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Sepsis

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Abstract

Sepsis, severe sepsis, systemic inflammatory response and other related manifestations represents a medical condition with high morbidity and mortality rate globally. It was estimated that beyond 30 million people affected as reported by WHO report of 2018. Despite of satisfactory diagnostic biomarkers, loss of human life's continues which mainly rise from infection, inflammation or due to long-term stay in ICU's. Out of different prognostic biomarkers, PCT comes to be a reliable marker for the early diagnosis of sepsis and its related manifestations. This review gives an outlook to the explanation of sepsis – its pathophysiology, etiology, and its diagnostic marker.

Keywords – Sepsis, Procalcitonin (PCT), C-reactive protein (CRP), Cytokines, Systemic Inflammation.

Introduction

More than 800,000 episodes of sepsis, severe sepsis and septic shock occurs each year in United States, estimated from National Census Projections and Medicare databases [8]. Hence, believes to be rising; while factors adding to such rising includes enhanced number of immuno-compromised patients, aging population, using life-sustaining technologies and resistance to various antimicrobial agents, effecting treatment of nosocomial and community acquired infections [9]. Sepsis is current cause of infection related deaths, mostly, influenced by age of targeted population. In sepsis, morality rate shows minimal peak in neonates with progressive hike between 20-70 ages, finally with a dramatic elevation after 75 years. Poor outcomes remained, despite of the usage of new antimicrobials and better supportive care suggesting a requirement of different treatment approach for lowering morality from sepsis and related syndromes. For the diagnosis of sepsis and its severity, various biomarkers have been suggested such asProcalcitonin (PCT), C - reactive protein (CRP), Tumor necrosis factor-alpha (TNF-α), Cytokine biomarkers (IL-6 and IL-8), etc. While PCT was considered

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to be better for diagnosis due to sensitivity, high selectivity and helpful in early diagnosis of such conditions. Also helpful in differentiating between bacterial infections and viral infections.

Sepsis

Sepsis is considered as the presence of various number of bacteria in blood, which divides and cause body to response in such manner that results in organ dysfunction. In previous consensus conferences, sepsis is mentioned as only one organ dysfunction [3] which further modified to be as a multi-organ dysfunction condition. In 2016, the 'Third International Consensus Definitions Task Force' defined; "Sepsis, as a life threating organ dysfunction caused by host response to an infection which results in injury to host's own tissues and organs." [1] While, septic shock is described as "A subset of sepsis underlying circulatory and cellular metabolism abnormalities that are profound enough to substantially increase mortality than sepsis condition alone" [2]. Further, redefined as systemic inflammatory response to infectious condition. Overall, sepsis described as host response to an infection that resulted due to presence of various cytokines and other modulators, released through immune response to an infectious condition, observed as an association of systemic inflammation [3].

Epidemiology

Sepsis and its related manifestations found to be a common cause of mortality in ICU's followed by late diagnosis as well as treatment, enhanced mortality rate [5]. In India, an observational study conducted in four intensive therapy units (ITUs) for time-period from June 2006 to June 2009, suggested that out of 1,385 ITUs patients, 731 were found to be suffering from sepsis condition [6, 7]. Thus, concluding that sepsis patients to be likely found in India ITUs and considered to be higher rate as compared with western literature [6]. Similarly, study conducted on US population suggested sepsis to be fatal condition, with annual increased mortality rate as compared with mortality rate of acute myocardial infarction condition, and incidence projected with an increase by 1.5% per annum [8].

Pathophysiology

Previously, sepsis is characterized as an exaggerated hyper-inflammatory condition, associated with organ failure, resulting in death of patients. Presently, it is belief that sepsis represents both pro- and anti-inflammatory responses with changes in non-immunological pathways including, cardiovascular, neuronal, hormonal, bioenergetics, and metabolism

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coagulation, which have prognostic significance, and organ dysfunction (Figure.1). Tissue injury or an infection activates local immune response, a general part of wound healing (host's defense mechanism), while in some cases, activates spillover of inflammatory mediators; resulting in manifestations- hypothermia/fever, leukopenia or leukocytosis, and tachycardia [10]. Respective to individual-immune response; a bacteria, fungi, parasites or viruses may results in sepsis. While, it can progress to severe sepsis, resulting in dysfunction of renal, cardiovascular, hematologic, hepatic system along with unexplained metabolic acidosis condition. On further account; some inflammatory mediators also bestows change in vasodilation process, a case of progression in sepsis, which may leads to occurrence of hypotension and hypo-perfusion or both indicating septic shock condition [9]. Consequently, complexity of biological and clinical conditions of such patients are associated with age, underlying comorbidities, and current infection level. Research is going to continuous to find the principal alteration of sepsis. Researcher are studying in the field of dysregulated coagulation, cellular dysfunction and metabolic alteration.to investigate the immunopathology process which is related with morbidity and mortality.

