Procalcitonin as a Diagnostic Test for Sepsis: Health Technology Assessment in the ICU

David J. Gattas and Deborah J. Cook

Elevation in the serum concentration of procalcitonin (PCT) is associated with systemic infection. This association has led to the proposed use of PCT as a novel biomarker of bacterial sepsis. The advantages and limitations of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definitions of sepsis are an important consideration that affects the impact of any diagnostic test for sepsis and these issues are discussed. Our main objective is to perform a systematic health technology assessment of PCT as a diagnostic test for sepsis. In an adult intensive care unit (ICU) population, we identify a specific and important question—can PCT accurately distinguish sepsis in patients with systemic inflammatory response syndrome (SIRS) who have a suspected infection? Likelihood ratios are calculated from published data to attempt to find the best answer. The published evidence does not support a general claim that PCT is a useful decision support tool for diagnosing sepsis in patients who have SIRS. Procalcitonin has a slightly better ability to exclude the diagnosis of sepsis. The role for using PCT testing in the ICU will continue to evolve along with our understanding and definition of sepsis.

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PROCALCITONIN (PCT) is a 116 amino acid protein and the precursor of the hormone calcitonin. The complete sequence of PCT has been known since 1984,1,2 and the gene encoding it was characterized in 1989.3 Current interest in the protein in critical care medicine stems from the original report in 1993 that elevations in the serum concentration were associated with bacterial sepsis in children.4 In that report, elevations of up to 1,000 times the normal range were described in association with proven severe bacterial infection. The normal range for serum PCT is less than 0.5 ng/mL. This evaluation of PCT levels in critically ill adults summarizes features that are pertinent to the effectiveness of a diagnostic test for sepsis and then systematically reviews the PCT literature in a format compatible with previously published guides.5-11

DIAGNOSING SEPSIS

The Definition Problem

The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definitions for sepsis and its related syndromes were proposed 10 years ago12 (see Table 1). They have helped maintain our focus on the cardinal importance of the host response to infection in the evolution of sepsis. This focus has been rewarded by recent and overdue advances in the treatment of sepsis such as activated protein C,13 insulin,14 and corticosteroids15 that all target the host response to infection.

However, the ACCP/SCCM definitions leave something to be desired as the reference standard for the diagnosis of sepsis. The limitations of the definitions are often raised in critical care medicine,16 and new conferences to discuss our evolving understanding of sepsis and our conceptual framework occur periodically. The broader topic of using biomarkers in sepsis management also continues to evolve.17,18 The case for and against the 1992 definitions is summarized in Table 1. Our perception of the accuracy of any diagnostic test for sepsis may be substantially altered if the goalposts (the definition of sepsis) are moved in the future.

Sepsis Therapy

Therapeutic agents that are specific and efficacious for treating sepsis are not yet widely established and disseminated. This is relevant to determining the potential impact of a new diagnostic test for sepsis. If a test result has a low capacity to usefully alter treatment, and therefore outcome, it argues against conducting that test.

HOW DOES PROCALCITONIN PERFORM IN THE PRECLINICAL AND LABORATORY SETTINGS?

In the absence of a gold standard for diagnosing sepsis, the construct validity of using PCT in this setting assumes great importance.

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Potentially Clinical Use?

Does Procalcitonin Have a Range of Potential Clinical Use?

As PCT has emerged into clinical use, it has been evaluated in a wide variety of clinical settings. It is proposed that hyperprocalcitonemia is relatively specific for bacterial sepsis. Mild elevations (0.5-2 ng/mL) are associated with viral infections, chronic inflammation, and systemic inflammatory response syndrome (SIRS). In the case of viral infection, this claim is based on conclusions drawn from very small subsets of patients in the original reports that measured PCT levels in neonatal and pediatric patients with infection.

