PROCALCITONIN: Contributing to improved clinical decision making

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Sepsis/Sepsis Biomarkers/Procalcitonin
Major Cause of Morbidity & Mortality World Wide

- 10th **leading** cause of death overall
- More than **750,000 cases** of in US annually
- Mortality was **8 x higher** than other reasons for hospitalization
- Sepsis **survivors live only ½ as long as predicted age**

AHRQ: Sepsis Admissions are on the Rise

AHRQ’s Nationwide Inpatient Sample 2000-2009

- Hospital stays with a *principal* diagnosis of septicemia increased *146%*
- *Secondary* diagnosis increased by *66%,* as determined by a search of.

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SIRS Criteria

- Clinical Manifestations defined by ACCP/SCCM:
  - Temperature > 38°C or < 36°C.
  - Heart rate > 90 bpm.
  - Respiratory rate:
    - >20 breaths/min.
    - $\text{paCO}_2 < 32 \text{ mm Hg}$.
  - WBC > 12,000/mm$^3$, $< 4,000$/mm$^3$, or $>10\%$ immature (band) forms.
  - New onset confusion.
  - Blood glucose > 150 in absence of diabetes.

Making the Diagnosis

- Tachycardia – 718 possibilities
- Tachypnea - 371 possibilities
- Increased/Decreased Temperature – 1380 possibilities
- Increased/Decreased WBC – 350 possibilities

541 possible diagnosis with 2 or more of the criteria!!!
Acute infection:

- Acute bacterial meningitis
- Acute respiratory distress syndrome (ARDS)
- Acute myocardial infarction (AMI)
- Acute pancreatitis
- Acute pulmonary embolism
- Acute rheumatic fever
- Acute renal failure
- Acute salicylate intoxication
- Acute systemic lupus erythematosus (SLE)
- Acute toxoplasmosis

Possible Diagnoses:

- 3-Quinuclidinyl Benzilate/Weapons
- Acute coronary syndrome
- Acute chest pain
- Acute deep vein thrombosis
- Acute endocrine disorders
- Acute gastrointestinal bleeding
- Acute myocardial infarction
- Acute pulmonary embolism
- Acute respiratory distress syndrome
- Acute renal failure
- Acute salicylate intoxication
- Acute systemic lupus erythematosus
- Acute toxoplasmosis

Possible Symptoms:

- Angina pectoris
- Asthma
- Bronchitis
- Dyspnea
- Fatigue
- Headache
- Nausea
- Vomiting
- Confusion
- Delirium
- Hypotension
- Hypertension
- Tachycardia
- Bradycardia
- Hypothermia
- Hyperthermia

Possible Interventions:

- Administration of oxygen and positive end-expiratory pressure (PEEP)
- Administration of intravenous fluids and inotropic support
- Administration of medications for pain control
- Administration of medications for arrhythmia management
- Administration of medications for infection management
- Administration of medications for pain control
- Administration of medications for respiratory distress
- Administration of medications for cardiovascular support
- Administration of medications for fluid and electrolyte management

Possible Complications:

- Cardiac failure
- Shock
- Pulmonary edema
- Renal failure
- Multiorgan failure

Possible Preventive Measures:

- Early recognition and treatment of acute conditions
- Routine monitoring of vital signs and laboratory parameters
- Prophylactic use of medications for prevention of complications
- Education of patients and caregivers on signs and symptoms of acute conditions
- Early discharge planning and follow-up

Possible Outcomes:

- Complete recovery
- Improved functional status
- Reduced hospital stay
- Prevention of complications
- Improved quality of life

Possible Research Areas:

- Development of new therapeutic agents for acute conditions
- Enhancement of preventive strategies
- Improvement of diagnostic tools for early detection
- Development of population-based interventions
- Development of predictive models for risk stratification

Possible Future Directions:

- Integration of telemedicine and telehealth services for improved access
- Development of precision medicine approaches for individualized treatment
- Implementation of electronic health records for improved data management
- Enhancement of patient and caregiver education programs
- Development of community-based support systems for long-term care
Diagnostic Accuracy of SIRS Criteria

- Critical Care - Zhao (2012):
  - The diagnostic performances of the two definitions range from modest to good

- Critical Care – De Kruif (2010):
  - “Clinician judgment” of sepsis correct 73% of time

- AJCCM – Harbarth (2001):
  - Clinicians’ clinical diagnosis of sepsis were correct 77% of time

Zhao H et al., Crit Care Med. 2012 Jun;40(6):1700-6
De Kruif et al., Crit Care Med. 2010 Feb;38(2):457-63
Harbarth et al., Amer J Crit Care Med. 2001 Aug 1;164(3):396-402.
Importance of Focused Antimicrobial Use

• Worldwide, drug-resistant organisms are increasing
  • *C. difficile*, *MRSA*, *Acinetobacter* species, *Klebsiella pneumoniae* carbapenemase-producing organisms

• Well documented causal relationship between antimicrobial misuse and the emergence of antimicrobial – resistance.
  • Overuse of antibiotics increases costs.
  • Unchecked antibiotic consumption increases risks of drug-related adverse events.

