Appropriateness of procalcitonin guided antimicrobial therapy utilization in hospitalized veteran patients

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The speaker has no actual or potential conflicts of interest in relation to this presentation.
OUTLINE

• Medical Center Overview
• Background/Literature Review
• Purpose
• Methods
• Results
• Self-Assessment Questions
• Q&A Session
CLEMENT J. ZABLOCKI VETERANS AFFAIRS MEDICAL CENTER (ZVAMC)

- Located in Milwaukee, WI
- Associated with Medical College of Wisconsin
- Unique users – 63,444
  - 185 acute care beds (Medical/Surgical/Psychiatry/Rehab/SCI)
    - Inpatients treated - 7,717
  - 113 long-term care beds
- Antimicrobial Stewardship Program
  - Prospective audit
  - Antibiotic protocols and restrictions
  - IV to PO conversions
BACKGROUND

Inappropriate antimicrobial use

- Bacterial or viral etiology is difficult to predict based on clinical signs and symptoms$^1$
- 30-50% of antimicrobials used in the inpatient setting are inappropriate$^2,3$

Unnecessary and inappropriate antimicrobial use leads to negative outcomes$^1$

- Increased bacterial resistance
- Increased drug-related adverse events
- Increased health-care associated costs
Infection biomarkers are useful when determining the potential etiology of undifferentiated infections:

- Erythrocyte Sedimentation Rate (ESR)
- C-Reactive Protein (CRP)
- Cytokines
- Fever
- Leukocytes
- Procalcitonin (PCT)
PROCALCITONIN (PCT)\textsuperscript{1,5,6}
PROCALCITONIN ASSAY

VIDAS® BRAHMS PCT

- Enzyme-linked fluorescent immunoassay (ELFA) for the quantitative measurement of PCT with results in 20 minutes
- FDA approval in 2008: to aid in the risk assessment of critically ill patients on the first day of ICU admission for progression to severe sepsis or septic shock in conjunction with other lab findings and clinical assessments
- FDA expanded approval in 2016: to help assess the response of septic patients to treatment by comparing baseline PCT measurement with a PCT value taken on day four
ProCAP

- **Design:** Prospective, single-blinded, randomized study [n=200 with community acquired pneumonia (CAP)]
- **Purpose:** evaluate the impact of serial PCT testing and antibiotic discontinuation following PCT level results of less than 0.25 ng/mL to reduce antibiotic duration in CAP
- **Results:** no difference in mortality between PCT guided therapy and control despite a reduction in mean duration of antibiotic therapy in the PCT group (6.2 ± 6.2 days vs. 14.2 ± 7.3 days, p<0.001)

LITERATURE REVIEW

ProHOSP\textsuperscript{1}

- **Design**: multicenter, non-inferiority, randomized controlled trial of ERs in 6 Swiss tertiary care hospitals [n=1359 presenting with lower respiratory infection (LRTI)]

- **Purpose**: assess the utility of a PCT algorithm in reducing antibiotic exposure without increasing adverse outcome risk in patients with LRTIs

- **Results** (PCT compared to control):
  - Reduction in mean duration of antibiotic exposure (5.7 vs. 8.7 days; relative change -34.8%, 95% CI -40.3% to -28.7%)
  - Reduction of 8.2% in the incidence of antibiotic-related adverse effects without an increase in adverse outcomes (95% CI -12.7% to -3.7%)

*Clin Infect Dis.* 2015; rr(5): 651-662
ZVAMC INITIAL PCT LEVEL ALGORITHM

Suspected Infection

No
- Immunosuppressed
- Post-transplantation
- Trauma/post-surgery
- Invasive fungal infection
- Localized infection (abscess)

PCT Indicated?

Yes
- Lower Respiratory Tract Infection (CAP, HCAP, HAP, VAP, AECOPD)
- Severe sepsis and septic shock

≤0.25 ng/mL
- Bacterial etiology highly unlikely
  - Antibiotics strongly discouraged. Consider alternative diagnosis. Repeat PCT if holding antibiotics and no clinical improvement

0.25-0.5 ng/mL
- High clinical suspicion for infection*

>0.5 ng/mL
- Bacterial etiology highly likely
  - Initiate antibiotics to cover possible organisms
  - Obtain daily PCT levels. Refer to follow-up algorithm

* High clinical suspicion for infection includes patients with a high clinical suspicion for infection and a PCT level of 0.25-0.5 ng/mL.
ZVAMC INITIAL PCT LEVEL ALGORITHM

\[
\leq 0.25 \text{ ng/mL}
\]

Bacterial etiology highly unlikely

Antibiotics strongly discouraged. Consider alternative diagnosis. Repeat PCT if holding antibiotics and no clinical improvement.
*Continue empiric antimicrobials and redraw a level after 12 hours to assess for a subsequent rise in PCT.*
ZVAMC INITIAL PCT LEVEL ALGORITHM

1. >0.5 ng/mL
2. Bacterial etiology highly likely
3. Initiate antibiotics to cover possible organisms
4. Obtain daily PCT levels. Refer to follow-up algorithm
• PCT levels are not indicated if antimicrobial therapy has been discontinued, if the source of the infection has been identified, or if the infection is well controlled

• PCT levels are not recommended for more than 5 days

• Patients should be treated for a duration based on established guidelines for the diagnosed infection
Consider obtaining daily PCT levels in order to assess for trends in patients with an unidentified source of infection. It is recommended that decisions based on PCT levels be performed every other day in order to assess for trends in PCT levels. Daily changes to antibiotic regimens based on PCT are not recommended.

