How to Manage Antibiotics like a Pro with Procalcitonin

Matthew Exline, MD MPH
Director, Medical Intensive Care Unit
Objectives

• Discuss the physiology of procalcitonin (PCT) as related to bacterial infections

• Compare procalcitonin levels to other physiologic and biologic markers of infection

• Understand the use of procalcitonin concentrations in antibiotic cessation
Disclosures

- I sit on our sepsis response task force and preach early antibiotics
- I write for **ALOT** of antibiotics in ICU
- I sit on our antimicrobial utilization committee and preach stopping abx
- I am a **TOP** utilizer of procalcitonin at OSU
- No commercial affiliations to disclose
A Busy Morning

- 68 yo with newly diagnosed cardiomyopathy secondary to amyloidosis and atrial fibrillation develops new onset hypotension
  - T 96.5 HR 97 BP 86/49 RR 24
- His nurse is called with his morning Hgb 5.8 mg/dl (down from 8.5 the day before)
- His abdomen is tense
- Over the morning he has increased work of breathing and hemodynamic instability
- His mental status worsens and he is intubated for airway protection
Interventions

- A CT abd/pelvis reveals a retroperitoneal hematoma
- He receives 6u PRBCs
- He is started on norepinephrine
- He is started on empiric antibiotics for possible aspiration during intubation
- His bedside echo estimates an ejection fraction of 30%
Why Don’t Patients Read the Book?

• He has evidence of cardiogenic, hypovolemic, and septic shock
• On day 2, his norepi gtts is weaned down and he is on minimal ventilator settings
• His hemoglobin has stabilized off heparin
• The pharmacists wants to know if you are continuing antibiotics…
He got better with antibiotics

I have another etiology for shock

He has a white count and GPC on sputum

He’s so tenuous

I can tell them to evaluate at 72-hours and leave it for weekend team
Antibiotic Dilemmas

CMS mandated sepsis bundle (SEP-1)

CDC emphasis on antibiotic stewardship

Mt Foster Parry Savoia False Cape Renard Wandel
CMS Mandated Sepsis Care

• Within 3 hours
  – Measure lactate
  – Obtain cultures prior to antibiotics
  – Administer antibiotics
  – Administer 30cc/kg fluids (if hypotensive)

• Within 6 hours (if hypotensive)
  – Apply vasopressors
  – Assess volume status
  – Repeat lactate
Does the Antibiotic Choice Matter?

261 ED patients with sepsis
Mortality for “inappropriate abx” in ED 50%
Mortality for appropriate abx in ED 32.5% (p=n/s)

Table 6. In-hospital mortality: Time from triage to appropriate antibiotics

<table>
<thead>
<tr>
<th>Cutoffs</th>
<th>Number</th>
<th>Mortality, %</th>
<th>Difference, %</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>Probability of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 hr</td>
<td>41</td>
<td>19.5</td>
<td>13.7</td>
<td>0.30</td>
<td>0.11–0.83</td>
<td>.02</td>
<td>.13 vs. .29</td>
</tr>
<tr>
<td>&gt;1 hr</td>
<td>220</td>
<td>33.2</td>
<td>5.4</td>
<td>0.54</td>
<td>0.29–1.03</td>
<td>.06</td>
<td>.22 vs. .31</td>
</tr>
<tr>
<td>≤2 hrs</td>
<td>124</td>
<td>28.2</td>
<td>5.4</td>
<td>0.54</td>
<td>0.29–1.03</td>
<td>.06</td>
<td>.22 vs. .31</td>
</tr>
<tr>
<td>&gt;2 hrs</td>
<td>137</td>
<td>33.6</td>
<td>9.2</td>
<td>0.53</td>
<td>0.27–1.01</td>
<td>.05</td>
<td>.23 vs. .34</td>
</tr>
<tr>
<td>≤3 hrs</td>
<td>172</td>
<td>27.9</td>
<td>9.2</td>
<td>0.53</td>
<td>0.27–1.01</td>
<td>.05</td>
<td>.23 vs. .34</td>
</tr>
<tr>
<td>&gt;3 hrs</td>
<td>89</td>
<td>37.1</td>
<td>9.2</td>
<td>0.53</td>
<td>0.27–1.01</td>
<td>.05</td>
<td>.23 vs. .34</td>
</tr>
<tr>
<td>≤4 hrs</td>
<td>200</td>
<td>28.5</td>
<td>10.8</td>
<td>0.62</td>
<td>0.31–1.24</td>
<td>.18</td>
<td>.25 vs. .34</td>
</tr>
<tr>
<td>&gt;4 hrs</td>
<td>61</td>
<td>39.3</td>
<td>10.8</td>
<td>0.62</td>
<td>0.31–1.24</td>
<td>.18</td>
<td>.25 vs. .34</td>
</tr>
<tr>
<td>≤5 hrs</td>
<td>218</td>
<td>30.7</td>
<td>1.8</td>
<td>0.82</td>
<td>0.37–1.79</td>
<td>.62</td>
<td>.27 vs. .29</td>
</tr>
<tr>
<td>&gt;5 hrs</td>
<td>43</td>
<td>32.6</td>
<td>1.8</td>
<td>0.82</td>
<td>0.37–1.79</td>
<td>.62</td>
<td>.27 vs. .29</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