• Antimicrobial agent development is on the decline

• 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
SIRS Criteria

- Clinical Manifestations defined by ACCP/SCCM:
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  - WBC $>12,000/\text{mm}^3$,
    $<4,000/\text{mm}^3$, or $>10\%$ immature (band) forms.
  - New onset confusion.
  - Blood glucose $>150$ in absence of diabetes.

SIRS/Sepsis/Severe Sepsis/Septic Shock

- Sepsis is SIRS plus a known or suspected infection. (27% mortality)
- Severe Sepsis is sepsis associated with organ dysfunction, hypoperfusion, or hypotension. (32% mortality)
- Septic Shock is sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities. (54%)

- May include:
  - Lactic acidosis.
  - Oliguria.
  - An acute alteration in mental status.
  - Others.

Plasma Markers for Diagnosis of Sepsis

- Procalcitonin
- CRP
- IL-6
- Lactate

The world leader in serving science
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

After P. Linscheid, Endocrinology 2003

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

Morgenthaler N. et al., Clin Lab 2002, 48: 263-270
Expression

Calcitonin in healthy persons

Calcitonin

PCT in bacterial infection

Calcitonin

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

PCT Kinetics

- Rapid kinetics: rises 3h after bacterial invasion
- Peak: 6-12h
- Half-life: ~ 24h

Procalcitonin Interpretation

- No “universal” cut-off
- PCT cut-offs depend on the general clinical situation of the patient

Normal Values

- 0.05
- 0.5
- 2
- 5
- 10
- 100

Clinical Condition

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

Potential Limitations of PCT

Low PCT levels in the presence of bacterial infection may occur:

• Early in the course of infection

• Sub acute Endocarditis

• Localized infections
Potential Limitations of PCT

- Newborn < 48hr - increased PCT values (physiological peak)
  - On 3rd day after birth, normal adult reference ranges apply

- Primary inflammation syndrome following trauma: multiple trauma, extensive burns, major surgery (cardiac, transplant, abdominal)
  - Rapid decrease (half-life 24hr) in the absence of bacterial infection

- Medullary C-cell cancers of the thyroid, pulmonary small-cell carcinoma and bronchial carcinoma

- Prolonged circulatory failure (eg: cardiogenic shock, hemorrhagic shock, thermal shock)

- Treatments that can cause a cytokine storm e.g. OKT3, anti-lymphocyte globulins, etc.
PCT in the Emergency Department
PCT in the Emergency Department

- **PCT:**
  - ED staff often examining patient in earliest hours of disease progression.\(^1\)
  - Helps improve estimation risk of severe sepsis and of mortality.\(^1\)
  - Sensitivity and specificity over 80%.\(^1\)
  - NPV 92% or higher.\(^2\)

- If start is delayed 24 to 48 hours, therapy significantly less effective.\(^1\)
- Several medical conditions are very similar to sepsis.
- There are also several common diseases that can cause sepsis.
  - Peritonitis, pneumonia, pyelonephritis/urinary tract infections, soft tissue infections, gastroenteritis, meningitis, aspiration, and limited bacteremia.

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PCT in the Intensive Care Unit
Gray Zone = Delayed diagnosis and treatment of an infection, compared with excess antibiotic use, multi-drug resistance and increased costs.¹

Unmet need for clinical or laboratory tools to distinguish between SIRS and the various forms of sepsis.²

PCT:

- Early production.³
- Sharp increases.³
- More sensitive to resolution of infection.³
- Correlates with host response to microbial infection.⁴

Guidelines recommended that serum PCT levels could be employed as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentations.⁵

References:

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

- **PCT** can aid in the **diagnosis** and **severity stratification** in patients suspected of sepsis, severe sepsis, and septic shock.
- **Clinical symptoms** of sepsis and other noninfectious disease conditions are often similar
- **In multiple studies**, PCT has demonstrated a high sensitivity and specificity for the differentiation of sepsis from SIRS (Systemic Inflammatory Response Syndrome)
- **PCT levels** can be useful for the management of patients after surgery or transplant and in peritonitis

PCT correlation to Patient Prognosis

- In sepsis initial PCT values > 1 ng/ml
- Rapid decline to PCT values < 1 ng/ml associated with good prognosis
- No or slow decline, not getting < 1 ng/ml associated with poor prognosis
- In SIRS no or only short-time increase > 1 ng/ml

Serial measurement of PCT provides a clearer picture of the patient’s response to antibiotic treatment.