- **≤0.25 ng/mL**
  - Low suspicion for ongoing infection or decreasing/stable PCT
  - Strongly consider **discontinuing** antimicrobial therapy

- **0.25-0.5 ng/mL**
  - Low suspicion for ongoing infection or decreasing/stable PCT

- **>0.5 ng/mL**
  - Strongly consider **continuing** antimicrobial therapy.
  - If PCT continues to rise or not adequately decrease despite broad-spectrum antimicrobials, consider other sources of infection or resistant organisms
ZVAMC FOLLOW-UP PCT LEVEL ALGORITHM

- \(<0.25\, \text{ng/mL}\)
  - Low suspicion for ongoing infection or decreasing/stable PCT
  - Strongly consider **discontinuing** antimicrobial therapy
- \(0.25-0.5\, \text{ng/mL}\)
ZVAMC FOLLOW-UP PCT LEVEL ALGORITHM

0.25-0.5 ng/mL

High suspicion for ongoing infection or decreasing/stable PCT

>0.5 ng/mL

Strongly consider **continuing** antimicrobial therapy.

If PCT continues to rise or not adequately decrease despite broad-spectrum antimicrobials, consider other sources of infection or resistant organisms.
PURPOSE

• To assess the long-term appropriateness of initial and serial PCT testing and the impact of PCT testing on antibiotic management in the Intensive Care Unit (ICU) and Emergency Department (ED) per the ZVAMC PCT protocol
OUTCOMES

Primary outcome:

• Appropriate utilization assessment of PCT testing in the ED and ICU per the current PCT protocol in patients with LRTIs and/or sepsis

Secondary outcomes:

• Antibiotic duration
• Antibiotic de-escalation (antibiotic days saved)
• Total and ICU length of stay (LOS)
• Readmission at 30 days
• Economic analysis (antibiotic cost)
METHODS: STATISTICS

Primary outcome:
  • Chi-square

Baseline characteristics:
  • Chi-square, Fisher’s exact test, 2-sample t-test

Secondary outcomes:
  • Antibiotic duration: Negative binomial regression
  • Antibiotic de-escalation (antibiotic days saved): Poisson regression
  • Total and ICU LOS: Negative binomial regression
  • Readmission at 30 days: Chi-square
  • Economic analysis (antibiotic cost)
STUDY DESIGN

Quality assurance, single-center study

Intervention:

- Implementation of pharmacy-assisted PCT serial ordering and guidance of antimicrobial therapy per protocol for patients with PCT tests drawn in the ED or ICU

Retrospective review
October 1 – December 31, 2014

Prospective review with intervention
October 1 – December 31, 2015
STUDY DESIGN

Data collected:

- Patient demographics
- PCT level
- Diagnosis at time of test
- Signs/symptoms related to sepsis and/or LRTI
- Systemic Inflammatory Response Syndrome criteria
- Pertinent microbiology
- Antimicrobial therapy
- Total and ICU LOS
- 30-day readmission rates
**INCLUSION/EXCLUSION CRITERIA**

**Inclusion Criteria**
- Female or male veteran
- Age ≥ 18 years
- PCT in ED or ICU during retrospective or prospective time frames
- Diagnosis of LRTI and/or suspected sepsis

**Exclusion Criteria**
- Patients with >24 hours of appropriate antimicrobial therapy prior to initial PCT level
- Febrile neutropenia
- Acute and chronic graft-versus-host disease (GVHD)
- Immunosuppression
- Chronic steroid use (defined as >3 months of prednisone 7.5 mg/day or of a prednisone equivalent)
- End stage renal disease (CrCl <15 ml/min)
- Pregnancy, post-partum
- Immediately post-surgery, trauma, and/or burns
RESULTS

Retrospective Group (2014)

n = 62 assessed

n = 27 excluded

n = 35 included

Not indicated (n=7)
Chronic steroid use (n=5)
ESRD (n=2)
Post-surgery (n=3)
>24 hr approp. abx (n=10)
RESULTS

Prospective Group (2015) n = 80 assessed

- n = 33 excluded
  - Not indicated (n=14)
  - Chronic steroid use (n=6)
  - ESRD (n=6)
  - Post-surgery (n=2)
  - >24 hr approp. abx (n=5)