Abx < 1h
80.5% survive
Abx > 1h
66.8% survive
Antibiotic Stewardship

• Dedicating necessary human, financial and information technology resources.

• Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours)

• Monitoring antibiotic prescribing and resistance patterns

• Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff

• Education: Educating clinicians about resistance and optimal prescribing

CDC - Core Elements of Hospital Antibiotic Stewardship Programs
Antibiotic Resistance Kills

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least 🌧️2,049,442 illnesses, 🔧23,000 deaths

*bacteria and fungus included in this report

Estimated minimum number of illnesses and death due to *Clostridium difficile (C. difficile)*, a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least 🌧️250,000 illnesses, 🔧14,000 deaths

WHERE DO INFECTIONS HAPPEN?
Antibiotic-resistant infections can happen anywhere. Data show that most happen in the general community; however, most deaths related to antibiotic resistance happen in healthcare settings, such as hospitals and nursing homes.
Procalcitonin (PCT) – Super Hero!

• By Day:
  – Mild mannered 116AA peptide responsible for calcium metabolism released by thyroid

• By Night:
  – Highly specific marker of systemic bacterial infection released by many different tissues

Morgenthaler N. et al., Clin Lab 2002, 48: 263-270
Is Procalcitonin New?

PCT Clinical Trials in English by Year
Where is Procalcitonin?
EVERYWHERE!

Fig. 1. Increase of plasma and tissue content of ICT in sepsis. The percent increase of detected ICT content is expressed as a ratio of septic vs. control tissues. The ratio was calculated from values expressed in pg ICT/g wet weight of control and septic tissues.
What causes Procalcitonin release?

• Systemic bacterial infections are associated with high PCT serum concentrations (Assicot Lancet 1993)

• Infections with low PCT
  – Viral
  – Localized bacterial
  – Fungal (candida) (Raineri J Int Care 2017 5:58)
When is procalcitonin elevated?

![Graph showing kinetic profiles of different biomarkers of bacterial infection.](image)

Kinetic profiles of different biomarkers of bacterial infection.
Adapted from Meisner M.¹

Vidas B.R.A.H.M.S Manufacturers Website
Can Procalcitonin Prognosticate in Sepsis?

PCT increases with severity of illness

PCT in patients that do not survive (solid) versus survivors (dashed)

Meisner Crit Care 1999 3:49
Limitations

• Limitation is delay in turn around time
  – At OSU 3-4 hours usually

• Can be falsely elevated
  – Massive inflammatory response (burns, cardiac arrest, severe shock)
  – Some non-bacterial infections
  – Immune stimulatory therapy
  – ESRD
How Good is Procalcitonin?