- **Decreasing PCT levels** in patients with sepsis indicate effective treatment of the underlying infection
- **Persistently elevated PCT levels** indicate a possible treatment failure
- **When integrated into the management of septic patients**, PCT can help clinicians to manage septic patients more efficiently
PCT shown to improve Accuracy of Clinical Diagnosis

IL-6, IL-8 or CRP without impact on accuracy of clinical diagnosis

Harbarth S. AJRCCM 2001
PCT in Abx Stewardship
Effect of Procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomized, single-blinded interventional trial: Study Design

Patient inclusion by intention to treat with antibiotics

LRTI (CAP, AECB, Bronchitis, Asthma)

Randomization

Standard Week (without PCT result) N=119

Treatment is up to the discretion of the treating Physician

Follow-up after 10-14 days

PCT Week N=124

Low PCT values recommendation not to treat

PCT (ng/ml)

Antimicrobial Treatment?

<0.1 NO!

0.1-0.25 No

0.25-0.5 Yes

>0.5 YES!

Clinical and PCT control after 6-12h

Christ-Crain et al., Lancet 2004, 363(9409) : 600-607
Effect of Procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomized, single-blinded interventional trial: Study Results

**Key Takeaways:** Reduction of antibiotic prescription by ~50%. No difference in outcomes.

<table>
<thead>
<tr>
<th>Category</th>
<th>Standard group</th>
<th>PCT group</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>92</td>
<td>47</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>AECOPD</td>
<td>55</td>
<td>25</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>33</td>
<td>10</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>31</td>
<td>19</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Others</td>
<td>20</td>
<td>14</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Admittance</th>
<th>Hospital LOS</th>
<th>Outcome</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=119)</td>
<td>74</td>
<td>11</td>
<td>64</td>
<td>3</td>
</tr>
<tr>
<td>PCT Group (n=124)</td>
<td>80</td>
<td>11</td>
<td>65</td>
<td>3</td>
</tr>
</tbody>
</table>

Christ-Crain et al., Lancet 2004, 363(9409): 600-607
Effect of Procalcitonin-Based Guidelines vs. Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial

Journal of the American Medical Association.
2009;302(10):1059-1066

Objective:

- Examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes.
ProHosp: 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 without negative impact on outcomes (non-inferiority)

ProHosp - Study Design

Multicenter, non-inferiority, randomized controlled trial

• Patients
  - 1381 patients with LRTI randomized to administration of antibiotics based on PCT algorithm
  - Cutoff ranges for initiating or stopping antibiotics (PCT group) or standard guidelines (control)
  - 6 academic/non-academic ED

• Outcome Measure
  - Composite adverse outcomes of
    ▪ Death,
    ▪ All Cause ICU admission
    ▪ Disease-specific complications,
    ▪ Recurrence/Relapse within 30 days
  - Antibiotic exposure and adverse effects from antibiotics

ProHosp – JAMA 2009 (Schuetz et al)

**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 „Overruling“ in case of:**
  - Respiratory or hemodynamic instability
  - Life-threatening comorbidity
  - Need for ICU admission
  - **PCT < 0.1 µg/l:** CAP with PSI V or CURB >3, COPD with GOLD IV
  - **PCT < 0.25 µg/l:** CAP with PSI >IV or CURB >2, COPD with GOLD > III
  - Localised infection (abscess, empyema)
  - 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 >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: Primary Endpoint (Safety)

Overall Adverse Outcome (30 days)

PCT 15.4% vs. Control 18.9%, RD -3.5%,

- **Death**
  - 5.1% vs. 4.8%,
    - Risk Difference 0.3%

- **All cause ICU admission**
  - 6.4% vs. 8.7%,
    - Risk Difference -2.3%

- **Disease-specific complications**
  - 2.5% vs. 2.0%,
    - Risk Difference 0.5%

- **Recurrance/Readmission**
  - 3.7% vs. 6.5%,
    - Risk Difference -2.8%

- *The 95% CI for the risk difference excludes an excess risk in the PCT group of 7.5% or more satisfying the pre-defined noninferiority criterion.*
Results: Secondary Endpoint (Superiority)

Reduction of Abx exposure in subgroups of patients:
- CAP \(\Rightarrow 32.4\%\) reduction,
- AECOPD \(\Rightarrow 50.4\%\) reduction,
- Acute bronchitis \(\Rightarrow 65.0\%\) reduction

Schütz et al., JAMA.2009;302(10):1059-66
Summary of Results

• PCT guided algorithm in patients presenting to the ED with LRTI, compared to conventional guided practices resulted in:

  – Similar rates of adverse outcomes (non-inferiority)
  – Mean antibiotic exposure was significantly lower
  – Antibiotic-associated adverse effects were significantly lower

_Schütz et al., JAMA.2009;302(10):1059-66_
ProRATA – Lancet 2010 (Bouadma et al.)