Role of Cytokines:

In the pathophysiology of sepsis and its related syndromes, a complex array of intermediary pathways has been describe involving various happenings including inflammation, vascular endothelial injury, coagulation factors activation, and fibrinolysis inhibition may contribute to the organ dysfunction, further leading to death. In sepsis condition, WBCs secretes a network of proinflammatory cytokines in large variation; commonly includes TNF-α –variety of interleukins and inflammatory prostaglandins (IL-1β, Il-6, IL-8) [11]. In addition, elevated blood levels of soluble cytokine receptors are also observed. During sepsis, elevated levels of such proinflammatory cytokines persists for a prolonged period and alteration of helper T-cells ratio may be linked with multiple-organ failure [11].

Role of Coagulation:

In sepsis condition, coagulation process and inflammatory events appears to be directly or indirectly related while low concentrations of APC (a significant inhibitor of thrombin), and TFPI have been reported [12]. In sepsis condition, coagulation system and platelets are found to be highly activated except factor XII is reduced. While in contrast, most of the coagulation factors are depleted in severe sepsis which further lowers in septic shock condition [13]. Protein C, a natural antithrombin produced in liver, founds to be in lower concentrations at an onset of fever during sepsis which worsens with the progression of such condition. In

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addition, it was observed that patients suffering from septic shock had lowest concentration of Protein C resulting in 100% mortality [9, 14].

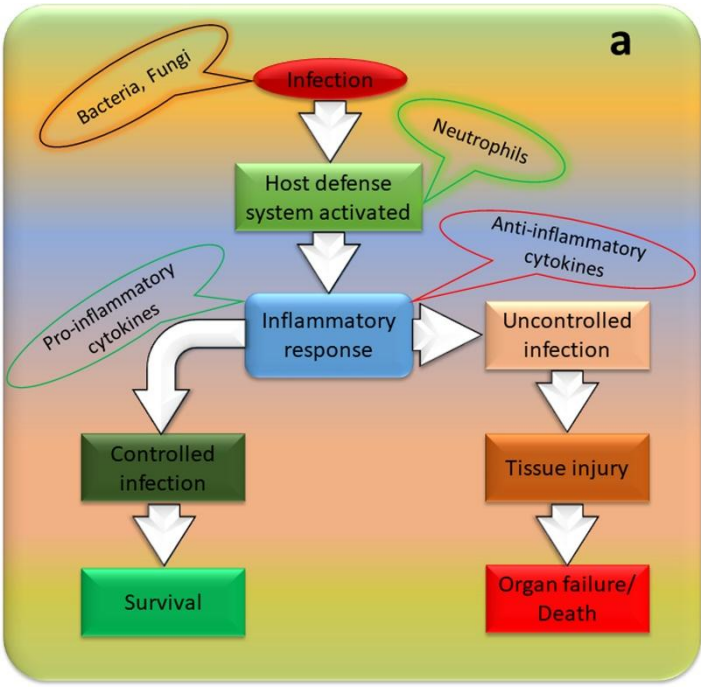

Figure 1. A schematic representation of pathophysiology of sepsis [15].

Causative Agents

Bacterial infections, found to be most common in sepsis, can trigger various chemical reactions; effecting lungs, urinary tract and abdominal area [2]. While, some are also found to be due to fungal infections or agent that may cause systemic inflammatory response syndrome (SIRS). The bacteria can be either gram-negative or gram-positive but majority, found be of gram-negative bacilli including *Eschericchia coli*, *Klebsiella Pneumonia*, *Enterobacter*, *Pseudomonas aeruginosa* etc. While, few of gram-positive bacteria includes *Streptococcus Pneumonia*, *Streptococcus pyogenes*, *Streptococcus aureus*, *Enterococcus* etc. While Candida, most frequent fungi which causes sepsis.