• Let’s look at what we have now
  – qSOFA
  – CBC
  – Markers of Inflammation
    • CRP, IL-6
  – Lactate
  – Cultures
Sepsis Definitions

- SIRS, qSOFA, and sepsis definitions all lack specificity
  - Definitions rely on clinicians suspicion of infection

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Sensitivity of clinical tools to predict clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICU admission</td>
</tr>
<tr>
<td>Prehospital setting (%/IQR)</td>
<td></td>
</tr>
<tr>
<td>qSOFA score ≥ 2</td>
<td>36.3 (26.6–47.2)</td>
</tr>
<tr>
<td>SIRS criteria</td>
<td>68.8 (57.9–77.9)</td>
</tr>
<tr>
<td>Sepsis definition</td>
<td>50 (39.3–60.7)</td>
</tr>
<tr>
<td>ED’s triage (%/IQR)</td>
<td></td>
</tr>
<tr>
<td>qSOFA score ≥ 2</td>
<td>31.2 (22.2–42.1)</td>
</tr>
<tr>
<td>SIRS criteria</td>
<td>58.8 (47.8–68.9)</td>
</tr>
<tr>
<td>Sepsis definition</td>
<td>42.5 (32.3–53.4)</td>
</tr>
</tbody>
</table>

Data are presented as percentages and interquartile range (IQR). qSOFA score ≥ 2 items: RR ≥ 22/min; SBP ≤ 100 mmHg; GCS ≤ 15 or decline from baseline. SIRS criteria ≥ 2 items: RR > 20/min, HR > 90/min, temperature ≥ 38.3 °C or ≤ 36 °C. Sepsis definition: SIRS criteria plus one of the following item: SBP < 90 mmHg, GCS ≤ 15 or decline from baseline, oxygen saturation < 90%. ED: emergency department, ICU: intensive care unit.
Leukocytosis in Sepsis

- Detection of leukocytosis (leukopenia) is hallmark of sepsis
- Limitations include:
  - Not sensitive (may miss up to 12%)
  - Non-specific: stress response, steroids, etc.
- In Day 1 post-op CABG patients
  - Increased WBC sens 63% spec 24%
  - Fever sens 24.5% spec 83.3%
  - Combined sens 14.3% spec 91.5%

Kumar Indian Heart J 2005 59:316
C Reactive Protein

- Acute phase reactant synthesized by liver
- CRP is not specific for sepsis, but...
  - High CRP may indicate more severe infection
  - Improvement with CRP in first 48 hours indicates response to infection
- Overall, not a good biomarker for sepsis

Samraj Shock. 2013 40: 358
IL-6 in Sepsis

• Secreted by lymphocytes and macrophages in response to “danger molecules”

• Responsible for fever, synthesis of neutrophils, and synthesis of inflammatory proteins

• May correlate with prognosis and duration of sepsis
Procalcitonin outperforms other biomarkers

N = 72 children with pneumonia

Table 2  Validity coefficients of tests for selected cut off points in the discrimination between bacterial (including mycoplasma and bacterial + viral coinfections) and viral pneumonia

<table>
<thead>
<tr>
<th></th>
<th>Bacterial</th>
<th>Viral</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Pos pred value</th>
<th>Neg pred value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT &gt; 0.5 μg/l</td>
<td>41/43</td>
<td>10/29</td>
<td>95%</td>
<td>60%</td>
<td>80.3%</td>
<td>88.4%</td>
</tr>
<tr>
<td>PCT &gt; 1 μg/l</td>
<td>37/43</td>
<td>4/29</td>
<td>86%</td>
<td>87.5%</td>
<td>90.2%</td>
<td>80%</td>
</tr>
<tr>
<td>PCT &gt; 2 μg/l</td>
<td>27/43</td>
<td>1/29</td>
<td>62.7%</td>
<td>96%</td>
<td>96.4%</td>
<td>60%</td>
</tr>
<tr>
<td>CRP &gt; 20 mg/l</td>
<td>38/43</td>
<td>15/29</td>
<td>88.4%</td>
<td>40%</td>
<td>71.6%</td>
<td>66.6%</td>
</tr>
<tr>
<td>CRP &gt; 60 mg/l</td>
<td>30/43</td>
<td>7/29</td>
<td>69.8%</td>
<td>52%</td>
<td>81.1%</td>
<td>58.1%</td>
</tr>
<tr>
<td>IL-6 &gt; 100 pg/ml</td>
<td>12/20</td>
<td>2/12</td>
<td>66%</td>
<td>83%</td>
<td>85.7%</td>
<td>55.5%</td>
</tr>
<tr>
<td>WBC &gt; 15 000 (×10⁶/l)</td>
<td>28/43</td>
<td>6/29</td>
<td>65.1%</td>
<td>79.3%</td>
<td>82.3%</td>
<td>60.5%</td>
</tr>
</tbody>
</table>

