Comparing Biomarkers in Used in Infection, Sepsis, and Septic Shock: What is the Role of Procalcitonin

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Disclosure

• No financial disclosures
  o No financial gain from pharmaceutical companies
  o No stock ownership

• Historically, I have partnered with the healthcare companies bioMerieux (Vitek), Carefusion, Cardinal Health, TheraDoc, and ICNet to help them with special projects at their requests

• Information presented is based on my interpretation of the evidence and clinical experience
Objectives

- Provide a synopsis of currently available biomarkers used in infectious disease
- Compare and contrast common biomarkers to determine which marker or group of markers can provide the clinician with effective diagnostic information and risk stratification
- Attendees will be able to assess if their current biomarker choices provide their clinicians with optimal clinical effectiveness
Diagnoses of the Patient

Exam findings

Suspicion of infection

Ancillary services

Lab

Infection requiring treatment?

Infectious Agent

• Bacteria
• Virus
• Fungus....

Severity

Treatment plan

Biomarkers

WBC
CRP
Lactate
Procalcitonin
Others
Biomarker

• Anything that can be used as an indicator of the physiological state of an organism, even temperature is considered a biomarker.

• NIH: Any characteristic that is objectively measured and evaluated as an indicator of normal biologic process, pathogenic process, or pharmacologic response to a therapeutic intervention

• Over one hundred seventy six (176) biomarkers studied for the diagnosis or management of infection and sepsis

• Biomarkers
  • Infection
  • Cancer
  • Cardiac
The Biomarker Catch

• The clinical phenotype of a patient with significant infection/sepsis generally is similar to that of a patient with systemic inflammatory response caused by non-infectious” inflammation
• Difficult to differentiate bacterial, viral, and fungal
• Affected by immunosuppressed patients
• Autoimmune diseases
• Anti-inflammatory, disease modifying, steroids
Marker Categories

- Proinflammatory markers of the immune system
- Proteins produced in response to infection and/or inflammation
- Markers of abnormal coagulation
- Markers of end organ function
Proinflammatory cytokines of the immune system

- Tumor Necrosis Factor (TNF)
- Interleukin-1 (IL-1)
- Interleukin-6 (IL-6)

Faix JD, Established and Novel Biomarkers of Sepsis, Biomarkers Med., 2011 (5)2, 117-130
TNF, IL-1, & IL-6

- Primary cytokines that mediate the initial response of the immune system to injury or infection
- Major source is the activated macrophage
- All have been studied extensively
- IL-6 has the most attention; more reliably measured in the plasma (original proof of concept)
- IL-6 is useful in autoimmune rheumatic disorders and malignancies
- Neither is specific enough to be useful clinically, especially alone

Faix JD, Established and Novel Biomarkers of Sepsis, Biomarkers Med., 2011 (5)2, 117-130
Proteins produced in response to infection &/or inflammation

Produced in response to proinflammatory cytokines TNF and IL-1

- Interleukin-8 (IL-8)
- Monocyte chemo-attractant Protein-1
- C-reactive protein (CRP)
- Pentraxin-3
- Lipopolysaccharide-binding protein
- Complement C3b and C5a
- Procalcitonin (PCT)
Markers of abnormal coagulation

• D-dimer
• Protein C
• Plasminogen activator inhibitor-1
Markers of abnormal coagulation

• Consumption of coagulation factors and platelets along with inhibition of the fibrinolytic system results in microvascular fibrin deposits resulting in interruption of blood flow and end organ damage
• D-Dimer is the most common fibrin related marker and is used in DIC scoring
• D-Dimer in conjunction with PCT may be useful in other diagnoses
• Protein C was used with drotrecogin-alfa (Xigris) as a surrogate marker in therapy
• Problem with markers of coagulation is that late sepsis or septic shock has already occurred
Markers of end organ dysfunction

• Lactate
• Membrane microparticles
Lactate (lactic acid) is produced when body experiences inadequate tissue perfusion – a defining parameter of late sepsis

