



Sepsis, Inflammation, Trauma and Emergency Medicine

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Abstract

Sepsis, a common condition encountered in hospital environments remains an important cause of death at intensive care units and emergency departments. A marked increase in serum procalcitonin as an important biomarker during the course of a septic process often indicates an exacerbation of the illness, and a decreasing level is a sign of improvement. Inflammation is an important area related to sepsis and trauma. A synergistic relationship can develop between the activation of the innate immune system and the loss of organ barrier functions. There are many complex factors such as genetic and physical agents, mediators and effectors involved in the development of organ failure both in trauma. These factors can lead to susceptibility of patients to post-traumatic organ failure. The patient's immune surveillance could fail to eliminate the pathogen, allowing it to spread and there is a pro-inflammatory mediator release with, inappropriate activation.

Keywords

Sepsis, Inflammation, Trauma and Emergency medicine

Introduction

Sepsis

The recently updated definitions of sepsis have moved away from the centrality of inflammation and the Systemic Inflammatory Response Syndrome (SIRS) criteria which have been shown to be non-specific. Sepsis is now defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection". The Quick (q) Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score is proposed as a surrogate for organ dysfunction and may act as a risk predictor for patients with known or suspected infection, as well as being a prompt for clinicians to consider the diagnosis of sepsis.

The authors of *The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)* reviewed and updated sepsis definitions, benefiting from the advances in understanding of the pathobiology which have occurred since the last revision [1]. Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the Systemic Inflammatory Response Syndrome (SIRS) criteria [1].

Thus, in an earlier study, sepsis, was defined as infection-induced Systemic Inflammatory Response Syndrome (SIRS) involves multiple mechanisms, including the release of cytokines, the activation of complement systems, coagulation systems and fibrinolytic systems [2].

Dysregulation of the hemostatic system due to the interaction between the coagulation system and the inflammatory response is a strong predictor of mortality in patients with severe sepsis [2]. Sepsis is the leading cause of mortality especially in non-cardiological critically ill patients with as many as 20 million annual cases of sepsis worldwide and a mortality rate of around 35% [3].

Sepsis and its complications have a significant and increasing impact on health sector, and are one of the leading causes of mortality. Endogenous immunoglobulin levels

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may have a different impact on the mortality risk of sepsis patients based on their severity. In patients with moderate organ failure, the simultaneous presence of low levels of IgG, IgA and IgM was a consistent predictor of both acute and post-acute mortalities [4].

The incidence of sepsis is increasing in all areas of the world. In general, sepsis occurs in approximately 2% of all hospitalizations in developed countries [5]. Severe sepsis is a common, frequently fatal, and expensive condition. Epidemiological studies indicate an incidence of severe sepsis approximately 751,000 sepsis cases per year in the United States. The influence of sepsis on expenses in the health care system is very large due to the requirements of staff access and multiple treatments [5].

Early prevention, antibiotics therapy, and combined treatments is important as discussed by Huanusied the concept of holistic integrative medicine [6].

Procalcitonin has been proved to be superior biomarker in terms of diagnosing sepsis and predicting clinical outcome and the use of procalcitonin should be considered within the context of the clinical workup including patient history, physical examination and other laboratory findings. Integrating use of procalcitonin into practice in the early golden hours of sepsis diagnosis and antibiotic stewardship program would be beneficial [7]. Advances in the understanding of the innate immune response could be potential therapeutic targets for sepsis since mechanisms involved in the clearance of pathogen toxin from the circulation and potential interventions could be aimed at enhancing clearance mechanisms [7].

Inflammation, innate immunity and neutrophils

Immunologic abnormalities can provoke multiple organ failure in severely injured patients and can manifests in two forms, which follow a biphasic pattern [8]. The first phase, in addition to the injury by trauma, organ damage is caused by the immune system during a systemic inflammatory response, In the second phase the patient is more susceptible for sepsis due to host defense failure or immune paralysis [8]. The innate immune system is an immunomonitor and has a very prominent role in organ failure after trauma. Polymorphonuclear phagocytes and monocytes are the main effector-cells of the innate immune system that are involved in organ failure and are controlled by cytokines, chemokines, complement factors and specific tissue signals major torso trauma can prime and activate Polymorphonuclear Neutrophils (PMNs) within 3 to 6 hours after injury and post-injury priming of PMNs may create an early vulnerable window during which a second event (e.g., a secondary operation or delayed hemorrhage) activates exuberant PMN cytotoxic superoxide anion O_2^- -release, rendering the injured patient at high risk for multiple organ failure [9].