Arch Dis Child 2001;84:332–336
PCT has good sensitivity / specificity

Figure 3. Receiver-operating-curve analysis of serum calcitonin precursors (solid circles) vs. interleukin-6 (solid triangles), C-reactive protein (open circles), and lactate (open triangles) concentrations. Values are shown for all time points (n = 272; 101 values at admission, 74 values on day 2, and 97 values on day of discharge or death) for the diagnoses of sepsis, severe sepsis, or septic shock.

Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit.
Muller, Beat; Becker, Kenneth; MD, PhD; Schachinger, Hartmut; Rickenbacher, Peter; Huber, Peter; Zimmerli, Werner; Ritz, Rudolf

Lactate a Marker of a Sick Patient (and maybe a good hospital)

- Lactic Acid is not pathologic, but may indicate inadequate tissue perfusion / anaerobic metabolism
- Lactate is not specific for sepsis

<table>
<thead>
<tr>
<th>Lactate Group (mmol/L)</th>
<th>Compliant Lactate Measured ≤ 6 hr</th>
<th>Noncompliant Lactate Measured &gt; 6 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Hypotension</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Total, n (Died n/%)</td>
<td>OR* (95% CI) [p]</td>
</tr>
<tr>
<td>≤ 2 (referent)</td>
<td>1,302 (301/23.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt; 2 to ≤ 3</td>
<td>1,009 (242/24.0)</td>
<td>1.04 (0.87–1.24)</td>
</tr>
<tr>
<td>&gt; 3 to ≤ 4</td>
<td>693 (158/22.8)</td>
<td>0.99 (0.80–1.21)</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>996 (289/29.0)</td>
<td>1.38 (1.16–1.65)</td>
</tr>
</tbody>
</table>

OR = odds ratio.
*Odds ratio based on generalized estimating equation population-averaged logistic regression model.
Blood Cultures and Sepsis

• Blood cultures should be drawn within 3 hours of identification of sepsis
  – Before antibiotics (per CMS)
  – Without delaying antibiotics (per Surviving Sepsis)

• Positive cultures provide marker of infection, causative organisms, and antibiotic sensitivities

If they are positive
Only about 30% have a positive blood culture

Only 50% have any positive culture

Martin et al, NEJM 2003:348;1546-54
Culture Negative Sepsis

- Positive cultures provide not just diagnostic information, but prognostic information

Table 5 Outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Culture-negative patients (n = 415)</th>
<th>Culture-positive patients (n = 586)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>149 (35.9)</td>
<td>258 (44.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>139 (33.5)</td>
<td>232 (39.6)</td>
<td>0.049</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, days¹</td>
<td>3.0 (1.0-7.0)</td>
<td>4.0 (1.0-8.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Duration of ICU stay, days</td>
<td>4.0 (2.0-8.0)</td>
<td>4.0 (2.0-9.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Duration of hospital stay, days</td>
<td>12.0 (7.0-21.0)</td>
<td>15.0 (7.0-27.0)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

¹A total of 326 culture-negative patients and 448 culture-positive patients were mechanically ventilated during the ICU stay. ICU, intensive care unit.
What Do We Know So Far

• We need to give early / effective antibiotics
• We need to limit antibiotic usage
• Procalcitonin is a small peptide that is release in response to systemic bacterial infections
• Procalcitonin outperforms other biomarkers of bacterial infection
• How can we use procalcitonin?
Utilization of Procalcitonin

• Location
  – Ambulatory
  – Emergency Room
  – Inpatient

• Antibiotic Use
  – Initiation
  – Cessation

• Protocol
  – Absolute cut-off
  – Relative decreases
Procalcitonin In Ambulatory Care

• Limited utility in non-systemic infections
  – Questionable utility in cellulitis or upper respiratory tract infections


• Existing testing may be adequate
  – UA for cystitis

• Turn around time may limit utility

• Best studied in lower respiratory tract infections
458 patients with LRTI “in need of antibiotics”
  – Dx: Colds, sinusitis, pharyngitis, otitis, bronchitis, influenza, COPD/asthma exacerbation, CAP