• Distinguishes infection from sepsis and septic shock

• Useful in prognosis of septic shock
# Biomarker Summary

<table>
<thead>
<tr>
<th>Marker</th>
<th>Differentiate Bacteria</th>
<th>Clinical Usefulness</th>
<th>Availability</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF, IL-1, IL-6</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>IL-8</td>
<td>No</td>
<td>++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Pentraxin-3</td>
<td>No</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>LPS Binding</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+++++</td>
</tr>
<tr>
<td>C3b &amp; C5a</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>+++++</td>
</tr>
<tr>
<td>CRP</td>
<td>No</td>
<td>+</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>CD64</td>
<td>No</td>
<td>++</td>
<td>+</td>
<td>+++++</td>
</tr>
<tr>
<td>TREM-1</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>+++++</td>
</tr>
<tr>
<td>PCT</td>
<td>Yes</td>
<td>+++++</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>Lactate</td>
<td>No</td>
<td>+++</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>No</td>
<td>+</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>Protein-C</td>
<td>No</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
</tbody>
</table>
## Comparison of Clinical Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Specificity Bacterial Infection</th>
<th>Sensitivity Inflammation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>+</td>
<td>+++</td>
<td>Simple Inexpensive</td>
<td>Sensitivity for bacteria Non-specific for bacterial infection All inflammation &amp; infections Disease states/drug - 596</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>++</td>
<td>++</td>
<td>Inexpensive Moderately specific</td>
<td>All inflammation &amp; Infections Slow induction (peak &gt;24h) No correlation with severity</td>
</tr>
<tr>
<td>Lactate</td>
<td>+</td>
<td>+</td>
<td>Inexpensive Reliable marker of perfusion Prognosis &gt; Sepsis</td>
<td>Must be in sepsis to be elevated Very poor specificity for bacterial infection</td>
</tr>
<tr>
<td>Procalcitonin (PCT)</td>
<td>++++</td>
<td>+</td>
<td>Specificity for bacteria Favorable kinetics Rise/half-life Correlates with severity of illness Antibiotic use</td>
<td>Education Instrument for Lab More expensive than WBC, CRP, and lactate</td>
</tr>
</tbody>
</table>

Diagnostic accuracy of PCT compared to other biomarkers used in sepsis for bacteria

- **Sensitivity: 89%**
- **Specificity: 94%**
- **NPV: 90%** / **PPV: 94%**

- PCT levels accurately differentiate sepsis from noninfectious inflammation*
- PCT has been demonstrated to be the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infectious cause

What is Procalcitonin and its role in sepsis management?
Bacterial induction and release from all tissues

Healthy Individuals

Systemic response to 
**bacterial infection**

PCT Kinetics

- Rapid kinetics: detectable 3 hours after infection has begun, with a peak after 12 to 24 hours
- Peak values up to 1000 ng/ml
- Half-life: ~ 24 hours

Procalcitonin

- PCT is induced in systemic inflammatory reactions
- Bacterial infections release much greater quantities of PCT compared to non-bacterial etiologies
- PCT induction and release is in direct proportion to the bacterial insult to the body
- Viral infections, autoimmune diseases, transplant rejections, and allergic reactions generally do not induce PCT
- PCT is therefore an “indirect marker” of a bacterial infection: PCT a measurement of the body’s inflammatory response to the bacteria
PCT Interpretation

- PCT thresholds depend on clinical situation of the patient
- Correlates with bacterial burden or bacterial load

Non-Bacterial Stimuli

- Primary inflammation syndrome following trauma: multiple trauma, extensive burns, major surgery (abdominal and transplant)
- Severe pancreatitis or severe liver damage (1ng/ml)
- Prolonged circulatory failure: IE severe multiple organ dysfunction syndrome (MODS) (1.4ng/ml)
- Medullary or C-cell cancers of the thyroid, pulmonary small-cell carcinoma and bronchial carcinoma
- Newborn < 48hr - increased PCT values (physiological peak)
PCT response to bacterial challenge

Elevated or rising PCT values
  • Systemic response to bacterial infection
    o Progressing infection
    o Immune system is overwhelmed
  • Risk of significant disease progression

Low PCT values in presence of clinical presentation
  • Self-limiting infection
  • Non-bacterial etiology
  • Early phase of infection
Aiding Sepsis Risk Assessment

• PCT levels above 2 ng/ml indicate a higher risk for progression to sepsis or septic shock
• PCT levels below 0.5 ng/ml indicate a low likelihood of progression to sepsis or septic shock
• Suggest a baseline with daily levels for 72 hours resulting in 4 PCT values
Aiding Septic Patient Management

