INTRODUCTION

Sepsis remains one of the leading causes of mortality in critically ill patients in the ICU. Over the last decade there has been a demonstrable significant reduction in mortality from severe sepsis and septic shock through the use of performance metrics and collaborative quality improvement efforts that facilitate the incorporation of the latest scientific and clinical advancements into bedside practice. As scientific knowledge and clinical expertise continue to grow as to the treatment of patients with sepsis, and new innovative technologies and approaches are developed, continued efforts must be made to translate this into improved patient care ***(Levision et al., 2011)***.

During sepsis, a wide array of endogenous humoral and cellular mediator systems are activated, including complement, coagulation and fibrinolytic systems, with the release of cytokines and lipid mediators such as eicosanoids, platelet-activating factor, and endothelin-1. The inflammatory response involves the activation of endothelial cells, platelets, macrophages, monocytes and neutrophils generating oxygen and nitrogen radicals. Also, the activation of sympathoadrenal axis (with increased level of norepinephine), the activation of rennin-angiotensin-aldosterone system (with increased level of angiotensin II), and increase in the vasopressin levels are often part of host response. These mechanisms largely responsible for the clinical manifestations of sepsis, finally lead to tissue

hypoxia, which represents the common pathway of organ dysfunction ***(Kotch et al., 2001)***.

Multiple Organ Dysfunction Syndrome (MODS) has been described as a “disease of medical progress" or the unwanted outcome of successful shock resuscitation. MODS refer to the presence of altered organ function in a severely ill patient, so that homeostasis cannot be maintained without Intervention. In the ICU, the incidence of single organ failure approaches 48%. The lung is the most common organ to develop obvious clinical failure, followed by the liver, kidney, gastrointestinal tract and cardiovascular system. The physiologic definition is severe acquired dysfunction of at least two organ systems lasting at least 24 to 48 hours in the setting of sepsis. Both the number of dysfunction organs and the duration of the dysfunction are critical to the condition. The mortality increases proportionally with number and duration of dysfunction ***(Irwin and Rippe, 2010)***.

The diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature of the signs and symptoms of sepsis. However, the early diagnosis and stratification of the severity of sepsis is very important, increasing the possibility of starting timely and specific treatment. Biomarkers can have an important place in this process because they can indicate the presence or absence or severity of sepsis, and can differentiate bacterial from viral and fungal infection and systemic sepsis from local infection. Other

potential uses of biomarkers include roles in prognosis, guiding antibiotic therapy, evaluating the response to therapy and recovery from sepsis, differentiating Gram-positive from Gram-negative microorganisms as the cause of sepsis, predicting sepsis complications and the development of organ dysfunction (heart, kidneys, liver or multiple organ dysfunction) ***(Pierrakos and Vincent, 2010).***

The past two decades have seen a remarkable growth in our understanding of sepsis and the complex interconnection of multiple biological pathways involved in septic process. Despite initial enthusiasm with "disease modifying agents", the early administration of appropriate antibiotics and early hemodynamic resuscitation remain the corner stone of the management of patients with sepsis.

This resuscitation of patients with sepsis should be based on the best current scientific evidence and coordinated by intensives with expertise in managing these complex patients ***(Marik, 2011)***.

Aim of the Work

This work aims to discuss pathophysiology, diagnosis and management of multiple organ failure resulting from sepsis for critically ill patients in intensive care units.

Chapter One
PATHOPHYSIOLOGY OF SEPSIS AND MODS

Sepsis is a complex condition starting from an infective stimulus and resulting in an exaggerated immune response. The inflammatory response that was initiated to fight the infection ultimately leads to damage of various organs throughout the body.

