Interpreting biomarkers in infectious diseases in intensive care unit: the potential role of procalcitonin

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Contribution: (I) Conception and design: Z Molnar; (II) Administrative support: F Hawchar; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Life threatening organ dysfunction in the critically is always due to or accompanied with some kind of dysregulated immune response. This is not the privilege of sepsis only, as the host response is not specific for the type of the insult. Therefore, similar reactions are provoked by both infectious or non-infectious injuries. This similarity in the host response makes differential diagnosis difficult and often leads to false interpretation of biomarkers that have been used in diagnosing sepsis and infection for several decades. Today we understand that damage and pathogen associated molecular patterns, the PAMPs and DAMPs, are more-or-less identical regardless of the type of the insult. One of the most studied biomarkers in this field is procalcitonin (PCT). It is true, that absolute values show a huge scatter amongst patients admitted with similar diseases and conditions due to the individual response of patients for a given insult, therefore difficult to interpret, but this holds true for any biomarker. However, due to its half-life of 24 hours, evaluating the kinetics of PCT based on a series of regular measurements makes it a potentially very useful marker on the intensive care unit. It can help the clinician's decision making in several ways. It may be used for the diagnosis of infection; assessing antibiotic appropriateness; diagnosing cytokine storm and evaluating the patient's inflammatory response in general, both in infections and after non-infectious injuries. PCT may also help to provide additional information to indicate adjunctive immunomodulation therapies, such as immunoglobulins or extracorporeal cytokine removal, etc., in several shock states. The aim of this review is to put PCT in a different context as reported previously and provide the pathophysiological rationale of why and how one should use it at the patients' bedside.

Keywords: Sepsis; biomarkers; intensive care unit (ICU); procalcitonin (PCT)

Received: 30 November 2018; Accepted: 11 December 2018; Published: 17 December 2018.
View this article at: http://dx.doi.org/10.21037/jeccm.2018.12.04

Introduction

Sepsis is now defined as a life-threatening organ dysfunction caused by dysregulated host response to infection, which may be associated with circulatory and cellular/metabolic dysfunction resulting in high risk of mortality (1). The latter condition is referred to as ‘septic shock’. However, it is not only infection, but several other non-infectious type insults that can cause dysregulated inflammatory response resulting in organ dysfunction. Nevertheless, regarding early management of septic patients, as recommended by the Surviving Sepsis Campaign guidelines, the early recognition of infection, adequate antimicrobial therapy and fluid resuscitation may contribute to positive outcomes and survival benefit (2). Although critical illness caused organ dysfunction can be detected via objective signs of organ failure/dysfunction, in the sepsis context the fundamental question is to decide whether the critical illness is due to infection or not?
Dysregulated host response: what does it mean?

It was Janos Selye, originally from Hungary, who in 1936 discovered, that animals exposed to different acute non-specific ‘nocuous’ agents, such as cold, surgery, etc., developed a typical syndrome, which appeared to be independent of the nature of the damaging agent (11). Later he called this condition stress. Today we know, that this non-specific response is directed by the immune system, it is also independent from the insult, let it be infectious or non-infectious in origin, and reflect the patient’s individual response to the injury—exactly the way Selye described stress response.

The immune system consists of two main components, the innate and the adaptive immunity. This complex network relies on the balance between pro-, and anti-inflammatory mechanisms. The innate immunity recognizes a broad spectrum of pathogens via ‘pathogen associated molecular patterns’ (PAMPs), and produces a pro-inflammatory response, in order to eradicate the potentially dangerous invading pathogens. The role of the anti-inflammatory (guided by adaptive immunity) is to keep this war localized and/or under control. It was a surprising new aspect that mechanical damage of tissues such as trauma, burns, ischemia-reperfusion, pancreatitis, major surgery, etc., may also result in a cytokine storm. Immune response for a non-infectious insult is referred to as “damage-associated molecular patterns” (DAMPs) (12).

When we are healthy, the antagonistic forces are in balance in our body, as symbolized by yin and yang (Figure 1). In Chinese philosophy, yin and yang describes how antagonistic forces may actually be complementary, interconnected, and interdependent, and how they may give rise to each other as they interrelate to one another. This becomes clear when we concern the acid/base, pro-/anti-coagulation and oxidant/anti-oxidant balance. Nobody knows it better than us, critical care physicians, how an imbalance in homeostasis (acid-base) or hemostasis (pro-, anti-coagulation) can cause life threatening situations.

