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Q&A

The Role of Procalcitonin in Diagnosis of Sepsis and Antibiotic Stewardship: Opportunities and Challenges

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Sepsis was recently redefined as "a life-threatening organ dysfunction caused by dysregulated host-response to systemic infection" based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). The incidence of sepsis is increasing despite global initiatives, with a mortality ranging from 30% to 50%. A timely diagnosis of sepsis is pivotal for prompt recognition and appropriate intervention. Each hour of delay in administration of antibiotics results in an increase of 7.6% mortality for septic shock, yet overdiagnosis and inappropriate use of broad-spectrum antibiotics contribute to the emergence of antibiotic resistance. Diagnosis of sepsis is a clinical challenge. Early signs of systemic inflammation such as fever, tachycardia, and leukocytosis are not specific to sepsis. Traditionally, anaerobic and aerobic blood cultures were used to detect and identify the presence of bacterial infection; however, approximately 40% of patients with sepsis are culture-negative. Other biomarkers such as C-reactive protein (CRP;[11] inflammatory) and lactate (organ dysfunction) are not early indicators and lack specificity. There is increasing evidence that support the use of procalcitonin (PCT) for diagnosis of bacterial sepsis and act as a guide to discontinue antibiotic therapy. Yet, there are concerns about the efficacy, safety, and availability of PCT. We have asked 5 experts with different roles in this field to share their thoughts on the challenges of PCT-guided diagnosis and antibiotic therapy.

1. What are the challenges in sepsis diagnosis?

Joshua Hayden: In clinical journals, the question is "What are the challenges in defining sepsis?" Systemic inflammatory response syndrome (SIRS) criteria have been removed from the new Sepsis-3 definition after 25 years. A clinical syndrome that is this hard to define, not surprisingly, is difficult to diagnose. It is worth noting that the only laboratory values that currently count toward the diagnosis of sepsis are lactate and those included in the Sequential Organ Failure Assessment (SOFA) score, including platelets, bilirubin, and creatinine.

Todd Dorman: Early identification appears critical for the avoidance of further deterioration in clinical status and subsequent outcome. Presently, there are no good ways to identify septic patients. Previously, SIRS criteria were used but have now been shown to both over- and underdiagnose by ap-

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[11] Nonstandard abbreviations: CRP, C-reactive protein; PCT, procalcitonin; SAPS, Stop Antibiotics on Procalcitonin Guidance; SHEA, Society for Healthcare Epidemiology of America; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; IDSA, Infectious Disease Society of America; ICU, Intensive care unit; AUC, area under the curve.

proximately 15% in both directions. The SOFA and qSOFA (quick SOFA) scores in Sepsis-3 have been retrospectively validated and are still undergoing prospective evaluation.

Bradley Langford: Rather than a singular entity, sepsis is a complex clinical syndrome resulting from a multifaceted pathophysiological host response to infection. Even with the recently updated Sepsis-3 definitions aimed at improving its early identification and management, the main diagnostic challenge is a lack of gold-standard clinical or laboratory criteria to accurately identify sepsis.

Mark Downing: Early antibiotics and goal-directed therapy (intravenous fluids, mechanical ventilation, and vasoactive agents) have been shown to improve outcomes in patients with sepsis, where the mortality rate can be >30%. It is therefore critical to make an early diagnosis and differentiate sepsis from other conditions that can cause multiorgan dysfunction, where these therapies may be counterproductive. Unfortunately, the gold standard for making a diagnosis in sepsis is isolating the organism in the microbiology laboratory, which usually takes several days or does not occur at all due to the limitations of current culture techniques.

Carey-Ann Burnham: There are several challenges in the diagnosis of sepsis. The first challenge can be to determine if the patient's symptoms are attributable to an infection, and if so, the causative agent of the infection and optimal antimicrobial therapy for that agent. As it has been well described, delays in administration of appropriate antimicrobial therapy in the setting of sepsis result in less favorable clinical outcomes, and broad spectrum antibiotics are typically given as soon as sepsis is suspected. The gold standard for detection of blood stream infection is blood culture. However, blood cultures are negative in a large proportion of septic patients. In addition, blood cultures typically require 24 h or more of incubation before a positive result, so broad spectrum antimicrobial therapy must be initiated before these results are available.