During the onset of sepsis, the inflammatory system becomes hyperactive, involving both cellular and humoral defense mechanisms. Endothelial and epithelial cells, as well as neutrophils, macrophages and lymphocytes produce powerful inflammatory mediators especially Tumor Necrosis Factor α (TNF-α), Interleukin-6 (IL-6), IL-1 and IL-8. Simultaneously, robust production of acute phase proteins such as C-reactive protein occurs, and humoral defence mechanisms such as the complement system are activated, resulting in production of pro-inflammatory mediators, including C5a, the complement split product. C5a ultimately enhances cytokine and chemokine production. Furthermore the coagulation system becomes activated through various mechanisms, often resulting in disseminated intravascular coagulopathy ***(Qureshi and Rajah, 2008)***.

The hallmarks of sepsis are excessive inflammation, excessive coagulation and suppression of fibrinolysis. In addition endogenous Activated Protein C (APC), which modulates coagulation, control inflammation and support fibrinolysis is also decreased. There is considerable variability in response which is almost certainly to a large degree genetically determined. Those with a tendency to produce excessive cytokines and TNF will have a greater inflammatory response. Simultaneously, the initial vascular damage result in neutrophil activation, neutrophil-endothelial cell adhesion, and further elaboration of inflammatory cytokines. In tissues already prone to dysfunctional oxygen uptake and metabolism, this vascular injury promotes further tissue hypoxia through regional hypoperfusion. This uncontrolled cascade of inflammation and coagulation fuels the progression of sepsis, resulting in tissue hypoxia and ischemia with resultant organ dysfunction and death ***(Qureshi and Rajah, 2008).***

Pro-inflammatory mediators facilitate inflammation by promoting endothelial cell-leukocyte adhesion, inducing the release of arachidonic acid metabolites and complement activation. In addition, pro-inflammatory mediators also promote coagulation by increasing tissue factors and membrane coagulants, inhibit anticoagulant activity by decreasing thrombomodulin and inhibit fibrinolysis. In contrast, anti-inflammatory mediators inhibit inflammation by inhibiting TNF-α, augmenting acute-phase reactants and immunoglobulins and

inhibiting T-lymphocyte and macrocyte functions. Anti-inflammatory mediators also inhibit activation of the coagulation system by cytokines. The anti-inflammatory response serves as a negative feedback mechanism to downregulate the synthesis of pro-inflammatory mediators and modulates their effects, thereby restoring homeostasis. SIRS is the result of an excessive pro-inflammatory response, whereas a Compensatory Anti-inflammatory Reaction (CARS) is the result of inappropriate immunosuppression. If an imbalance develops between SIRS and CARS, homeostasis is violated ***(Ramnath et al., 2006)***.

I- Definition of sepsis:

Two major consensus conferences have defined sepsis. The first, in 1992, put forth the concept of the Systemic Inflammatory Response Syndrome (SIRS), recognizing that lethally altered pathophysiology could be present without positive blood cultures. The SIRS criteria are represented by two or more of the following ***(Remick, 2007)***:

1) Body temperature > 38°C.
2) Heart rate > 90 beats per minute.
3) Respiratory rate >20 breaths per minute or arterial CO_2 tension less than 32 mmHg or a need for mechanical ventilation.
4) White blood count > 12,000/ mm^3 or > 10% immature forms.

Sepsis represents SIRS that has been induced by an infection. Severe sepsis is sepsis with dysfunction of a least one organ or organ system, and septic shock is severe sepsis with hypotension.

The 2001 International Sepsis Definitions Conference modified the model of SIRS and developed an expanded view of sepsis after revisiting the literature. This conference developed the concept of a staging system for sepsis based on four separate characteristics designated by the acronym PIRO. ***P*** stands for the Predisposition, indicating pre-existing co-morbid conditions that would reduce survival. ***I*** is the Insult or infection, which reflects the clinical knowledge that some pathogenic organisms are more lethal than others. ***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 a system such as the coagulation system ***(Remick, 2007)***.

