyema
  - Mediastinitis

- **Intracellular pneumonia pathogens** (Mycoplasma, Chlamydia)
  - But PCT usually elevated with Legionella

---

**Differences in PCT Elevation by Pneumonia Pathogen**

*Multicenter cohort of 1735 adults hospitalized with CAP*

![Graph showing differences in PCT elevation by pneumonia pathogen](image)
Accuracy for Distinguishing SIRS vs Sepsis

*Meta-analysis of 30 studies and 3,244 patients*

- AUC 0.85
- Sensitivity: 77%
- Specificity: 79%


Challenges in Measuring Procalcitonin Accuracy

- No reliable gold standard for diagnosing bacterial pneumonia or sepsis
  - Many pneumonia and sepsis patients never have a pathogen identified
  - Isolated organism not always causative pathogen
    - **Difficult to quantify “sensitivity/specificity”**

- Instead, benefit is most convincingly measured through randomized intervention studies utilizing PCT to **decrease** unnecessary antibiotic exposure without harming patients
**Lower Respiratory Tract Infections: ProHOSP**

*Multicenter RCT of 1359 adults in Switzerland presenting to ER with CAP, COPD exacerbation, or acute bronchitis*

- ↓ Mean antibiotic duration of antibiotics (5.7 vs 8.7 days)
- No difference in adverse events
- PCT algorithm overruled in ~20% of cases

![Procalcitonin (PCT) algorithm for stewardship of antibiotic therapy in patients with UTI](image.png)

Schuetz, JAMA 2009; 302: 1059-66

**U.S. Multicenter Trial: ProACT**

- Multicenter U.S. study conducted from Nov 2014-May 2017
  - Predominantly urban academic hospitals
  - All with high adherence to Joint Commission pneumonia core measure
  - All did not use PCT in routine care

- Enrolled adults in the ED with initial diagnosis of acute lower respiratory tract infection where there was uncertainty about the need for antibiotics

- Intervention: PCT guidelines according to ProHOSP

Huang, NEJM 2018; 379:236-49
ProACT: Results

Mean 4.2 days with PCT vs 4.3 days with usual care (p=0.87)

No difference in rate of serious adverse events

Similar results in all prespecified subgroup analyses

Huang, NEJM 2018; 379:236-49

Why Different Findings in ProHOSP vs ProACT?

- **Difference in adherence rates**
  - Higher adherence with ProHOSP (more rigorous intervention feedback)
  - ProACT used quality improvement principles (e.g. letters to providers; embedding PCT algorithms into EHR and guidelines); reasons for nonadherence queried but no other questions or recommendation

- **Lower severity of illness in ProACT**
  - Fewer patients admitted to the hospital (47% vs 93% with ProHOSP)
  - Less CAP (20% vs 68% vs ProHOSP), more asthma, COPD, bronchitis

- **Guidelines recommend 5-10 days of antibiotics for COPD exacerbations → common reason for overruling PCT algorithm in ProACT**

- **Improving antibiotic stewardship and trend towards shorter courses**
  - ProACT enrolled primarily academic centers with robust antibiotic stewardship
  - Default CAP treatment course now 5 days
Caution: Procalcitonin for Severe COPD Exacerbations

Multicenter French RCT of 302 adult patients with severe acute COPD exacerbations requiring ICU admission

Daubin, Intensive Care Med 2018; 44:428-37

Procalcitonin for Respiratory Infections: Bottom Line

- In the current era, PCT may not have a substantial impact on antibiotic prescribing rates for suspected respiratory infections beyond good antibiotic stewardship principles

- Use of PCT for acute COPD exacerbation remains controversial → may be safer to simply give antibiotics and not check PCT in these patients (particularly for severe exacerbations requiring ICU care)
  - Patients may benefit from anti-inflammatory effects of antibiotics
  - PCT levels with bacterial infections may be lower in COPD

