Procalcitonin and other biomarkers for infectious disease

Infectious Diseases in Clinical Practice
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Disclosures

• I have no financial disclosures
• I will not discuss off-label uses of medications or unapproved laboratory tests
Content and Learning objectives

• Discuss how biomarkers may be used to guide diagnosis of infection and antibiotic therapy
• Define procalcitonin and explain its characteristics
• Recognize the limitations of procalcitonin and other biomarkers as an effective tool for making treatment decisions

Outline

• Definition and assay characteristics
  • Lactate
  • ESR / CRP
  • Procalcitonin
• Data for use of procalcitonin in sepsis
• Data for use of procalcitonin in lower respiratory tract infection
• Summary and recommendations
Scope of the problem

- Sepsis is diagnosed in 1.7 million adults per year
- Bacterial infections account for ~50% of cases of sepsis
- Clinicians cannot hold antibiotics while awaiting cultures, and cultures are not perfectly sensitive
- A rapid, low cost assay that is both sensitive and specific for bacterial infection would be a welcome addition to sepsis diagnosis and management

Intensive Care Med, 43 (2017), pp. 304-377

Why use biomarkers?

- as a diagnostic tool – “is this patient septic?”
- as a tool for staging of disease severity – “how should we triage?”
- as an indicator of prognosis – “what is the most likely outcome?”
- for prediction and monitoring of clinical response to therapy – “how can we know if this is working?”
Usual biomarkers for infection

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Produced By</th>
<th>Infectious Triggers</th>
<th>Non-infectious Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>Bone Marrow</td>
<td>Any infection (bacteria, viruses, fungi, etc)</td>
<td>Surgery, steroids, neoplasia, trauma</td>
</tr>
<tr>
<td>CRP</td>
<td>Liver</td>
<td>Any infection; endocarditis, osteomyelitis</td>
<td>Autoimmune, IBD, surgery, trauma</td>
</tr>
<tr>
<td>Lactate</td>
<td>Anaerobic metabolism</td>
<td>Sepsis</td>
<td>Trauma, surgery, burns, seizure, ischemia, DKA, toxic ingestion, cirrhosis</td>
</tr>
</tbody>
</table>


Lactate levels correlate with mortality in sepsis

Lactate is not specific for infection

![Graph showing lactate levels in infected and non-infected individuals](image)


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**ESR and CRP**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRP</th>
<th>ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Activates complement, acts as an opsonin for various pathogens</td>
<td>Fibrinogen mediates coagulation and inflammation</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Dying cells release cytokines, causing liver to produce CRP</td>
<td>Fibrinogen causes RBCs to clump, ESR is indirect measure</td>
</tr>
<tr>
<td>Rate of rise</td>
<td>Rapid rise 4-6 hrs, peaks 1-2 days, normalizes 3-7 days after stimulus ends</td>
<td>Slow rise, peaks 7-10 days, half-life of weeks after stimulus ends</td>
</tr>
<tr>
<td>Specimen needed</td>
<td>Serum/plasma, stable ~7 days</td>
<td>Fresh whole blood, test same day</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>High</td>
<td>Low/moderate</td>
</tr>
</tbody>
</table>

Value of ESR/CRP for infectious diseases

- When you suspect active infection, may be helpful to check and trend CRP
- Normal value does not rule out infection, elevated level does not rule in

<table>
<thead>
<tr>
<th>Variable</th>
<th>RD (n=32)</th>
<th>Infection (n=20)</th>
<th>Malignancy (n=6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR, mm/h</td>
<td>65 (8-120)</td>
<td>73 (30-109)</td>
<td>80 (40-140)</td>
<td>NS</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>26 (1-109)</td>
<td>64 (9-394)</td>
<td>71 (9-317)</td>
<td>0.009*</td>
</tr>
</tbody>
</table>

RD: rheumatic disease

*Difference between RD vs Infection p=0.006, RD vs Malignancy p=0.055 in post-hoc analysis