Antibiotics discouraged for PCT ≤ 0.25 ug/L (recommended PCT > 0.25)

Patients were called within 2-4 hours and informed of results
  – Patients with negative PCT were retested in 24 hours

Primary outcome – symptoms limiting daily activity

Secondary outcome – antibiotic usage
PCT reduced antibiotic usage

• Patients in PCT arm with 0.1 day increase in symptoms

• Antibiotic Usage
  – Standard therapy – 97%
  – Procalcitonin – 25%

• Side Effects – Diarrhea
  – Standard therapy (antibiotic group) – 33%
  – PCT – 20%

• Compliance with withholding antibiotics 85% in PCT arm
  – 15% of time docs gave abx anyway

• Repeat PCT likely unnecessary
  – Only 7% of patients with low initial PCT had repeat that was higher / needed abx
How much does PCT change minds?

- 550 patients with respiratory tract infections
- Doc determined need for abx and then checked PCT
- In both PCT and control arm, doc thought abx were needed ~ 30% of the time

### TABLE 2

Initial clinical decisions, procalcitonin (PCT)-guided recommendations and final clinical decisions in the intervention group

<table>
<thead>
<tr>
<th>Initial decision</th>
<th>PCT determination</th>
<th>Reassessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 days</td>
<td>28 days</td>
</tr>
<tr>
<td><strong>No antibiotic (n=191)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.25 ng·mL⁻¹ PCT</td>
<td>191</td>
<td>182</td>
</tr>
<tr>
<td>≥0.25 ng·mL⁻¹ PCT</td>
<td></td>
<td>177</td>
</tr>
<tr>
<td><strong>Antibiotic (n=84)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.25 ng·mL⁻¹ PCT</td>
<td>36</td>
<td>44</td>
</tr>
<tr>
<td>≥0.25 ng·mL⁻¹ PCT</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>
How could I use PCT in Clinic?

• Well studied in respiratory tract infections
• Testing with call back to patient for antibiotics works well
  – Cut off of 0.25 ug/L is safe
• Does not appear to add value in patients you do NOT want to treat with abx
• May help limit abx in patients that you are thinking of treating
Procalcitonin in ED

- Multiple ED studies with over 3000 patients enrolled total
- Focus generally on decision to start antibiotics on patients
- Limitations include
  - Turn around time
  - Follow-up for patients discharged
  - Bias to treatment in patients being admitted
Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections

The ProHOSP Randomized Controlled Trial

- 1359 patients in tertiary ED in Switzerland
- Use of PCT for both initiation and stopping of abx in "severe" lower respiratory tract infections
  - CAP, COPD exacerbation, bronchitis, other
  - > 90% of patients treated as inpatients
- Rapid < 1-hour PCT levels performed on all patients
  - Cut-off 0.25 ug/L for treatment
  - PCT repeated days 3, 5, 7, and discharge
- Overruling of PCT suggestion possible for ICU patients / hemodynamic instability
PCT Reduces Antibiotic Use in ED

- Outpatient antibiotic use
  - Standard Care 59%, PCT 33%
- Hospitalized patients
  - Standard Care 90%, PCT 78%
Use of PCT is Safe in the ED

Table 2. Rates of Combined Adverse Outcomes and Mortality by Randomization Group

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of Patients</th>
<th>Risk Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCT Group (n = 671)</td>
<td>Control Group (n = 688)</td>
</tr>
<tr>
<td>All patients (intention-to-treat)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall adverse outcome</td>
<td>103 (15.4)</td>
<td>130 (18.9)</td>
</tr>
<tr>
<td>Death</td>
<td>34 (5.1)</td>
<td>33 (4.8)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>43 (6.4)</td>
<td>60 (8.7)</td>
</tr>
<tr>
<td>Recurrence/rehospitalization</td>
<td>25 (3.7)</td>
<td>45 (6.5)</td>
</tr>
<tr>
<td>Disease-specific complication</td>
<td>17 (2.5)</td>
<td>14 (2.0)</td>
</tr>
</tbody>
</table>

- Adverse effect from antibiotics
  - Standard Care 28.1% PCT 19.8%
How Compliant Were They?