- PCT may still have benefit in patients with suspected CAP who are sick enough to be hospitalized
  - Due to high morbidity of CAP, prudent to use PCT to shorten antibiotic duration on the back-end rather than withhold up-front
  - Low PCT may help in withholding antibiotics in low-risk patients where clinical picture/lab testing is suggestive of viral infection
2019 IDSA/ATS CAP Recommendations

- “We recommend that empiric antibiotic therapy should be initiated in adults with clinically suspected and radiographically confirmed CAP regardless of initial serum procalcitonin level (strong recommendation, moderate quality of evidence)”

- “Several studies have demonstrated that the duration of antibiotic therapy can be reduced in patients with CAP with the use of a procalcitonin-guided pathway and serial procalcitonin measurement compared with conventional care, but in most cases the average length of treatment was greatly in excess of current U.S. standards of practice as well as the recommendations of these current guidelines.... Serial procalcitonin measurement is therefore likely to be useful primarily in settings where the average length of stay for patients with CAP exceeds normal practice (e.g., 5–7 d).”


Procalcitonin in the ICU: PRORATA

- Check procalcitonin daily

- 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

   Boudama, Lancet 2010;375:463-474
Procalcitonin in the ICU: PRORATA

621 ICU patients randomized to daily procalcitonin vs usual care, 7 ICUs, France

- Control (N=314)
- Procalcitonin (N=307)

**Fewer days of antibiotics**

No difference in LOS or Mortality

---

Boudama, Lancet 2010;375:463-474

---

Procalcitonin in the ICU: SAPS

Guidelines for continuing or stopping of antibiotics

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

- Decrease by ≥80% peak threshold, or ≤ 0.5 µg/L
  - STOP ANTIBIOTICS

- Decrease by <80% peak threshold, or > 0.5 µg/L
  - CONTINUE ANTIBIOTICS

---

Procalcitonin in the ICU: SAPS

1575 ICU patients with sepsis randomized to daily procalcitonin vs usual care, 15 ICUs, Netherlands

- Fewer days of antibiotics
- No difference in LOS
- Lower Mortality!

Control (N=785)  Procalcitonin (N=761)

Median Days of Antibiotics  ICU Length of Stay  Mortality (28-day)


PCT-Guided Antibiotic Discontinuation In ICU Patients and Mortality

Meta-analysis of 5000 patients from 16 RCTs

- But results driven mainly by trials with high protocol adherence
  - Low Certainty Evidence (High Risk of Bias)

Pepper, Chest 2019 Feb 14 (ePub)
How Not To Use Procalcitonin: Daily ICU Screening (PASS Trial)

- RCT in Denmark enrolling adults within 24 hours of ICU admission
- PCT taken immediately and every morning while in ICU
- Intervention: if “alert PCT” ≥1.0 and not decreasing at least 10% from prior day:
  - Substantially increase antibiotic spectrum, and/or
  - Intensify diagnostic effort to find source.
- Antibiotic escalation mandatory, except if:
  - Clear contraindication, or
  - Clear microbiologic result explaining infectious state

PASS Trial: An Antibiotic Stewardship Nightmare

- Overall, no benefit:
  - Did not improve time to appropriate abxs
  - Increased number of cultures taken, but not other diagnostic or radiologic studies
  - No difference in mortality

- Evidence of harm:
  - Substantially increased piperacillin-tazobactam and ciprofloxacin use
  - Increased ICU LOS by 1 day
  - Increased rate of mechanical ventilation
  - Increased rate of renal dysfunction

Jensen, Crit Care Med 2011; 39: 2048-58
2016 Surviving Sepsis Campaign Recommendations

- “We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence)”

- “We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to be have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence)”

Rhodes, Crit Care Med 2017; 45:486-552

Procalcitonin as a Prognostic Marker in Sepsis: MOSES study

*Prospective U.S. multicenter cohort study of 858 patients with sepsis admitted to ICU → PCT measured daily for 5 days*

*Failure of PCT to Decline >80% → 2-fold Increased Mortality Risk*

Schuetz et al, Crit Care Med 2017; 45:781-89
Procalcitonin in Immunocompromised Patients

