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The Use of Procalcitonin Monitoring in Critically Ill Adults for Early Identification and Treatment of Sepsis

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Abstract

Sepsis is the leading cause of death in critically ill and rapidness of identification is crucial to prevent circulatory collapse, multisystem organ failure, and death. The International Surviving Sepsis Guidelines supports the early implementation of empiric antimicrobial therapy. The inappropriate use or overuse of antimicrobials results in increased antibiotic resistance, increased healthcare costs, adverse drug events, and antibiotic-induced colitis. The use of a biomarker specific to bacterial sepsis would allow the clinician to diagnose sepsis early and monitor response to antimicrobial therapy, understanding the need to escalate, descalate, or discontinue therapy. Procalcitonin has been proposed as such specific biomarker; able to differentiate sepsis syndrome from systemic inflammatory response. Studies to date show mixed results regarding the effectiveness of procalcitonin to identify, stage, and monitor response to treatment of sepsis. Procalcitonin is not a gold standard in the diagnosis of sepsis; however, it is an important adjunct to other physiological clinical markers.

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Significance of the Problem

Sepsis is the leading cause of mortality in the critically ill. Rapidness in the identification of sepsis is crucial to prevent progression to circulatory collapse, multisystem organ failure, and death (Tang, Eslick, Craig, & McLean, 2007). The signs used for identification of sepsis such as tachycardia, fever, tachypnea, and leukocytosis are all nonspecific and difficult to distinguish from the clinical presentation of noninfectious conditions such as systemic inflammatory response syndrome (SIRS); a very common condition in critical patients with burns, trauma, and surgery (Tang et al., 2007). Barriers encountered in the clinical identification of sepsis encompass the inability of many patients to describe their symptoms due to altered level of consciousness, atypical appearance of clinical findings in the presence of immunological incompetence, and the presence of other medications that alter the hemodynamic response (Jensen et al., 2008).

To improve prognosis in the critically ill patient with sepsis, the International Surviving Sepsis Campaign (ISSC) guidelines support implementing early antimicrobial therapy that is active against the identified causative process (Jensen et al., 2011). Initial treatment for presumed sepsis involves the use of empiric broad spectrum antibiotic therapy, which frequently results in antibiotic overuse, antibiotic resistance, and increased healthcare costs (Nobre, Harbarth, Graf, Rohner, & Pugin, 2008). In practice, 10 to 14 days of antibiotic treatment are common among critical patients in the intensive care unit (ICU). If the length of antibiotic treatment is unnecessary, it predisposes the patient to a higher risk of allergic reactions, drug adverse effects, and antibiotic-induced colitis (Hochreiter et al., 2009).

An important consideration involves not only the early identification of sepsis and early treatment, but the appropriate treatment for the causative pathogen. Theoretically, an ideal biomarker would provide the clinician an early warning that the antimicrobial of choice is not appropriate or effective (Jensen et al., 2011). Blood culture analysis poses considerable delays to

diagnosis and results take 24 to 48 hours to yield results. Biological markers of inflammation such as leukocytes or C-reactive protein (CRP) can be elevated for reasons other than sepsis and are slowly released after progression of infection, which makes them unacceptable for rapid identification and management of sepsis (Sinha, Desai, Mantri, & Kulkarni, 2011).

The ISSC guidelines of 2008 define sepsis as the presence of infection with systemic manifestations including: temperature > 38.3 C or < 36 C, heart rate > 90 or 2 standard deviations (SD) above the normal value for age, tachypnea, edema or positive fluid balance, altered mental status, hyperglycemia, leukocytosis or leukopenia, normal WBC count with > 10% immature forms, CRP > 2 SD above normal, procalcitonin > 2 SD above normal, and arterial hypotension. Severe sepsis is defined as the presence of sepsis along with tissue hypoperfusion and organ dysfunction, evidenced by hypoxemia, acute lung injury, oliguria, elevated creatinine, coagulopathy, ileus, hyperbilirubinemia, thrombocytopenia, and hyperlactatemia. Finally, septic shock is defined as sepsis induced hypotension in spite of fluid resuscitation (Dellinger et al., 2008).