It is the same regarding the inflammatory forces. Normally the balance is maintained between pro-, and anti-inflammation, and they function at a baseline level of activity to protect us from our environment during our everyday life. When we fall ill, both the pro-, and anti-inflammation increases its activity, they act in a parallel manner, the above-mentioned balance is maintained, and after 5–6 days we usually recover from injuries, or community acquired infections, and the activity of our immune system returns to its baseline (13). Why? Because we are healthy. It may sound a paradox, but we are still healthy even when we have fallen ill. This is why the SIRS concept was false, as SIRS is a physiological response, required to overcome the insult.
However, in the context of sepsis, pro-inflammatory forces overwhelm anti-inflammation and the response goes out of control, becomes uncontrolled and dysregulated (14). These patients can die due to fulminant septic shock during the early course of their disease.

**Diagnosing infection at the bedside—use kinetics over absolute values**

As mentioned above, sepsis is not a definitive disease, thus from the patient’s treatment point of view it may be an irrelevant issue whether a given patient is septic or not. The key question is whether the critically ill condition is due to infection or not?

The way it usually works in everyday practice is the following: we recognize that the patient is critically ill via the objective signs of organ dysfunction and commence basic and organ specific resuscitation, regardless of the actual diagnosis, which is often unknown at the time. The main question in this sepsis context is, whether the symptoms are due to infection or not? If infection is highly likely then source control should be initiated as soon as possible (15). However, if infection is unlikely, then antimicrobial therapy, surgery should be withheld due to the undesired adverse effects (15).

Unfortunately, diagnosing infection is not always easy. Although clinical signs are very important but on their own may be insufficient. Classical indicators of infection, such as fever/hypothermia, leukocytosis/leukopenia, tachycardia and hypotension are non-specific indicators of infection, frequently observed in every critically ill patient with or without infection. Therefore, inflammatory biomarkers have been investigated for decades in order to improve our diagnostic accuracy (5). However, despite the promising results, biomarkers have their own limitations. One of the major misconceptions regarding inflammatory biomarkers is that they are often referred to as ‘sepsis’ or ‘infectious’ biomarkers, which is a big mistake. As it was discussed earlier, both PAMPs and DAMPs can trigger inflammatory immune response in a very similar manner and this is one of the reasons why biomarkers will never have 100% sensitivity and specificity for diagnosing infection or sepsis, and they will never be able to clearly differentiate the inflammatory response for infection from host response for non-infectious insults.

There are more than 200 so called inflammatory biomarkers potentially available today, but undoubtedly PCT and C-reactive protein (CRP) are the most commonly used (5). CRP’s greatest limitation is its long half-life and slow response time. It reaches its maximum concentration around 48 hours after a certain insult, hence follows the change of the patients’ condition with a considerable delay. Moreover, CRP concentrations are elevated in most ICU patients with a huge scatter, making interpretation of the results even more difficult (16).

In contrast, PCT can be detected within 4–6 hours after the initial insult and reaches its peak concentration within 24 hours. In case of adequate treatment (for example in sepsis) or during an uncomplicated course after major surgery, the levels follow a reduction of roughly 50% per day (17). Several studies compared CRP to PCT and found that the latter differentiates bacterial infections from other etiologies with a higher sensitivity and specificity (18), also showed to have a good prognostic value regarding outcome (19). However, interpreting PCT values is not easy either.

Numerous studies report that PCT values correlate with severity of sepsis and septic shock (20). According to Clec’h et al., patients with septic shock had an almost 10 times higher median PCT levels compared to non-septic shock patients (21). If we look at their data more closely, it is important to acknowledge that although there is a statistically significant difference of 14 (0.3–767) in septic shock vs. non-septic shock: 1 (0.15–36) ng/mL, but there is also a huge overlap between the two groups due to the huge scatter of the data, indicating individual variations in the response for the insult. In a subsequent study from the same group the median PCT value in medical vs. surgical patients differed both in SIRS: 0.3 (0.1–1.0) vs. 5.7 (2.7–8.3), and in septic shock: 8.4 (3.6–76.0) vs. 34.0 (7.1–76.0) ng/mL (22). However, the same phenomenon as previously can also be observed, regarding the scatter and overlap of the data. Therefore, one rightly assume that absolute values may significantly differ between populations of patients (both severity and etiology), but regarding the individual patient, a single measurement of PCT is of limited value.

