Procalcitonin – A Way to a Better Antibiotic Stewardship in the Adult Population:

A Literature Review

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MASTERS OF NURSING

By

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To the Faculty of Washington State University:

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Abstract

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Procalcitonin (PCT) is a relatively new diagnostic test in the United States. PCT results have been useful in early identification of severe bacterial infections, and differentiating systemic inflammatory response syndrome (SIRS) from sepsis. PCT was approved by the Federal Drug and Administration (FDA) in 2008, as an adjunct test to physical assessments and laboratory findings. PCT may be used concomitantly with C-reactive protein (CRP), blood culture, complete blood count (CBC), or cerebrospinal fluid (CSF) analysis, to assist in detecting progression to sepsis and septic shock in critically-ill patients. PCT is typically ordered upon initial presentation in a patient with signs and symptoms of systemic infection, such as fever of unknown origin, chills, tachycardia, tachypnea, confusion, and decreased urinary output. Low PCT (<2ng/L) signifies that the patient’s symptoms are caused by a process or agent other than bacteria and points to an early localized infection that has not yet spread systemically, or to a minor systemic inflammatory response. High levels of PCT (>2 ng/L) indicate sepsis, with a greater likelihood of progression to septic shock if left untreated. Although not FDA approved for such use, decreasing serial PCT levels have been documented with successful antibiotic therapy. This literature review was conducted to evaluate PCT testing and its
future as a gold standard in practitioners' efforts to combat antibiotic resistance and improve antibiotic stewardship.

Key Words: Procalcitonin, procalcitonin-based guidelines, sepsis, severe bacterial infection, antibiotic stewardship, fever of unknown origin, SIRS
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Procalcitonin – A Way to a Better Antibiotic Stewardship in Adult Population:

A Literature Review

Introduction

Overuse of antibiotics is a significant problem in our health care system. It is a multifaceted issue as it affects patients' healthy gastrointestinal flora, contributes to the emergence of multi-drug-resistant pathogens, and adds to already high medical costs. The issue of overuse creates an urgency to develop methodologies that either negate or limit antibiotic use.

Riedel (2012) recognizes sepsis as the 11th leading cause of death and a monumental healthcare expense of over $17 billion in the United States today. While blood cultures remain important in identifying the offending agent, their usefulness as a rapid diagnostic tool leaves a lot to be desired for the mere turnaround time of minimum 48 hours. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been utilized as inflammatory markers for decades. Their lack of specificity for sepsis and infection have proven to be less useful than originally thought (Riedel, 2012).

Fast and accurate diagnosis is extremely important as septic patients who do not receive an appropriate antibiotic treatment in the first hour of onset of hypotension are at increased risk for increased morbidity and mortality (Kumar et al., 2006). A retrospective cohort study reviewed medical records of 2,731 patients in 14 intensive care units in 10 hospitals. Rapid and appropriate antibiotic treatment was associated with an increased survival to discharge. Only 50% of septic shock patients received appropriate antimicrobial treatment within 6 hours of the onset of hypotension. Each hour of delay in antimicrobials resulted in 7.6% decrease in survival.
Harbarth and colleagues (2001) agreed that differentiating sepsis from non-infectious causes of SIRS, such as trauma, burns, pancreatitis, hemorrhage, hypothermia, or surgery, remains challenging in the critically ill. Schuetz et al. (2011) concurred that PCT levels should assist providers in determining if the antibiotic therapy is required and what the duration of such therapy should be, according to continuous monitoring of PCT levels.