II- Etiology of sepsis:

Although gram-negative bacteremia is commonly found in patients with sepsis, gram-positive infection may affect 30-40% of patients. Fungal, viral and parasitic infections are usually encountered in immunocompromised patients. Sources of bacteremia leading to sepsis include the urinary, respiratory, GI tracts, skin and soft tissues (including catheter sites). The source of bacteremia is unknown in 30% of patients.

Escherichia coli is the most frequently encountered gram-negative organism, followed by Klebsiella pneumoniae, Enterobacter aerogenes or cloacae, Serratia marcescens, Pseudomonas aeruginosa, Proteus mirabilis, Providencia, and Bacteroides species. Up to 16% of sepsis cases are polymicrobic. Gram-positive organisms, including methicillin-sensitive and methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis, are associated with catheter or line-related infections ***(Brenner, 2006)***.

III- Mechanism of sepsis:

A- Innate immunity and inflammation in early sepsis:

Host defenses can be categorized according to innate and adaptive immune system responses. The innate immune system responds rapidly by means of pattern-recognition receptors [e.g. Toll-Like Receptors (TLRs)] that interact with highly conserved molecules present in microorganisms. For example, TLR-2 recognizes a peptidoglycan of gram-positive bacteria, whereas TLR-4 recognizes a lipopolysaccharide of gram-negative bacteria. Binding of TLRs to epitopes on microorganisms stimulates intracellular signaling, increasing transcription of pro-inflammatory molecules such as Tumor Necrosis Factor α (TNF-α) and interleukin-1β, as well as anti-inflammatory cytokines such as interleukin-10. Pro-inflammatory cytokines up-regulate adhesion molecules in neutrophils and endothelial cells. Although activated neutrophils kill microorganisms, they also injure

endothelium by releasing mediators that increase vascular permeability, leading to the flow of protein- rich edema fluid into lung and other tissues. In addition, activated endothelial cells release nitric oxide, a potent vasodilator that acts as a key mediator of septic shock ***(Russell, 2006)***.

B- Specific and amplification of the immune response by adaptive immunity:

Microorganisms stimulate specific humoral and cell-mediated adaptive immune responses that amplify innate immunity. B cells release immunoglobulins that bind to microorganisms, facilitating their delivery by antigen-presenting cells to natural killer cells and neutrophils that can kill the microorganisms. T-cell subgroups are modified in sepsis. Helper (CD_4^+) T cells can be categorized as type 1 helper (Th1) or type 2 helper (Th2) cells. Th_1 cells generally secrete pro-inflammatory cytokines such as TNF-α and interleukin-1β and Th_2 cells secrete anti-inflammatory cytokines such as interleukin-4 and interleukin-10, depending on the infecting organism, the burden of infection, and other factors ***(Russell, 2006)***.

C- Aberrant mediator production:

The inflammatory response represents an important, central component of sepsis because elements of the response drive the physiological alterations that become manifest as the

systemic inflammatory response syndrome. An appropriate inflammatory response eliminates the invading microorganisms without causing damage to tissues, organs, or other systems ***(Remick, 2007)***.

1- Hyper inflammatory response.

2- Blunted inflammatory response.

3- Unknown inflammatory response.

1- Hyperinflammatory response:

Several years ago, many basic science investigators and clinicians believed that the problem of sepsis was directly related to the exuberant production of pro-inflammatory molecules. The problem seemed rather simple: inflammation was excessive. The solution was easy: blunt inflammation, and save lives. This concept was driven by four pieces of information. First, septic patients with increased levels of specific mediators such as Tumor Necrosis Factor (TNF) are at increased risk for death. Second, injection of TNF molecules into experimental animals results in widespread inflammatory alterations and tissue injury similar to that observed in septic patients. Third, experimental animals injected with lethal doses of endotoxin display elevated levels of the same mediators. Finally, inhibition of these specific mediators improves survival in endotoxin shock models. Together, these observations launched a series of clinical trials aimed at blocking TNF or

Interleukin (IL)-1. The results of these clinical trials are not satisfactory ***(Osuchowski et al., 2006)***.

