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Can procalcitonin levels indicate the need for adjunctive therapies in sepsis?

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ABSTRACT

After decades of extensive experimental and clinical research, septic shock and the related multiple organ dysfunction still remain the leading cause of mortality in intensive care units (ICUs) worldwide. Defining sepsis is a difficult task, but what is even more challenging is differentiating infection-induced from non-infection-induced systemic inflammatory response-related multiple organ dysfunction. As conventional signs of infection are often unreliable in intensive care, biomarkers are used, of which one of the most frequently investigated is procalcitonin. Early stabilisation of vital functions via adequate supportive therapy and antibiotic treatment has resulted in substantial improvements in outcome over the last decades. However, there are certain patients who may need extra help, hence modulation of the immune system and the host's response may also be an important therapeutic approach in these situations. Polyclonal intravenous immunoglobulins have been used in critical care for decades. A relatively new potential approach could be attenuation of the overwhelming cytokine storm by specific cytokine adsorbents. Both interventions have been applied in daily practice on a large scale, with firm pathophysiological rationale but weak evidence supported by clinical trials. The purpose of this review is to give an overview on the pathophysiology of sepsis as well as the role and interpretation of biomarkers and their potential use in assisting adjunctive therapies in sepsis in the future.
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1. Introduction

Diagnosing and treating severe bacterial infections and related multiple organ dysfunction in the intensive care unit (ICU) is one of the biggest challenges in critical care medicine. As these patients correspond to a very heterogeneous population, varying in aetiology and severity, universally applicable diagnostic criteria and treatment protocols for sepsis are difficult to define. Nevertheless, sepsis has become a very important public health issue all around the world for several reasons. The incidence of sepsis has increased during the past decades, with mortality rates of 20–50%, and sepsis appears to be the single most important reason for hospitalisation [1–3]. Therefore, improving outcome is of utmost importance for patients and healthcare providers alike. Unfortunately, more than 30 years of extensive clinical research resulted in mainly non-significant results. According to a recent review of 72 prospective randomised trials with mortality being the primary endpoint, 55 ended up with non-significant results, also including several studies on adjuvant therapies [4,5]. Promising positive results of single-centre studies were often contradicted later by large multicentre trials [5]. Heterogeneity of the populations studied and diversity in clinical practice may be just two of the most important limitations of multicentre trials leaving us disappointed regarding several promising interventions. However, it is important to acknowledge that 'absence of evidence' may not necessarily mean the 'evidence of absence'.

Nevertheless, early detection of infection-induced critical illness and the immediate start of resuscitation in parallel with adequate antimicrobial therapy undoubtedly give the best possible chance for survival and received strong recommendation by the Surviving Sepsis Campaign guidelines [6]. However, whilst recognising organ failure is relatively easy, diagnosing the underlying infection remains a challenge. Owing to the non-specific properties of conventional signs of infection, such as body temperature and white blood cell count, for decades biomarkers have been searched for to aid diagnosis. One of the most studied biomarkers of the last decade is procalcitonin (PCT) [7]. Its role in assisting antibiotic therapy has been studied extensively [8,9], but it may also have a potential role in guiding adjunctive therapies in the critically ill.

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Modulation of the immune system and the host's response has also been the focus of research interest. However, anti-inflammatory therapies, such as anti-cytokines, anti-oxidants, etc., have also been tested, but the results were disappointing [10,11]. Nevertheless, at least theoretically, attenuating the cytokine storm in the early phase of critical illness may provide some benefits by counterbalancing the overwhelming pro-inflammatory response [12]. This concept provides the rationale of why the so-called 'adjuvant therapies' may have a role in these patients.

The purpose of the current review is to summarise the background of why diagnosing sepsis, or to be more precise infection, remains an everyday challenge for ICU physicians, and how PCT could be used to aid decision-making, including the commencement of adjunctive therapies.

2. Sepsis is not a 'definitive' disease

Defining sepsis is not simple. The idea of 'sepsis syndrome' was conceived in 1980, during the protocol writing of one of the first prospective randomised trials in sepsis, performed by Bone et al., and was based on the inclusion criteria of that study [13,14]. The classical signs of 'sepsis syndrome', such as fever/hypothermia, leukocytosis/leukopenia, tachycardia and hypotension, meant a very large and non-specific group of patients. A few years later a consensus conference was brought together and the 'consensus criteria' for several definitions were published in 1992 [15]. This concept was also questioned and criticised [16]. In the most current Surviving Sepsis Campaign guidelines, a more robust and detailed definition has been created, but fundamentally it is still following the previous concept of the Bone criteria [6].