Procalcitonin

• Procalcitonin (PCT): Peptide pre-hormone of calcitonin
  • CT secreted by thyroid C-cell as response to hypercalcemia
  • Normal PCT values negligible in healthy adults (< 0.05 ng/dl)

Procalcitonin discovery

• 1983: calcitonin is elevated in toxic shock, bacterial meningitis
• 1990: “calcitonin-related peptide” elevated in sepsis
• 1993: procalcitonin in sepsis
  • Produced by many body tissues in sepsis
  • Continuum of PCT level from no infection → mild infection → severe sepsis
  • Non-infectious stimuli as well, but transient

Mechanism

• Bacterial infection $\rightarrow$ IL-1, IL-6, and tumor necrosis factor-$\alpha$ $\rightarrow$ stimulates PCT production
• Viral infection $\rightarrow$ interferon-$\gamma$ $\rightarrow$ no stimulation of PCT

![Diagram of PCT production and response](image)

Characteristics

• Rises at 3 – 6 hrs, peaks 12 -24 hrs
• Correlated with infection severity
• Levels decline 50% over 24 hours
• Assay time $\sim$30 mins
• Cost $\sim$25

![Box plot of PCT levels](image)
### Reasons for inaccurate result

#### False Positives
- Severe stress
  - Birth
  - Trauma/post-op
  - Burn
- Non-bacterial cytokine storm
  - Malaria
  - Systemic fungal infection
  - GVHD
- Dysregulated PCT
  - Meds (IL-2, Anti-thymocyte globulin)
  - Paraneoplastic (carcinoid, medullary thyroid, SCLC, etc)

#### False Negatives
- Very early infection
- Intracellular bacteria
  - Mycoplasma
  - Legionella
- Localized / indolent infection
  - Subacute bacterial endocarditis
  - Occult abscess
  - Osteomyelitis

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### Procalcitonin – rationale for use

**Procalcitonin can aid decisions about antimicrobial initiation and/or de-escalation**

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- Redundant coverage: 10%
- Spectrum not indicated: 4%
- Noninfectious or nonbacterial: 33%
- Colonization or contamination: 16%
- Duration too long: 34%
- Adjustment not made: 3%

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Where Data Exists for PCT

Clinical setting for PCT use

<table>
<thead>
<tr>
<th>Setting</th>
<th>Abx initiation</th>
<th>Abx duration, days median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>64% vs 84%</td>
<td>7 (4–10) vs 10 (7–13)</td>
</tr>
<tr>
<td>Outpatient*</td>
<td>23% vs 63%</td>
<td>7 (5–8) vs 7 (6–8)</td>
</tr>
<tr>
<td>ED</td>
<td>73% vs 88%</td>
<td>7 (4–10) vs 10 (7–12)</td>
</tr>
<tr>
<td>ICU</td>
<td>100% vs 100%</td>
<td>8 (5–15) vs 12 (8–18)</td>
</tr>
</tbody>
</table>

*Mainly trials of URI, bronchitis, COPD exacerbation

Procalcitonin – ICU

- PCT >1 ng/mL had sensitivity 89%, specificity 94% for the diagnosis of sepsis (PPV 94%, NPV 90%) in the ICU

<table>
<thead>
<tr>
<th></th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>CRP</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>IL-6</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>Lact</td>
<td>58</td>
<td>61</td>
</tr>
</tbody>
</table>

2007: PCT to diagnose sepsis

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic odds ratio</th>
<th>(95% CI)</th>
<th>Patient populations</th>
<th>Forest plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon (2004)</td>
<td>24.58</td>
<td>(7.96-75.94)</td>
<td>Hospitalised patients</td>
<td></td>
</tr>
<tr>
<td>Uzzan (2006)</td>
<td>15.70</td>
<td>(5.10-27.09)</td>
<td>ICU/surgical/trauma patients</td>
<td></td>
</tr>
<tr>
<td>Jones (2006)</td>
<td>9.86</td>
<td>(5.72-17.01)</td>
<td>Emergency department patients</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11.31</td>
<td>(7.29-17.53)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2013: PCT to diagnose of sepsis