Sepsis, severe sepsis, and septic shock cause progressively higher elevations in serum PCT, even as high as 1,000 ng/mL. This relationship is very intriguing and worthy of investigation. Many observational pilot studies have been published.
and they constitute much of the current literature on the clinical use of PCT. Pancreatitis, burns, postcardiopulmonary bypass, neutropenia, and posttransplantation are several examples of patient populations that have been subjects for PCT studies. The range of potential uses for PCT is very wide and encompasses any area of clinical medicine in which there is diagnostic uncertainty regarding the presence or absence of infection. Additionally, using PCT as a prognostic and stratification tool in sepsis has shown promise. This indication is not elaborated on here; the use of PCT in general intensive care unit (ICU) populations as a diagnostic test is the focus of this assessment.

WHAT IS THE IMPACT OF PCT CLINICALLY?
What Are the Specific Questions For Which We Need Answers?

Following the large body of published short reports and initial experiences with using PCT, our next task should be to articulate the specific questions that clinicians need answered accurately. Larger, more rigorous studies can then be designed to evaluate how well PCT answers those questions. Like much other health technology, this intermediary stage between the development of PCT and its subsequent dissemination and clinical use is lacking. Redressing this imbalance is the raison d’être of the health technology assessment process.

There are questions for which we do not need the answers. For example, it is not necessary to order a diagnostic test that can accurately distinguish septic shock from SIRS or from normal. These conditions are easily distinguishable at the bedside. It also is not necessary to know that PCT is superior to another biomarker of sepsis if one is not already in the habit of ordering that test or if that biomarker is not widely established as a means to define, diagnose, monitor, or treat sepsis.

Important questions concern the accurate differential diagnosis of conditions that are similar in clinical appearance but that differ in treatment. Distinguishing septic shock from cardiogenic shock is one example and there is a small amount of literature addressing that question. By far the most common and relevant question is the distinction between SIRS and sepsis. Intensivists encounter this scenario very frequently and in many different forms: “This postoperative patient has a fever and tachycardia, but do they have sepsis or SIRS?” “My patient has a new positive sputum culture, but is this organism causing a systemic infection right now?” and so on. The scope of this assessment is confined now to this specific and important question:

Among a Group of Patients With SIRS Who Are Suspected of Having an Infection, Can PCT Accurately Distinguish Those Who Have Sepsis?

Methods

The authors are solely responsible for the literature searching and assessment process. There are no conflicts of interest. Evidence was identified with a Medline search, using “procalcitonin” as a keyword; the search was restricted to human studies published in the English language.

The author (D.J.G.) selected abstracts that referred to the diagnostic accuracy of PCT in adult ICU populations. Selected articles were then examined according to their ability to satisfy 3 conditions that we deemed essential for our purposes: (1) Did the researchers use the ACCP/SCCM definitions for sepsis (or present data enabling their calculation)? (2) Were the subjects (at least in part) adult ICU patients who were clinically suspected of having an infection? and (3) Was the data presented in a way that allows a 2 × 2 table to be derived (diagnostic/nondiagnostic PCT value vs SIRS/sepsis)? Positive and negative likelihood ratios were then calculated from the 2 × 2 table.

Results

The results of the literature review are listed in Table 2. Aoui et al29 showed impressive likelihood ratios, but there is a difference in the population studied here. Cardiac surgery patients with a temperature greater than 38°C on the second postcardiac surgical day were enrolled, irrespective of whether there was clinical suspicion of infection or not. This is a deviation from the precise target population we have identified as our primary interest, but we decided not to exclude this study from the assessment; it is a convincing and useful result in this population in this study. Harbarth et al30 is among the most rigorous and specific studies aimed precisely at answering the question we have posed here. It indicated a good ability for PCT to exclude sepsis when below the cut-off value, but
the positive likelihood ratio (LR) value (4.4) is much less than in the Aoui et al study. A LR of this magnitude would raise a pretest probability of 40% to 50% by roughly 30%. The only other study that indicated some usefulness in answering our question was by Selberg et al. This smaller study provided few details on the inclusion criteria. At a high cut-off value (PCT 3.3 ng/mL), the LRs (LR+/LR− 4.8/0.17) showed potential usefulness. Fourteen of 22 patients in the sepsis group, however, had severe sepsis; the pretest likelihood in this population would be expected to be high. A significant contribution to management by the PCT result would be unlikely.