**Problem Statement**

There are a few laboratory tests that healthcare providers may order to assess for an ongoing infectious process, such as CBC, CRP, ESR, and blood cultures. These tests are not sensitive or specific for bacterial infection and sepsis. Blood culture results are available after 24-72 hours, and the true results are highly dependant on the correct method of collection as well as the use of the correct media that will encourage growth of the offending agent. The uniqueness of PCT, unlike other laboratory tests, lies in that PCT elevation is rapid and significant (4-6 hours) once triggered by a bacterial infection. CRP and ESR in contrast, are elevated within 24 hours or longer. Serum PCT levels can be drawn with an initial blood draw and its point-of-care test has a 20-minute turnaround time. The decision time to initiate an antibiotic is, therefore, dramatically reduced. Likewise, PCT levels decline by half within 24 hours of antibiotic-achieved infection control or an effective host immune response (Riedel, 2012). Without PCT, the patient potentially would continue on an extended course of a broad-spectrum antibiotic for several days before the blood cultures would identify the exact offending agent and reveal the antibiotic sensitivity. In the mean time, the healthcare provider would be
inclined to add or switch antibiotics according to the patient’s status, until the source organism became evident. Treatment efforts must be focused on early identification and treatment of systemic inflammatory response syndrome (SIRS) and bacterial infection, as well as careful and selective initiation of antibiotic treatment and rapid de-escalation of antibiotic treatment, once the patient’s condition improves.

Methods

The literature search for this review was conducted using Medical Literature On-Line (MEDLINE), accessed through the PubMed website. An advanced search and cross-reference of 24 Washington State University WorldCat databases was also utilized through the Washington State University online library. Studies reviewed were written in English and found in peer-reviewed articles. Key words used to initiate the literature search were procalcitonin, biomarkers, sepsis, procalcitonin-guided protocols, procalcitonin in antibiotic stewardship, randomized controlled trials with procalcitonin, economic evaluation, and procalcitonin algorithms for antibiotic therapy decisions. The literature review was limited to studies completed between years 2008-2012, with an exception of Habarth et al., (2001), an article that played a primary role in getting the FDA approval for Procalcitonin testing in 2008. The PubMed search yielded 477 potential articles, of which 83 were chosen for review from clinical trials and 20 from the procalcitonin literature review. Based on the problem statement, a total of 10 articles were reviewed and organized into three sections: PCT – A Better Laboratory Test (3 articles), Cost-effectiveness of PCT Testing (1 article), and A Better Antibiotic Stewardship (6 articles).
Theoretical Framework

Leavell and Clark’s Levels of Prevention Model emphasizes the importance of health promotion and health maintenance, as well as disease prevention at various stages (See Figure 1). The theory hypothesizes that any disease or injury occurs on a continuum between health and advanced disease (Nursing Theories, 2012). With a timely intervention at any point on this continuum, the disease process can be slowed and/or stopped to prevent a further deterioration in health. There are three levels of prevention: primary, secondary, and tertiary. PCT testing would be considered a secondary measure, as the goal is to diagnose early and treat appropriately severe bacterial infections and SIRS before signs and symptoms of sepsis and septic shock set in.

Literature Review

PCT – A Better Laboratory Test

PCT is a biomarker with excellent specificity for sepsis (Harbarth et al., 2001), while other laboratory values, such as WBC, band count, CRP, sputum and urine culture, are non-sensitive, non-specific and unreliable. All seriously ill patients will have an elevated CRP secondary to inflammation. In addition, CRP levels may be altered by administration of immunosuppressive therapy (Riedel, 2012). Vital sign changes and other signs and symptoms may mimic sepsis; but in reality this pseudosepsis could be a manifestation of numerous other conditions, such as gastrointestinal (GI) hemorrhage, pulmonary embolism, acute myocardial infarction (AMI), acute pancreatitis (edematous or hemorrhagic), diuretic-induced hypovolemia, and relative adrenal insufficiency.
Cunha, 2012). Hypotension and increased lactate levels are late signs of septic shock and signify organ hypoperfusion (Riedel, 2012).