- Despite exclusion criteria in PCT trials, PCT production **not impaired by neutropenia or immunocompromising states**
- Observational studies suggest PCT discriminates bacterial infection in cancer patients
- Specific scenarios include:
  - Bacterial infection in febrile neutropenia
  - Tumor fever in non-neutropenic cancer patients
  - Bacterial vs fungal infections in BMT patients

1. Schuttrumpf, Ann Hematol 2003
2. Sakr, Infection 2008
3. Shomali, Cancer 2012
4. Koya, Bone Marrow Transpl 2012

Caveats about Procalcitonin in Oncology Patients

- Unknown whether PCT algorithms studied in trials applies to neutropenic / BMT patients
  - Typically treat for longer durations - what is the right cutoff at which antibiotics can be stopped?
- Oncology patients have more reasons for false positives
  - Antilymphocyte / anti-thymocyte globulin, granulocyte transfusions, alemtuzumab, anti-CD3 antibodies, etc.
Procalcitonin and COVID-19

1099 hospitalized patients with COVID-19 in China

PCT >0.5 Corresponds to 5-Fold Higher Risk of Severe COVID-19

Meta-analysis of 4 studies

Guan, NEJM 2020; 382:1708-20

Lippi, Clinica Chimica Acta 2020; 191-91
Interpreting High Procalcitonin with COVID-19

Bacterial co-infection, or generalized inflammatory activation?

Early Thoughts:
- PCT on admission is likely useful for early risk assessment
- Monitoring PCT may be useful for detecting progression
- Unclear whether it can help identify bacterial co-infection
- ATS/IDSA CAP Co-Chairs: endorse using low PCT early in course of a patient with confirmed COVID-19 to guide withholding or early stopping of antibiotics, especially among patients with less severe disease

C-Reactive Protein vs Procalcitonin

Meta-analysis of 9 studies

CRP:
- AUC 0.73
- Sensitivity 80%
- Specificity 61%

PCT:
- AUC 0.85
- Sensitivity 80%
- Specificity 77%

Metlay and Waterer, Ann Intern Med 2020; Aug 18

Tan, J Cell Biochem 2019;120
CRP-Guided Antibiotic Therapy for Outpatient COPD Exacerbations

*Multicenter RCT of 653 patients in 86 general medical practices in England and Wales using POC CRP testing*

- Antibiotics discouraged for CRP <20 mg/L
- Antibiotics recommended for CRP 20-40 if purulent sputum or anyone with CRP >40

Anthonisen Criteria:
- Increased dyspnea
- Increased sputum volume
- Increased sputum purulence

CRP algorithm decreased antibiotic utilization (48% vs 70%) with no evidence of harm (including hospitalizations, pneumonia diagnoses, death)

Butler, NEJM 2019; 381:111-120

---

CRP-Guided Antibiotic Therapy for GNR Bacteremia

*Multicenter RCT of 504 adults with GNR bacteremia in 3 Swiss hospitals comparing CRP protocol (discontinue antibiotics once 75% decline from peak) vs fixed 7 days or 14 days*

CRP-Guided Group

Fixed 7-Days

Fixed 14-Days

Median 7 days with CPR protocol; no difference in 30-day clinical failure rates

von Dach, JAMA 2020; 323:2160-69
CRP is Predictive of COVID-19 Severity Too

209 patients initially hospitalized with nonsevere disease in China

AUC 0.84 for predicting progression to severe disease

Other Sepsis Biomarkers

Biomarkers studied for diagnostic accuracy for sepsis with >300 patients (other than PCT or CRP)