The LRs in other studies listed in Table 2 indicated that there was a negligible change in the pretest likelihood of sepsis as a consequence of the PCT results. Ruokonen et al conducted a large study, comprised entirely of the target population, the objective of which was to distinguish sepsis from SIRS in consecutive adult ICU admissions. There was no effect (LR+ 1.2) on the probability of disease if the PCT value was above the optimum cut-off level (0.8 ng/mL). Like the Harbarth et al study, this study showed a slightly better ability to rule out the diagnosis of sepsis (LR− 0.6). Studies by Suprin et al, Ugarte et al, and Wanner et al also yielded LRs that were unlikely to assist a clinician in diagnosing sepsis; the ability of PCT to exclude sepsis was slightly better. Notably, in the study by Giamarellos-Bourbolis et al, visual inspection of the scatter plot of PCT results seemed to indicate that no patients with SIRS had PCT values below the cut-off value to diagnose sepsis. This leads to estimated LRs that actually detracted from the predictive ability of clinical and standard laboratory assessment alone.

We conclude that studies are inconsistent and inconclusive, casting doubt on whether PCT can

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient Population</th>
<th>Inclusion Criteria</th>
<th>n (Total)</th>
<th>n (Target)*</th>
<th>PCT Cut-Off Value (ng/mL)</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoui et al29</td>
<td>Cardiac surgery</td>
<td>Temperature &gt; 38°C 48 hours after cardiac surgery; not restricted to clinically suspected infection</td>
<td>97</td>
<td>97</td>
<td>1</td>
<td>18</td>
<td>0.16</td>
</tr>
<tr>
<td>Giamarellos-Bourbolis et al32</td>
<td>General ICU</td>
<td>Not specified</td>
<td>119</td>
<td>67</td>
<td>1</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Harbarth et al30</td>
<td>General ICU</td>
<td>Consecutive admissions with SIRS and suspected of having an infection</td>
<td>78</td>
<td>78</td>
<td>1.1</td>
<td>4.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Ruokonen et al33</td>
<td>General ICU</td>
<td>Consecutive admissions; new fever in the ICU and suspected of having an infection</td>
<td>208</td>
<td>208</td>
<td>0.5</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Selberg et al31</td>
<td>Medical ICU</td>
<td>Not specified</td>
<td>33</td>
<td>33</td>
<td>0.5</td>
<td>1.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Suprin et al34</td>
<td>Medical ICU</td>
<td>Diagnosed with infection or SIRS clinically; organ dysfunction present</td>
<td>95</td>
<td>95</td>
<td>2</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Ugarte et al35</td>
<td>General ICU</td>
<td>All consecutive admissions (except postelective surgery)</td>
<td>190</td>
<td>190</td>
<td>0.6</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Wanner et al36</td>
<td>Trauma ICU</td>
<td>All trauma ICU admissions with injury severity score &gt;9</td>
<td>405</td>
<td>108</td>
<td>1.5</td>
<td>3.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

NOTE. See text for a brief explanation of likelihood ratios.
* n (target) represents the number of patients with either sepsis or SIRS. Normal controls and other groups excluded.
† LR+ is the likelihood ratio for the presence of sepsis if PCT is above the cut-off value.
‡ LR− is the likelihood ratio for the presence of sepsis if PCT is below the cut-off value.
accurately distinguish sepsis from SIRS. PCT appears to perform better at ruling out sepsis when the value is not elevated than diagnosing sepsis when it is elevated.

**Likelihood ratios**

LRs are one of the accuracy measures that tell us about the properties of a diagnostic test. Although much less commonly referred to than measures such as sensitivity, specificity, and predictive values, LRs are powerful and directly useful to a clinician. LR quantitates the magnitude and direction of the change in the pretest probability brought about by a given test result. If the pretest probability is known (or estimated by clinical opinion), the posttest probability of disease may be calculated.