• ProHOSP had excellent compliance with protocol
  – 90.8% followed protocol
    • Includes 11.5% were PCT level was ignored due to clinical instability

• Providers were more likely to disregard recommendations for duration rather than initiation of therapy
Is this physiology or psychology?

**COMMUNITY-ACQUIRED PNEUMONIA**
Antibiotic duration - 5d min, defervesce 48-72h, and ≤ 1 sign of clinical instability (Moderate recommendation, level II evidence, IDSA/ATS 2007)

**COPD**
Antibiotics if all 3 cardinal symptoms* (Evidence B) or 2 symptoms if one is sputum purulence (Evidence C), for 5-10 days (Evidence D) (GOLD 2015). *Increased dyspnea, sputum volume, sputum purulence

**ASTHMA**
Antibiotics not generally recommended for the treatment of acute asthma exacerbations (Evidence B) (NIH Expert Panel Report 3, 2007); Do not initiate antibiotics (GINA 2015)

**ACUTE BRONCHITIS**
Antibiotics not recommended for uncomplicated bronchitis (CDC/ACP 2016)

**Fig. 1** ProACT guidelines. The ProACT Coordinating Center provided posters of this Figure to all centers. Other study education, in-service training, and promotion materials contain the same content.
How could I use PCT in ED?

• Well studied in lower respiratory tract infections
• Similar to ambulatory can call back patients with prescription
  – Cut off of 0.25 ug/L is safe
• Can be used on both patients being admitted and discharged home
Can procalcitonin help inpatient?

- Multiple studies with greater than 5000 patients participating
- Generally continuity of care from ED to ICU including medical wards
- Strategies focusing on both initiation (similar to primary care and ED) and duration of therapy
- Limitation
  - How to handle critically ill patients?
  - How to make timely decisions on initiation of therapy?
What to do for COPD Exacerbations?

-or-

PCT versus “Green Phlegm”

• 208 patients admitted for COPD exacerbations
• PCT measured on day of admission
  – PCT 0.1 ug/L abx strongly discouraged
  – PCT > 0.25 ug / L abx encouraged

(CHEST 2007; 131:9–19)
PCT for Hospitalized COPD

• No difference in
  – Hospital LOS
  – ICU transfers
  – Future exacerbations
  – Changes in FEV1
  – Re-hospitalizations

*(CHEST 2007; 131:9–19)*
Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial


- 1575 admitted to the ICU on antibiotics
  - Excluded: severe immune suppression, endocarditis, severe viral/mycobacteria/parasitic
- PCT measured baseline and then daily
- Suggested abx stopped for either:
  - PCT decreased by > 80% baseline
  - PCT ≤ 0.5 ug/L
- Primary outcome consumption of antibiotics
We can use this on sick patients

- 82% severe sepsis
- 18% septic shock
- 81% mechanically ventilated
- 9% on dialysis
- 96% on vasopressors
- 54% on steroids
Can we reduce ICU antibiotics?

• Antibiotic Consumption
  – Standard 9.3 (5.0-16.5) days
  – PCT 7.5 (4.0-12.8) days

• Reinfection (with same bacteria)
  – Standard 2.9%
  – PCT 5%

• Compliance
  – 44% stopped within 24-hours
  – 97% stopped within 48-hours
Checking Procalcitonin Saves Lives

- **28-Day Mortality**
  - Standard care 25%, PCT 19.6%

- **1-Year Mortality**
  - Standard care 40.9%, PCT 34.8% (difference 6.1%)

\[ \text{NNT} = 16! \]
Procalcitonin in Critically Ill Patients

• Meta-Analysis of PCT-guided therapy versus usual care
• Differentiated studies into:
  – Initiation – PCT determined starting of abx
  – Cessation – PCT determined duration of abx
  – Mixed – PCT for both start and stop decision
• 15 studies of critically ill patients including 6037 patients
• In ICU studies, use of PCT reduced total antibiotic days by an average of 1.65 days [0.89 – 2.41]
Procalcitonin Improves Survival in Cessation Studies

