Disclosures

• Society for Advancement of Blood Management
• Instrumentation Laboratories
Objectives

• Global incidence of Sepsis
• Why the need for early intervention?
• What test does UMC have and are we using it?
Global incidence of Sepsis

• Global healthcare issue that kills more people than Cancer, Sepsis still not widely known.
• (30,000,000 affected by Sepsis yearly) 30% - 50% Mortality

• 258,000 people die yearly – 1 every 2 minutes
• (more deaths than prostate CA, breast CA, AIDS combined)

• IN U.S alone admissions for Sepsis increased 3 fold over last decade
• (Same time period, Stroke and MI remained stable)
CDC numbers on Sepsis (U.S. numbers)

- CDC statistics center estimates:
  - 621,000 admissions in year 2000
  - Death rate 154,159
  - 1,141,000 admissions in 2008
  - Death rate 2007 > 207,427
Cost of Sepsis on the U.S.

- Sepsis is MOST expensive condition treated in U.S. hospitals.
- $20,000,000,000 in 2011 – increasing 11.9% annually

- Currently, no rapid diagnostic test available done at bedside
Emerging Sepsis biomarkers

- 2 most commonly used blood protein biomarkers for diagnosing infections that might lead to Sepsis,
  - C-reactive protein (CRP)
  - Procalcitonin (PCT)
- CRP is not sufficiently specific for diagnosing sepsis
- PCT – biomarker whose levels increase precipitously w/bacterial infection. **PCT** elevates prior to rise in Lactic Acid & more specific test for Sepsis.
How does Procalcitonin Testing Work?

• From Package Insert;
Procalcitonin (PCT) is the prohormone of calcitonin. Whereas calcitonin is only produced in the C cells of the thyroid gland as a result of hormonal stimulus, PCT is secreted by different types of cells from numerous organs in response to proinflammatory stimulation, particularly bacterial infection.

• Increased PCT levels may be observed in severe illness such as polytrauma, burns, major surgery, prolonged or cardiogenic shock.

• PCT levels may not be elevated in patients infected by certain atypical pathogens, i.e. Chlamydophila & Mycoplasma pneumoniae.
How does Procalcitonin Testing Work?

PCT concentration above 0.25 ng/mL can indicate clinically relevant bacterial infection, requiring antibiotic treatment.

At a PCT concentration > 0.5 ng/mL, in a patient with signs & symptoms of systemic inflammatory response (SIRS) should be considered a risk factor for the development of severe sepsis or septic shock.

Sepsis is an excessive reaction of the immune system & coagulation system to an infection.

Risk assessment after initial diagnosis & treatment of severe sepsis & septic shock in ICU aids in distinguishing patients at low risk for adverse outcomes & who could be discharged from the ICU, from patients at high risk who may need care escalation.
How does Procalcitonin Testing Work?

PCT levels can increase quickly, specifically in patients with a serious bacterial infection. *Morality Rates increase 7.6 per hour.*

PCT is therefore an important marker enabling differentiation between bacterial infection and other causes of inflammatory reactions.

Resolution of the septic infection can be accompanied by a decrease in the PCT concentration which returns to normal w/ half-life of 24 hrs

Continuous decline of PCT is indicative of effective source control measures and safe de-escalation of antibiotic therapy.
## Markers of Sepsis

<table>
<thead>
<tr>
<th>Marker</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactate</strong></td>
<td>Lactate is a general marker, lacks specificity for infection.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCT</strong></td>
<td>Marker of bacterial infection. No POC PCT tests available, lab PCT is expensive with long turnaround times.</td>
<td>Sepsis Test Panel (Lactate, CRP, PCT) - Applicable for initial screening and as an aid in diagnosis. - Provides positive indication of bacterial infection. - Guides antibiotic therapy and will allow fast identification of patients who are non-septic and will aid in the decision to discontinue antimicrobial therapy.</td>
<td></td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>A few single-plex POC CRP tests are available. Typically tested in the central laboratory with longer turnaround times.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Meta-studies showed better diagnostic accuracy for PCT than CRP to discriminate SIRS from sepsis; Surrogate biomarker to guide antibiotic therapy; Well studied biomarker (< 600 studies).
- Rises transiently in patients with some nonseptic inflammatory conditions; Mixed results with fungal infections; Limited value in case of viral infections.
- Good value to rule out sepsis if level remains low; Inexpensive and widely available.
- Nonspecific for sepsis (marker of inflammation); Slow kinetic; Suppressed by corticosteroids.
Antimicrobial Use & Misuse
Acute Care Setting

Appropriate Use

Inappropriate Use

“Just to be sure”


How did we get this way?
CMS SEP-1: 3 and 6 hour bundles

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION †:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

† “time of presentation” is defined as the time of earliest chart annotation consistent with all elements severe sepsis or septic shock ascertained through chart review.
Impact of Procalcitonin-Guided Antibiotic Management on Antibiotic Exposure and Outcomes: Real-world Evidence

Michael R. Broyles

1Department of Clinical Pharmacy and Laboratory Services, Five Rivers Medical Center, Pocahontas, Arkansas

Results. A total of 985 patients (pre-PCT-A group) were compared with 1167 patients (post-PCT-A group). Antimicrobial stewardship alone (pre-PCT-A) resulted in a median days of therapy (DOT) of 17 (interquartile range [IQR], 8.5–22.5) vs 9.0 (IQR, 6.5–12) in the post-PCT-A group (P < .0001). Secondary outcomes were also significantly reduced in the post-PCT-A group.

