Examining the Diagnostic Value of Procalcitonin

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EDITORIAL

Examining the Diagnostic Value of Procalcitonin and C-Reactive Protein in Sepsis: A Recent Comprehensive Perspective

Pemeriksaan Nilai Diagnostik Procalcitonin dan Protein C-Reaktif pada Sepsis: Perspektif Komprehensif Terbaru

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ABSTRACT

Sepsis is a global health problem characterized by organ dysfunction caused by dysregulation of the host's response to microbial infection. Sepsis remains the leading cause of morbidity and mortality in intensive care units worldwide. Early diagnosis and proper management are essential to improve patient outcomes. This comprehensive review examines the diagnostic value of two widely used inflammatory biomarkers – procalcitonin (PCT) and C-reactive protein (CRP) – in diagnosing and managing sepsis. PCT generally outperforms CRP in early sepsis diagnosis and distinguishing bacterial infections from other inflammatory causes. However, CRP remains a valuable marker for ongoing monitoring and evaluation of response to therapy. We also discuss the limitations of these two biomarkers and highlight the importance of interpreting results in the context of patient clinical presentation. In conclusion, the combined use of PCT and CRP, along with careful clinical assessment, can improve the accuracy of sepsis diagnosis and guide more effective management strategies.

Keywords: C-reactive protein; Procalcitonin; Sepsis.

ABSTRAK

Sepsis adalah masalah kesehatan global, ditandai adanya disfungsi organ yang disebabkan oleh disregulasi respon inang dalam menanggapi infeksi mikroba. Sepsis tetap menjadi penyebab utama morbiditas dan mortalitas di unit perawatan intensif di seluruh dunia. Diagnosis dini dan manajemen yang tepat sangat penting untuk meningkatkan hasil pasien. Tinjauan komprehensif ini mengkaji nilai diagnostik dari dua biomarker inflamasi yang banyak digunakan - procalcitonin (PCT) dan C-reactive protein (CRP) - dalam diagnosis dan manajemen sepsis. PCT umumnya mengungguli CRP dalam diagnosis dini sepsis dan dalam membedakan infeksi bakteri dari penyebab inflamasi lainnya. Namun, CRP tetap menjadi penanda yang berharga untuk pemantauan berkelanjutan dan evaluasi respons terhadap terapi. Kami juga membahas keterbatasan kedua biomarker ini dan menyoroti pentingnya interpretasi hasil dalam konteks presentasi klinis pasien. Kesimpulannya, penggunaan gabungan PCT dan CRP, bersama dengan penilaian klinis yang cermat, dapat meningkatkan akurasi diagnosis sepsis dan memandu strategi manajemen yang lebih efektif.

Kata Kunci: C-reactive protein; Procalcitonin; Sepsis.

Sepsis is a life-threatening clinical condition with widespread physiological and biochemical abnormalities. The Third International Consensus (Sepsis-3) currently defines sepsis as "organ dysfunction caused by a dysregulated host response to infection," emphasizing for the first time the critical role of both innate and adaptive immune responses in the development of the clinical syndrome.[1] Approximately 49 million people are affected by sepsis each year and an estimated 11 million deaths are attributable to this syndrome, accounting for 19.7% of all deaths worldwide.[2] Globally, mortality rates appear to be decreasing on average. However, up to 25% of patients still succumb to sepsis. In septic shock, a subgroup of sepsis characterized by profound circulatory, cellular, and metabolic abnormalities, hospital mortality rates approach 60%.[3] Defining "sepsis" comprehensively has been the subject of constant development and refinement over the past decades.[1,4,5] The incidence of sepsis has been steadily increasing since the first consensus definition (Sepsis-1) in 1991, reaching an estimated 49 million cases of sepsis and 11 million sepsis-related deaths worldwide in 2017. These data have led the World Health Organization (WHO) to declare sepsis a global health priority.6 According to the latest report from the Global Sepsis Alliance (2023), sepsis affects more than 50 million people annually and is responsible for an estimated 11 million deaths worldwide.7 Recent epidemiological studies revealed that these figures may be even higher in low- and middle-income countries, where sepsis accounts for up to 85% of all infection-related deaths.[8] This alarming increase in incidence can be attributed to a variety of factors: (1) an increasing average age among patients, especially in Western countries; (2) an increase in the number of invasive procedures; (3) the widespread use of immunosuppressive drugs and chemotherapy; and (4) antibiotic resistance.[8] Despite significant advances in therapeutic management, septic patients have a high risk of in-hospital mortality, accounting for approximately 20% of all-cause deaths globally. Although our understanding of the origin, pathophysiology, and immunological mechanisms of sepsis has made progress over the past three decades. The determining factors are the timing of correct diagnosis and initiation of causal, supportive, and adjunctive measures. This implies that increasing awareness of sepsis and promoting quality improvement initiatives in the field of sepsis effectively improve patient survival, along with the development of new diagnostics and interventions.[9]