- 30 studies, 3244 patients
- Pooled sensitivity was 0.77 (95% CI 0.72–0.81) and pooled specificity was 0.79 (95% CI 0.74–0.84)

Lancet Infect Dis, 13 (2013), pp. 426-435

PCT to trend treatment response in severe sepsis

Multicenter RCT ~600 ICU patients

Primary endpoint: all-cause mortality and antibiotic-free days


<table>
<thead>
<tr>
<th>Procalcitonin group (n=207)</th>
<th>Control group (n=214)</th>
<th>Between-group absolute difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>65 (21.2%)</td>
<td>64 (20.4%)</td>
<td>0.0% (-6 to 6.2)</td>
</tr>
<tr>
<td>60-day mortality</td>
<td>92 (30.0%)</td>
<td>92 (26.1%)</td>
<td>3% (-2.1 to 9.7)</td>
</tr>
<tr>
<td>Number of days without antibiotics</td>
<td>14.3 (9.1)</td>
<td>11.6 (8.2)</td>
<td>2.7 (1.4 to 4.1)</td>
</tr>
<tr>
<td><strong>Secondary endpoints (days 5–28)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>20 (6.5%)</td>
<td>16 (5.1%)</td>
<td>1.4% (-2.3 to 5.1)</td>
</tr>
<tr>
<td>Suppression</td>
<td>106 (30.4%)</td>
<td>97 (29.9%)</td>
<td>3% (-3.6 to 11.0)</td>
</tr>
<tr>
<td>Number of days without mechanical ventilation</td>
<td>16 (11.1)</td>
<td>16 (10.9)</td>
<td>-0.7 (-2.4 to 1.1)</td>
</tr>
<tr>
<td>SOFA score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>7.5 (4.4)</td>
<td>7.2 (4.4)</td>
<td>0.3 (-0.4 to 1.0)</td>
</tr>
<tr>
<td>Day 7</td>
<td>4.1 (4.2)</td>
<td>4.0 (4.2)</td>
<td>0.1 (-0.6 to 0.8)</td>
</tr>
<tr>
<td>Day 14</td>
<td>2.8 (3.5)</td>
<td>2.8 (3.5)</td>
<td>0.0 (-0.6 to 0.7)</td>
</tr>
<tr>
<td>Day 21</td>
<td>2.1 (3.3)</td>
<td>1.9 (3.1)</td>
<td>0.2 (-0.4 to 0.4)</td>
</tr>
<tr>
<td>Day 28</td>
<td>1.5 (2.0)</td>
<td>0.9 (2.4)</td>
<td>0.6 (0.0 to 1.1)</td>
</tr>
<tr>
<td>Length of stay in ICU from inclusion (days)</td>
<td>15.9 (16.1)</td>
<td>14.4 (14.1)</td>
<td>1.5 (9.0 to 3.9)</td>
</tr>
<tr>
<td>Length of stay in hospital from inclusion (days)</td>
<td>26.1 (19.3)</td>
<td>26.4 (19.3)</td>
<td>-0.3 (-3.2 to 2.7)</td>
</tr>
<tr>
<td>Multidrug-resistant bacteria</td>
<td>55 (17.9%)</td>
<td>52 (16.6%)</td>
<td>3.1% (-4.6 to 7.2)</td>
</tr>
<tr>
<td>Days of antibiotic exposure per 1000 patient days</td>
<td>653</td>
<td>812</td>
<td>-159 (-105 to -131)</td>
</tr>
</tbody>
</table>

PRORATA

- 23% relative reduction in days of antibiotic exposure
- Antibiotic-sparing mainly obtained by shortening duration

<table>
<thead>
<tr>
<th></th>
<th>PCT group (n=307)</th>
<th>Control group (n=314)</th>
<th>Between group abs difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days without Abx</td>
<td>14.3 (9%)</td>
<td>11.6</td>
<td>2.7 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Days of Abx exposure</td>
<td>653</td>
<td>812</td>
<td>-159 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

