Biomarkers and the Red Hot Swollen Joint

Eric VonHerbulis MS, DPM

Biomarkers

- Accurate and available
- Enhance clinical assessment
- Aid in decision making

Biomarkers in Infection

- Erythrocyte Sedimentation Rate - ESR
- C-reactive protein - CRP
- Procalcitonin - PCT
ESR

- Most commonly used and best studied
- Onset in 24-48 hours
- Peak in 7 days
- Resolution in several weeks

ESR and Osteomyelitis

- Kaleta et al
  - ESR > 70mm/hr
    - Sensitivity 89%
    - Specificity 100%
- Michail et al
  - ESR > 67mm/hr
    - Sensitivity 84%
    - Specificity 75%
- Fleischer et al
  - ESR > 60mm/hr
    - Sensitivity 68%
    - Specificity 70%
- Ertugrul et al
  - ESR > 65mm/hr
    - Sensitivity 88%
    - Specificity 73%

CRP

- More sensitive than ESR to acute phase response
- Onset 12-24 hours
- Peak in 2-3 days
- Half-life of 19 hours
CRP and Osteomyelitis
- Fleischer et al
  - CRP > 3.2 mg/dL
  - OR 10.8
- Michail et al
  - CRP > 1.4
  - Sensitivity 85%
  - Specificity 83%

PCT
- Distinguishes infectious from inflammatory
- Onset in 3-4 hours
- Peaks in 6-24 hours

PCT and Osteomyelitis
- Limited studies
  - Small N
  - Contradictory findings
- Michail et al
  - Cutoff 0.30 ng/mL
  - Sensitivity 81%
  - Specificity 71%
  - Inferior to ESR and CRP
Red Cell Distribution Width

- Reported as part of the CBC
- Used in the evaluation of anemia
- Inflammation contributes to elevation
- Strong association with ESR and CRP

RDW and Disease

- Associated with adverse outcomes
  - Heart failure
  - Acute coronary syndrome
  - Myocardial infarction
  - Peripheral arterial disease
  - Venous thromboembolism
  - Cancer
  - Kidney Disease
  - Hip Fracture

- Prognostic for mortality in infection
  - Pneumonia
  - Necrotizing fasciitis
  - Sepsis

RDW and Osteomyelitis

- 276 patients
  - 60% male
  - 59 years (32-93)
- 159/276 (57.6%) + osteomyelitis

<table>
<thead>
<tr>
<th></th>
<th>Osteomyelitis (+)</th>
<th>Osteomyelitis (-)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60</td>
<td>56</td>
<td>0.94</td>
</tr>
<tr>
<td>Male Sex (%)</td>
<td>62.9</td>
<td>56.4</td>
<td>0.277</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>15.9</td>
<td>14.6</td>
<td>0.0003</td>
</tr>
<tr>
<td>ESR (mm/hr) (N=163)</td>
<td>103.0</td>
<td>80.0</td>
<td>0.047</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>10.8</td>
<td>11.3</td>
<td>0.046</td>
</tr>
<tr>
<td>WBC (tho/µL)</td>
<td>10.5</td>
<td>9.2</td>
<td>0.03</td>
</tr>
<tr>
<td>CRP (mg/dL) (N=158)</td>
<td>8.4</td>
<td>5.9</td>
<td>0.39</td>
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Area under ROC curve (cm²)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR⁺</th>
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<th>PV⁺</th>
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<td>RDW ≥ 14.9 %</td>
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<td>58%</td>
<td>1.47</td>
<td>0.68</td>
<td>0.67</td>
<td>0.53</td>
<td>2.230</td>
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<td>ESR ≥ 83 (mm/hr) (N=163)</td>
<td>59%</td>
<td>56%</td>
<td>1.36</td>
<td>0.72</td>
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<td>Hgb ≤ 11 (g/dL)</td>
<td>56%</td>
<td>57%</td>
<td>1.31</td>
<td>0.77</td>
<td>0.84</td>
<td>0.49</td>
<td>1.704</td>
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<td>WBC ≥ 9.7 (tho/µL)</td>
<td>56%</td>
<td>57%</td>
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<tr>
<td>CRP ≥ 7.1 (mg/dL) (N=158)</td>
<td>53%</td>
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<td>1.10</td>
<td>0.91</td>
<td>0.80</td>
<td>0.45</td>
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RDW and Osteomyelitis

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<tr>
<th>ESR</th>
<th>Cut-off value (mm/hr)</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Keita et al</td>
<td>70</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>Ertugrul et al</td>
<td>65</td>
<td>88%</td>
<td>73%</td>
</tr>
<tr>
<td>Fleischer et al</td>
<td>60</td>
<td>88%</td>
<td>70%</td>
</tr>
<tr>
<td>Michal et al</td>
<td>67</td>
<td>84%</td>
<td>75%</td>
</tr>
<tr>
<td>VonRheinbals et al</td>
<td>83</td>
<td>92%</td>
<td>56%</td>
</tr>
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**SIRS and Sepsis**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>SIRS</td>
<td>Systemic inflammatory response syndrome (SIRS)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Sepsis occurs when SIRS is caused by infection</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis-induced hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities</td>
</tr>
</tbody>
</table>