This confusion regarding the definition leaves us with obvious uncertainties. It is difficult to know for sure in which patients we should start antibiotics or commence adjuvant therapies, which is still based on the physician's 'gut feeling' rather than objective parameters during our everyday practice.

3. Pathophysiology: from localised insult to 'cytokine storm'

The immune system is a complex network and the immune response to pathogens relies both on innate and adaptive components. The first line of defence against invaders consists of physical barriers such as the skin [17,18] and the mucous membranes of the respiratory [19], gastrointestinal [20] and genitourinary [21] tracts. The second line of defence is the rapidly acting innate immune system (including the complement system, sentinel phagocytic cells and natural killer cells), which plays a modulatory role on the adaptive immune system [22]. The innate system acts by broad recognition of antigens, mainly by triggering pathogen-associated molecular patterns (PAMPs) of lipopolysaccharide (LPS) elements on the surfaces of invading pathogens.

When a local response escalates into a systemic immune response, activation of several signalling pathways on different receptors will generate a 'cytokine storm' [23]. It was a very important discovery that following trauma, burns, ischaemia/reperfusion injury, pancreatitis, major surgery, etc., the same or similar molecules are released mainly from the mitochondria. These are called 'damage-associated molecular patterns' (DAMPs). Therefore, it has now become clear that following cellular injury, similar proteins (DAMPs) will be released as during bacterial infection (PAMPs) because the genetics, and hence the proteins released, are very similar in bacteria and in the mitochondria [24].

In most cases, the PAMP- and DAMP-induced pro- and anti-inflammatory forces swing into action alongside with each other, but remain in balance and after a certain period of time their activity returns to baseline and the infection is resolved. However, in critically ill patients this balance is disturbed and either the pro- or anti-inflammatory forces overwhelm each other and the localised insult becomes systemic. As a result, vital organs, distant from the site of the initial insult, become affected in an unpredictable manner. If two or more vital organs are affected it is termed multiple system organ failure. The processed is briefly summarised in Fig. 1. Organ dysfunction mainly means a DAMP-based imbalance between oxygen delivery (DO_2) and consumption (VO_2), resulting in a persistent non-specific inflammatory response. This process exhausts resources of defence against infection. Therefore, some adjunctive interventions are targeted to attenuate the DAMP-based overwhelming pro-inflammatory forces (i.e. cytokine adsorption), whilst other approaches boost immunological defence against the invading pathogens (i.e. immunoglobulins).

4. Diagnostic challenges

Recognising a 'septic patient' per se is based on two main pillars. The first is evaluation of vital organ functions and the degree of organ dysfunction via objective clinical signs [19]. The second is the attempt to verify the aetiology of critical illness, in other words whether or not it is due to infection. However, answering this question remains one of the most difficult tasks in our daily practice. There is not, and most probably will never be, one single marker that is able to diagnose sepsis, mainly due to its very colourful manifestation and the heterogeneity of patients.

4.1. Conventional markers of inflammation/infection

It has been shown and accepted that early initiation of adequate antibiotic therapy is of utmost importance, with the chances of survival reducing by the hour [25]. Therefore, diagnosing infection as early as possible has a pivotal role in efficient patient management. Traditionally, physicians use clinical signs, body temperature, white blood cell count and microbiological data to diagnose infection. However, clinical signs, which are the most important evidence in recognising organ dysfunction, are non-specific and non-sensitive markers of a bacterial infection. Fever and leukocytosis also have very poor sensitivity and specificity, being not much better than just flipping a coin. Microbiology is the gold standard for confirming pathogens, but the results come back late, at least 24–48 h after sampling. New molecular biology techniques can shorten the detection time of microbes but these cannot differentiate between colonisation and clinically relevant infection [26–28]. This is why we need laboratory tests that are sensitive and specific enough to indicate bacterial infection within hours of its onset. These biologically active substances are called biomarkers.

4.2. The role of biomarkers at the bedside

There are several useful biomarkers in clinical practice and extensive research is still ongoing to find better ones [1]. However, no biomarker can answer all questions alone with 100% sensitivity and specificity in severe sepsis and septic shock owing to the overlapping pathomechanism of PAMPs and DAMPs discussed in detail above [29].

The two most commonly used markers in infection/sepsis diagnostics are PCT and C-reactive protein (CRP) [30]. Despite their popularity, there are still many pros and cons, with no clear answers regarding their usefulness and interpretation in guiding patient management, including adjunctive therapies.