For any test result (eg, PCT > .5 ng/mL), there is a probability of receiving that result from a patient with the disease (sepsis) and a probability of getting that result in patients without the disease (eg, with SIRS). The ratio of these 2 likelihoods is the LR. When the pretest probability is converted to odds and multiplied by the LR, we obtain the posttest odds. This then may be converted back to the posttest probability. A nomogram is available to aid in this calculation, and there are simple ways to make estimates of the calculation.

As a memory guide and rule of thumb (presented as LR:change in probability, diagnostic effect of test result): a LR of 1/10 (0.1): large decrease, usually conclusive in ruling out the diagnosis; a LR of 1/5 (0.2): moderate decrease, often some help in ruling out the diagnosis; a LR of 1/2 (0.5): minimal decrease, usually minimal help; a LR of 1: no change, none; a LR of 2: minimal increase, usually minimal help; a LR of 5: moderate increase, often some help in confirming the diagnosis; a LR of 10: large increase, usually conclusive in confirming the diagnosis. Recommended reading regarding LR: Users’ Guide to the Medical Literature.

**Do PCT Results Affect Clinical Confidence?**

The prevailing conditions in which clinical decision making occurs in sepsis are ripe for the introduction of accurate, timely, and useful diagnostic information. There is widespread recognition that early treatment of the source of infection is crucial, but avoiding the inappropriate or exces-

sive usage of antibiotics and other therapies is also a desirable goal. The limitations of clinical diagnosis combined with these competing management goals have created a significant demand for our question to be answered. Emerging therapies in sepsis will also create a need to pinpoint the individual patients who are most likely to benefit from receiving them, particularly if these therapies have potential risks and/or are expensive.

There are no data describing the effect of PCT testing on clinical confidence regarding the presence or absence of infection. It is likely, however, that a perception by clinicians of decreased diagnostic uncertainty has been a driving factor in the dissemination of PCT so far. As shown earlier, the published evidence does not support a general claim that PCT can reliably distinguish sepsis from SIRS in adult ICU patients. PCT is definitely novel and interesting, and there certainly is an association between hyperprocalcitonemia and sepsis syndromes. Unfortunately, its promise as a useful decision support tool has not been realized at this time. Therefore, we believe that PCT levels may influence clinician behavior to an extent that is out of keeping with its poor predictive or diagnostic properties.

**Do PCT Results Affect Treatment Decisions?**

There are no data specifically addressing the question of whether PCT influences clinical decisions. Altered clinical confidence is likely to have some effect on decision making. Biomarkers such as PCT are used as supplements to clinical judgment. There is little capacity for a PCT result to alter a clinical decision otherwise felt to be clearly necessary, and rightfully so. The situation in which we might expect PCT to exert its strongest influence on therapy is one following clinical assessment, in which there is uncertainty in the mind of a clinician regarding 2 potential courses of action in a sepsis diagnostic problem. For example, when faced with a new positive sputum culture and inconclusive clinical support for ventilator-associated pneumonia, there is likely to be a strong desire to acquire some extra information that can help with the decision to start, continue, or stop antibiotic therapy. This review argues against ordering PCT in this clinical scenario because this is when the predictive ability of PCT is at its lowest. An
elevated PCT result will alter pretest probability very little, if at all.

CONCLUSION: SHOULD I PERFORM PROCALCITONIN TESTING IN MY PATIENTS?

The answer to this question may change as data evolve, along with our understanding and definition of sepsis. Current evidence indicates that PCT is incapable of providing accurate or useful information to help with the difficult diagnosis of sepsis among a group of adult ICU patients with SIRS who are suspected of having an infection. The use of PCT for the purposes of prognosis and stratification are additional potential uses of PCT that may develop over time, but cannot be recommended currently. Researchers may include PCT in future descriptions, if not definitions, of subgroups of sepsis patients. Meanwhile, clinicians who are considering using this technology in their own ICU should prospectively identify the clinical question that is driving the use of PCT. Critical appraisal of the literature, combined with careful audits of the local impact of using PCT in practice, will provide the basis for the rational implementation of this new technology.

REFERENCES