2. Is procalcitonin (PCT) a good diagnostic, prognostic, and/or monitoring marker for sepsis?

Carey-Ann Burnham: In the setting of sepsis, there is a great need for a biomarker that is rapidly produced and easy to measure. PCT has strengths and limitations as a biomarker, and the value of measuring PCT depends on the specific clinical situation. Compared to blood cultures, PCT has the advantage in that results may be available within a few hours. Plasma PCT rises within about 3–6 h of the initial clinical manifestations of sepsis and falls when severe infection resolves. In the setting of the emergency department, PCT may have value as an early predictor of systemic infection. Data on the utility of PCT to predict pneumonia are mixed. Thus, depending on the clinical setting and pretest probability, serial PCT measurements may provide evidence to support the decision to initiate antimicrobial therapy or for discontinuation of antimicrobial therapy. PCT may be used as a component in care pathways or algorithms for evaluation of sepsis.

Joshua Hayden: Good is a relative term. Aspartate aminotransferase was a good marker for myocardial infarction before creatine kinase-MB, which was good until cardiac troponin, which (some would say) was good before high-sensitivity troponin. PCT is one of the best markers the laboratory can offer for the diagnosis, prognosis, and monitoring of sepsis. It is not perfect, nor should we expect it to be given the challenge of diagnosing sepsis. Still, meta-analyses have shown that it has value in the diagnosis of sepsis (AUC 0.85) and it contributes prognostic information, which is why its use has been approved in the United States.

Todd Dorman: Unfortunately, it is not. Early studies gave the impression that it might be good for diagnosis and monitoring of sepsis. Over time, the studies have shown that PCT is not a good diagnostic tool. Hope remains that it can be used to deescalate therapy, with the strongest data seen in the bacterial pneumonia population.

Mark Downing: There is some controversy over whether PCT is a good marker for sepsis. A recent Cochrane Review of the previous data published this year could not find a benefit in using PCT with regards to mortality, reinfection, clinical severity, or antimicrobial use. However, this

review did not include a more recent multicenter, randomized, open-label trial in the Netherlands that was able to demonstrate a 20% decrease in mortality in the PCT arm (de Jong et al. 2016 Lancet Infectious Disease). In this trial, critically ill patients on antibiotics were randomized to either routine care or daily PCT measurements with instructions to stop antibiotics if the level passed either an absolute or a relative threshold. Infectious Diseases Society of America (IDSA) guidelines, published last year, recommend serial PCT measurements in the Intensive Care Unit (ICU) to reduce antimicrobial use based on limited evidence.

Bradley Langford: From a clinical utility perspective, I think this is controversial. Although PCT concentrations have been shown to correlate well with sepsis severity, the important question is whether this biomarker can add value by improving the management of sepsis. Given the heterogeneity of patients studied and cut-point values used, and lack of gold-standard reference, the sensitivity and specificity of PCT vary widely between studies. Also, given the urgency for rapid and aggressive treatment of sepsis, the efficacy and safety of PCT as a diagnostic tool to help guide initiation of treatment is questionable. Although there is growing evidence to support PCT-guided initiation of antibiotic therapy in respiratory tract infections, this practice does not seem to be beneficial in critically ill patients with suspected infection. However, where PCT appears to show some promise in the management of sepsis is in guiding earlier discontinuation of antimicrobial therapy.

3. What are the major limitations in clinical interpretation of PCT?

Todd Dorman: PCT is increased by many inflammatory states (i.e., surgery, paraneoplastic, autoimmune disease) and so it is not specific for infection. Furthermore, it is primarily increased in bacterial infection, possibly missing sepsis from other causes such as viral mediated disease. Importantly, some viruses, through upregulation of interferon, may cause PCT concentrations to be suppressed.