- The prospective, parallel-group, open-label
- 5 MICU, 2 SICU
  - 5 university hospitals
  - Suspected bacterial infection
  - N = 621

- Exclusion
  - <18 years
  - Pregnancy
  - ICU LOS < 3 days
  - BMT
  - Chemotherapy induced neutropenia
  - Infections were long-term, treatment is recommended

ProRATA: PrimaryEndpoints

- Mortality at 28 and 60 days (non-inferiority)
  - non-inferiority safety margin of 10%
- Number of days without antibiotics by day 28 (superiority)

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>PCT Group (n=307)</th>
<th>Control Group (n=314)</th>
<th>Between group absolute difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>65 (21.2%)</td>
<td>64 (20.4%)</td>
<td>0.8%</td>
<td>NA</td>
</tr>
<tr>
<td>60-day mortality</td>
<td>92 (30.0%)</td>
<td>82 (26.1%)</td>
<td>3.8%</td>
<td>NA</td>
</tr>
<tr>
<td># days without antibiotics</td>
<td>14.3 (9.1)</td>
<td>11.6 (8.2)</td>
<td>2.7%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

## ProRATA: Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PCT Group (n=307)</th>
<th>Control Group (n=314)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse (%)</td>
<td>20 (6.5)</td>
<td>16 (5.1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Superinfection (%)</td>
<td>106 (34.5)</td>
<td>97 (30.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Days without MV (%)</td>
<td>16.2 (11.1)</td>
<td>16.9 (10.9)</td>
<td>0.47</td>
</tr>
<tr>
<td>ICU LOS, d</td>
<td>15.9 (16.1)</td>
<td>14.4 (14.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospital LOS, d</td>
<td>26.1 (19.3)</td>
<td>26.4 (18.3)</td>
<td>0.87</td>
</tr>
<tr>
<td>Multi-resistant bacteria</td>
<td>55 (17.9)</td>
<td>52 (16.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>AB exposure/1,000 days</td>
<td>663</td>
<td>812</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**No significant difference between number and type of organ dysfunctions**

In ICU patients studied in this trial, a strategy of PCT guidance for AB treatment compared with standard guidelines was

- Non-inferior regarding 28 and 60 days all cause mortality
- Superior, enabling more days alive at 28d without antibiotics