Conclusion. The addition of PCT in a facility with an established stewardship program resulted in a significant reduction in antibiotic exposure and adverse outcomes. PCT may improve antibiotic management when diagnostic clarity and resolution of infection are lacking.
Sepsis = Two SIRS Criteria in presence of Infection

- Temperature > 100.4F (38C) or < 96.8F (36C)
- Heart rate > 90 beats/minute
- Respiratory rate > 20 breaths/minute or PaCO$_2$ < 32 mm Hg
- WBC
  - > 12,000/mm$^3$
  - < 4000/mm$^3$
  - > 10% immature (band) forms
Using this decision tree; there results were:
- Treated 1167 patients from 01/2011 – 12/14
  **47% reduction in Days/Therapy**
  **Days/Therapy dropped from 17 to 9**
- Mortality dropped 62%
  75 deaths in Pre – PCT
  35 deaths in Post – PCT
- 30 day readmissions rates dropped 50%
  204 Pre – PCT   119 Post - PCT
Understanding PCT Kinetics

- Rises 3-6 hours after bacterial infection
- Peak occurs 12-24 hours
- Half life of PCT is 24 hours
- Can take 24 hours of appropriate antibiotic therapy to see reduction in serum PCT
- PCT production and serum concentrations will decrease by up to 50% per day with appropriate antibiotic treatment
- If antibiotic therapy is inadequate, PCT levels will remain high

**B•RA•H•MS PCT** is a sensitive and specific biomarker of the inflammatory response to bacterial infection.

What differentiates B•R•A•H•M•S PCT from the other 175+ biomarkers?

- Sensitivity 89%/Specificity 94%
- Evaluate bacterial burden
- Not affected by corticosteroids
- Can use with disease modifying drugs
- Use with other drugs affecting inflammatory mediators
- Not affected by most autoimmune diseases
- Not affected by decreasing immune function/oncology therapy
### Sepsis/AKI presenting at UMC

<table>
<thead>
<tr>
<th>Row Labels</th>
<th>Count of clasf_desc</th>
<th>Sum of LOS, d</th>
<th>Average of LOS, d</th>
<th>Min of LOS, d</th>
<th>Max of LOS, d</th>
<th>Sum of tot_chg_amt</th>
<th>Sum of tot_pay_amt</th>
<th>Sum of Diff (chgs - pd)</th>
<th>Average of % Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE KIDNEY FAILURE, UNSPECIFIED</td>
<td>4242</td>
<td>26039</td>
<td>6.14</td>
<td>0</td>
<td>125</td>
<td>$176,139,941</td>
<td>$36,102,628</td>
<td>$140,037,312</td>
<td>24.15</td>
</tr>
<tr>
<td>OTHER SPECIFIED SEPSIS</td>
<td>68</td>
<td>1134</td>
<td>16.68</td>
<td>1</td>
<td>89</td>
<td>$7,948,964</td>
<td>$1,171,798</td>
<td>$6,777,166</td>
<td>21.11</td>
</tr>
<tr>
<td>SEPSIS, UNSPECIFIED ORGANISM</td>
<td>662</td>
<td>6874</td>
<td>10.38</td>
<td>0</td>
<td>75</td>
<td>$50,751,633</td>
<td>$9,694,080</td>
<td>$41,057,553</td>
<td>25.06</td>
</tr>
<tr>
<td>Grand Total</td>
<td>4972</td>
<td>34047</td>
<td>6.85</td>
<td>0</td>
<td>125</td>
<td>$234,840,538</td>
<td>$46,968,506</td>
<td>$187,872,032</td>
<td>24.23</td>
</tr>
</tbody>
</table>

- **Inpatient days:** 8008
- **Average LOS:** 16.68
- **Hospital Charges:** $187,872,032
- **Reimbursement:** $46,968,506

Aggressively working on obtaining Rapid ID laboratory equipment. Quest send out test; 4-5 Days TAT With Rapid ID 4-5 hours
Is PCT testing Cost Effective?

In a three nation study, review of Antibiotic (AB) overuse Antibiotic resistance (ABR) & C Diff (CDI) were analyzed.

PCT testing reduced ABR 6% & CDI 21%  Savings $1410 patient

In COPD population ABR, CDI cases were reduced with PCT testing by 50%    Savings, $2843 per patient

Conclusion: Outcomes were more sensitive to the impact of PCT guided strategy on the number of intensive care & general hospital days. Taken together, PCT guided testing reduces ABR & CDI cases and generate cost savings & patient hospitalized days.

