Procalcitonin Levels to Promote Responsible Antibiotic Use

Judy Neubrander, EdD, FNP-BC
Western Carolina University
School of Nursing

Learning Objectives

- To understand the issues associated with the increase in antibiotic resistance
- To learn what procalcitonin levels are and how they can be used for antimicrobial stewardship
- Review the literature that supports using procalcitonin levels in respiratory tract infections and sepsis patients
- Discuss real life data from the use of procalcitonin levels at Haywood Hospital

Disclosure Statement of Financial Relationships:
No financial relationship in the last 12 months with a manufacturer of products or services that will be discussed in the CE activity I am presenting.

Preventing Antibiotic Resistance

- Antibiotic resistance is the inevitable result of natural selection but is promoted by inappropriate antibiotic use by prescribers and patients
- Over 50% of antibiotic prescriptions in the outpatient setting are estimated to be unnecessary
  - Prescribed for conditions often caused by viruses (e.g. acute bronchitis where 80% are prescribed antibiotics)
  - Particular problem because of patient pressure
- Up to 50% of antibiotics use in hospitals is estimated to be inappropriate or unneeded as well
Antibiotic Resistance Threats 2016

- 2 million people a year acquire antibiotic (ABX) resistant infections (>23,000 of these die as a direct result)
- Estimates in cost vary from 20 billion in direct healthcare cost with 35 billion in lost productivity (2008)
- Core Actions
  - Prevent infections from occurring and prevent the spread
  - Track resistance
  - Improve the use of ABXs
  - Promote development of new ABXs and new diagnostic tests for resistant bacteria
- ABXs are among the most commonly prescribed medications


Preventing Antibiotic Resistance

- The length of treatment for most infections has been poorly studied and treatment durations are likely inappropriately long
  - Increased cost, likelihood of adverse effects, potential effect on hospital length of stay
- Appropriate use of ABX is necessary
  - Associated with drug toxicity
  - Increased drug resistance
- Increased lengths of stay, costs, and mortality are associated with multi-drug resistant organisms
- Collateral damage such as Clostridium difficile-associated diarrhea

Clostridium Difficile

- Categorized as “Urgent Threat” by CDC
- Many cases can be prevented
  - One study found in 126 consecutive patients with hospital associated C difficile infections
  - 73.8% of patients had at least 1 preceding course of antibiotics that was deemed inappropriate
- Directly related to ABX use and resistance
  - At least 250,000 illnesses and 14,000 deaths per year
  - 17,000 children per year (73% from doctor's offices and received antibiotic in 12 weeks prior usually for ear, sinus, or URI), mostly cephalosporins/beta-lactams
Antibiotic Stewardship

- The #1 important action to slow down development of drug resistant organisms is to change the way antibiotics are used.

- Antibiotic Stewardship:
  - ALWAYS use ABX appropriately and safely
  - ONLY when they are needed to treat disease
  - CHOOSING the right antibiotics and to administer them in the right way in every case

- Many different ways to approach stewardship
  - Use of procalcitonin levels is one way to reduce antibiotic use

Can Procalcitonin Help? Is There “Hope for Hype”?

Biomarkers to Guide Therapy for Bacterial Infections

- Several biomarkers have been identified with the potential to help diagnose local and systemic infections and guide antibiotic therapy

- Procalcitonin is the most extensively studied biomarker

Question 1) What are 2 other biomarkers being studied for post-op determination of SIRS?
What is Procalcitonin (PCT)?

- Prohormone of calcium modulating hormone calcitonin
  - Calcitonin is secreted by the C-cells of the thyroid after hormonal stimulation
- Synthesis of calcitonin is inhibited by cytokines and endotoxin
- PCT levels rise substantially in response to triggers released during bacterial and systemic infections
  - Endotoxin and inflammatory cytokines
  - Starts to rise at 4 hours and peaks between 8 and 24 hrs
  - Peaks 36 hrs after endotoxin challenge
  - Short half-life of 24 hrs independent of renal function
- Normally has a plasma level of < 0.05 ng/mL.

Role of PCT in the absence of infection

Release of calcitonin in the context of endocrine regulation:

- Synthesis in healthy persons in the C-Cells of the thyroid

Role of PCT in sepsis

- Alternative (cytokine-like) pathway during sepsis: 'Hormokine'
  - Bacterial toxins (gram+/-) and cytokines stimulate production of procalcitonin in all parenchymal tissues
  - Non endocrine tissue (ie liver, lung, brain etc.) do not have endocrine granules where calcitonin can be stored.
- PCT is immediately released into the bloodstream
A hormone that becomes a cytokine...