What we may use is the change of PCT over time. Tsangaris et al. evaluated PCT kinetics by measuring its levels daily in patients who had already been treated on the ICU and had a sudden onset of fever (23). A two-fold increase was found from the day before to the day when there was a sudden onset of fever in patients with later proven infection, but there was no change in PCT in patients with fever without the infection. Their results were confirmed by our observational study in which we also found that an increase in PCT from the day before
(t₁) to the day when infection was suspected (t₀) predicted infection, while in patients in whom infection was not proven, PCT remained unchanged (Figure 2) (24). A PCT increase of >88% from t₁ to t₀ that had an area under curve (AUC) of 77% with a sensitivity of 75% (65–84%) and specificity of 79% (60–92%) to indicate infection. It is important to note that neither the absolute values nor the change of white cell count, body temperature or CRP from t₁ to t₀ could predict infection and had an AUC of around 50% for all parameters.

Patients requiring prolonged ICU stay most likely to acquire immunosuppression. In these cases, PCT can also be used, but interpretation requires special attention. It has been demonstrated that in patients with secondary peritonitis with a series of recurrent infections, although PCT increased when infections occurred, but the peak values were lower and lower, insult after insult (25). Charles et al. found a similar pattern: during the first infectious insult the mean of PCT concentrations was 55 ng/mL, but despite a similar clinical picture, during the second infectious insult, the mean value was several-fold lower (6.4 ng/mL) (26).

These findings give strong evidence that PCT values are affected by several factors (individual response, etiology, time, etc.), and support the concept of interpreting PCT kinetics instead of choosing a fix cut-off value at the bedside.

**PCT-assisted antibiotic therapy**

Due to the relatively fast reacting features of PCT kinetics it may be used to assist antimicrobial therapy in several ways.

One of the first studies by Christ-Crain et al. found that antibiotic therapy guided by admission PCT levels resulted in a 50% (44% vs. 83%) reduction in antibiotic exposure in patients admitted to the emergency ward with acute respiratory symptoms (6). Subsequent multicentre trials adjusting antibiotic therapy as indicated by PCT-kinetics also found a 2-day decrease in antibiotic exposure, when antibiotics were stopped in case of a 80–90% decrease in PCT levels (7,27,28). Hochreiter et al. and Schroeder et al. conducted trials on high risk surgical patients with suspected infection. They found significant reduction of antibiotic therapy and shorter ICU stay where PCT-guided therapy was followed during the postoperative period (29,30).

Although, there are other studies that could not find significant benefits of this approach (3,31), but there were important methodological differences between these and the previously mentioned studies. Jensen et al. tested primarily antibiotic escalation and applied fixed values of PCT to indicate intervention (9). Shehabi et al. designed an excellent study, but they expected to detect a 4-day reduction in antibiotic exposure (10). Therefore, although they observed a 2-day benefit in the PCT-group, but the study was underpowered to show such a difference.

Nevertheless, a recent trial-based analysis of the SAPS-trial (28), indicates that the impact of a PCT-assisted antibiotic management approach, not just shortens antibiotic exposure but may also be related to lower in hospital mortality and cost effectiveness (32).

**Monitoring treatment efficacy**

It goes without saying that monitoring the inflammatory response of critically ill patients at the bedside on a daily basis in a reliable manner, would be of utmost importance. However, there is no such thing as ‘immunometer’ for that purpose that has been agreed upon as gold standard. There are hundreds of biomarkers on the market that could potentially be measured in the clinical routine, but they are expensive tests and data on their usefulness to monitor patient progress is limited. Therefore, each institute should take their choice of the one or two biomarkers for their daily routine they prefer and familiar with. In our institute we use PCT as our monitor to evaluate the patients’ inflammatory response and we measure it on a daily basis in almost every patient. In addition to this we specifically use PCT kinetics to indicate antibiotic appropriateness and to
indicate adjunctive therapies in patients with multiple organ failure and persisting cytokine storm.