England, Netherlands & Germany
Broyles Study (Turn Around Time)

Impact of Procalcitonin-Guided Antibiotic Management on Antibiotic Exposure and Outcomes: Real-world Evidence

Michael R. Broyles

Broyles TAT @ 1 hour

What is UMC Lab TAT?

<table>
<thead>
<tr>
<th>SUMMARY</th>
<th>ORD-COL</th>
<th>COL-REC</th>
<th>REC-REP</th>
<th>ORD-REP</th>
<th># of Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg</td>
<td>465.6</td>
<td>25.9</td>
<td>80.1</td>
<td>571.6</td>
<td>2136</td>
</tr>
<tr>
<td>Median</td>
<td>50.0</td>
<td>15.0</td>
<td>66.0</td>
<td>164.0</td>
<td>2136</td>
</tr>
</tbody>
</table>

| PROCALCITONIN           |         |         |         |         |             |
|                         |         |         |         |         |             |
| ORD-COL                 | 465.6   | 25.9    | 80.1    | 571.6   | 2136        |
| COL-REC                 | 66.0    | 2136    |         |         |             |
| REC-REP                 | 571.6   | 2136    |         |         |             |
| ORD-REP                 | 2136    |         |         |         |             |

How many PCT tests has UMC Lab run?

<table>
<thead>
<tr>
<th>total Procalcitonin tests from</th>
<th>range 0.5 to 2.0</th>
<th>above 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/23/2018 to 10/31/2018</td>
<td>1786</td>
<td>334</td>
</tr>
</tbody>
</table>

VIDAS® 3
Compact immunoanalyzer with full traceability and automation.
Procalcitonin (PCT) Result

In which range below does the patient’s PCT result fall?

- **< 0.1 ng/mL**
  - Sepsis not likely
  - Consider nonbacterial diagnosis
  - Repeat PCT testing in 12-24 h as needed
- **0.1 - 0.23 ng/mL**
  - Sepsis not likely
  - Local bacterial infection possible
  - Consider repeat PCT testing every 24 h to evaluate for early cessation of therapy
- **0.24 - 0.5 ng/mL**
  - Sepsis likely, unless other causes are known
  - Consider repeat PCT testing every 24 h to evaluate for early cessation of therapy
- **> 0.5 but ≤ 2 ng/mL**
  - Sepsis very likely
  - Significant systemic inflammatory response
  - Consider repeat PCT testing every 24 h to evaluate for early cessation of therapy
- **2.01 – 9.99 ng/mL**
  - Sepsis likely
  - Consider repeat PCT testing every 24 h to evaluate for early cessation of therapy
- **≥ 10 ng/mL**
  - Sepsis very likely
  - Significant systemic inflammatory response
  - Consider repeat PCT testing every 24 h to evaluate for early cessation of therapy

**Interpretive Guidelines: Likelihood of Systemic Infection (Sepsis)**

**Antibiotic Therapy (Rx) Guidelines**

- Strongly Discouraged
- Discouraged
- Encouraged
- Strongly Encouraged

**Serial PCT Results and 28-Day Mortality Risk Assessment**

Consider serial PCT testing and determination of Delta-PCT on Day 4 to assess 28-day all-cause mortality risk:

\[ \Delta \text{PCT, } \% = \frac{\text{PCT}_{\text{Day 0 or 1}} - \text{PCT}_{\text{Day 4}}}{\text{PCT}_{\text{Day 0 or 1}}} \times 100 \]

**Notes**
- If PCT result is not available on Day 0, use PCT result on Day 1.
- If more than one PCT result is available on Day 0 (or Day 1), use the highest value.
- If more than one PCT result is available on Day 4 (4th day after diagnosis), use the most recent value.

**Example**: Calculation and interpretation of Delta-PCT (\(\Delta\text{PCT}\))

\[ \Delta \text{PCT} = \frac{100 - 20}{100} = 0.8 \times 100 = 80\% \]

- **20% Mortality Rate @ Decline ≤ 80%**
- **50% Mortality Rate @ Decline = 80%**
- **90% Mortality Rate @ Decline > 80%**

- Patient’s PCT Decline = 80%
- 2-fold increase in mortality

**Based on the PCT result and other clinicopathologic findings, is the patient’s diagnosis consistent with severe sepsis/septic shock?**

- **Yes**
  - Determine \(\Delta\text{PCT, } \%\) Between Day 0 or 1 and Day 4
  - Is the \(\Delta\text{PCT, } \%\) ≤ 80%?
    - **Yes**
      - Therapy as appropriate
      - 28-Day all-cause mortality risk is decreased
    - **No**
      - Standard of care therapy

- **No**
Procalcitonin

Is Procalcitonin Ready for Prime Time?

Definitely proven its worth at UMC