Intervention and Intended Outcome

Serum procalcitonin (PCT) has been proposed as both a specific and sensitive early biomarker in the presence of bacterial sepsis (Jensen et al., 2008). PCT is a 116-aminoacid peptide and a precursor of calcium homeostasis. It is synthesized by thyroid C cells naturally; however, in the presence of sepsis, it is extra-thyroidal in origin. PCT is theoretically able to discern infectious from noninfectious causes of SIRS; additionally, PCT levels do not rise in response to viral infections (Riedel, Melendez, An, Rosenbaum, & Zenilman, 2011; Tang et al., 2007; Uzzan, Cohen, Nicolas, Cucherat, & Perret, 2006).

PCT is released in response to bacterial toxins and bacteria-specific proinflammatory mediators such as IL-6, tumor necrosis factor, and interleukin 1b. PCT is released in the bloodstream 2 to 6 hours after bacteria or its byproducts are present and levels plateau at 8 to 24

hours. PCT levels in the postoperative patient only increase transiently for 12 to 24 hours, unlike other markers such as leukocytes or CRP, which stay elevated for longer. Studies have reported that following PCT levels, a biomarker that can mirror the severity of the disease, could prove useful to evaluate antibiotic response. Decreased levels of PCT suggest an appropriate response to antimicrobial therapy (Jensen et al., 2008; Schuetz et al., 2012).

Statement of the Clinical/PICO Question

Is the use of procalcitonin level monitoring in critically ill adults an effective tool for early identification and treatment of sepsis?

Critical Analysis of the Evidence Related to the Clinical Question

Sinha et al. (2011) studied a group of 40 ICU patients to assess the usefulness of PCT as a biomarker for sepsis in the critically ill adult. The authors found a statistically significant correlation between the presence of sepsis and a PCT level between 0.5 and 2 ng/mL ($p < 0.0001$). PCT levels > 2 ng/ml had 86% sensitivity and 95% specificity, whereas levels of 0.5 ng/mL had a sensitivity of 90% and specificity of 84%. The study concluded that PCT levels above 2 ng/mL are effective markers of sepsis. Falsely elevated levels of PCT were identified in the presence of cardiogenic shock, trauma, major surgery, pancreatitis, and severe burns. The study recommended the cutoff of 10 ng/mL to identify sepsis with coexisting cardiogenic shock. Limitations of the study involved the small sample size and the lack of serial PCT measurements (Sinha et al., 2011).

A prospective study by Ruiz-Alvarez et al. (2009) aimed to evaluate the diagnostic and prognostic value of PCT in 103 critically ill patients with suspected sepsis in the ICU. Serum PCT values were higher on patients with sepsis when compared to their non-infected cohort ($p < 0.001$) and levels correlated with the degree of severity of sepsis. The non-infected, sepsis, severe sepsis, and septic shock groups had average PCT levels of 0.3, 1.1, 1.9, and 9.1 ng/mL respectively ($p < 0.001$). PCT sensitivity was established at 83% and specificity at 62%. The best

cutoff value for supporting the diagnosis of sepsis was 0.32 ng/mL. PCT values were significantly and independently associated with the presence of infection in the multivariate logistic regression model. PCT levels showed no statistical difference between survivors and non-survivors; therefore, a prognostic value could not be established. The study concluded that PCT was an accurate diagnostic parameter in differentiating SIRS from sepsis and PCT levels could be used to categorize degrees of infection. The main limitation of the study is that a single PCT level was collected on admission and correlation of one value to analyze outcome is suboptimal (Ruiz-Alvarez et al., 2009).

Nobre et al. (2008) conducted a randomized controlled trial (RCT) of 79 patients using an antimicrobial treatment algorithm based on daily fluctuation and evolution of serum PCT levels to potentially shorten duration of antibiotic therapy in patients with severe sepsis and septic shock. In the PCT group, patients' antibiotic therapy was given according to PCT guidance and control patients were treated under standard practice. All patients had baseline and daily PCT levels performed for the first seven days. Every subject received antibiotic therapy based on the suspected source of infection and local sensitivities and the antibiotic spectrum was narrowed when possible. The investigators did not interfere with the duration of therapy in patients in the control group but placed stopping rules for the intervention group based on serum PCT levels to encourage discontinuation of antibiotics.