Mortality, injury and cytokines

Mortality rate in sepsis remains high despite the current advances in medical science, technology and practice. Diagnosis should occur quickly and treatment is highly important in reducing the morbidity and mortality associated with sepsis. At-times the diagnostic uncertainty still remains high despite the available clinical information. Thus, a laboratory test with more specificity is essential.

The Surviving Sepsis Campaign developed an extensive database to assess the efficacy of the overall effect of its guidelines on clinical practice and patient outcome from January 2005 through March 2008, Data regarding the administration of recombinant human activated protein C in adult severe sepsis was evaluated [10].

The Surviving Sepsis Campaign developed guidelines for the administration of recombinant human activated protein C in adult severe sepsis. However, it is not clear how these impacted clinical practice or patient outcome The Surviving Sepsis Campaign goal was to develop an extensive database to assess the efficacy of the overall effect of its guidelines on clinical practice and patient outcome. Of patients with severe sepsis in the database, 1,009 of 15,022 (8%) received recombinant human activated protein C. Recombinant human activated protein C was administered within 24 hrs of the onset of sepsis in 76% (771 of 1009) of patients. Patients in North America (7.1%) and Europe (6.8%) were more likely to receive recombinant human activated protein C than patients in South America (4.2%, $p < 0.001$).

There was a statistically significant increase over time in the percentage compliance with the institution of a recombinant human activated protein C administration policy from the first, second, and eighth quarters and also a statistically significant increase in the actual administration rates of recombinant human activated protein C over the same timeline with administration rates of recombinant human activated protein C in the last quarter [10]. Thus, recombinant human activated protein C use was associated with a significant improvement in hospital mortality in patients who participated in the Surviving Sepsis Campaign [10]. Every clinician should be able to recognize the signs and symptoms of sepsis, along with early management strategies to expeditiously provide appropriate care and decrease resultant morbidity and mortality [10]. Troponin elevation in patients with sepsis confers poorer prognosis and is a predictor of mortality. However, further studies are needed to evaluate if more aggressive treatment of this subset of patients, or utilizing new therapeutic approaches will improve mortality [11].

Serum troponin concentrations have been examined,

including sepsis [11]. Left ventricular diastolic dysfunction and right ventricular dilatation are the echocardiographic variables correlating best with concomitant high-sensitivity troponin-T concentrations. Left ventricular diastolic and right ventricular systolic dysfunction seem to explain the association of troponin with mortality in severe sepsis and septic shock [11].

IL-7 has been shown to increase lymphocyte proliferation, expression of lymphocyte adhesion molecules, lymphocyte function-associated antigen 1 and very late antigen-4, interferon- γ production, and CD28 expression on splenic CD8+ T cells [12]. Combined treatment with IL-7 and anti-programmed cell death 1 antibody (anti-PD-1) produced additive effects on CD28 expression, lymphocyte proliferation, and splenic secretion of interferon- γ . Thus, there are differences in immunomodulatory actions between IL-7 and anti-PD-1, and provides a potential rationale for combining IL-7 and anti-PD-1 in the therapy of sepsis [12].

A recent multinational randomized controlled trial has also demonstrated the potential efficacy of this therapeutic agent for septic DIC [13]. Sepsis may be regarded as an uncontrolled inflammatory and procoagulant response to infection and the hemostatic changes in sepsis range from subclinical activation of blood coagulation to acute disseminated intravascular coagulation DIC [13]. A subgroup analyses of activated protein C, antithrombin, and thrombomodulin trials demonstrated that overt coagulation activation is strongly associated with the best therapeutic effect of the inhibitor and antiplatelet drugs, including acetylsalicylic acid, P2Y₁₂ inhibitors, and glycoprotein IIb/IIIa antagonists, may reduce organ failure and mortality in the experimental model of sepsis without a concomitant increased bleeding risk [13]. This area should be supported by solid clinical data and, the efficacy of anticoagulant and antiplatelet agents needs further large-scale prospective, interventional, randomized validation trials [13].

