ADVANCES IN BIOMARKER TESTING FOR SEPSIS AND BACTERIAL INFECTIONS

ERIC H GLUCK MD JD FCCP FCCM
DIRECTOR OF CRITICAL SERVICES
SWEDISH COVENANT HOSPITAL
DISCLOSURES:

Speaking engagements and consulting:

• Thermo Fisher Scientific, Middletown, VA
• Roche Diagnostics, Indianapolis, IN
• bioMerieux, Durham, NC
OBJECTIVES

• Define ‘infection’
• Describe the biology and kinetics of procalcitonin and other biomarkers used in the evaluation of sepsis
• Discuss the ability to use biomarker levels for mortality prediction in severe sepsis and septic shock patients
• Illustrate biomarker clinical utility when used to tailor individualized patient treatment in LRTI and Sepsis
WHAT IS AN INFECTION?

Infection exists when the body thinks it does

• We co-exist with 5,000,000,000 bacteria

• They are essential for our survival

• If kept in check this situation is mutually beneficial

• When the body reacts to a non-self organism for the purpose of containing or eliminating it, then there is a state of infection
TREATING INFECTION – THEN AND NOW

• Diagnosis of infection was based mostly on gut feeling. Corroboration with objective evidence was poor 60 years ago and remains poor today

• Antibiotics are prescribed not titrated
  ▪ Most antibiotic regimens are based on duration not on individual response

• Severity of infection involves
  ▪ Immunocompetency of patient
  ▪ Duration of infection prior to presentation
  ▪ Size of bacterial burden
  ▪ Site of infection
  ▪ Nutritional and functional status
  ▪ etc
TREATING INFECTION – THEN AND NOW

• The duration of antibiotic therapy should be dictated by response to treatment
• White cell count and macromarkers are not sensitive enough nor specific enough to provide this
  2/3 of pts in the ICU have SIRS criteria
  1/4 of pts in a typical ICU have sepsis
TREATING INFECTION – THEN AND NOW

- The innate immune system cannot always differentiate sepsis from damage, since the latter is often part of the process.
- Therefore the signal for infectious inflammation and sterile inflammation is often non specific.
ROLE OF BACTERIA IN HEALTH AND DISEASE

DOSE RESPONSE TO BACTERIAL PRESENCE

HOST RESPONSE TO INFECTION VS. INFLAMMATION

Diacovich & Gorvel. Bacterial manipulation of innate immunity to promote infection. Nature Reviews Microbiology 8, 117-128 (February 2010)
LOCAL AND SYSTEMIC RESPONSE TO INFECTION

Site of Infection
Local innate inflammatory response

Loss of containment. Sepsis.

Secondary Response
Liver, spleen, bone marrow, brain

Antibiotics and Fluids

Subsequent modulation by anti-inflammatory agents

IL-6
IL-1
PCT

‘Bystander’ Injury

CRP
PCT
DEFINING SEPSIS: THEN & NOW

THEN
- SIRS
- Severe Sepsis
- SIRS + Infection
- Septic Shock

NOW
- Infection
- Sepsis
- Sepsis + Organ Failure
- Severe Sepsis + Hypotension
- ↓BP + LA ≥ 2mmol/L
- Modified Sepsis
- Modified Septic Shock

SOFA ≥ 2
PCT KINETICS PROVIDE IMPORTANT INFORMATION ON PROGNOSIS OF SEPSIS PATIENTS

- Clinical symptoms alone are often insufficient for early and accurate diagnosis

- PCT levels can be observed within 3-6 hours after an infectious challenge with a peak up to 1000 ng/ml after 6-12 hrs. Half-life ~24hrs

- Specific to bacterial origin of infection and reflects the severity of the infection

ADDING PCT RESULTS TO CLINICAL ASSESSMENT IMPROVES THE ACCURACY OF THE EARLY CLINICAL DIAGNOSIS OF SEPSIS

- 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

KINETICS OF PROCALCITONIN

- Rapid and sustained response to bacterially induced systemic inflammation
- Half-life: 24 hours
- If the pathogen is not contained, infection spreads and the body up-regulates proinflammatory mediators