When PCT group patients had an admission baseline PCT level >1 ug/L, a decrease of 90% of baseline by day 5, or an absolute PCT value < 0.25 ug/L, investigators encouraged the practitioners to discontinue antibiotics. For patients that had a baseline level <1 ug/L, providers were encouraged to discontinue antibiotics when PCT levels were < 0.1 ug/L on day 3 and clinical evaluation excluded presence of infection. The study found that the PCT group had a lower median antibiotic duration of 6 versus 10 days ($p= 0.003$) and shorter median ICU length of stay of 3 versus 5 days ($p= 0.003$) when compared to the control group. The average number

of days alive without the use of antimicrobials for the PCT group was 17.4 ± 7.6 versus 13.6 ± 7.6 days for the control group ($p= 0.04$). The probability of having antimicrobial therapy discontinued sooner for the PCT group was twofold higher ($p= 0.009$) (Nobre et al., 2008).

In summary, PCT showed accuracy in the initial diagnosis of sepsis. The potential reduction in number of antibiotic days can lead to a decrease in cost, length of ICU stay, and antibiotic exposure. Though the patients received daily PCT measurements in the clinical study context, the frequency could be decreased to baseline, day 3, 5, and 6 to adhere to the algorithm recommendations and contribute to cost effectiveness. This study was conducted in Switzerland where the cost of 3 PCT measurements was $177. When compared to the savings established by stopping the antibiotics earlier, plus a potential shorter ICU stay, this test could be established as a cost-saving measure. There was no difference in 28-day mortality, clinical cure, or infection relapse between both groups. Limitations of the study included the small sample size and the exclusion of immunocompromised patients, those with complicated infections, or patients with infections that are known to require prolonged antimicrobial therapy (Nobre et al., 2008).

The systematic review and metaanalysis by Uzzan et al. (2006) aimed to determine the usefulness of PCT as a diagnostic marker for sepsis and septic shock in ICU, as well as in the post operative and trauma settings. Twenty-five studies were reviewed with PCT sensitivities ranging from 42 to 97% and specificities from 48 to 100%. The cutoff values of PCT-based diagnosis of sepsis ranged between 0.6 to 5 ng/mL. PCT was found to have a global diagnostic accuracy (DA) odds ratio (OR) of 15.7 with 95% confidence interval. In other words, PCT had almost a sixteen-fold higher chance to be positive in infected than non-infected patients ($p < 0.0001$). If used as a rapid adjunct screening test, PCT can assist the clinician in identifying the infected patient that should be given empiric antimicrobial therapy. “PCT is not a gold standard for infection but may make this diagnosis easier especially in the emergency context of systemic inflammation or shock” (p. 2001). Two limitations of this analysis should be considered. Some

of the studies reviewed used the term sepsis as a mixture of sepsis, severe sepsis, and septic shock; posing the risk of misclassification of study subjects. Additionally, the introduction of excessive heterogeneity by merging studies dealing with different samples, settings, and prognoses can be problematic, since diagnostic tests can have different accuracies at different phases of disease (Uzzan et al., 2006).

Riedel et al. (2011) conducted a study to identify the usefulness of PCT testing in patients in the emergency department (ED) as a predictive marker of bacteremia in febrile individuals. A sample of 295 patients were grouped according to positive or negative blood cultures, and there were significant differences in PCT levels between both groups ($p= 0.00007$). Statistical differences in PCT levels were also found in patients with positive blood cultures for pathogens when compared to patients with positive blood cultures due to contaminants ($p= 0.01$). The PCT cutoff value relative to a positive blood culture for a pathogen was identified at 0.1475 ng/mL, with a sensitivity of 75% and specificity of 78.9%.

In individuals without bacteremia or sepsis, PCT levels were 0.1 ng/mL or less. A value of < 0.1 had 96.3% negative predictive value for bacteremia in ED patients when compared to the use of blood cultures alone. Levels between 0.1 and 1 ng/mL could not predict either the presence or absence of sepsis; therefore, blood cultures and other supportive clinical data to rule out bacteremia were required. The study also supported the relationship between elevated levels of PCT and number of blood culture sets positive for the pathogen detected. Typically more positive culture sets suggest a more serious blood infection. However, one important limitation to note is that only 16 patients in the study had positive blood cultures (Riedel et al., 2011).