Bradley Langford: The adage to "treat the patient, not the laboratory test" applies here. As there is no perfect biomarker for infection, there is a need to consider the clinical and microbiological scenario when applying the results of a PCT assay to a patient. The host response for each patient will differ significantly from one patient to another with a similar infection. For this reason, single PCT concentration alone appear to be less useful than serial testing for those with sepsis. There is also a need to consider the possibility of falsely increased (e.g., due to recent trauma, surgery) or falsely reduced (e.g., due to localized bacterial infection) concentrations.

Mark Downing: PCT does not replace clinical judgement. In fact, in the above mentioned de Jong study that has shown the most positive evidence to date, the protocol was not followed in over 50% of patients. Antibiotics were continued despite a PCT concentration that was low enough to indicate therapy should be stopped. PCT does not replace routine microbiologic testing in terms of making a diagnosis, and it is not yet clear how effective it is as a stand-alone prognostic marker.

Carey-Ann Burnham: The prognostic value of PCT can vary depending upon the threshold that is used as a positive result and even with the type of infection; gram-negative infections typically result in higher values than gram-positive or fungal infections. PCT does not inform the specific etiology of infection, and thus microbiologic data are still needed for optimization of antimicrobial therapy. A physiological increase in PCT can be observed in settings other than infection; for example, increases may be observed in postoperative patients as a result of inflammation from surgery.

Joshua Hayden: One of the major limitations in the United States has been the availability (and cost) of PCT. As a result, clinicians are less comfortable integrating this laboratory value into their decision-making. Furthermore, even when PCT is available, it is rarely offered 24 hours/day, seven days/week with a turnaround time that allows it to factor into clinical decision making. A marker that can help you decide the necessity of antibiotics is not terribly helpful if you get results back six hours after you already did or did not start treatment. The lack of an affordable and true random access platform for PCT has certainly limited its adoption and clinical use.

4. How does PCT compare to other sepsis biomarkers (i.e., C-reactive protein, lactate)?

Bradley Langford: PCT seems to be superior to most other biomarkers in terms of differentiating bacterial sepsis from noninfectious or nonbacterial conditions. PCT has a greater specificity compared to CRP, which tends to rise in response to a wider range of inflammatory stimuli. Additionally, its early detectability and faster drop after resolution of infection make PCT a more optimal choice compared to CRP. Although lactate is a good marker of sepsis severity, it lacks specificity. Finally, probably most importantly, there is a greater volume of data supporting the clinical utility of PCT in antimicrobial stewardship compared to other biomarkers.

Mark Downing: PCT is thought to be more specific for bacterial infections. CRP is increased in several inflammatory conditions that are not infectious, and lactate is a

measure of tissue ischemia, which also could have a non-infectious cause.

Joshua Hayden: Compared to other markers, PCT is the most expensive. At the same time, it also has potential to provide the most value for treating patients with sepsis and it is worth noting that the cost of treating sepsis far outweighs the costs of diagnosing and monitoring it. PCT is more specific than CRP and offers earlier insight compared to lactate. When CRP is increased solely as a result of sepsis, it is an attractive, cost-effective marker. Unfortunately, CRP can be increased by a range of stimuli and this limits its value in the diagnosis and monitoring of sepsis. Lactate, on the other hand, is an excellent marker of end organ damage (whether from sepsis or something else). Unfortunately, by the time lactate is increased the "golden hours of treatment" are past or rapidly disappearing. PCT is an earlier indicator relative to lactate—seeing fire is a good way to know your house is burning down, but seeing smoke gives you more time to run.

Todd Dorman: CRP is too overly sensitive and thus if used clinically would likely lead to overuse of antibiotics. The half-life of CRP is too long for clinical utility as well (approximately 19 h). For those patients in septic shock, lactate appears to be a decent biomarker for mortality, although far from perfect. The concerns with PCT are that it lacks clinically useful sensitivity and specificity for sepsis.

Carey-Ann Burnham: CRP and lactate are more widely available than PCT. The studies on the relative sensitivity and specificity of other sepsis biomarkers are mixed, but, in general, PCT is a more specific marker for sepsis compared to CRP or lactate. It can be challenging to compare these studies as a result of the different methodologies and interpretive criteria used for the assays between different investigations.

5. There is increasing evidence on the use of PCT-guided de-escalation of antibiotic therapy. What are your thoughts regarding its efficacy, safety, and availability?