Gluck (n. d.) indicated a PCT value of <0.5ng/mL will correctly dismiss a sepsis diagnosis 98% of the time. Continuous rise of serum PCT is associated with poor patient outcome, while a documented continuous fall of serum PCT signifies the recovery of the patient’s immune system and an appropriate antibiotic selection by the provider. A provider may chose to start a patient on a broad spectrum antibiotic with a documented high suspicion of bacterial infection, despite normal or mildly elevated levels (0.5-1.5ng/mL) of PCT. In this case, continuous monitoring of PCT and prompt discontinuation of antibiotics is indicated after the second normal PCT level is received in 12-24 hours. PCT values of >2.0ng/mL would necessitate continuation of antibiotics and daily measurements of PCT. Serial monitoring of PCT after the initial 24 hours of onset of illness is implemented to evaluate the effectiveness of the prescribed antibiotics (Gluck). Again, declining PCT values are encouraging of the patient’s recovery, while persistent high PCT values indicate a need to change the prescribed antibiotic treatment plan. Elevated WBC, band count, CRP, and body temperature will not resolve as rapidly as the serum PCT level, which will drop with correct treatment of the imposing infection (Gluck). After the PCT normalizes and remains <0.5ng/mL for 48 hrs, antibiotic treatment may be discontinued (Gluck).

Antibiotics administration as the standard care of an infected or septic patient are currently prescribed for fixed durations, from 10-14 days (Heyland et al., 2011). Johanesen, Jensen and Lundgren (2011) described a problematic situation where critical ICU patients are admitted with and remain on empiric broad spectrum antibiotics for
extended periods of time, until providers have a clear indication that infection is not contributing to patient’s already high morbidity and mortality risk. With serum PCT levels, clinicians are now able to assess individual patient’s responses to prescribed antibiotic therapy.

Harbarth and colleagues (2001) studied 78 ICU patients admitted with SIRS and possible infection. The superiority of PCT over other biomarkers (Interleukin-6 and Interleukin-8) was confirmed; PCT had the highest discriminative value with an area under the curve 0.92, a sensitivity of 97%, a specificity of 78%, with a positive predictive value (PPV) of 94%, a negative predictive value (NPV) of 88%, with a confidence interval of (CI) 0.85-1.0 when used to differentiate SIRS from sepsis. When added to standard clinical impression and common laboratory values used to rule out sepsis (body temperature, blood pressure, CBC, and CRP), PCT values improved diagnostic accuracy of sepsis from 77% to 94% (See figure 2).

PCT levels cannot be used in patients with end-stage renal disease (ESRD) and hemodialysis to detect early bacterial infection and sepsis. Although PCT elimination is not well understood at this time, these patients have high levels of PCT despite negative blood cultures (Riedel, 2012). Elevated PCT levels have been linked to SIRS, localized bacterial infections, autoimmune disease, inhalation injury, burns, trauma, surgery, pancreatitis, heat stroke, some cancers, as well as viral, parasitic, and fungal infections (McGee & Baumann, 2009). The differentiating factor in afore mentioned situations, besides astute clinical judgment, would be the degree of elevation (0.5-2ng/L) rather than elevation alone, and would require serial measurements of PCT to rule out sepsis.
Persistent high levels of PCT (0.5-2ng/L and greater) are diagnostic of sepsis, severe sepsis, and septic shock.

**Cost-effectiveness of PCT Testing**

Heyland, Johnson, Reynolds and Muscedere (2011) evaluated the economic and clinical impact of PCT guided antibiotic therapy. The authors reviewed 5 intensive care unit-based randomized controlled trials that compared PCT guided antibiotic treatment versus the usual care of a septic ICU patient (n = 947). The combined results confirmed the reduction in antibiotic exposure in the PCT arm (weighted -2.14 days, p < .00001), no difference on effect on mortality in PCT arm versus the control group (risk ration 1.06, p = .59), and no difference in lengths of stay in ICU (weighted mean difference -1.50, p = .25) or hospitalization (-1.86, p = .21). Cost analysis was done in Canadian dollars, with the conversion rate applied as Can$ 1.00 = USD$ 1.02 (MSN Money, 2013). Economic analysis revealed a potential cost saving of approximately $480.00 USD per patient per clinical course, while using an average-cost antibiotic. PCT-guided antibiotic treatment would accumulate great monetary savings, while promoting a safe and prudent antibiotic therapy. Limitations of this study are the narrow inclusion criteria (no prior antibiotics, ICU-presenting infections only), majority of patients with a medical diagnosis, low provider compliance with PCT-guided algorithm, and fixed durations of usually prescribed antibiotics in the control group (Heyland et al., 2011).