<table>
<thead>
<tr>
<th>Biomarker [ref]</th>
<th>No. of patients</th>
<th>Sepsis definition</th>
<th>Study population</th>
<th>Reference group</th>
<th>Sensitivity/specificity (%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin (4)</td>
<td>702</td>
<td>Positive blood cultures</td>
<td>Pediatric ICU patients with infection</td>
<td>Non-infected critical care patients</td>
<td>84/83</td>
<td>0.75</td>
</tr>
<tr>
<td>Inter-alpha inhibitor protein</td>
<td>579</td>
<td>Positive blood cultures</td>
<td>Nonhealthy with sepsis</td>
<td>Nonhealthy with risk factors for sepsis</td>
<td>89/99</td>
<td>0.9</td>
</tr>
<tr>
<td>G-reactive protein A1</td>
<td>525</td>
<td>ACIP 1992</td>
<td>ED patients with sepsis</td>
<td>ED patients with suspected infection (with and without SIRS)</td>
<td>NR</td>
<td>Logistic regression analysis</td>
</tr>
<tr>
<td>Bacitracin/LPS binding protein</td>
<td>525</td>
<td>ACIP 1992</td>
<td>ED patients with sepsis</td>
<td>ED patients with suspected infection (with and without SIRS)</td>
<td>NR</td>
<td>Logistic regression analysis</td>
</tr>
<tr>
<td>CD64</td>
<td>688</td>
<td>International Sepsis Definitions Conference 2001</td>
<td>Non-selected ICU patients with sepsis</td>
<td>ICU patients admitted without sepsis</td>
<td>89/87</td>
<td>0.94</td>
</tr>
<tr>
<td>Selnesprotein P</td>
<td>376</td>
<td>ACIP 1992</td>
<td>Non-selected population with sepsis or septic shock</td>
<td>Healthy individuals</td>
<td>NR</td>
<td>(no test)</td>
</tr>
<tr>
<td>Enzyme-linked immunosorbent assay</td>
<td>376</td>
<td>ACIP 1992</td>
<td>Surgical patients without infection or admission</td>
<td>Surgical patients with SIRS without sepsis</td>
<td>80/82</td>
<td>0.66</td>
</tr>
<tr>
<td>Syndecan-1</td>
<td>512</td>
<td>International Sepsis Definitions Conference 2001</td>
<td>Trauma patients (6 h after admission) without sepsis</td>
<td>Trauma patients without sepsis</td>
<td>NR</td>
<td>(logistic regression analysis)</td>
</tr>
<tr>
<td>Progesterone</td>
<td>440</td>
<td>Sepsis-3</td>
<td>ICU patients with sepsis</td>
<td>ICU patients without sepsis</td>
<td>89/79</td>
<td>0.76</td>
</tr>
<tr>
<td>K-11</td>
<td>506</td>
<td>SIRS and organ dysfunction; systolic blood pressure &lt; 90 mmHg, or lactate 2 mmol/L, plus infection</td>
<td>ED patients with suspected sepsis</td>
<td>ED patients with SIRS and organ dysfunction; systolic blood pressure &lt; 90 mmHg, or lactate &gt; 4 mmol/L, without infection</td>
<td>NR</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Wang, Open Forum Infect Dis 2020; 7:ofaa153

Pierrakos, Crit Care 2020; 24:287
Summary

- PCT is an imperfect, but potentially useful biomarker of bacterial infection
- However, no biomarker (including PCT) is accurate enough to use to justify withholding empiric antibiotics in patients with evidence of serious infection
- PCT can help safely reduce antibiotic use in critically ill patients on the “back-end”
- Utility of PCT for respiratory infections is likely low in the current era with good antibiotic stewardship and short recommended antibiotic courses for pneumonia
- PCT-guided antibiotic therapy has not been as well studied in immunocompromised patients, but the test can be useful as an adjunct to diagnosing infection
- CRP is less specific than PCT for bacterial infection, but CRP-guided algorithms can reduce antibiotic exposure in outpatients with COPD
- Both PCT and CRP can help risk-stratify patients with COVID-19
- Many other biomarkers have been studied, but none are ready for “prime time”

Thank You!

For all the lives we touch
Clean hands protect our patients. Always perform hand hygiene and help others do the same.

crhee@bwh.harvard.edu