Bradley Langford: Antimicrobial resistance is a rapidly growing public health threat. It is of particular concern in ICUs owing to the density of broad-spectrum antimicrobial use, where there is strong selective pressure to drive high levels of antimicrobial resistance. Prolonged duration of therapy is a known risk factor for antimicrobial resistance, a practice that is perpetuated given the lack of high-quality evidence regarding optimal treatment length and in some cases an unfounded concern about the insufficiency of a shorter treatment course. PCT-guided discontinuation of antibiotic therapy may help provide some objectivity to the often-subjective decision regarding antibiotic duration. There are now several studies supporting the concept that PCT algorithms aimed at monitoring response to antibiotic therapy can help reduce the use of these agents without any adverse impact on length of stay or mortality. As a result, the IDSA/Society for Healthcare Epidemiology of America (SHEA) Antimicrobial Stewardship Guidelines and Surviving Sepsis Campaign Guidelines have recommended PCT testing to guide antibiotic discontinuation (albeit weak recommendations). The above mentioned recent de Jong trial, Stop Antibiotics on Procalcitonin Guidance (SAPS), is the largest study to date that adds further support to this approach. In fact, this trial found a reduced risk of mortality in the PCT-guided group. It is possible that earlier identification of alternative (nonsepsis) diagnoses and reduced antimicrobial exposure can reduce the risk of mortality, but these data should be interpreted with caution. These findings have not been replicated in other prospective studies. Although it is promising to see reduced usage of antibiotics without increased mortality, key aims of reduced antibiotic use are to help decrease the risk of antimicrobial resistance, *Clostridium difficile* infection, and other adverse effects of antibiotics. Unfortunately, the majority of trials performed to date are not powered to detect or did not thoroughly examine these important outcomes.

Carey-Ann Burnham: In patients who appear septic, empiric broad-spectrum antimicrobial therapy is usually initiated. In patients with negative blood cultures, it can be difficult to establish an endpoint to this therapy. When interpreted in the appropriate clinical context, serial PCT measurements may be one piece of evidence to support de-escalation of antibiotic therapy. Additional data are needed to better inform how PCT can best be used to tailor antimicrobial therapy and the overall efficacy of this approach.

Todd Dorman: The literature is mixed on this topic. The most recent guidelines for sepsis published in early 2017 state, "We suggest that measurement of PCT levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence)". However, it should be noted that the most recent Cochrane Systematic review (2017) shows there are limited data to support even this role at the present time. It may have a role in deescalating therapy in the isolated circumstance of the cultures being negative.

Mark Downing: The recent Cochrane review did not find a reduction in antimicrobial usage in studies using PCT. However, it did identify a significant amount of

harm associated with using PCT to guide therapy. Beyond showing a decrease in mortality, the de Jong trial was able to reduce antimicrobial use from 7 days in the control arm to 5 days in the PCT-guided therapy arm. Testing is not routinely available in most centers in Canada.

Joshua Hayden: There is an understandable reluctance to deescalate antibiotic therapy based on a laboratory value. However, the data coming out of a range of trials, most recently SAPS, show that de-escalation reduces antibiotics usage and decreases (or in some studies leaves unchanged) mortality. Less unnecessary antibiotic usage is a very, very good thing in healthcare. Unfortunately, the SAPS trial, like others, had a 50% noncompliance rate among providers in the PCT-guided arm. In spite of data showing that PCT-guided reduction of antibiotics is safe and effective, substantial barriers exist to the widespread implementation of this approach.

6. What are the limiting factors that prevent widespread use of PCT in sepsis and antibiotic stewardship?

Carey-Ann Burnham: There are several factors limiting widespread use of PCT in sepsis management. The first is test availability. If results cannot be provided quickly, the assay is of limited use. In addition, depending on the clinical context, the assay can have suboptimal sensitivity and specificity for sepsis. For example, patients in the ICU have a high likelihood of severe infection and sepsis, but these patients may have a systemic inflammatory response as a result of trauma, which can complicate the interpretation of PCT values.