Harbarth et al. AJRCCM 2001
Jensen JU, Crit Care Med 2006;34:2596-602
Schuetz P, Gluck EH et al., Crit Care Med, 2013, 17:R115
Serial Procalcitonin Predicts Survival in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study

Philipp Schuetz, MD, MPH; Robert Birkhahn, MD; Robert Sherwin, MD; Alan E. Jones, MD; Adam Singer, MD; Jeffrey A. Kline, MD; Michael S. Runyon, MD, MPH; Wesley H. Self, MD; D. Mark Courtney, MD; Richard M. Nowak, MD; David F. Gaieski, MD; Stefan Ebmeyer, MD; Sascha Johannes, PhD; Jan C. Wiemer, PhD; Andrej Schwabe, PhD; Nathan I. Shapiro, MD, MPH
- Procalcitonin is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on the first day of ICU admission for progression to severe sepsis and septic shock
- Aiding assessment of mortality risk
- Recent FDA clearance includes using PCT to aid in antibiotic therapy decisions in the ICU, ED and patient wards
## INSIGHT FOR LRTI THERAPY DECISIONS

<table>
<thead>
<tr>
<th>PCT Plasma Concentration</th>
<th>Antibiotics Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.50 ng/mL</td>
<td>Antibiotics Strongly Encouraged</td>
</tr>
<tr>
<td>&gt;0.25 – 0.50 ng/mL</td>
<td>Antibiotics Encouraged</td>
</tr>
<tr>
<td>0.10 – 0.25 ng/mL</td>
<td>Antibiotics Discouraged</td>
</tr>
<tr>
<td>&lt; 0.10 ng/mL</td>
<td>Antibiotics Strongly Discouraged</td>
</tr>
</tbody>
</table>
INSIGHT FOR SAFELY DISCONTINUING ANTIBIOTICS

CHANGE IN PCT CONCENTRATION

Decline from peak PCT >80% and Clinical Improvement

CURRENT PCT CONCENTRATION

Discontinue Antibiotics
Sepsis ≤ 0.50 ng/mL
LRTI ≤ 0.25 ng/mL

Important Considerations:
PCT Assay Sensitivity and Low-end Performance

Normal Range for B·R·A·H·M·S PCT: 0.05 ng/mL
USE OF PCT AT MY HOSPITAL

• Early adaptor
• In use for 8 years
• Over 200 levels drawn per month
USE OF PCT AT MY HOSPITAL

- Antibiotics are discouraged by pharmacy if the PCT is negative X 2 at onset of infection or during the treatment
CASE 1

- Patient presents with nausea, vomiting and abdominal pain
- Liver function tests are found to be abnormal with an obstruction type pattern
- WBC is elevated but without a left shift
- Lipase is normal
- Pre test probability strongest for ascending cholangitis
CASE 1: BIOMARKER EVALUATION

- Patient is resuscitated initially
- With 3 L of Normal Saline
- Antibiotics are started
- Cultures are obtained

<table>
<thead>
<tr>
<th>Date</th>
<th>Lactate</th>
<th>PCT</th>
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<tbody>
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<td>0</td>
<td>6.5</td>
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<tr>
<td>0.25</td>
<td>4.0</td>
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</tr>
<tr>
<td>0.5</td>
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<tr>
<td>1</td>
<td>1.8</td>
<td>10.7</td>
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<td>2</td>
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<td>3</td>
<td>5.7</td>
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<td>4</td>
<td>2.3</td>
<td></td>
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<tr>
<td>5</td>
<td>1.4</td>
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</tbody>
</table>
Case 1: Biomarker Evaluation

- Patient is resuscitated initially with 3 L of Normal Saline
- Antibiotics are started
- Cultures are obtained
Case 1: Biomarker Evaluation

<table>
<thead>
<tr>
<th>Date</th>
<th>0</th>
<th>0.25</th>
<th>0.5</th>
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</tr>
<tr>
<td>PCT</td>
<td>0.2</td>
<td>10.7</td>
<td>10.7</td>
<td>5.7</td>
<td>2.3</td>
<td>1.4</td>
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</table>
CASE 1: CLINICAL FOLLOW UP

- The patient's blood pressure stabilized after 3 L of normal saline. He never required blood pressure support with vasopressors.