Unnecessary and prolonged antibiotic therapy adds to the cost of healthcare in that it increases complications from administering such therapy. The expense of treating medication-induced allergic drug reactions, antibiotic-induced colitis, and multi-resistant
bacterial infections is ever significant in today’s healthcare worldwide (Hochreiter et al., 2009). Nobre et al. (2008) asserted that more studies are necessary to determine the exact cost benefit of PCT-guided antibiotic treatment in comparison with empirical antibiotic treatment. Nobre and colleagues (2008) hypothesized that a shorter antibiotic course, shorter length of stay in ICU, and shorter hospitalization in general, as allowed by the PCT-guided treatment, would clearly offset the cost of PCT testing – USD$177/3 tests.

A Better Antibiotic Stewardship

An observational quality survey study was completed by Albrich et al. (2012) in 10 medical centers in Switzerland, 3 in France, and 1 in the United States. The study population (N = 1,759) was a mixture of emergency department and outpatient office visit patients with the chief complaint of lower respiratory tract infection (LRTI). Patients (n=1,520) were confirmed to have a LRTI, and of those, 1,208 (79.5%) received a minimum of one antibiotic. The baseline PCT levels were drawn at the time of diagnosis and serially monitored during the antibiotic therapy. The initiation and duration of antibiotic therapy, compliance with the PCT-guided algorithm (Figure 3), and patient outcomes were all monitored. Thirty-day phone follow-up interviews were conducted and any changes in the patients’ expected course of treatment was investigated and documented. The study results indicated that following a PCT-guided algorithm reduced the duration of antibiotic treatment by approximately 20% in comparison with the standard treatment (7.4 days vs 5.9 days, P < .001). Not initiating antibiotics on a low PCT level of < 0.25ng/L and appropriate termination of antibiotic therapy when PCT level decreased to < 0.25ng/L were found safe. There were no indications of heightened
mortality or untoward events with application of this methodology. The study strengths were the large sample size, and the inclusion of different levels of care. The limitation of this international study may be that provider compliance with PCT-guided algorithm was 81%, 19% of the patients PCT-guided algorithm was overruled secondary to more complicated clinical presentations, and the uneven number of medical centers surveyed in each country, as it would be difficult to appropriately generalize findings to all countries involved (Albrich et al., 2012).

Schuetz et al. (2009) conducted the ProHOSP, multicenter, noninferiority (prove that PCT is not inferior to the current evidence-based practices), large randomized controlled trial with 1,359 emergency department patients from 6 Swiss hospitals. Patients were 18 years of age or older. The chief complaint was variable stages of lower respiratory tract infections (LRTI). Antibiotic administration occurred in both, the PCT-guided algorithm group (Figure 2) and control group. The intervention arm relied on PCT levels for treatment, while the control group relied on evidence-based practice guidelines. Adverse effects monitored included death, ICU admission, disease-specific complications, and recurrence of LRTI that required an antibiotic or hospital readmission. Also monitored were antibiotic exposure, to include the duration of antibiotic therapy, adverse effects from antibiotics, and length of hospital stay. The study concluded that the PCT-guided group did not have a 30-day higher risk of adverse effects than the control group (95% CI). A drastic decrease in overall antibiotic exposure was observed in PCT group, 5.7 vs. 8.7 days. The rate of adverse affects such as nausea, diarrhea, and rash were decreased by 8.3% while following the PCT guidance. The strength of this trial lies in a large sample size studied and partially blinded outcome assessment. The limitations
of the study may be physicians’ knowledge of the trial may have triggered a Hawthorne effect in that they prescribed less antibiotics compared to what their usual prescriptive habits. The spillover effect may have altered the prescribing habits of physicians involved with the control group patients in this trial.