- Multiple PCT measurements over consecutive days aids in assessing the response to empiric antibiotic therapy.
- As infection is controlled, PCT will decline daily.
- The Procalcitonin Monitoring Sepsis Study (MOSES) showed that sustained PCT elevation is an independent risk factor for mortality.
- PCT level decline less than 80% from baseline within four days is associated with increased all-cause mortality, especially with initial PCT is greater than 2 ng/ml.
67 Y/O female
CC: Mild mental confusion, c/o pain in neck, shoulders, upper and lower back, and other diffuse arthralgia’s

Medical History:
Recurrent Urinary Tract Infections
Hypertension
Migraine headaches
Depression NOS
Generalized Anxiety D/O
Fibromyalgia
Restless leg syndrome
Osteoporosis

Chlorthalidone 25mg daily
Lisinopril 10mg daily
Verapamil 240mg daily
Sumatriptin 50mg prn
Milnacipran 50mg bid
Sertraline 50mg daily
Pregabalin 150mg bid
Clonazepam 0.5mg prn bid
Pramipexole 1mg HS
Nitrofurantoin 100mg bid
Hydrocodone/Acetamin 7.5mg/325mg prn q 4 hours
**UA collection**
- Mini-Cath - clogged
- Required 4 attempts

**Urinalysis**
- Nitrite positive
- WBC: 5
- Bacteria 4+
- Dark yellow
- Clarity: cloudy

**Other Lab**
- WBC: 9.6 x 1000
- PCT: 0.05ng/ml
BE: UTI and Lactate Specificity

PCT
Lactate
Troponin

STEMI + 2 Stents

BP 142/82
BP 90/58
BP 98/60

Day 1 @ 0800
Day 2 @ 0700
Day 2 @ 1700
Day 2 @ 1800

0.05
0.05
0.05

1.51
73 Y/O female
CC: dysuria, fever, nausea/vomiting
Temp 103.4
Hx: Recurrent UTI’s last 3 years
RR 19
BP 142/84
HR 95
WBC 28.4 w/4 bands
Lactate 1.9 mmol/L
SrCr 1.6 mg/dl w/ BUN 38
Mini-cath UA
- Nitrite positive
- Leukocyte esterase positive
- 4+ bacteria

75 Y/O female
CC: dysuria, fever, nausea/vomiting
Temp 102.8
Hx: Recurrent UTI’s last 4 years
RR 18
BP 156/86
HR 91
WBC 26.4 w/4 bands
Lactate 1.8 mmol/L
SrCr 1.8 mg/dl w/ BUN 34
Mini-cath UA
- Nitrite positive
- Leukocyte esterase positive
- 4+ bacteria
HW & CK

HW

PCT 9.3

Ceftriaxone 1gm every 24 hours

CK

PCT 8.1

Levofloxacin 500mg every 24 hours
Cardiovascular status: 126/83 - 83
Replace levofloxacin with meropenem
Repeat PCT in 12 hours
56 Y/O male, construction worker
Asthma since childhood
CC: SOB, productive cough, malaise, fever
Duration of 12-14 days
Azithromycin Z-Pak
Benazepril 20 mg daily
Nebivolol 5 mg daily
Citalopram 20 mg daily
Furosemide 80 mg daily
Omeprazole 20 mg daily
Prednisone 5 mg daily
Mometasone 220 mcg daily
Albuterol MDI prn q 4 hours for SOB/wheezing

Question:
What is your Tx plan if the procalcitonin was 0.7?
Now:
Would your plan be different if the procalcitonin was 17?
JW clinical course

Day 1 (22 hours)
- Temp 101.8
- BP 138/82
- RR 22
- WBC 22.4 x 1000
- Bands 10
- Lactate 2.1 mmol/L

Day 2
- Temp 103.6
- BP 106/62
- RR 26
- WBC 28.8
- Bands 12
- Lactate 5.6 mmol/L
- PCT 86 ng/ml
- Blood gases