Table 1. Causative Agents of Sepsis (Gram-negative):

Bacterial agents	**Site of Infection**
Eschericchia coli	UTIs, prostatitis, and peritoneal infections
Klebsiella pneumonia	UTIs, prostatitis, and peritoneal infections
Enterobacter	UTIs
Pseudomonas aeruginosa	Infected burn wounds
Proteus	UTIs

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Bacteroidesfragilis	Peritoneal infections

Table 2. Causative Agents of Sepsis (Gram-positive):

Bacterial agents	**Site of Infection**
Streptococcus pneumonia	Pneumonia and meningitis
Streptococcus pyogenes	Skin and soft tissue infections
Staphylococcus aureus	Skin and soft tissue infections
Enterococcus	UTIs

Diagnosis

Diagnosis of sepsis requires a high index of suspicion, through physical examination, along with history of patients, laboratory investigation and close follows of the patient's hemodynamic state. Worldwide, variousprecautionarymethods have been practiced in hospitals, although, overall its mortality rate remains high; due to infection from various pathogens. Hence, it becomes an ultimate requirement to diagnose its inception, in early stages, in order to prevent from severity of such condition. Conventional methods, including blood culture reports, further, followed by molecular diagnostics technique, are multi-step analysis as well as time-consuming; hence carrying the main disadvantage. Due to critical and high mortality rate, it is necessary for immediate treatment of sepsis condition, in response to such drawbacks; lab-based diagnosis have been developed to facilitate better healthcare. A huge number of bio-sensors have been adapted for the diagnosis of sepsis using various biomarkers includingProcalcitonin (PCT), C - reactive protein (CRP), Tumor necrosis factor-alpha (TNF-α), and Cytokine biomarkers (IL-6 and IL-8), etc. [16] due to their high accuracy, specificity, sensitivity, and both positive and negative prognostic values [18]. On comparison with other biomarkers, procalcitonin (PCT) performance found to be superior in sepsis diagnosis [19]. Approved by FDA, PCT assay is commercially available for the assessment of developing severe sepsis in critically ill patients upon the first day to ICUs. As compared to other biomarkers. In the study of S. Gupta *et al.*, PCT considered as a most reliable as well as promising biomarker, hence accurately differentiate between culture-negative and culture-positive sepsis [21].

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Procalcitonin

Procalcitonin, and its cleavage products, discovered in 1975 while its structure briefly described by Le Moullec*et al.*, a peptide consisting of 116 amino acids; further cleaved to calcitonin [22,23], giving molecular weight of 14.5 kDa; produced in C-cells of thyroid cells (Figure.2). In normal state, less amount of PCT released in circulations, giving normal plasma PCT levels of approximately 5-50pg/mL [26]. It's centrally half-life in serum is approximately 22-33 hours.

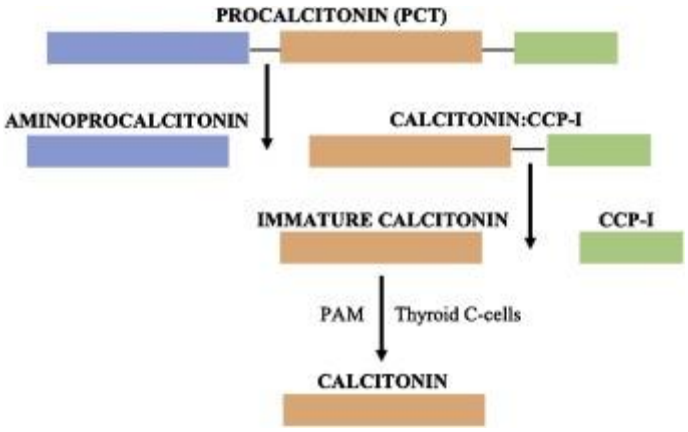

Figure 2. Schematic representation of PCT and calcitonin superfamily precursor molecules [25].