Schuetz et al. (2011) reviewed 14 randomized controlled trials that included a total of 4,467 patients with varied acuity of primary care, emergency department, and intensive care. They sought to evaluate the use of PCT algorithms in adult patients suffering from respiratory tract infections and sepsis (See Table 1). Their results further reinforced the safety profile of PCT, as mortality levels between PCT and control groups were not significantly different (0.73-1.14, 95% CI). Lower levels of exposure to antibiotics were noted, as low-acuity patients did not receive antibiotics. Antibiotic treatments prescribed to moderate to high-acuity patients were of shorter duration, when therapy was de-escalated based on consecutive decline of serum PCT levels. The limitation of the study is that all randomized control trials were done in Europe. Further United States-based, multicenter studies were recommended for PCT algorithms, and authors proposed an acuity-based algorithm (Schuetz et al., 2011).

A systematic literature review was reported by Agarwal & Schwartz (2011) that evaluated the safety of PCT and its effectiveness in guiding the antibiotic therapy in intensive care patients (N = 1,476). Antibiotic use was strongly discouraged for PCT levels <0.25ng/L, and discouraged for PCT levels <0.5ng/L. PCT levels > 0.5 indicated a need for antibiotic, where antibiotic was strongly encouraged with PCT elevations >/= 1ng/L. The results confirmed that PCT-guided antibiotic therapy reduces overexposure to antibiotics in intensive care units (greatest mean difference in days -3.8, p > .001)
and may decrease patients’ length of stay (in 2 out of 5 studies). Mortality and re-infection risks were not significantly different in the PCT algorithm and the control group. The limitation of these studies is the lack of cost-effective analysis with the PCT guided methodology and all studies were conducted in Europe (Agarwal & Schwartz, 2011).

A randomized, controlled, open interventional trial of severely septic intensive care unit (ICU) patients was reported by Nobre et al. (2008). Two hundred and eighty-two patients were initially screened, and 79 were randomized to the PCT group or the control group using a computer-based random number generation. In the PCT arm all 79 patients had a baseline and a daily PCT until the 7th day or until antibiotic discontinuation. The initial PCT values were not communicated to the prescribing physicians. All patients received initial antibiotic treatment, as dictated by the local bacterial resistance patterns. Patients in the control group were initially treated with a variety of broad spectrum parenteral antibiotics depending on their indication. In this population, culture results determined antibiotic choice; however the duration of antibiotic treatment was not altered. In the PCT group, antibiotics were stopped on day 3 if the PCT level declined 90% or more from the baseline, where the baseline PCT was <1ng/L. If the baseline PCT was ≥1ng/L, the antibiotic was stopped on day 5, provided again that the latest PCT level declined by 90% or more from the baseline. Limitations of this study include a single-center study, small sample size, the uneven number of dropouts in the two groups, low baseline levels of PCT in a small group of patients included in the study, and no compliance analysis with PCT algorithm. The study concluded that following the PCT algorithm is safe, lessens the duration of antibiotic
treatment days (median 6.0 days vs 9.5 days), and allows for shorter ICU and hospital lengths of stay (4 days vs 7 days) as compared to the control group (Nobre et al., 2008).

The PRORATA trial was conducted in a multicenter, prospective, parallel-group, open-label trial in France (Bouadma et al., 2010). The trial included 7 ICUs in 5 university-affiliated hospitals, and one medical-surgical ICU in a general hospital. Of 1,315 eligible patients, 630 underwent the trial and computer-generated randomization 1:1 to PCT and control group. The results of this trial did not confirm that following PCT-guided protocols to treat patients with suspected bacterial infections shortened the length of stay in ICUs. However, the PCT-guided algorithm for antibiotic treatment was reported to decrease antibiotic exposure, with no substandard outcomes when compared to standard antibiotic treatments. The authors mentioned limitation of this study included 53% of patients in PCT group did not undergo the PCT algorithm due to the physician decision to stop or not start antibiotics, even when they were indicated by the established protocol, only 10% of the study sample were surgical patients, use of the open trial design, participation of only 8 ICUs, and a higher number of subjects from the PCT group died days 29-60. Regardless, the number of days without antibiotics were higher in PCT group (14.3 vs. 11.6, p < 0.0001), with an absolute difference of 2.7 days, 95% CI, with the similar 28-day mortality rate of 21.2% vs. 20.4%. (Bouadma et al., 2010).