Müller B. et al., JCEM 2001

Calcitonin:
Source of production in healthy people

PCT:
Source of Production in Septic Patients

Procalcitonin Levels

- A minor increase (<0.5 ng/mL) is observed in local infections with a low probability for systemic infection (sepsis)
- Moderately elevated levels (0.5-2 ng/mL) indicate that sepsis is possible with a small risk for progression to severe sepsis
- Highly elevated levels (2-10 ng/mL) indicate that sepsis is very likely with a high risk for progression to severe sepsis
- Very high values (>10 ng/mL) are almost exclusively due to severe sepsis or septic shock

Comparison to Current Markers

- Advantages
  - Faster than C-reactive protein (CRT) which begins to rise after 12-24 hrs and peaks at 48 hrs
  - PCT production is not impaired by neutopenia or other immunosuppressive states
  - Not affected by steroids like WBC
  - Able to differentiate between bacterial vs. viral infection (viruses actually suppress PCT production)
  - Rapid decline with immune control on infection (half-life of 24 hours), a daily decrease of about 50%
  - Faster than cultures, more reliable (direct stimulation by cytokines)
Limitations

- Situations where PCT elevations may be due to a non-bacterial cause:
  - Newborns (<48-72 hours; >72 hours interpret level as usual)
  - Massive stress (severe trauma, surgery, cardiac shock, burns)
  - Treatment with agents which stimulate cytokines
    - OKT3, injection therapy TNFα, IL-2, anti-lymphocyte globulins
  - Malarias and some fungal infections
  - Prolonged, severe cardiogenic shock or organ perfusion abnormalities
  - Some forms of vasculitis and acute graft vs. host disease
  - Certain cancers: medullary CT-cell cancers of the thyroid, pulmonary small-cell carcinoma and bronchial carcinoma

Uses for Procalcitonin Levels

- Respiratory Tract Infections (RTIs) including chronic obstructive pulmonary disease (COPD), pneumonia, asthma, bronchitis
  - Inpatient
  - Outpatient
- Sepsis & Septic Shock Prediction
  - FDA approved
- Newer: Post-Operative Use, Pediatrics

Procalcitonin Procedure

- Upon admission, PCT levels are tested in ED patients suspected of having a significant bacterial infection
  - Suspected pneumonia, LRTI including bronchitis or COPD exacerbation, or sepsis
- Test results are available in 20 mins
- Patients are assessed for either a probable bacterial infection or not probable bacterial infection
- Procalcitonin algorithm followed (serial results obtained)
  - If antibiotics (ABX) not started, another PCT is checked to make sure it did not elevate
  - If ABX started, PCT is checked to make sure pt is decreasing appropriately, when normalized, ABX stopped
Evidence: Respiratory Infections

- Ventilator-associated pneumonia (VAP)
  - PCT may be useful in the diagnosis of VAP
  - Multinational, randomized trial (n=101); PCT guidance reduced duration of therapy by about 27% (p=0.038)
  - Number of mechanical vent-free days alive, ICU free days alive, length of hospital stay and mortality rate on day 28 were similar

- Prospective, randomized trial of LRTIs comparing PCT management vs. control in adults
  - 8 studies-COPD, CAP, VAP, U/LRI (2), LRI (3); n=3431
  - All used similar algorithms, cutoffs, and assays
  - Exclusions (n=243): CF, tuberculosis, nosocomial pneumonia, severely immunocompromised

Evidence: Low Acuity Patients

- PCT guidance resulted in lower prescription rates by:
  - 40% to 75% in primary care patients with upper and lower RTIs
  - 60% to 75% in patients with acute bronchitis
  - 30 to 45% in patients with exacerbation of COPD

- No increase in mortality or any other adverse outcome in any of the individual trials

- Neither mortality or other adverse events surface when pooling data in the meta-analyses
**LRTI Initial Antibiotic Use Algorithm**

<table>
<thead>
<tr>
<th>PCT Value</th>
<th>Antibiotic Use Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1 µg/L</td>
<td>Strongly Discouraged</td>
</tr>
<tr>
<td>0.1-0.24 µg/L</td>
<td>Discouraged</td>
</tr>
<tr>
<td>0.25-0.5 µg/L</td>
<td>Encouraged</td>
</tr>
<tr>
<td>&gt;0.5 µg/L</td>
<td>Strongly Encouraged</td>
</tr>
</tbody>
</table>

*Consider alternative diagnosis*

*Repeat PCT in 6-12 hours if antibiotics not begun and no clinical improvement*

*If clinically unstable, immunosuppressed or high risk consider reassessing (PSI Class IV-V, CURB=2, BOLD III or IV)*

Repeat every 2-3 days to consider early antibiotic cessation.