Heper et al. (2006) conducted a study to establish the diagnostic value of distinguishing sepsis from severe sepsis and septic shock in the first 72 hours post admission in 39 patients. Additionally, the authors aimed to evaluate the trajectory of sepsis in survivors versus non-survivors, to establish the prognostic value of PCT monitoring. The diagnosis and grading of

sepsis was based on the criteria from the American College of Chest Physicians and the Society of Critical Care Medicine consensus. Patients were evaluated on admission, at 24, 48, and 72 hours and PCT levels were drawn at these times. When PCT levels were compared between the different grades of sepsis, they were found to be significantly different; PCT levels were lower in the sepsis group and higher in the severe sepsis group ($p= 0.001$, $p= 0.009$). For this study, the severe sepsis and septic shock groups were combined under the category of severe sepsis.

Levels of PCT at the seventy-second hour were higher in patients who died compared to those who recovered ($p= 0.032$). For the purpose of discrimination between sepsis and severe sepsis, the PCT level of > 1.35 ng/ml had 88.9% sensitivity and 70% specificity. PCT levels were found to be higher in the severe sepsis group at all times. It was difficult to establish an exact PCT value for the diagnosis of sepsis. The study concluded that PCT levels increase as sepsis worsens. The findings suggested that elevated PCT levels at 72 hours might suggest refractory sepsis and possibly a poor outcome (Heper et al., 2006). The authors of this RCT did not disclose limitations in their study; however, it is important to note that the severe sepsis and septic shock groups were combined under the severe sepsis term; which complicates the comparison of this study's findings to others that classified infected patients under the standard categories.

A randomized controlled trial by Hochreiter et al. (2009) aimed to establish the role of serum PCT monitoring for guiding length of antimicrobial therapy in 110 surgical ICU patients. Both the PCT-guided and control groups had PCT levels monitored daily and received antibiotic treatment based on confirmed or suspected bacterial infections. For subjects in the PCT-guided group, antibiotics were discontinued if the patients were clinically improved, had PCT levels < 1.0 ng/mL, or decreased by 25-35% from baseline value over three days. The study results showed that in the PCT-guided group, antibiotic therapy was 5.9 ± 1.7 days shorter ($p <0.001$) and the ICU length of stay was shorter with 15.5 ± 12.5 versus 17.7 ± 10.1 days in the control

group (p = 0.046). The study concluded that PCT-guided therapy was able to shorten the length of antibiotic treatment and ICU length of stay. No limitations of the study were presented; however, one of the authors served as a consultant and had received payments from BRAHMS, the manufacturer of PCT assays (Hochreiter et al., 2009).

Schuetz et al. (2012) conducted a systematic review of 14 RCTs regarding the use of clinical algorithms using PCT levels in the management of sepsis and respiratory infections in primary care, the ED, and ICUs. This review found a marked reduction in the use of antibiotics in all settings; however, for the purposes of this particular paper, the author will concentrate on the findings pertaining to critically ill adults. The algorithms varied between studies, but some commonalities were established. First, in the most critical patients, PCT levels were used to determine when to discontinue antibiotic therapy and not when to start treatment. Second, when PCT levels trended down, there was an adequate correlation with resolution of bacterial infection, allowing for early discontinuation of the antimicrobial agent before the typical course was completed. Third, when PCT levels decreased to < 0.5 ug/L or by at least 80-90% from baseline measurements, and the patient was clinically improved, it was recommended to stop antimicrobial therapy. For the post operative critical patient, the threshold of •1 ug/L was used to discontinue therapy. Fourth, if treatment was withheld initially, PCT levels were monitored in 6 to 12 hours. In the high risk acute patient in the ICU, algorithms called for empiric antimicrobial therapy without delaying treatment for a PCT measurement (Schuetz et al., 2012).

This review suggested that the use of a PCT-guided algorithm for antimicrobial therapy is effective at reducing rates of antibiotic use in patients with bronchitis, acute exacerbation of COPD, pneumonia, and sepsis. Many of the studies reviewed were carried out in Europe, and they should be repeated in the US to ascertain if this practice would be appropriate based on population, practice, and different pathogenic makeup. An important limitation to consider is that

in an attempt to minimize bias, the authors included a small number of RCTs in their review, which could have excluded a large body of literature (Schuetz et al., 2012).