Joshua Hayden: The limited availability (and cost) of PCT as well as reluctance to deescalate antibiotics based on PCT results. This can create an almost perfect storm where expensive testing is done but it adds no value to patient care. If the testing is not offered with rapid turnaround time, clinicians would have already taken action (right or wrong) before they have the results, making the testing mostly worthless. Furthermore, since clinicians are reluctant to de-escalate antibiotics based on PCT, the testing done for this purpose is truly money down the drain.

Bradley Langford: Firstly, cost is a consideration in terms of whether the possible benefits of PCT testing justify the expenditures and resources used. Secondly, uncertainty about the generalizability of previous study results may prevent the implementation of PCT in individual hospitals. The local prescribing culture may play a major role in the impact of this biomarker. We know that duration of therapy generally tends to be longer than guideline recommendations, but in hospitals where duration of therapy is already optimized, PCT-guided antibiotic discontinuation may be of less benefit. It is reassuring, however, that a reduction in antibiotic utilization was found in the de Jong trial, as this study took place in the Netherlands, where antibiotic stewardship is already strongly emphasized. Thirdly, the low rates of adherence to PCT algorithms in many studies raises concern about the utility of this approach if clinicians are likely to frequently override the protocol.

Todd Dorman: Lack of clinical utility and thus a poor value calculation with cost exceeding value.

Mark Downing: There needs to be more "real-world" evidence to support its use. The argument is that it may work well in certain studies where patients are carefully selected and the protocol is adhered to, but it is unclear if it can be routinely used in antimicrobial stewardship programs in a manner that is safe, effective, and cost effective.

7. What factors should the laboratory keep in mind before implementing PCT testing for sepsis diagnosis and antibiotic stewardship?

Mark Downing: It needs to be defined up front who will order the testing and in which patients. Just as with troponin and D-Dimer, it is important that clinicians are educated in selecting the correct patients for the test and interpreting the test within the entire clinical picture. Introducing PCT testing should be viewed as a quality improvement initiative, where the organization can review its efficacy and safety after its implementation to determine whether it is of use.

Todd Dorman: At this point in time, at best there is a weak recommendation for its use in de-escalation strategies only. In this era of cost-conscious care, more data are needed from high-quality research projects before this is made routinely available.

Carey-Ann Burnham: If a laboratory is planning to implement PCT as a component of antimicrobial stewardship, it is critical to work closely with key clinical stakeholders, including Critical Care, Infectious Diseases, and the Emergency Department, to create criteria for when PCT will be measured and how the results will be used. Ideally, PCT measurements could be incorporated as part of clinical decision support tools within the electronic medical record, including thresholds for when antimicrobial use would be endorsed or discouraged. Education on the limitations of PCT as a marker for sepsis must be a component of the roll-out of the assay.

Joshua Hayden: Over-utilization and underaction are major issues. Ordering PCT in the setting of trauma or following major surgery when it can be nonspecifically

increased, for instance, are inappropriate uses of the test. Clinical laboratories should think carefully about implementing PCT in tandem with ordering controls (restricted users, patient populations, etc.). This requires close interactions with hospital epidemiologists and infectious disease physicians. Fortunately, these interactions are exactly what is needed to ensure that the results of PCT are appropriately impacting patient management (the underaction piece). It is essential that clinical laboratories be a part of larger hospital committees (sepsis committee, antimicrobial stewardship, etc.) where they can help provide education on proper ordering and interpretation of PCT.

Bradley Langford: A business case should be taken into account considering not only the cost of testing and antibiotic use but also the downstream impact of reduced antibiotic use (e.g., antimicrobial resistance, *Clostridium difficile*). There should be discussions about which patients are eligible to have PCT testing (e.g., ICU, emergency department), and recommendations on how PCT should not be used (e.g., there is evidence that PCT testing to facilitate antibiotic escalation in sepsis is not useful and may have an adverse effect on antibiotic use and patient outcomes). Daily rounds and antimicrobial stewardship rounds in the ICU should incorporate a discussion of the patient's PCT concentration, if applicable, to ensure that results are being acted upon in a timely manner. Finally, from a quality improvement perspective, an analysis should be planned to ensure PCT testing has a positive impact on patient care.

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