Procalcitonin is used as a diagnostic marker of sepsis condition; founds to be elevated in serum under such condition [24]. It has been proved to best marker for differentiating between bacterial and viral infection; mainly evaluating severe bacterial infection [24, 25]. PCT levels may not increase in local-infection condition, while its reaction is mainly observed if infection, further, followed by systemic inflammation response. The study of Assicot*et al.*, effectively differentiate pediatric patients suffering from sepsis than those of localized bacterial infection and also, from those suffers with viral infections [26]. Similarly, another study suggested that localized infection or infection without systematic inflammation may not or slightlyenhance PCT levels [27]. For supporting Assicot*et al.*, data, a study conducted by Gendrel et al, observed that PCT levels elevates in meningitis patients, infected from bacteria while its levels were not elevated in meningitis patients with viral infections [28]. Further, it was concluded that the decision scale for PCT guided antibiotic therapy with PCT to be as a decision marker [18].

PCT production in Sepsis

During severe systemic infections, PCT is probably released by extra-thyroid tissues while, during sepsis, itsexact site of production is still unknown/uncertain. This conclusion was

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based upon the patient's history of thyroidectomy; as they were still able to produce PCT during severe infection [26]. In human mononuclear leukocytes, PCT mRNA expression is stimulated by endotoxin and pro-inflammatory cytokines [29], indicating mononuclear cytokines are probable source of PCT in sepsis condition. As reported by Dandona*et al.*, PCT released into circulation in 4 hours after a single bolus release of endotoxins, released by bacteria [30]. After 6 hours, PCT levels hiked and remains at its peak level for nearly about 24 hours, a parallel conduct of TNF-α. Hence, these findings suggests that elevation in PCT is probably mediated by endotoxin and cytokines. The precise pathophysiology of PCT function and its secretion remains to be elucidated, also, it amplifies nitric oxide synthesis in vitro, similar to TNF-α manner and interferon-γ [31]. From the previous finding, PCT considers to be better as well as reliable marker for the diagnosis of sepsis condition.

Comparison of Procalcitonin with CRP

Previous studies suggested that PCT as a relevant marker as compared with other diagnostic markers such as C-reactive protein (CRP), lactate or others pro-inflammatory cytokines.It reports that PCT determines specificity, better sensitivity, positive predictive value, as well as negative predicted value on comparing with CRP values [32, 33].CRP concentration level in serum can be misleads and fail to the testing of severe sepsis. In the case of general infection or acute onset of sepsis, CRP level may be secretion in response to several type of stimuli, as in case of, various type of traumas or inflammation. After both, major or minor surgery, CRP level may be rise to >50mg/ml. However, in the both forms of sepsis; acute sepsis or severe sepsis, there may be similar type of moderate elevation of CRP (50- 100 mg/L or less). Such diagnoses may leads to inappropriate treatment which may result in fatal consequences. Various studies suggests, during sepsis, elevation of serum CRP levels may takes up to 1-2 weeks. On its contrary, PCT elevates during severity of sepsis and reaches its maximum in patients with septic shock, as studies suggested. In addition to this, PCT levels demonstrates significant results in sepsis and its related syndromes i.e. severe sepsis and septic shock. The study of Luzzani*et al*., suggested for PCT prediction, the receiver operation distinctive curve was 0.925 for PCT as compared with 0.677 for CRP [34]. As factors that enhance PCT levels are not due to infection itself but also the infection by severe systemic reactions. In addition, PCT levels reflects sepsisseverity and its outcomes whereas, levels of CRP was not always reflected. On such conclusions, PCT being mentioned as an indicator of systemic inflammation conditions such as sepsis, and severe sepsis .While CRP levels, during sepsis, can be considered for its diagnosis but due to its less reactivity and sensitivity cannot be

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describes as a reliable marker for such condition. On concluding, CRP is not considered to be a main prognostic marker in ICUs and for critically ill patients while PCT founds to be better and shows a close correlation with severity of infection and organ dysfunction.

Conclusion

Sepsis, due to severity and high mortality rate, considers to be a challenging situation in nowadays. Thus, it an urgent need to search methods which emphasize on its sensitivity and the speed of diagnosis, in early onset of disease. Various studies suggested many biomarkers for its diagnosis, out of which, PCT appears as aconsistent marker for diagnosing prognosis and severity of sepsis. On comparing with CRP, PCT shows maximum elevation in the sepsis patients and helpful in early diagnosis of such patients.

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