A systematic review and meta-analysis of seven PCT-guided algorithms suggested that their use in the management of sepsis decreases antimicrobial duration of treatment and allows for more antibiotic-free days. Three of the seven studies reported the total duration of antimicrobial therapy and it was found to be lower in the PCT-guided group by approximately 4 days ($p < 0.001$) leading to almost 3 extra antibiotic-free days in the 28 day follow up ($p < 0.00001$). One study gathered information regarding cost effectiveness and found that PCT-based strategies reduced the cost of antibiotic treatment by 17.8% ($p < 0.01$). Similar mortality, hospital length of stay, number of ventilator-free days, and rates of superinfection or persistent infection were comparable between the PCT-guided algorithm patients and the control groups (Kopterides, Siempos, Tsangaris, Tsantes, & Armaganidis, 2010).

The review's conclusions encouraged practitioners to tailor the treatment of sepsis with the use of PCT as a biomarker instead of treating the patient based on empiric rules alone. It is important to point out that mortality in critically ill patients is multifactorial and the adjustment of one variable, such as early discontinuation of antibiotics, rarely results in decrease of overall mortality. The findings need to validated by other RCTs, since studies reviewed here excluded organisms that were difficult to treat needing prolonged antimicrobial therapy. Other limitations include the small number of studies reviewed and the fact that not all the studies presented data on the same outcomes making comparisons challenging. In conclusion, the use of PCT-guided therapy is associated with reduced antibiotic exposure without compromising outcomes, but it is still inadequately validated for antibiotic control (Kopterides et al., 2010).

Jensen et al. (2011) performed the Procalcitonin And Survival Study (PASS) which aimed to establish whether early PCT monitoring and the use of an obligatory protocol for antimicrobial management would result in efficient and appropriate choice of antimicrobial agent

in the treatment of sepsis and improve 28-day survival in comparison to standard clinical judgement. The study also aimed to identify whether the duration of organ failure and ICU length of stay could be decreased. A total of 1200 adult patients who were judged to have infection were included during the first 24 hours of their ICU admission. Subjects were excluded if they had bilirubin levels > 40 mg/dL or triglycerides > 1000 mg/dL. Patients in the PCT-guided group were given therapy directed by clinical guidelines and PCT levels with an obligatory algorithm for intervention whereas the standard-of-care-only group was given antimicrobial treatment based on clinical guidelines alone.

For the PCT-guided group, the 'alert procalcitonin' was used to prompt the clinician to either start or increase antimicrobial therapy in the event of uncontrolled or refractory infection. This alert was identified as PCT •1 ng/mL at baseline. For the control group, standard empiric therapy was chosen according to the suspected pathogen and the potential site of infection. The PCT-guided group had a longer median length of antibiotic therapy and were more likely to have more frequent blood cultures drawn in the first 24 hours but they did not have more invasive procedures or imaging studies ($p < 0.001$). Twenty-eight day mortality analysis showed no difference in survival between the 'alert procalcitonin' and the 'non-alert procalcitonin' group. The time of death of non-survivors from both groups were comparable. Having an 'alert procalcitonin' at baseline was an independent predictor of 28-day mortality and having frequent alerts on the first five days was associated with increased risk of severe sepsis, septic shock, persistent, and progressive infection. The PCT-guided group spent 65.5% days on the ventilator compared to 60.7% for the standard-of-care group ($p < .001$). The average ICU length of stay was longer in the PCT group compared to the control group, 6 versus 5 days ($p = .004$). Additionally, the PCT-guided group had lower glomerular filtration rates and required dialysis and inotropic or vasopressor therapy for longer. No difference was found in frequency of organ failure in either group on day twenty-eight or day of discharge (Jensen et al., 2011).

The study data suggested that the use of a PCT monitoring in real time and the algorithm of therapeutic antimicrobial interventions did not improve survival, resulted in longer ICU length of stay, and higher use of broad spectrum antimicrobials. There were also increased costs due to the performance of the test itself, increased use of broad spectrum antibiotics, additional culture samples, more ventilator and dialysis days, and increased ICU length of stay. The use of PCT-guided algorithms suggested a harm effect based on the higher use of broad-spectrum antimicrobials possibly causing more end-organ target damage. PCT sensitivity was established at 59% using a cutoff of 1.0 ng/mL for diagnosis of sepsis, suggesting that this is not a reliable test. Significant study limitations involve the nature of low microbial resistance in the Danish hospitals where the study took place. Many patients had severe infections, but not all had blood stream infections, which are the most powerful stipulations for PCT increase. The cutoff for interventions of 1.0 ng/mL might have reduced the frequency of potential intervention in the early phase of the disease This number was chosen based on previous studies that established this as a cutoff for identifying sepsis in the critically ill as well as for determining mortality. Lastly, the inclusion criteria for the study was not well defined and described as ‘broad’ (Jensen et al., 2011).