- n = 47 included
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Retrospective (n=35)</th>
<th>Prospective (n=47)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.46 ±12.85</td>
<td>71.13 ± 11.39</td>
<td>0.8035</td>
</tr>
<tr>
<td>Male</td>
<td>33 (94.29%)</td>
<td>45 (95.74%)</td>
<td>0.7632</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRTI</td>
<td>22 (62.9%)</td>
<td>33 (70.2%)</td>
<td>0.4833</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6 (17.1%)</td>
<td>6 (12.8%)</td>
<td>0.5791</td>
</tr>
<tr>
<td>Both</td>
<td>7 (20.0%)</td>
<td>8 (17.0%)</td>
<td>0.7300</td>
</tr>
<tr>
<td>COPD diagnosis</td>
<td>12 (34.29%)</td>
<td>26 (55.32%)</td>
<td>0.0526</td>
</tr>
<tr>
<td>Undetectable PCT level (&lt;0.05 ng/mL)</td>
<td>8 (22.86%)</td>
<td>23 (48.9%)</td>
<td>0.0215*</td>
</tr>
<tr>
<td>Detectable PCT level (ng/mL)</td>
<td>0.221±4.85</td>
<td>0.164±6.30</td>
<td>0.4439</td>
</tr>
</tbody>
</table>
ANTIBIOTIC ACTION PER PROTOCOL

% of patients (%)

- **Continued**
  - Retrospective: n=11
  - Prospective: n=11
  - P-value = 1.0

- **OFF protocol**
  - Retrospective: n=12
  - Prospective: n=15
  - P-value = 0.5661

- **Discontinued**
  - Retrospective: n=12
  - Prospective: n=21
  - P-value = 0.1260
## Antibiotic Days

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Retrospective (n=36)</th>
<th>Prospective (n=47)</th>
<th>P-value</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic duration (days)</td>
<td>6.94±8.75</td>
<td>4.26±4.41</td>
<td>0.0706</td>
<td>-40%</td>
</tr>
<tr>
<td>Antibiotic days saved*</td>
<td>6.42±0.79 (n=12)</td>
<td>6.33±0.86 (n=21)</td>
<td>0.9273</td>
<td>-7.06%</td>
</tr>
</tbody>
</table>

Total saved antibiotic cost due to de-escalation of antibiotics: $1126.40

*low initial PCT level or serial levels showing decline
MEAN TOTAL LENGTH OF STAY (LOS)

Total LOS*  

Days

Retrospective: 10.83
Prospective: 7.6

Negative binomial regression percent change = 0.701; p-value = 0.054

*Total LOS is truncated at 30 days
MEAN ICU LENGTH OF STAY (LOS)

Negative binomial regression percent change = 0.808; p-value =0.6244
READMISSIONS AT 30 DAYS

Percentage of patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Total readmission</th>
<th>Infection-related readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>n=3</td>
<td>n=0</td>
</tr>
<tr>
<td>Prospective</td>
<td>n=16</td>
<td>n=3</td>
</tr>
</tbody>
</table>

P-value = 0.0073
P-value = 0.3137
CONCLUSIONS

• PCT can reduce the duration of antibiotic days overall and increase the number of antibiotic days saved when compared to guideline antibiotic durations

• The number of patients impacted by antibiotic days saved is increased when a pharmacist is involved in the monitoring and follow-up of PCT

• A pharmacist monitoring PCT levels has the potential to decrease total LOS if protocol is followed
LIMITATIONS

• Small sample size
• Only conducted in patients who were in the ED and ICU at the time of the initial lab draw
FUTURE DIRECTIONS

• Implement pharmacy-assisted PCT follow-up into ZVAMC antimicrobial stewardship protocol and/or clinical pharmacist work-flow
• Education to providers regarding PCT protocol and how to interpret/act upon results
• Expansion of study timeframe to achieve power
ASSESSMENT QUESTION #1

Which of the following disease state combinations is procalcitonin clinically indicated for?

A. Suspected sepsis and/or lower respiratory tract infections
B. Cellulitis and/or onycholysis
C. Otitis externa and/or otitis media
D. Sinusitis and/or nasopharyngitis
ASSESSMENT QUESTION #1

Which of the following disease state combinations is procalcitonin clinically indicated for?

A. Suspected sepsis and/or lower respiratory tract infections
B. Cellulitis and/or onycholysis
C. Otitis externa and/or otitis media
D. Sinusitis and/or nasopharyngitis
Based on current literature, procalcitonin is associated with which of the following?

A. Reduced mortality
B. Increased length of stay
C. Reduction in the duration of antibiotic therapy
D. Increased number of antibiotic-related adverse effects
ASSESSMENT QUESTION #2

Based on current literature, procalcitonin is associated with which of the following?

A. Reduced mortality
B. Increased length of stay
C. Reduction in the duration of antibiotic therapy
D. Increased number of antibiotic-related adverse effects
ACKNOWLEDGEMENTS

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REFERENCES


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