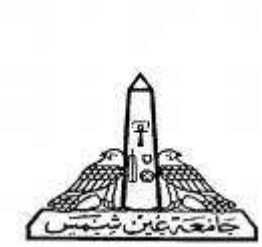

Recent Trends in the Treatment of Hemodynamic Derangement in Sepsis

An essay
Submitted for partial fulfillment of Master degree in pharmacology & therapeutics

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2011

الاتجاهات الحديثة فى علاج عدم انتظام ديناميكية الدم في حالات التقيح

مقال توطئة للحصول علي
درجة الماجستير في الأدوية و العلاج

مقدمه من

الطبيبة / ساره عادل احمد خضر

(بكالوريوس الطب و الجراحة) ٢٠٠٥

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Introduction

Sepsis is a critical problem with significant morbidity and mortality even in the modern era of critical care management. Multiple derangements exist in sepsis involving several different organs and systems, although controversies exist over their individual contribution to the disease process. Septic patients have substantial, life-threatening alterations. Despite intense efforts, sepsis remains a serious clinical problem, accounting for thousands of deaths every year ***(Remick, 2007).***

Systemic Inflammatory Response Syndrome (SIRS) is a response to wide variety of severe clinical insults as massive trauma, burns, pancreatitis, major surgery or infection and manifested by 2 or more of these criteria. The body temperature is more than 38°C or less than 36°C, and heart rate is above 90 beats per minute. Regarding the respiratory rate it is more than 20 breaths per minute or a need for mechanical ventilation. Lastly white blood cells greater than 12,000/mm3 or less than 4000/mm3 or more than 10% immature form ***(Khan and Salzman, 2007)***.

Sepsis is a serious medical condition that is characterized by a whole-body inflammatory state (SIRS) with the presence of a known or suspected infection. The 2001 International Sepsis Definitions Conference modified the model of SIRS, and developed the concept of a staging system for sepsis based on four separate characteristics represented by the acronym **PIRO**. **P** stands for the predisposition, indicating the pre-existing co-morbid conditions that would reduce survival. **I** stands for the insult or infection. **R** represents the response to the infectious challenge, including the development of SIRS. The last letter **O** stands for organ dysfunction and includes organ failure as well as the failure of different systems such as the coagulation system ***(Levy et al., 2003).***

Severe sepsis is sepsis associated with organ dysfunction which can be indicated by hypoperfusion leading to arterial hypoxia (partial pressure of oxygen (PaO2)/ inspired fraction of oxygen (FIO2) <300) or Hypoperfusion abnormalities such as lactic acidosis > 4 mmol/l, acute oliguria (urine output <0.5 ml/kg/h), or acute alteration in mental status. Increased ventilation requirements and increased creatinine >0.5 mg/dl indicate lung and kidney dysfunction. A rise in hepatic enzymes and hyperbilirubinemia (plasma total bilirubin >4mg/dl are detectable. Abnormal coagulopathiese (interntional normalization ratio (INR) >1.5 or partial thromboplastin (PTT)

>60s) and thrombocytopenia (platelet count <100,000/ml) are also indicators of organ dysfunction ***(Rivers et al., 2001).***

Septic shock is a subset of severe sepsis and defined as severe sepsis induced hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities; systolic blood pressure of <90 mm Hg, or a reduction of ≥ 40 mm Hg from baseline and mean arterial pressure (MAP) <65 mm ***(Remick, 2007).***

Sepsis is caused by bacterial infection that can begin anywhere in the body. The common places where an infection might start include the bowel which is usually seen with peritonitis and the kidneys with upper urinary tract infection. The liver and the gall bladder are one of the common places where infection may start. Additionally the lungs and the skin aren't spared. The lungs can be seen with bacterial pneumonia and the skin with cellulitis. Sepsis may also accompany meningitis. In children, sepsis may accompany infection of the bone (osteomyelitis). In addition, the common sites of infection in hospitalized patients include intravenous lines, surgical wounds, surgical drains, and sites of skin breakdown such as bedsores (decubitus ulcers) ***(Enrione and Powell, 2007)***.

Huge advances have been made in the field of sepsis in terms of pathophysiology, epidemiology, diagnosis, monitoring, and therapeutics. Despite these changes, mortality rates remain unacceptably high and continued progress, particularly in early and adequate treatment is urgently needed which will be discussed in this article.