There is growing evidence that inappropriate antibiotic (AB) therapy can lead to serious adverse events. To improve diagnostic accuracy, biomarkers have become the focus of intensive research. A comprehensive meta-analysis has evaluated more than 50 potential biomarkers for the diagnosis of sepsis, with procalcitonin (PCT) and C-reactive protein (CRP) emerging as two of the most promising candidates.[10] Procalcitonin (PCT) is one of the most widely studied inflammatory biomarkers[11] and can differentiate bacterial from viral infections in critically ill patients.[12,13] PCT, a precursor of the hormone calcitonin, shows high specificity for systemic bacterial infections. Meanwhile, CRP, an acute-phase protein produced by the liver in response to inflammation, has long been used as a general indicator of infection and inflammation. Whether CRP and PCT represent good predictors of sepsis severity, as well as sepsis-related mortality, remains controversial.[14] In 2004, several study groups suggested no prognostic impact of CRP and PCT measurements in patients with sepsis or septic shock. However, the prognostic role in the current sepsis-3 era requires further investigation. In particular, the role of CRP and PCT during sepsis or septic shock, stratified by disease progression or clinical improvement, has not been investigated. Furthermore, the emergence of new technologies and multimodal approaches in sepsis diagnosis has opened new opportunities while raising new questions about the optimal role of these biomarkers in clinical practice. In this context, this editorial aims to comprehensively evaluate the diagnostic value of PCT and CRP in sepsis based on the current literature. We will explore the strengths and limitations of each biomarker, assess their value in various clinical contexts, and discuss potential synergies between them. In addition, we will discuss challenges in the use of these biomarkers and explore promising future research directions.

By understanding in depth the role of PCT and CRP in the diagnosis of sepsis, we hope to provide valuable insights for clinicians in optimizing the use of these biomarkers, which may ultimately improve patient outcomes and reduce the global burden of sepsis.

Procalcitonin: High Specificity for Bacterial Sepsis

Procalcitonin (PCT), a polypeptide, is one of the biomarkers that has shown the highest reliability in the early diagnosis of sepsis, especially bacterial etiology.[15] In bacterial sepsis, serum PCT increases 100–1000-fold within 4 hours after the onset of systemic infection and peaks between 8 and 24 hours.[16] PCT is a peptide consisting of 116 amino acids with a molecular weight of 14.5 kDa. Its production is regulated by the calcitonin 1 (CALC-1) gene on chromosome 11.[17] However, production is activated in all parenchymal tissues in response to bacterial infection, mediated by the cytokines interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-β).[18] These other tissues cannot cleave PCT to its mature form, calcitonin, leading to PCT accumulation. In contrast, PCT production is attenuated by interferon-γ which is mainly secreted in response to viral infection.[19] This characteristic makes PCT a more specific marker for bacterial infection. All currently available assays for PCT quantification are based on immunoassay techniques. The first commercially available PCT assay was the BRAHMS PCT LIA® (Thermo Fisher, Hennigsdorf, Germany), a manual luminometric immunoassay. A more sensitive and rapid automated test known as BRAHMS PCT Kryptor®) (Thermo Fisher, Hennigsdorf, Germany) was subsequently developed, which was first approved by the FDA in 2008 for use in the diagnosis of severe sepsis and septic shock.[20] Other tests have since been developed, such as the PCT immunoturbidimetric test (DiaSorin Liaison, Vidas, Roche E601, and Siemens Advia Centaur), and the Diazyme immunoturbidimetric test (on the Abbott Architect c16000, Siemens Advia 2400, Roche Cobas C501

and Beckman Coulter AU5800).[21] The test methods can use Electro Chemiluminescence with a test time of 18 minutes and a detection limit of 0.06 ng/mL, the Enzyme-Linked Fluorescence Immunoassay method takes 20 minutes with a detection limit of 0.09 ng/mL, and the Time-Resolved Amplified Cryptate method. Emission (TRACE) takes longer, namely 50 minutes with a detection limit of 0.06 ng/mL.[22,23]

C-Reactive Protein: High Sensitivity but Less Specific

C-reactive Protein (CRP) was discovered by Tillett and Francis in 1930. The name CRP arose because it was first identified as a substance in the serum of patients with acute inflammation. CRP is an acute-phase protein, synthesized by the liver, and has become a widely used biomarker because of its high sensitivity to inflammation and infection.[24,25] CRP increases sharply after an acute inflammatory reaction or tissue injury 6-8 hours and peaks at levels of up to 350-400 mg/L after 48 hours and has a half-life of 19 hours.[25] CRP is not affected by diurnal variations. Therefore, CRP is very useful for establishing the diagnosis of inflammation and infectious diseases. The gene encoding CRP is located on chromosome 1.[26] The CRP molecule consists of 5-6 identical non-glycosylated polypeptide subunits, consisting of 206 amino acid residues, and are non-covalently bound to each other to form a disk-shaped molecule with a molecular weight of 110-140 kDa, each unit has a molecular weight of 23 kDa. Immunoassays and laser nephelometry are methods for measuring CRP levels and are inexpensive, accurate, and rapid. For the detection of lower CRP levels (0.3 to 1.0 mg/L), high-sensitivity CRP methods are recommended because conventional CRP detection tests are less accurate. High-sensitivity CRP only indicates the testing process used, allowing detection of lower CRP levels and not a different, or more specific, differential diagnosis.[27]

Challenges and Limitations

Although PCT and CRP have proven to be very useful, challenges remain in their interpretation and application. Individual variation, comorbid conditions, age, and other factors can influence the levels of these two biomarkers.[28] Therefore, it is important to always interpret test results in the full clinical context. In the future, further research is needed to optimize the use of PCT and CRP in various clinical scenarios. The development of diagnostic algorithms that combine these two biomarkers with other clinical parameters may improve the accuracy of diagnosis and management of patients with inflammatory conditions. Another challenge that needs to be overcome is the variability in measurement methods and cut-off values for PCT and CRP between institutions.

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