A systematic review and meta-analysis of eighteen studies evaluated the accuracy of PCT for sepsis diagnosis. The studies were grouped according to the Sackett and Haynes’ classification of training and validation sets to allow clinicians to evaluate the generalizability of the studies’ findings. In the training set, the index test is developed in an ideal situation, whereas the validation set is tested in a more realistic clinical context. Seventy-six percent of the patients in this systematic review were included in the training set. The odds ratio (OR) and likelihood ratio (LR) of PCT were consistently low. The pooled diagnostic OR for PCT was 7.79, which suggests the test is unhelpful. PCT levels in the validation set showed greater variability and lower accuracy (Tang et al., 2007).

One considerable limitation of this review is the exclusion of all studies that assessed the ability of PCT in the diagnosis of septic shock, because it was believed that this condition could be diagnosed by clinical criteria alone. Tang et al. (2007) included a typical case mix of patients seen in medical and surgical critical care units as well as emergency departments but excluded all studies that were limited to restrictive patient groups such as burns, pancreatitis, or meningitis. Therefore, the findings could be applicable to common clinical settings but not to specific diseases. This systematic review did not evaluate the use of PCT as an adjunct bedside assessment for diagnosis and disease management. In summary, PCT levels had low diagnostic performance in the differentiation of SIRS and sepsis (Tang et al., 2007).

The Synthesis Answer to the Clinical Question

The literature review of 4 systematic reviews, 4 RCTs, and 3 prospective studies yielded a wide range of results regarding the use of PCT for early diagnosis and treatment of sepsis. The cutoff value for the identification of sepsis varied between 0.14 to 5 ug/mL, with the majority of studies supporting 0.14 to 2 ug/mL. One study suggested PCT levels > 10 ug/mL to rule in sepsis in the scenario of concurrent infection and cardiogenic shock. The diagnosis of sepsis was supported with an average PCT level of 1.1 ug/mL, 1.35 ug/mL to 1.9 ug/mL for severe sepsis, and > 9.1 ug/mL for septic shock. Additionally, PCT levels < 0.1 - 0.3 ug/mL generally excluded sepsis, except for patients with high risk for infection, in which case a PCT level < 0.5 ug/mL was necessary for exclusion. In the post surgical patient, a PCT level < 1 ug/mL excluded sepsis.

Discontinuation of antimicrobial therapy was encouraged with PCT levels < 0.5-1 ug/mL, or a baseline PCT drop of 25-90%. The use of PCT-guided algorithms for antibiotic treatment had mixed results. One systematic review found a decrease in antibiotic length of treatment, increase in the number of antibiotic free days, and decrease in ICU length of stay. However, the

PASS study found an increase in antibiotic days, hospital length of stay, ventilator days, dialysis days, and lower glomerular filtration rates. In the analysis of prognosis and mortality, no difference was found between the use of PCT-guided antibiotic algorithms versus empiric treatment. There was no difference in frequency of organ failure, infection relapse, or clinical course. There was not a statistically significant difference in PCT levels between survivors and non survivors; however, it was noted that high PCT levels at 72 hours of treatment was an indicator of refractory sepsis and poor outcome.

One systematic review strongly concluded that PCT values were not accurate in differentiating SIRS from sepsis. Two RCTs found PCT to be a test low in diagnostic value with a low sensitivity making it unreliable. Others studies found PCT to have modest contribution to diagnosis of sepsis. One systematic review suggested that PCT levels had a sixteen-fold higher chance to be positive in septic patients. Overall, PCT is not considered a gold standard diagnostic tool for sepsis but could be useful as an adjunct of other clinical data.