AIM OF the WORK:

The aim of this work is to:

- Identify the nomenclature of sepsis.
- Identify the Pathophysiology of sepsis.
- Identify the Pathophysiology of hemodynamic derangement in sepsis.
- Review various experimental animal models in sepsis.
- Review new strategies in treatment of sepsis.
- Review new strategies in treatment of hemodynamic derangement in sepsis.

Pathophysiology

To understand the targets and mechanism of action of different pharmaceutics regimen in sepsis, we have to highlight the pathophysiology of sepsis and its hemodynamic derangement complication.

I. Pathophysiology of sepsis:

Severe sepsis is associated with 3 integrated responses, activation of coagulation with endothelial dysfunction, impairment of fibrinolysis, and activation of inflammation. These 3 responses are due to variety of proinflammatory mediators, procoagulant factors, and inhibitors of fibrinolysis. Understanding the pathophysiology of severe sepsis and the network of cascading events that occur is important for critical care ***(Kleinpell, 2003)*.**

Activation Of Coagulation and endothelial dysfunction:

Normal hemostasis exists as a finely tuned balance where the blood typically remains liquid to allow free flow within the vessels. During inflammatory situations such as sepsis,

significant alterations occur at multiple levels within both the coagulation system and the cells that regulate this system. Septic patients frequently manifest disseminated intravascular coagulation (DIC) with consumption of platelets and prolongation of clotting times ***(Esmon, 2006)***.

Abnormalities in the coagulation system resulting from systemic illnesses, which cause local disturbances in hemostasis and the thrombotic potential of patients, have been described since the time of Virchow. Virchow's classic triad consists of changes in coagulability, endothelial cell injury, and abnormal blood flow. In septic patients, all three of these classic alterations are present and result in reduced blood flow to vital organs. Septic patients frequently have poor tissue perfusion leading to inappropriate use of oxygen which results into cytopathic hypoxia ***(Fink, 2001).***

The extrinsic pathway is the main initial coagulation process involved in sepsis-induced DIC and stimulation of the intrinsic pathway can also occur in sepsis through feedback mechanisms. Endothelial and monocytes generation of tissue factor (TF) is activated by bacterial products and endotoxin. Activation of TF is counteracted by a specific tissue factor pathway inhibitor (TFPI). The potential for TFPI substitution to

inhibit the activation of the coagulation cascade in sepsis requires further study. Thrombin generation is inhibited by antithrombin III (AT III) and the protein C-protein S system ***(Zeerleder et al., 2005).***

During sepsis, AT III is consumed and degraded by elastase. Protein C is activated by thrombomodulin and, with its cofactor protein S, inhibits factors Va and VIII a. The free level of protein S depends on the level of the C4b binding protein (C4 bBP), an acute-phase complement regulatory protein. During sepsis, protein C activity is significantly reduced, either by acute consumption or by thrombomodulin down-regulation, and increased levels of plasma C4 bBP inhibit protein S ***(Fourrier et al., 2005).***

A state of enhanced coagulation occurs in sepsis not only through stimulation of the coagulation cascade but also through a reduction in the levels of protein C and AT III, which are components of the normal anticoagulation system. These events lead to attenuation in anticoagulant function, resulting in the generation of thrombin and a procoagulant state**.** Continued formation of thrombin leads to a prothrombotic tendency with formation of microthrombi, which can impair blood flow and organ perfusion ***(Aird, 2001)***.

DIC frequently occurs in the course of severe systemic diseases, of which Gram-negative sepsis is the best known example. DIC can be defined as an acquired syndrome characterized by the activation of intravascular coagulation up to the level of fibrin formation, accompanied by secondary fibrinolysis or inhibited fibrinolysis. Endotoxin is the bacterial component eliciting a cascade of tissue factor dependent hypercoagulable reactions mediated by cytokines, including tumor necrosis factor-α (TNF- α) and IL-6. The clinical features of DIC include spontaneous or induced bleeding complications thrombotic complications, whereas multiple organ failure may be a result of intravascular fibrin formation. In addition, the generation of multiple proteolytically active enzymes of the clotting cascade may enhance inflammatory activity, which may worsen the systemic inflammatory syndrome ***(Zeerleder et al., 2005).***

In addition, the altered hemostasis allows blood to clot when it should not, clogging blood vessels and reducing blood flow. Because the liver produces fixed quantities of procoagulant factors, and the bone marrow releases a defined number of white blood cells into the circulation, local effects modulate the systemic coagulopathy. In other words, although the coagulopathy is systemic, the bleeding typically occurs in