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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.

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.

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