**Discussion**

Rodak (2012) predicts that the most stellar infection control programs of the future will have the PCT test added to their sepsis protocol. This test recognizes sepsis early, allowing providers to treat patients with antimicrobials early, which in turn
decreases sepsis-related mortality. Using serial PCT testing, providers can monitor antibiotic therapy closely and terminate treatment when symptoms begin to resolve, PCT levels decrease, and eventually normalize. A prudent antibiotic stewardship is a national and global healthcare goal with all the multi-resistant bacteria that have emerged and antibiotic-related side-effects, such as Clostridium difficile, on the rise. Reviewed studies that focused on antibiotic de-escalation strategies all confirm that significant decreases in antibiotic exposures are possible with adherence to the PCT-guided algorithm. Inferior outcomes and mortality did not increase while providers followed PCT levels, and ordered antibiotic therapy termination as soon as PCT levels lowered and patient’s symptoms indicated a pending recovery.

It is of utmost importance that providers use the resources available to them and take advantage of the potential economic and clinical benefits of PCT testing. With health on one side of the continuum, and septic shock on the other (Figure 1), PCT testing identifies early signs of bacterial infections and SIRS before the progression into irreversible end-organ damage and leave patients with debilitating long-term complications of sepsis. As secondary level of prevention, serial PCT testing allows for appropriate initiation, termination and de-escalation of antibiotic treatments.

**Conclusion**

Overuse of antibiotics, further emergence of multi-resistant pathogens, and the adverse effects of antibiotic treatments can be prevented by educating providers on new medical research, laboratory tests and guidelines that are aimed at limiting antibiotic therapy to true bacterial infections and shortening the course of antibiotic treatments. The majority
of the PCT studies reviewed were based in European healthcare centers. Recommendations for further research include large multicenter, large sample clinical trials in the United States, and utilizing PCT-guided algorithms. The evaluation should include measures of antibiotic treatment days, length of stay, morbidity and mortality as well as the economic impacts utilizing Procalcitonin to guide therapy.
Figure 1. Levels of prevention model (Exercise Is Medicine, 2012)
Figure 2. Clinical models with and without PCT (Harbarth et al., 2001)
Figure 3. Procalcitonin algorithm for stewardship of antibiotic therapy (Schuetz et al., 2009)
Figure 4. Procalcitonin: A Biomarker for Improved Infection Management. (Neath, n. d.)
### Table 1. An acuity-based PCT algorithm (Schuetz et al., 2011)

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- **Overruling the algorithm:**
  - Consider alternative diagnosis, or Abx if patients are clinically unstable, are at high risk (e.g., COPD GOLD III-IV), or have strong evidence of a bacterial pathogen.

- **Follow-up/other comments:**
  - Reasses patients’ condition and recheck PCT level every 2 to 3 days to consider early cessation of Abx.
  - Reasses patients’ condition and recheck PCT level every 2 days to consider cessation of Abx.
  - Empirical therapy recommended in all patients with clinical suspicion of infection.

- **Follow-up evaluation every 1 to 2 days:**
  - Consider alternative diagnosis; reassess patients’ condition and recheck PCT level every 2 days to consider cessation of Abx.

- **Follow-up evaluation every 2 to 3 days:**
  - Reasses patients’ condition and recheck PCT level every 2 to 3 days to consider early cessation of Abx.

- **Clinical reevaluation as appropriate:**
  - Consider treatment to have failed if PCT level does not decrease adequately.
References