- The lactate reduction indicated adequacy of resuscitation.

- The PCT often rises for 24 to 36 hours after the onset of treatment since it often requires that long for antibiotics to achieve cidal tissue levels.
CASE 2: SCENARIO I

• Presentation: Female with shortness of breath with modest hypoxia and bilateral patchy infiltrates on chest film.
  • WBCs are elevated with a modest shift to the left
  • Watery yellow tinged sputum production
  • No subjective fever
CASE 2: SCENARIO I

What would this pattern indicate?

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>Lactate</td>
<td>3.5</td>
<td>4.2</td>
<td>1.2</td>
</tr>
<tr>
<td>PCT</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
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</tr>
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</table>
CASE 2: SCENARIO II

This time the LA and PCT are both elevated suggesting that the patient has pneumonia. Sputum was positive for gram+ cocci in chains.

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>4.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT</td>
<td>0.15</td>
<td>3.8</td>
<td>2.9</td>
<td>1.8</td>
</tr>
</tbody>
</table>
CASE 3

• This patient presents with a 2 day history of diarrhea and fever to 102

• Patient had recently undergone a revision of a prior hip surgery and received 48 hours of prophylactic antibiotics
CASE 3: LAB DATA

WBC = 11.2

Bands = 14%

Temp = 101.2

HR = 107

Physical Exam - abdomen distended and tender diffusely
  Bowel sounds were hyperactive

Abdominal X-ray diffuse dilation of large bowel
## CASE 3: BIOMARKER EVALUATION

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>1.2</td>
<td>1.5</td>
<td>1.5</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>&gt;9</td>
<td></td>
<td></td>
<td>Expired</td>
</tr>
<tr>
<td>PCT</td>
<td>15.8</td>
<td>89</td>
<td>64</td>
<td>31</td>
<td>22</td>
<td>16</td>
<td>27</td>
<td>199</td>
<td>&gt;299</td>
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</tr>
</tbody>
</table>
CASE 4

- Patient presents with frequency and dysuria
- UA demonstrates + LE, +nitrites, 24 WBC per HPF, many bacteria
CASE 4: BIOMARKER EVALUATION

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>4.6</td>
<td>1.5</td>
<td>1.5</td>
<td>0.8</td>
</tr>
<tr>
<td>PCT</td>
<td>6.2</td>
<td>5.6</td>
<td>6.4</td>
<td>6.8</td>
</tr>
</tbody>
</table>
CASE 4: PART 2

- Ultrasound demonstrated a perinephric abscess
- The abscess was drained by interventional radiology
- Patient was placed on additional antibiotics
<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT</td>
<td>8.2</td>
<td>7.1</td>
<td>4.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>
CURRENT US GUIDANCE

IDSA 2016: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia

- For patients with HAP/VAP, we suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone (weak recommendation, low-quality evidence)

IDSA 2016: Implementing an Antibiotic Stewardship Program

- In adults in ICUs with suspected infection, we suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use (weak recommendation, moderate quality evidence)

SCCM 2017: Surviving Sepsis Campaign Guidelines

- 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 have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence)
D. Antimicrobial Therapy

14. We suggest that measurement of *procalcitonin* levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.

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).

XVIII. In Adults in ICU With Suspected Infection, Should ASPs Advocate Procalcitonin (PCT) Testing as an Intervention to Decrease Antibiotic Use?

Recommendation

In adults in ICUs with suspected infection, we suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use (weak recommendation, moderate quality evidence).

Comment: “…. If implemented, each ASP must develop processes and guidelines to assist clinicians in interpreting and responding appropriately to results, and must determine if this intervention is the best use of its time and resources.”

Adapted from: Barlam TF et al., Clinical Infectious Diseases 2016. [Epub ahead of print]
XXIV. Should Discontinuation of Antibiotic Therapy Be Based Upon PCT Levels Plus Clinical Criteria or Clinical Criteria Alone in Patients With HAP/VAP?