PCT is detectable in the serum within a few hours (2–4 h) after the onset of bacterial infection. It reaches its peak within 24 h and then starts to decline in the case of adequate treatment, with ca.

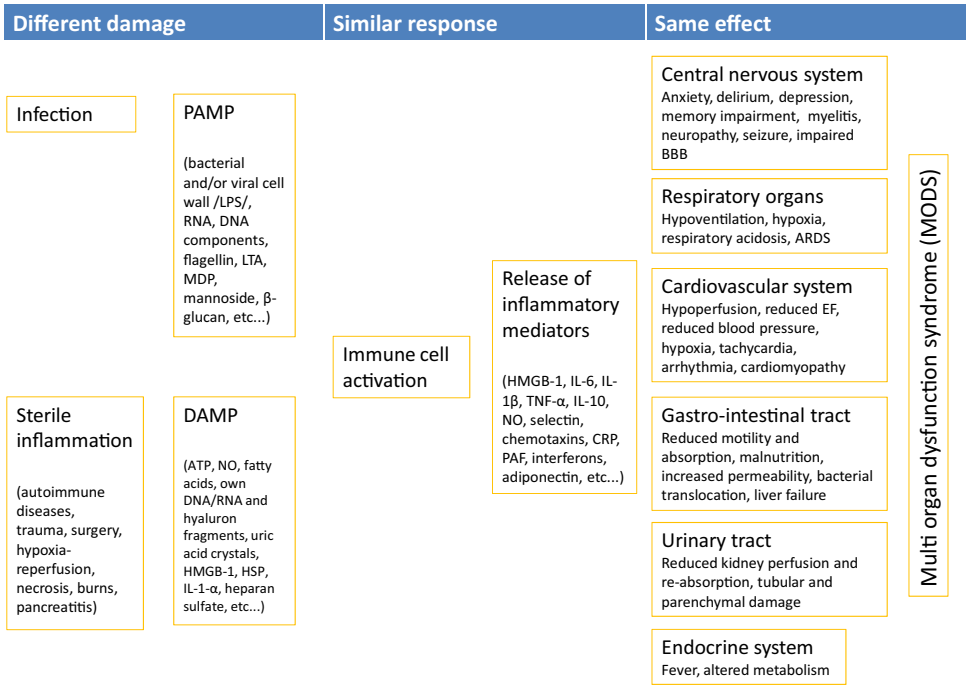

Fig. 1. Pathogenesis of sepsis and multiple system organ failure due to different insults. PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; LPS, lipopolysaccharide; LTA, leukotriene A; MDP, metal-dependent phosphohydrolase; HMGB-1, high-mobility group box 1; HSP, heat shock protein; IL, interleukin; TNFα, tumor necrosis factor-alpha; NO, nitrogen oxide; CRP, C-reactive protein; PAF, platelet-activating factor; BBB, blood–brain barrier; ARDS, adult respiratory distress syndrome; EF, ejection fraction. For explanation, see text.

50% daily drop according to its half-life [31]. In contrast, CRP has a similar but delayed response, and under certain circumstances it reaches its maximum value usually within 48 h. Furthermore, CRP levels are generally elevated in most ICU patients, making interpretation of CRP very difficult [32]. The other major problem with CRP in the ICU is its slow kinetics, in other words it lags way behind the actual events of the inflammatory process.

PCT differentiates bacterial infections from systemic inflammatory response of other aetiologies with higher sensitivity and specificity compared with CRP [33,34]. Discussing the available evidence on PCT–CRP comparison is beyond the aim of this manuscript, hence we will mainly focus on PCT in the coming paragraphs. There is considerable evidence that a PCT-supported policy in antibiotic treatment has several beneficial effects, such as reduced antibiotic prescription and exposure in lower respiratory tract infections, with similar clinical outcome and survival [35], and it may also shorten the duration of antibiotic treatment in the ICU [36].

5. Interpreting procalcitonin

As sepsis is often regarded as a 'definitive' disease, most physicians wish for a certain absolute value of biomarkers to diagnose sepsis/infection. However, based on the previously discussed pathomechanism (PAMP/DAMP/both), it should be acknowledged that sepsis is not a definitive disease, therefore it is impossible to have one single cut-off value for all conditions.

5.1. Sepsis is different in surgical and medical patients

PCT levels were found to be several times higher in surgical compared with medical patients with the same gravity of septic shock [37]. This indicates that the degree of the inflammatory response is different depending on aetiology [38–41].