PCT for lower respiratory tract infections (LRTIs)

Early data for PCT use for LRTIs

- 2004: PCT reduces antibiotic prescriptions for lower respiratory tract illnesses (LRTI) by 40%
- 2006: PCT reduces antibiotics for COPD (65%) and CAP (30%)
- No increase in adverse events

Pro-HOSP Study

• RCT of 1360 hospitalized adults with lower resp tract infection


PCT reduced antibiotic use for all forms of LRTI

• CAP: 32% abx reduction
• COPD: 50% abx reduction
• Bronchitis: 65% abx reduction
• No difference in mortality, ICU admission, or complications

Pro-VAP Study

• RCT of 100 pts treated for vent-associated pneumonia
• 27% reduction in antibiotic therapy in PCT group (15→10d)

Pro-ACT study

• 14 hospitals with “high adherence” to QI measures for pneumonia
• ED and inpatient clinicians educated about the use of PCT for LRTI
• Patients presenting with suspected LRTI then randomly assigned to serial PCT (with antibiotic use guideline) or standard care
PCT failed to influence antibiotic use in ED or hospital

A focus on mortality data

- 2018 systematic review and meta-analysis
- 26 randomized trials and 6708 patients
PCT assay thresholds

- No PCT level has been found to be perfectly sensitive or specific for detection of bacterial infection
- In most studies, PCT level of 0.25 or 0.50 has been used as a cut-off for discouraging ongoing antibiotic use
- Significant decline of PCT from baseline measurement (usually ~80%) has also been used
2019 systematic review and meta-analysis of 12 studies in 2408 patients with CAP that included etiologic diagnoses

Forest Plot for Sensitivity and Specificity with 95% CI. Pooled sensitivity is 0.55 (95% CI: .37–.71), pooled specificity is 0.76 (95% CI: .62–.86).

<table>
<thead>
<tr>
<th>PCT cut-off</th>
<th>Test Characteristic</th>
<th>Bacterial vs Viral CAP</th>
<th>Bacterial vs Non-bacterial / unknown CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.10 mg/mL</td>
<td>Sensitivity</td>
<td>81%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>52%</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>50%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>82%</td>
<td>94%</td>
</tr>
<tr>
<td>≥0.25 ng/mL</td>
<td>Sensitivity</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>67%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>53%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>78%</td>
<td>92%</td>
</tr>
<tr>
<td>≥0.50 ng/mL</td>
<td>Sensitivity</td>
<td>58%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>73%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>55%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>75%</td>
<td>92%</td>
</tr>
</tbody>
</table>

- Multicenter study of 1735 adults hospitalized with CAP, including 645 with a viral or bacterial pathogen detected
- 23% of patients with typical bacterial pathogens had PCT <0.25 ng/mL, 12% had PCT <0.1 ng/mL.

Other promising biomarkers?

- **Presepsin:**
  - Soluble CD14 subtype, released into the blood upon the activation of monocytes in response to infection
  - Meta-analysis of 19 studies (~3000 patients) showed similar sensitivity and specificity to procalcitonin for diagnosis of sepsis

- **Neutrophil CD64:**
  - Immunoglobulin receptor expressed on resting neutrophils that rises precipitously after exposure to pro-inflammatory cytokines
  - Meta-analysis of 26 studies (~4000 patients) found slightly better sensitivity and specificity for diagnosis of sepsis compared to PCT, but the studies included were very heterogeneous

**Summary**

- The utility of a biomarker is its capacity to provide information to guide clinical decision making for individual patients, in addition to other established and routinely available tests. There’s still no substitute for clinical judgement.
- Lactate, C-reactive protein and procalcitonin (PCT) are biomarkers that often correlate with presence of acute infection, but cannot rule in or rule out
- PCT has sensitivity and specificity in range of 55-75% for bacterial infections – not good enough as a stand-alone marker
- PCT may be more useful for de-escalation of antibiotics
- Newer biomarkers still being studied, not commercially available at present
Questions?

???