Recommendation:

For patients with HAP/VAP, we suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone

(weak recommendation, low-quality evidence)
### Table 1 Diagnostic Criteria for Sepsis
Infection, documented or suspected and some of the following:

**General:**
- Fever (>38.3°C), hypothermia (<36°C)
- HR >90 bpm
- Tachypnea
- Altered Mental Status
- Significant Edema or fluid balance (>20 ml/kg over 24h)
- Hyperglycemia >140 mg/dL in absence of DM

**Inflammatory variables:**
- Leukocytosis (WBC >12,000)
- Leukopenia (WBC <4000)
- Normal WBC >10% immature forms
- Plasma CRP above normal
- Plasma Procalcitonin above normal

**Hemodynamic Variables**
- Arterial hypotension
  (SBP < 90 mm Hg, MAP < 70 mm Hg or a SBP decrease > 40 mm Hg in adults)

**Organ Dysfunction variables:**
- Arterial hypoxemia PaO2/Fio2 < 300
- Acute oliguria (UOP < 0.5 mL/kg/hr for at least 2h despite adequate fluid resuscitation)
- Creatinine increase > 0.5 mg/dL
- Coagulation abnormalities (INR > 1.5 or PTT > 60s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count < 100,000)
- Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL)

**Tissue perfusion variables**
- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling

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

• Procalcitonin is a specific and sensitive biomarker reflecting the host response to a systemic bacterial infection

• PCT and lactate are complementary markers

• PCT is used in ED, ICU, and hospital floors and is used to help determine both the severity of illness and the adequacy of source control

• The change in PCT over time reflects the patient’s response to treatment and can aid in risk assessment for mortality in severe sepsis and septic shock patients
QUESTIONS?
<table>
<thead>
<tr>
<th>SOFA score</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FIO₂ (mm Hg)</td>
<td>&gt;400</td>
<td>&lt;400</td>
<td>&lt;300</td>
<td>&lt;200</td>
<td>&lt;100</td>
</tr>
<tr>
<td>SaO₂/FIO₂</td>
<td>≥21 to ≤30</td>
<td>≥14 to ≤20</td>
<td>≥6 to ≤14</td>
<td>≥3 to ≤6</td>
<td>≥1 to ≤3</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets 10⁹/mm³</td>
<td>&gt;150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2.0–5.9</td>
<td>6.0–11.9</td>
<td>&gt;12.0</td>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>No</td>
<td>MAP &lt; 70</td>
<td>Dopamine &gt;5 or dobutamine (any)</td>
<td>Dopamine &gt;15 or norepinephrine &gt;0.1</td>
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</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glasgow Coma Score</td>
<td>15</td>
<td>13–14</td>
<td>10–12</td>
<td>6–0</td>
<td>&lt;0</td>
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<tr>
<td><strong>Renal</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL) or urine output (mL/d)</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2.0–3.4</td>
<td>3.5–4.9 or &lt;500</td>
<td>&gt;5.0 or &lt;200</td>
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SOFA AND qSOFA

**SOFA**

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<tbody>
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<td>Respirations PaO₂/FiO₂ (mm Hg)</td>
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<td>&lt;400</td>
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<td>142-200</td>
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<tr>
<td>Coagulation Platelets x10³/mm³</td>
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<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
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<tr>
<td>Liver Bilirubin (mg/dL)</td>
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<td>1.2-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
<td>&gt;12.0</td>
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<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
<td>MAP &lt;70</td>
<td>Dopamine &lt;15 or dobutamine (any)</td>
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</tr>
<tr>
<td>CNS Glasgow Coma Score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
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<tr>
<td>Renal Creatinine (mg/dL) or urine output (mL/d)</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-3.4</td>
<td>3.5-4.9 or &lt;500</td>
<td>&gt;5.0 or =200</td>
</tr>
</tbody>
</table>

**qSOFA**

- Altered in mental status
- Decrease in systolic blood pressure of less than 100 mmHg
- Respiratory rate greater than 22 breaths/min