**Table 1 - Sepsis, SIRS, and MODS: Defining the terms**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>SIRS</td>
<td>Two or more of the following:</td>
</tr>
<tr>
<td></td>
<td>- Temperature &gt; 38°C or &lt; 36°C</td>
</tr>
<tr>
<td></td>
<td>- Respiratory rate &gt; 20 breaths/min</td>
</tr>
<tr>
<td></td>
<td>- Pulse oximetry &lt; 90%</td>
</tr>
<tr>
<td></td>
<td>- Mean arterial pressure &lt; 70 mm Hg</td>
</tr>
<tr>
<td></td>
<td>- White blood cell count &lt; 4000/mL or &gt; 12,000/mL</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Symptomatic response to an infection caused by 2 or more SIRS criteria as a result of an infection</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>Sepsis associated with organ dysfunction, hypoperfusion or hypotension</td>
</tr>
<tr>
<td>Multiple organ dysfunction syndrome (MODS)</td>
<td>Presence of altered organ dysfunction in an acutely ill patient</td>
</tr>
</tbody>
</table>

**CRP and Sepsis**

- **CRP**
  - Elevated in sepsis
  - Performs better than WBC and temp
  - May be used to monitor response to abx
  - Performs poorly distinguishing SIRS from sepsis

**PCT and Sepsis**

- **Specific marker of severe bacterial infection**
- **Useful in distinguishing SIRS from sepsis**
- **Serial monitoring predictive of mortality**
- **Successful in guiding treatment strategies**

- Approved by FDA for risk assessment of critically ill patients on admission for progression to severe sepsis and septic shock
Kim et al - Increase in RDW from baseline in first 72 hours is a strong independent predictor of mortality.
Biomarkers and Length of Hospitalization

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Hospitalization &gt; 7 days</th>
<th>Hospitalization &lt; 7 days</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (tho/μL)</td>
<td>12.64</td>
<td>9.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>15.44</td>
<td>15.36</td>
<td>0.6786</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>81.3</td>
<td>52.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>10.95</td>
<td>5.78</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Biomarkers and Readmission

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>30 day readmission</th>
<th>No readmission</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDW (admission)</td>
<td>15.46</td>
<td>15.95</td>
<td>0.0409</td>
</tr>
<tr>
<td>RDW (discharge)</td>
<td>16.24</td>
<td>15.80</td>
<td>0.0065</td>
</tr>
<tr>
<td>RDW (∆)</td>
<td>1.27</td>
<td>0.15</td>
<td>0.0009</td>
</tr>
<tr>
<td>WBC (discharge)</td>
<td>8.83</td>
<td>7.82</td>
<td>0.0713</td>
</tr>
<tr>
<td>ESR (N=544)</td>
<td>72.1</td>
<td>60.0</td>
<td>0.0038</td>
</tr>
<tr>
<td>CRP (N=531)</td>
<td>8.4</td>
<td>7.5</td>
<td>0.3665</td>
</tr>
</tbody>
</table>
Diagnosis of the Septic Joint

- **Gram stain**
  - Sensitivity of 29-65%
- **Culture**
  - Sensitivity of 75-95%
  - Results in 24-48 hours

CRP and the Septic Joint

- **CRP**
  - Cutoffs range from 1-20mg/dL
  - Sensitivity of 41-91%
  - Specificity of 15-85%
  - Cutoff of 0.5 mg/dL gives 99% sensitivity

ESR and the Septic Joint

- Elevated in all types of arthritis
- Statistically significant elevation with SA vs crystal and SA vs RA
- Very poor diagnostic discrimination
Synovial WBC and the Septic Joint
- Normal: < 180
- Non-inflammatory: 200-2000
- Inflammatory: 2000-50,000
- Septic: > 50,000

PCT and the Septic Joint
- Consistently discriminating
- Meta-analysis involving 583 patients
  - Cutoff 0.5 ng/mL
  - Sensitivity 65%
  - Specificity 88%
  - +PV 63%

Other markers of the Septic Joint
- Synovial glucose
- Synovial protein
- Lactate
- IL-6
- Synovial markers
RDW and the Septic Joint

- N = 2631
  - 429/2631 (18.17%) with + culture
- Mean age 59.5 years
  - < 65 years associated with septic joint
- 1322/2631 (56%) male
  - Not statistically significant

Biomarkers and the Septic Joint

- Statistically significant associations with
  - Age < 65
  - WBC
    - Left shift
  - CRP
  - Platelets
  - ESR
- Synovial fluid associations
  - ↓ lymphocytes, monocytes
  - ↑ neutrophils

RDW as a Biomarker

- Routinely reported, easily accessible without additional cost
- Diagnostic accuracy superior to ESR and CRP for osteomyelitis
- Associated with the development of sepsis following lower extremity infection
- Associated with 30 day readmission
Procalcitonin

- Valuable in the diagnosis of the septic joint
  - High positive predictive value at cutoff of 0.3-0.5 ng/mL
- Approved for risk stratification of critically ill
- Poor discrimination between SSTI and osteomyelitis