Unspecific PCT elevations can also be found in the absence of bacterial infection [42,43]. Mono induction of PCT due to DAMP-based surgical tissue injury is reflected in elevated PCT values after surgery, with a peak on the first postoperative day followed by a gradual decrease thereafter [44]. Theoretically, in surgical patients with infectious complications, DAMP and PAMP pathomechanisms take place at the same time resulting in a synergistic effect on the inflammatory response and a re-induction of PCT production with increasing levels. In contrast, in medical patients it is primarily the activation of PAMPs, resulting in a less extensive inflammatory response, hence lower PCT levels. For example, in a study by Clec'h et al., the median (interquartile range) PCT values in systemic inflammatory response syndrome in medical versus surgical patients were 0.3 (0.1–1.0) ng/mL vs. 5.7 (2.7–8.3) ng/mL, and in septic shock were 8.4 (3.6–76.0) ng/mL vs. 34.0 (7.1–76.0) ng/mL, respectively [37].

Furthermore, sepsis changes its 'face' with time. Charles et al. found different degrees of inflammatory response despite a similar clinical picture (i.e. organ dysfunction) in patients during their first compared with their second and third septic hit [45]. They investigated patients with primary and secondary bloodstream infections and found that the same gravity of infection indicated by the clinical picture was accompanied by a several times lower PCT maximum concentration in patients with the second event of infection compared with those with a primary event. This indicates that lower levels of PCT should be taken just as seriously in the case of a later onset of infection as higher values during the first hit. These data have been further supported by recent reports [46,47].

5.2. Kinetics over absolute values

Despite the above differences in the absolute values in different conditions, the kinetics may show a similar pattern and may also be more useful. Tsangaris et al. studied patients who were in the ICU for more than 10 days, who were free of infection and

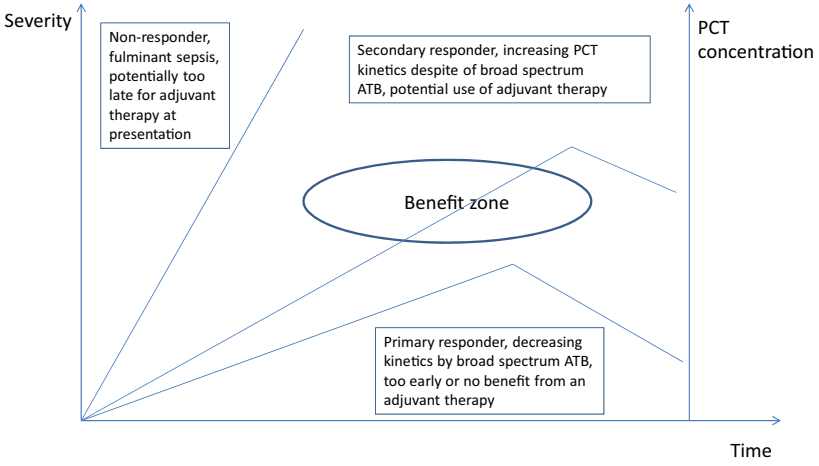

Fig. 2. Potential 'therapeutic window' as indication of adjuvant therapies in sepsis. ATB, antibiotics; PCT, procalcitonin. See text for explanation.

who presented with a new onset of fever [48]. PCT showed a minimum 2-fold increase in patients with proven infection from the day before to the day of fever onset. However, in patients without infection, PCT remained constantly low compared with previous days. They concluded that PCT values on the day of fever onset must be compared with values from the previous day to diagnose infection. Furthermore, in the case of a 'normal' clearance and the absence of re-induction, PCT values on the third day after the fever onset returning to the normal range were associated with better survival [48]. These are in accord with a recent pilot study by Öveges et al. [49]. In patients in the ICU, the change of PCT from the day before to the day when infection was suspected showed significant differences in cases when infection was proven compared with those in whom infection could not be proven. Although PCT values on the previous day were similar in both groups, there was a significant increase in patients with infection, whilst there was no change in the non-infection group [49]. These results indicate that PCT change (i.e. kinetics) may be more useful than absolute values in diagnosing infection.