The gold standard for proving antibiotic appropriateness of antibiotic therapy is the microbiological confirmation of the bacteria and its susceptibility. However, to obtain these results may take several days. At the early stage of suspected infection, currently there is no ‘perfect’ clinical sign or laboratory parameter that helps the clinician in deciding about antimicrobial therapy. We conducted an observational study (the EProK-study) where PCT was measured when the first dose of empirical antibiotics was given (t0), and then 8 hourly (t8, t16, t24) during the first 24 hours and then daily (33). There was a significant difference in the kinetics between patients receiving appropriate as compared to those receiving inappropriate antibiotic therapy. Receiver Operating Characteristic analysis revealed that a PCT elevation ≥55% within the first 16 hours (i.e., from t0 to t16) had an AUC for predicting inappropriate antibiotic treatment of 0.78 (95% CI: 0.66–0.85), P<0.001; from t0 to t24 a ≥70% increase had an AUC of 0.85 (0.75–0.90), P<0.001. These data suggest that early response of PCT within the first 24 hours of commencing empirical antibiotics in critically ill patients may help the clinician to evaluate the appropriateness of therapy, a concept which certainly will have to be tested in the future. Of note, hospital mortality was 35% in the appropriate and 65% in the inappropriate group (P=0.001), which provides further evidence that choosing inappropriate antibiotic therapy may seriously affect survival.

Translating these results into the everyday practice, we recommend two possible approaches. The first is, to measure the percentage change in PCT within the first 24 hours after starting antibiotic therapy and use the EProK data to decide on antibiotic appropriateness. Second, measure PCT level at the commencement of antibiotic therapy, then one more somewhere in between 12–16 hours later and another one after 24 hours. If one observes a ‘roof top’ type kinetics (Figure 3) in contrast to a continuous increase what we found in the inappropriate group in the EProK study, may support that the patient is getting appropriate treatment.

In critically ill patients who have received appropriate resuscitation, source control, and require organ support, but still don’t want to improve, indicating some sort of adjunctive therapy is sometimes considered (34). As there is no frank evidence on the indication of these treatment alternatives, guidelines usually do not recommend these therapies (2). However, clinicians still use immunoglobulins, high volume hemofiltration, plasmapheresis and recently extracorporeal cytokine removal (CytoSorb®, Cytosorbents, Germany), all over the world.

In a recent proof of concept prospective randomized pilot trial, we tested the efficacy of early extracorporeal cytokine removal with CytoSorb in patients with septic shock, with high PCT and high vasopressor need (35). The most dramatic effects as compared to controls were the dramatic decrease in PCT and vasopressor need within the first 12–24 hours of treatment.

Our results suggest that PCT may be a useful biomarker to monitor inflammation/cytokine storm in patients and also to help the physicians to target immunomodulatory adjuvant therapy to patients who may benefit the most.

Conclusions

PCT is a well-established and thoroughly investigated biomarker, which has been shown to help individualizing antibiotic management of critically ill patients that can have several potential benefits on both patient outcomes and cost

![Figure 3 Predicting antibiotic appropriateness from PCT kinetics. The figure demonstrates that after commencing empirical antibiotic therapy (at T0), PCT shows different kinetics in patient who receive appropriate as compared to those who receive inappropriate treatment. While there is continuous increase in PCT in the IA-group, in the A-group PCT reaches its peak somewhere between 12–16 hours and by T24 it already declining, regardless, whether the absolute values at T24 are higher than at T0 or not. The drawing is based on the results published in (33). PCT, procalcitonin; IA, inappropriate; A, appropriate.](image-url)
effectiveness. In addition to its role in antibiotic therapy it may also play an important part in the assessment of the inflammatory response in general, hence in several non-infectious conditions, and in combination with the clinical picture it may help in targeting adjunctive therapy to those patients who would benefit the most.

Acknowledgements

None.

Footnote

Conflicts of Interest: Z Molnar receives lecture honoria from ThermoFisher Scientific. F Hawchar has no conflicts of interest to declare.

References