# Antibiotic Stewardship Studies (n=4241)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study name</th>
<th>Research question</th>
<th>Setting</th>
<th>n=</th>
<th>Mortality Control vs PCT group</th>
<th>AB exposure Control vs PCT</th>
<th>Relative AB reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christ-Crain et al</td>
<td>ProRESP</td>
<td>Reduction of antibiotic prescription for LRTI in the ED?</td>
<td>ED, single center</td>
<td>243</td>
<td>4/119 (3.4%) vs 4/124 (3.2%)</td>
<td>10.7 vs 4.8*</td>
<td>55.1%</td>
</tr>
<tr>
<td>Christ-Crain et al</td>
<td>ProCAP</td>
<td>Reduction of antibiotic exposure in CAP in ED and hospital?</td>
<td>ED and hospital, single center</td>
<td>302</td>
<td>20/151 (13.2%) vs 18/151 (11.9%)</td>
<td>12.9 vs 5.7*</td>
<td>55.8%</td>
</tr>
<tr>
<td>Stolz et al,</td>
<td>ProCOLD</td>
<td>Reduction of antibiotic exposure in COPD exacerbation over 6 month?</td>
<td>ED, single center</td>
<td>208</td>
<td>9/106 (8.5%) vs 5/102 (4.9%)</td>
<td>7.0 vs 3.7*</td>
<td>47.1%</td>
</tr>
<tr>
<td>Briel et al,</td>
<td>PARTI</td>
<td>Safety &amp; reduction of antibiotic exposure in upper and lower RTI?</td>
<td>Primary Care, multicenter</td>
<td>458</td>
<td>1/232 (0.4%) vs 0/226 (0%)</td>
<td>6.8 vs 1.5*</td>
<td>77.9%</td>
</tr>
<tr>
<td>Nobre et al,</td>
<td>&quot;ProSEP&quot;</td>
<td>Reduction of antibiotic exposure in sepsis in the ICU ?</td>
<td>ICU , single center</td>
<td>79</td>
<td>8/39 (20.5%) vs 8/40 (20%)</td>
<td>9.5 vs 6**</td>
<td>36.8%</td>
</tr>
<tr>
<td>Schuetz et al,</td>
<td>ProHOSP</td>
<td>Safety &amp; feasibility in LRTI in a multcenter setting?</td>
<td>ED and hospital, multicenter</td>
<td>1359</td>
<td>33/671 (4.9%) vs 34/688 (4.9%)</td>
<td>8.7 vs 5.7*</td>
<td>34.5%</td>
</tr>
<tr>
<td>Stolz et al,</td>
<td>ProVAP</td>
<td>Reduction of antibiotic exposure in VAP in differnt ICUs ?</td>
<td>ICU, multicenter</td>
<td>101</td>
<td>12/50 (24%) vs 8/51 (15.7%)</td>
<td>9.5 vs 13***</td>
<td>26.9%</td>
</tr>
<tr>
<td>Kristoffersen et al</td>
<td>1-PCT</td>
<td>Reduction of antibiotic exposure for LRTI in Denmark?</td>
<td>ED and hospital, single center</td>
<td>210</td>
<td>1/107 (0.9%) vs 2/103 (1.9%)</td>
<td>6.8 vs 5.1*</td>
<td>25.0%</td>
</tr>
<tr>
<td>Hochreiter et al,</td>
<td>ProSICU</td>
<td>Guiding antibiotic therapy with PCT</td>
<td>Surgical ICU, single center</td>
<td>110</td>
<td>14/53 (26.4%) vs 15/57 (26.3%)</td>
<td>7.9 vs 5.9*</td>
<td>25.3%</td>
</tr>
<tr>
<td>Bouadma et al,</td>
<td>ProRATA</td>
<td>Reduction of antibiotic exposure for sepsis in different french ICUs ?</td>
<td>ICU, multicenter</td>
<td>621</td>
<td>64/314 (20.4%) vs 65/307 (21.2%)</td>
<td>11.6 vs 14.3***</td>
<td>18.9%</td>
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<tr>
<td>Burckhardt et al,</td>
<td>&quot;PARTI Germany&quot;</td>
<td>Safety &amp; reduction of only initial PCT Primary Care, multicenter</td>
<td>Primary Care, multicenter</td>
<td>550</td>
<td>0/275 (0%) vs 0/275 (0%)</td>
<td>36.7% vs 21.5%****</td>
<td>42.0%</td>
</tr>
</tbody>
</table>

Total: 4241 166/2117 (7.8%) vs 159/2124 (7.5%)

*mean; **median; ***antibiotic –free days, ****initial prescription of AB; AB; antibiotic; ED emergency department, ICU intensive care unit, CAP community-acquired pneumonia, COPD chronic obstructive pulmonary disease, VAP ventilator associated pneumonia
PCT Supported by...
**Use of Adjunctive Markers for the Evaluation of Fever**

- Procalcitonin level elevations of >0.5 ng/mL occur within 2–3 hrs of onset, with higher levels observed along the continuum from systemic inflammatory response (0.6 –2.0 ng/mL), severe sepsis (2–10 ng/mL), and septic shock (>10 ng/mL).
- Most importantly, viral infections, recent surgery, and chronic inflammatory states are not associated with an increment in procalcitonin levels.

**Recommendation for Using Biomarkers to Determine the Cause of Fever**

- Serum procalcitonin levels and endotoxin activity assay can be employed as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentations (level 2).
  - Level 2 : “reasonably justifiable by available scientific evidence and strongly supported by expert critical care opinion”

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*O*Grady NP et.al., Crit Care Med 2008; 36:1330-1349; ** Dellinger et.al., Crit Care Med 2008; 36:296-327
SCCM 2012

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock

**Antimicrobial Therapy**

- Antimicrobial therapy within 1 hr of septic shock (1B) or severe sepsis (1C) recognition
- Antimicrobial regimen should be reassessed daily for potential de-escalation (1B)
  - Use of low PCT or similar biomarkers to assist in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (2C)

- Weak recommendation in favor of an intervention indicates judgment that the desirable effects of adherence to a recommendations probably will outweigh the undesirable effects. Panel is not confident about the benefit vs. downside or they are closely balanced.
  - Weak recommendation “we suggest”

Dellinger R et al., Crit Care Med. 2013. 41:2 580-637.