PCT = 36 ng/ml
JW clinical course

Day 2 continued

- Increase fluids
- DC Levofloxacin
- Start Vancomycin
- Start Meropenem
- CPAP > Ventilator
- Sputum Gram stain: coagulase positive/gram-positive cocci in clusters
- 1st blood culture Gram stain: coagulase positive/gram-positive cocci in clusters
- Nasal culture plate: MRSA

Day 2 PM

- PCT 72 ng/ml
JW clinical course

Day 3

- Temp 101.2
- BP 120/68
- WBC 23.3 x 1000
- Bands 10
- Lactate 2.2mmol/L
- BP 120/68
- PCT 46 ng/ml
- Sputum: MRSA
- Blood Cx: MRSA
JW clinical course

Summary

JW Biomarker Trend

- PCT
- WBC
- Lactate

Admission Day 1 Day 2 Day 2.5 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8
• The pneumonia diagnosis is based on three pillars (1) clinical symptoms (2) tissue infiltration (3) signs of inflammation, suspicion of infection – elevated PCT is not absolutely essential, but be aware of significant elevations (1/3rd / 0.5ng/ml)

• Significant elevations in procalcitonin after 24 hours is always cause for concern and that the infectious organism is not being adequately treated
Retrospective Analysis: Before and After

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<th>2010 PCT implementation</th>
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<td>Implementation</td>
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</tr>
<tr>
<td>COPD</td>
<td>Education</td>
<td>COPD</td>
</tr>
<tr>
<td>Biliary tract</td>
<td></td>
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</tr>
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<tr>
<td>SSSI</td>
<td></td>
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</tr>
<tr>
<td>GU</td>
<td></td>
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</tr>
<tr>
<td>Septicemia</td>
<td></td>
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</tr>
<tr>
<td>Other</td>
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Inclusion and Exclusion Criteria

• **Inclusion:**
  - All patients with ID diagnosis requiring parenteral administration of antibiotics at onset of therapy
  - All age groups (pediatric through aged)

• **Exclusion:**
  - Patients admitted for surgical prophylaxis
  - Patients transferred to other facilities

• **Process Implemented:**
  - PCT at baseline (ED or admission) and every 24 hours and as needed
  - PCT placed in all ID related order sets and protocols

• **Pharmacy reviewed:**
  - All PCT orders
  - All antimicrobial orders
  - Communicated with prescribers to close loop of missed lab and/or therapy changes
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<td>Osteomyelitis</td>
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<td>GU</td>
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## Statistical Analysis

<table>
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<tr>
<th>Clinical factor</th>
<th>p-value</th>
<th>Applied test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.2505</td>
<td>Mann–Whitney U test</td>
</tr>
<tr>
<td>Gender</td>
<td>0.6149</td>
<td>Chi-square test Gender vs. time (before/after)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.9124</td>
<td>Mann-Whitney U test</td>
</tr>
<tr>
<td>Adverse drug events</td>
<td>4.47E-09</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>C difficile</td>
<td>0.002128</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>8.43E-06</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>30 day readmissions</td>
<td>9.39E-09</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Antimicrobial days of therapy per patient:</td>
<td>0.00018</td>
<td>Mann-Whitney U test</td>
</tr>
</tbody>
</table>
Five Rivers Medical Center

- **Outcomes Comparison:** Control Vs. Procalcitonin
- 4 years Pre (n=985) and Post Procalcitonin (n=1167) implementation with one year for education between patient groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre</th>
<th>Post</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Days of Therapy</td>
<td>16.43 DOT</td>
<td>9.52 DOT</td>
<td>P &lt; 0.00018</td>
</tr>
<tr>
<td>Mortality due to Infectious Diseases</td>
<td>6.9%</td>
<td>2.8%</td>
<td>P&lt; 0.000001</td>
</tr>
<tr>
<td>30-day Readmission for Infection</td>
<td>18%</td>
<td>9.5%</td>
<td>P &lt; 0.000001</td>
</tr>
<tr>
<td>C. difficile Rate</td>
<td>9.5%</td>
<td>0.9%</td>
<td>P &lt; 0.002128</td>
</tr>
<tr>
<td>Adverse Drug Events</td>
<td>16.2%</td>
<td>8.1%</td>
<td>P &lt; 0.000001</td>
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</tbody>
</table>
Questions

mrbroyles@suddenlink.net