See LRTI follow-up algorithm

---

**LRTI PCT Follow up Algorithm**

<table>
<thead>
<tr>
<th>PCT Value</th>
<th>Antibiotic Use Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1 µg/L or drop by &gt;90%</td>
<td>Cessation Strongly Encouraged</td>
</tr>
<tr>
<td>0.1-0.24 µg/L or drop by &gt;80%</td>
<td>Cessation Encouraged</td>
</tr>
<tr>
<td>0.25-0.5 µg/L</td>
<td>Cessation Discouraged</td>
</tr>
<tr>
<td>&gt;0.5 µg/L</td>
<td>Cessation Strongly Discouraged</td>
</tr>
</tbody>
</table>

*Consider continuing if clinically unstable*

*If PCT rising or not adequately decreasing consider possible treatment failure and reassess pt for other sites/sources of infection or evidence of resistant pathogen*

Repeat daily for 2 days then every 2-3 days afterward to consider early antibiotic discontinuation.

See LRTI follow-up algorithm

---

**Sepsis Initial Antibiotic Use Algorithm**

<table>
<thead>
<tr>
<th>PCT Value</th>
<th>Antibiotic Use Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.25 µg/L</td>
<td>Strongly discourage antibiotic</td>
</tr>
<tr>
<td>0.25-0.49 µg/L</td>
<td>Discouraged</td>
</tr>
<tr>
<td>0.50-1.0 µg/L</td>
<td>Encouraged</td>
</tr>
<tr>
<td>&gt;1.0 µg/L</td>
<td>Strongly Encourage</td>
</tr>
</tbody>
</table>

*Consider alternative diagnosis*

*Repeat PCT in 6-12 hours if antibiotics not begun*

*If clinically unstable, immunosuppressed or high risk consider overruling (PSI Class IV-V, CURB=2, BOLD III or IV)*

*Strongly consider antibiotic initiation in all patients with suspicion of infection.*

Repeat daily for 2 days then every 2-3 days after to consider early antibiotic discontinuation.

See Sepsis Follow-up algorithm
Sepsis PCT Follow up Algorithm

<table>
<thead>
<tr>
<th>PCT Value</th>
<th>Antibiotic Use Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.25 µg/L</td>
<td>Cessation Strongly Encouraged</td>
</tr>
<tr>
<td>0.25 - 0.49 µg/L or drop by &gt;80%</td>
<td>Cessation Encouraged</td>
</tr>
<tr>
<td>≥0.5 µg/L and decreased by &lt;80%</td>
<td>Cessation Discouraged</td>
</tr>
<tr>
<td>≥0.5 µg/L and rising or not decreasing</td>
<td>Cessation Strongly Discouraged</td>
</tr>
</tbody>
</table>

Consider continuation if clinically unstable

*A PCT value which is rising or not declining at least 10% per day is a poor prognostic indicator and suggests infection is not controlled
*Reason pt for other sites/sources of infection or evidence of resistant pathogen

Cost-Effectiveness

- PCT cost is ~2x CRP cost but provides greater clinical value if used for determination of cessation of antibiotics (current cost ~$24-25/test)
- A cost benefit analysis of use in ICU found cost savings depended on how frequently PCT was utilized and the cost of ABX which were discontinued
- Other studies have seen shortened durations in RTIs
- Depends on:
  - ↓ Complications of antibiotic use (C. difficile infection, drug toxicity, etc.)
  - ↓ ABX use
  - ↓ Blood cultures
  - Long term benefits in ↓ resistance to ABX and overall health care costs

Note:

- PCT cost is ~2x CRP cost but provides greater clinical value if used for determination of cessation of antibiotics (current cost ~$24-25/test)
- A cost benefit analysis of use in ICU found cost savings depended on how frequently PCT was utilized and the cost of ABX which were discontinued
- Other studies have seen shortened durations in RTIs
- Depends on:
  - ↓ Complications of antibiotic use (C. difficile infection, drug toxicity, etc.)
  - ↓ ABX use
  - ↓ Blood cultures
  - Long term benefits in ↓ resistance to ABX and overall health care costs
Key Principles of PCT Interpretation

- Interpret in the clinical context of the patient
- Serial measurements are preferred and provide more useful information
- Consider the process of the disease when evaluating the PCT values
- Be aware of conditions that may affect PCT levels
  - Trauma
  - Inflammation
  - Localized infections (osteomyelitis, localized abscess)

Conclusions

Where could PCT potentially be useful?

- In the ED to differentiate bacterial versus viral RTIs
- To determine antibiotic treatment length in RTIs
- Diagnosis, risk stratification, and monitoring of sepsis and septic shock in adults and children
- Monitoring response to antimicrobial therapy
- Differentiating viral vs. bacterial meningitis
- Inpatient and Outpatient, pediatric patients
- Diagnosis of bacterial vs. fungal infection in neutropenic patients
- Diagnosis of systemic secondary infection post-surgery
- Febrile infants to determine if bacterial infection

Question #2: Where is the evidence?

Key: + moderate evidence; ++ good evidence; +++ strong evidence; ? Evidence still undefined

Why did we add PCT at Haywood?