Trauma

Injury due to trauma can induce immune function changes, which can lead to both proinflammatory activation known as Systemic Inflammation Response Syndrome (SIRS) and an anti-inflammatory reaction with immunosuppression known as Compensatory Anti-inflammatory Response Syndrome (CARS). SIRS with proven infection is referred to as sepsis, however clinically it is often difficult to isolate the microbial inoculum, making the differential diagnosis between SIRS and sepsis difficult. This differential diagnosis is in turn crucial for further therapeutic decisions: is an antimicrobial therapy and aggressive search for a septic focus with all its side-effects necessary or is a focused symptomatic therapy of the SIRS the adequate treatment

concept? [13]. In multiple trauma situations, both syndromes can develop simultaneously, recently described as Mixed Antagonist Response Syndrome (MARS) [14].

The impact of trauma on neutrophil function was evaluated by Hazeldine [15]. With trauma-induced changes in neutrophil biology linked to the development of such post-traumatic complications as multiple organ failure and acute respiratory distress syndrome, an area of research within the field of trauma immunology that is gaining considerable interest is the manipulation of neutrophil function as a means by which to potentially improve patient outcome [15].

Neutrophils play an essential role in the body's innate immune response to infection. To protect the host, these phagocytic cells possess an impressive array of microbicidal weapons that can be brought to bear on an invading pathogen, including a variety of toxic oxygen radical species and proteolytic enzymes [16]. A three-stage development of SIRS was proposed as stage 1, a local production of cytokines in response to an injury or infection. Stage 2, the protective release of a small amount of cytokines into the circulation and stage 3 as the massive systemic reaction where cytokines become destructive by compromising the integrity of the capillary walls and flooding end organs [17].

Cytokines are generally viewed as a destructive development in the patient that generally leads to multiple organ dysfunction. However, cytokines also protect the body when localized and it will be necessary to study the positive effects of cytokines and their role in causing SIRS and to investigate the relationship between cytokines and their blockers in SIRS [17].

Measurements of Thioredoxin (Trx), Macrophage Migration Inhibitory Factor (MIF), IL-6, IL-8, IL-10 and Procalcitonin (PCT) in plasma from patients with SIRS/sepsis, neutropenic sepsis, healthy volunteers and Pre-oesophagectomy patients were evaluated [18]. Plasma levels of Trx, MIF, IL-6, -8, -10 and PCT were raised in patients with SIRS/sepsis. Comparisons between mediators suggested a unique correlation of Trx with MIF. Trx and MIF differed from cytokines and PCT in that levels were significantly lower in patients with neutropenia compared with the main SIRS/sepsis group. By contrast, IL-8 and PCT levels were significantly greater in the neutropenic patient group. The link between MIF and Trx highlighted in this study has implications for future investigations into the pathogenesis of SIRS/sepsis [18].

A recent clinical study reported the potential efficacy of supplement-dose antithrombin in septic Disseminated Intravascular Coagulation (DIC) and recombinant thrombomodulin has been newly developed and its efficacy for

DIC was reported. A recent multinational randomized controlled trial has also demonstrated the potential efficacy of this therapeutic agent for septic DIC [19].

Emergency department

The majority of trauma victims end-up being managed at least initially, in the Emergency Department (E.D) of health care facilities. This makes the E.D of any hospital a critical area in terms of assessment of quality of care [20]. The initial management of these patients is often challenging, requiring precise interpretation of symptoms and signs by specialized and experienced personnel, the utilization of high technology imaging modalities for accurate diagnosis, timely and appropriate resuscitation measures, frequent monitoring of response and timely consultation with the appropriate specialty [20]. The high death rate in this prior study is multifactorial. There is deficiency of trained manpower in trauma management; and the systemic deficiencies such as the lack of a trauma system, Pre-hospital care and intensive care facilities, are independent contributory factors. The factors responsible for late presentation at the definitive care center are multiple; and justify the fact that the public needs to be aware of the fact high speed and high velocity trauma of today's world is beyond the comprehension of alternative [20].

Conclusion

This paper has reviewed sepsis, and trauma and inflammation. A synergistic relationship can develop between the activation of the innate immune system and the loss of organ barrier functions. There are many complex of factors such as genetic and physical agents, mediators and effectors involved in the development of organ failure both in trauma. These factors can lead to susceptibility of patients to post-traumatic organ failure. Sepsis, a common condition encountered in hospital environments remains an important cause of death at intensive care units and emergency departments. A marked increase in serum procalcitonin during the course of a septic process often indicates an exacerbation of the illness, and a decreasing level is a sign of improvement. The patient's immune surveillance could fail to eliminate the pathogen, allowing it to spread and there is a pro-inflammatory mediator release with, inappropriate activation.

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