1.1.3 Cessation

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Events</th>
<th>%</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloos 2016</td>
<td>140</td>
<td>552</td>
<td>149</td>
<td>537</td>
<td>19.6%</td>
</tr>
<tr>
<td>de Jong 2016</td>
<td>149</td>
<td>761</td>
<td>196</td>
<td>785</td>
<td>25.0%</td>
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<tr>
<td>Deliberato 2013</td>
<td>2</td>
<td>42</td>
<td>4</td>
<td>39</td>
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<td>Hochreiter 2009</td>
<td>15</td>
<td>57</td>
<td>14</td>
<td>53</td>
<td>1.9%</td>
</tr>
<tr>
<td>Nobre 2008</td>
<td>8</td>
<td>39</td>
<td>8</td>
<td>40</td>
<td>1.0%</td>
</tr>
<tr>
<td>Oliveira 2013</td>
<td>16</td>
<td>49</td>
<td>15</td>
<td>45</td>
<td>2.0%</td>
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<tr>
<td>Schroeder 2009</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>13</td>
<td>0.4%</td>
</tr>
<tr>
<td>Shehabi 2014</td>
<td>30</td>
<td>196</td>
<td>26</td>
<td>198</td>
<td>3.4%</td>
</tr>
<tr>
<td>Stolz 2009</td>
<td>8</td>
<td>51</td>
<td>12</td>
<td>50</td>
<td>1.6%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1761</strong></td>
<td><strong>1760</strong></td>
<td><strong>55.5%</strong></td>
<td><strong>0.87 [0.77, 0.98]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events 371 427

Heterogeneity: $\chi^2 = 4.33$, df = 8 (P = 0.83); $I^2 = 0$

Test for overall effect: Z = 2.31 (P = 0.02)
Procalcitonin in Respiratory Infections

PCT Patients Had:
- Less antibiotics
- Fewer days of antibiotics
- Lower mortality
- Less side-effects
Procalcitonin in Respiratory Infections

PCT Patients Had:
- Less antibiotics
- Fewer days of antibiotics
- Lower mortality
- Less side-effects
Putting it All Together

• Ambulatory – PCT-guided protocols reduce antibiotic usage and antibiotic side effects
• ED – PCT-guided protocols reduce antibiotic usage in lower respiratory tract infections
• Inpatient / ICU – Use of PCT protocol may
  – Reduce antibiotic use
  – Reduce side effects of antibiotics
  – Improve survival when used for decisions on stopping abx
What Do Experts Say?

FDA News Release

FDA clears test to help manage antibiotic treatment for lower respiratory tract infections and sepsis

For Immediate Release

February 23, 2017
14. 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).

15. We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence).
How Should We Use Procalcitonin?

- PCT can help differentiate systemic infections from other non-infections sources of inflammation
- For “low risk” non-critically ill patients, antibiotics can be safely held if PCT is < 0.1 ug/L (0.25 ug/L borderline)
- For critically ill patients, antibiotics can be safely discontinued for PCT < 0.25 or 80% less than peak

Thermo Fisher Procalcitonin Package Insert
Our Patient

- Patient with on minimal ventilator settings, low dose vasopressors, and stable Hgb at 48-hours
  - PCT concentration 0.07 ug/L
  - Antibiotics held
- On ICU day #5 patient deteriorated
- Increasing norepinephrine requirements
  - Worsening cardiogenic shock?
  - Hypovolemia?
  - New infection?
Our Patient

• Patient with on minimal ventilator settings, low dose vasopressors, and stable Hgb at 48-hours
  – PCT concentration 0.07 ug/L
  – Antibiotics held

• On ICU day #5 patient deteriorated

• Increasing norepinephrine requirements
  – Worsening cardiogenic shock?
  – Hypovolemia?
  – New infection?

• Antibiotics were restarted for worsening shock
  – Repeat PCT 4.5 ug/L
Conclusion

- Procalcitonin can aid in determining which patients will benefit from antibiotics in a variety of clinical settings.
- Procalcitonin cannot replace your clinical judgement.
  - May help your existing markers for sepsis.
- In critically ill patients, antibiotics should not be delayed waiting for procalcitonin.
- Use of procalcitonin to stop antibiotics in the hospital will reduce today's antibiotic usage and may improve mortality.
Thank You

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