- Pneumonia vs. Heart Failure
  - Similar presentations of shortness of breath, rapid heart rate, coughing and wheezing
  - Both can produce infiltrates and hypoxia to varying degrees
  - Prevention of initiation of antibiotics
- Septis Pathway
- Shorten length of therapy with antibiotics
- Antibiotic stewardship-no ID docs or dedicated RPhs
- Where has it not been helpful?
  - UTI & Cellulitis

Haywood Initial MUE Data-May 2013

- We utilized prescribers with experience using PCT levels to assist with training
- Assessed whether “prevented ABX” or “shortened duration”
  - Of patients with PCT levels ≤ 0.5:
    - 44% of levels prevented antibiotics from being initiated
    - Of those patient’s the PCT level didn’t prevent ABX initiation or who didn’t have a PCT level on admit:
    - PCT level stopped antibiotics early 84% of the time
  - Overall prescribers followed guidance from the PCT level 76% of the time with 2 prescribers following it 100%
  - 13% of patients were patients with heart failure that the physician ordered the PCT level to determine if the patient also had pneumonia

2nd MUE: Study Population August 2013

- Assessed whether “prevented ABX” or “shortened duration”
  - Of patients with PCT levels ≤ 0.5:
    - 60% of levels prevented ABX from being initiated (16% increase)
    - Of those patient’s the PCT level didn’t prevent antibiotic initiation or who didn’t have a PCT level on admit:
    - PCT level stopped ABX early 11.1% of the time (↓ from 44%)
  - Overall prescribers followed guidance from the PCT level 67% of the time (↓ of 9%) with 1 prescriber following it 100% of the time
  - 8% of patients were patients with heart failure that the prescriber ordered the PCT level to determine if the patient also had pneumonia
**Reason for PCT**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>12</td>
</tr>
<tr>
<td>Septicemia</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
</tr>
<tr>
<td>Empyema</td>
<td>12</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>12</td>
</tr>
<tr>
<td>CSF</td>
<td>12</td>
</tr>
</tbody>
</table>

**PCT Protocol Use Results**

- Prevented Abx Use (no abx or none after initial PCT within 24 hr): 55.0%
- Stopped Abx Early (if not prevented): 11.1%
- Following Protocol Overall: 67.3%
- Following Protocol After Low Initial PCT: 60.0%

**Cost Analysis**

- **Total ABX and PCT Testing Costs**
  - Based on 60% protocol compliance
  - Extrapolated to 720 tests over 4 months (August-November 2013)
  - Estimated at $25 per PCT test

- Antibiotic cost alone: $12,458 for PCT > 0.1 and $21,252 for PCT < 0.1
Medwest Procalcitonin DUE

- **Challenges**
  - Some PCTs appeared to be drawn unnecessarily (on pts with cellulitis, DKA, concomitant UTI, etc.)
  - Some prescribers still want to treat all COPD exacerbations
  - No formal pharmacy procalcitonin monitoring program in place
  - High turnover of hospitalist staff, education is challenging

- **Positives**
  - All high PCTs correlated with bacterial infection (2 septicemias were caught with an initial level of 0.4 in ER that rose on the second PCT)
  - Our studies are in progress: “Assessment of Antibiotic Use in Small Community Hospital” and “Assessment of Procalcitonin Level Use in Small Community Hospital”
  - Doing well stopping ABX from being initiated, 1 patient was not admitted, high rate of stopping initial ABX based on protocol

Final Thoughts

- **Goals**
  - Increased pharmacist involvement
  - Improved decrease in duration of antibiotic treatment
  - Improvement in utilization of PCT test by prescribers

- **Cost Savings:**
  - Does not include prevention of unnecessary tests, blood draws
  - In addition to monetary benefits, focus on antibiotic stewardship benefits
  - Lessens patient risk for harm due to decreased IV access, risk for C. diff, etc.
  - Saves nursing and pharmacy time, improving efficiency
Patient Case

- Antibiotics initiated 08/04/14 in ER include:
  - Rocephin 1 gm IV daily
  - Levaquin 750 mg IV q24h
- Labs on 08/05/14 AM
  - PCT 0.10
  - WBC 10.5
  - Initially possible infiltrate on Chest X-ray
- Antibiotics discontinued
- Actual Dx:
  - Acute respiratory failure secondary to pulmonary edema & LV dysfunction
- Patients condition improved and discharged 08/08/14

Audience Questions #3 and #4

3) Based on what we know about PCT, if the initial PCT is negative and antibiotics are not initiated:
   a. When could a second PCT level be drawn?
   b. If it is elevated, when would you see approximately a 50% decline in PCT if the pt is being treated appropriately?

4) If this patient had a flu-like/viral infection, would the PCT level be elevated?