PCT kinetics may also be very useful in stopping antibiotic therapy according the patient's individual response. As indicated in the PRORATA trial, a >80% drop over a few days compared with the peak PCT value can be an important signal to discontinue antibiotic therapy, hence reducing antibiotic exposure significantly without affecting outcome [36]. Tailoring the length of antibiotic therapy according to biomarker levels is also recommended in the recent Surviving Sepsis Campaign guidelines [6]. These results suggest that PCT kinetics-based therapy may be superior to pre-set absolute values. Nevertheless, further studies are needed to reinforce the findings of the PRORATA trial.

6. When to commence adjuvant therapies?

In the world of evidence-based medicine, adjunctive therapies have a very difficult task to prove themselves. Mainly single-centre or small studies show therapeutic benefit on outcome, and these positive results are often contradicted by large multicentre trials. Nevertheless, from a pathophysiological point of view, most of these therapeutic modalities have a firm pathophysiological rationale. Despite the lack of clear evidence, adjuvant therapies are still frequently used all over the world in the everyday practice, but discussing them all would be well beyond the scope of this article.

The purpose of the current review is to show how a PCT-assisted approach can help to indicate the commencement of adjunctive therapies. We have chosen two alternatives: IgM-enriched immunoglobulins (Pentaglobin®; Biotest Pharma GmbH, Dreieich, Germany), which have long been used in our everyday practice; and a new possibility for cytokine adsorption (CytoSorb™; CytoSorbents Europe GmbH, Berlin, Germany).

Several properties of IgM-enriched intravenous immunoglobulins make this preparation suitable for immunomodulatory treatment in septic patients: it is able to facilitate the removal of apoptotic cells [50] and protect from endotoxin-related endothelial damage in parallel with successful antibiotic treatment [51]. Although there are no large prospective randomised trials to support their use on an evidence-based level, owing to the firm pathophysiological rationale it has been used for decades. However, the treatment is costly and there is frank evidence that patients can survive in large numbers simply getting supportive and appropriate antibiotic therapy. Nevertheless, there may be patients that benefit from IgM-enriched immunoglobulin treatments, but it is difficult to define when and in whom it should be commenced [52].

CytoSorb™ contains biocompatible, porous polymer polystyrene beads in a cartridge of ca. 300 mL that is able to adsorb a broad spectrum of cytokines in the 10–70 kDa range, both including pro- and anti-inflammatory cytokines [53–55].

As cytokine overproduction is a common feature in many life-threatening conditions in critically ill patients, such as sepsis, adult respiratory distress syndrome, major surgery in high-risk patients, trauma, viral infections, thermal injury, liver failure, acute pancreatitis, etc., the rationale for the use of a cytokine absorber theoretically should not be limited for sepsis only but for any critically ill conditions accompanied by a cytokine storm, hence an imbalance between the pro- and anti-inflammatory forces. Although at present there are only animal studies [56,57] and case reports [58–62], several prospective randomised trials are taking place worldwide [59].

Despite these positive results, the question remains why and when should we commence these therapies, if we do it at all, and which patients would benefit the most? By and large it follows some rationale that adjunctive therapies are indicated in the case of: (i) profound septic shock, indicated by high vasopressor requirement and multiple organ failure with at least two organs involved; (ii) no improvement within a few hours after the commencement of resuscitation and antimicrobial therapy; and (iii) when PCT values remain unchanged or increase in addition to not improving clinical conditions. This concept is summarised in Fig. 2. There is some evidence that PCT values reflect adequate or inadequate treatment within hours, or at least within the first 24 h, and kinetics may indicate appropriate or inappropriate treatment [63]. However, this assumption will have to be tested in future clinical trials. All we can say at the moment is that a multimodal,

individualised approach may help us to tailor these therapies better. The 'multimodal' approach means that several clinical and biochemical parameters are taken into account simultaneously, whilst 'individualised' refers to the interpretation of changes/kinetics of certain parameters such as PCT, rather than taking only 'fixed' absolute values into account.

7. Conclusion

Understanding the aetiology and the underlying pathology in sepsis and critical illness is essential to enable us to evaluate clinical signs and biomarkers in the right context. Several important issues should be taken into account during this evaluation, including the immunological background of the host response for different insults, summarised in the DAMP/PAMP concept. This also explains why biomarker levels may have different meanings due to different aetiology and why their kinetics, in other words their change over time, may provide more appropriate information than the absolute values. Designing future clinical trials based on recruiting patients with different aetiologies and then treated according to this concept may overcome the shortcomings of trials in the past and provide results on a more homogeneous group of patients and with more conclusive results. This may take us to a completely different strategy in our therapeutic management, leading us towards multimodal, individualised, goal-directed infection management in septic patients.

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