Ten of the studies reviewed used the BRAHMS PCT monitoring systems from Germany. Two studies used the rapid assay, one used the LIA, a manual assay, two studies used the Lumitest, which is now known as LIA. Five studies used the Kryptor, the automated assay. Only one study did not disclose its tool. Refer to the Appendix for the summary table.

Recommendations

Several recommendations can be implemented for the practicing provider caring for the critically ill adult with suspected sepsis.

• The diagnosis of sepsis must be based on the current ISSC guidelines, which include the use of PCT values to strengthen the diagnosis. PCT could be useful in an emergency setting to rule in or rule out bacteremia. Most importantly, providers should never delay the initiation of antimicrobial therapy while awaiting PCT results. If the clinical presentation and provider suspicion is high enough for sepsis, starting the therapy promptly is crucial.

• Providers should be cautious of PCT false positives in the presence of conditions such as cardiogenic shock, pancreatitis, burns, and major surgery. The studies reviewed recommended the PCT cutoff of 1 ug/mL for post operative patients and 10 ug/mL in the presence of suspected sepsis coexisting with cardiogenic shock. The use of PCT values in other conditions are beyond the scope of this paper.

• The use of PCT values in categorizing the stage and severity of sepsis can be a modest tool for the assessment of a critically ill adult. PCT monitoring is not considered the gold standard, yet there is evidence to support the use of baseline PCT and trends during antimicrobial therapy to assess patients' responsiveness to treatment. It would behoove the provider to use PCT as an adjunct tool in conjunction to clinical presentation and provider expertise.

• PCT can be useful for antimicrobial decision making when preliminary blood cultures are unavailable. In no way does the use of PCT monitoring exclude the usefulness of blood cultures in this setting. Having a PCT level can be useful when preliminary blood cultures are available and contamination is suspected. In this case, PCT levels would not rise and it can serve as supportive evidence not to start or discontinue antibiotic therapy.

• Presently, the use of PCT levels cannot be used to predict outcome or mortality. In the setting of critical care, there are numerous variables that contribute to mortality and survival. The alteration of one component alone, such as stopping antibiotic therapy earlier when PCT levels trend down, is unlikely to affect potential mortality or survival.

• Using the concept of 'alert procalcitonin,' PCT levels remaining > 1 ug/mL, could potentially be an adequate model to alert the clinician to reevaluate the patient for occult, refractory, or recurrent infections and consider alternate diagnoses or treatment modalities.

• The exclusion of sepsis should be considered with PCT levels < 0.25 ug/mL. However, it is necessary to follow up PCT levels if the provider chooses not to start antimicrobial therapy. Also, consider discontinuation of therapy if PCT levels decrease by 80-90% from baseline, in the

presence of clinical improvement. In summary, the use of PCT for diagnosis of sepsis and monitoring of effectiveness of treatment for sepsis is valuable as an adjunct tool to other clinical markers.

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Appendix

Author/Year	PCT & Antibiotic Initiation	PCT & Antibiotic Discontinuation	PCT to r/o sepsis
Sinha et al. (2011)	> 2 ng/mL, >10 ng/mL in cardiogenic shock	N/A	N/A
Ruiz-Alvarez et al. (2009)	1.1 ng/mL sepsis 1.9 ng/mL severe sepsis 9.1 ng/mL septic shock	N/A	< 0.3 ng/mL
Nobre et al. (2008)	N/A	Baseline >1 ug/L, □90% baseline on day 5 or absolute < 0.25 ug/L Baseline <1 ug/L, <0.1 on day 3	N/A
Uzzan et al. (2006)	0.6 - 5 ng/mL	N/A	N/A
Riedel et al. (2011)	0.1475 ng/mL	N/A	< 0.1 ng/mL
Heper et al. (2006)	>1.35 ng/mL to differentiate sepsis from severe sepsis	N/A	N/A
Hochreiter et al. (2009)	N/A	<1 ng/mL or □25-35% of baseline	N/A
Schuetz et al. (2012)	N//A	<0.5 ug/L or □80-90% of baseline <1 ug/L in post op	N/A

Author/Year	PCT & Antibiotic Initiation	PCT & Antibiotic Discontinuation	PCT to r/o sepsis
Kopteroides et al. (2010)	N/A	N/A	N/A
Jensen et al. (2011)	>1 ug/mL	N/A	N/A
Tang et al. (2007)	N/A	N/A	N/A