2- Blunted inflammatory response:

Another viewpoint would argue that septic patients failed to control the bacterial infection and died as a result of immunosuppression rather than immunostimulation. Recent work has shown that intensive care unit patients have reduced production of both TNF and IL-6 in response to endotoxin stimulation. Another study demonstrated that although TNF was reduced, IL-10 production was not impaired in patients with sepsis. These studies would indicate that the pro-inflammatory response could not be initiated, whereas the anti-inflammatory response continued unabated, producing the equivalent of a blunted inflammatory response. Patients with severe burns and sepsis exhibit defects in their T lymphocytes because the cells fail to proliferate in response to mitogenic stimuli and also fail to produce IL-2 or IL-12. Because blocking the inflammatory response with specific inhibitors was not tremendously effective, the possibility was raised that the patients required immunostimulation ***(Orozco et al., 2006)***.

3- Unknown inflammatory response:

The previous data would indicate that the inflammatory response in septic patients is complex and not as neatly defined as enhanced or decreased. Because of this heterogenous

response, some patients will benefit from blunting their inflammation, whereas others would be better served by augmenting their inflammatory response. Tailoring the therapy to the individual patient occurs with many diseases, and sepsis should not be an exception ***(Knight et al., 2004)***.

D- Cellular dysfunction:

Many cellular aspects become dysfunctional in sepsis and may be characterized as either excessive activation or depressed function. Excessive activation refers to cells that are primed such that they respond in a very vigorous manner to a second stimulus. An example of excessive activation would be neutrophils generating excess toxic products that cause damage to nearby cells. An example of depressed function would be neutrophils failure to phagocytose and clear invading pathogens. One of the current areas of active investigation concerning cellular function is the induction of cellular apoptosis or necrosis. The signaling mechanisms and molecules that induce apoptosis are currently being described in great detail by a number of investigators. Apoptosis and necrosis in the field of sepsis have been reviewed quite nicely in the recent past. Apoptosis may contribute to the pathogenesis of sepsis by delayed removal of those cells that should be removed, i.e, neutrophils, and early removal of those cells that should not be removed i.e. lymphocytes ***(Remick, 2007)***.

1- Lymphocyte apoptosis

2- Anergy.

3- Neutrophils hyperactivity.

4- Endothelial cell failure and apoptosis in other cells.

1- Lymphocyte apoptosis:

Lymphocytes are critical cells in the response to sepsis, and the interactions between the innate and adaptive immune system are becoming increasingly important. Pioneering studies have defined that septic patients have significant apoptosis of lymphocytes. These apoptotic lymphocytes were observed in virtually all lymphoid organs including the obvious locations, such as the spleen and thymus, but also in the gastric associated lymphatic tissue and essentially wherever collections lymphocytes exist. In septic patients, there is a combination of apoptotic and necrotic cell death. The importance of apoptosis in the pathophysiology of sepsis has been demonstrated in multiple studies ***(Wesche et al., 2005)***.

2- Anergy:

Anergy is a state of non-responsiveness to antigen. T cells are anergic when they fail to proliferate or secrete cytokines in response to their specific antigens. T-cell function was examined in patients with peritonitis and found that they had decreased Th1 function without increased Th2 cytokine production, which is consistent with anergy. Defective T-cell proliferation and cytokine secretion correlated with mortality.

Patients with trauma or burns have reduced levels of circulating T cells, and their surviving T cells are anergic ***(Hotchkiss and Karl, 2003)***.

3- Neutrophil hyperactivity:

Neutrophils are critical components of the innate immune response to infectious challenges. Neutropenic patients, regardless of the cause of the neutropenia, and patients with neutrophil dysfunction are at increased risk for the development of infectious complications. There is no question that an appropriate, robust neutrophil response benefits the patient and helps to eradicate an infectious focus. The difficulty lies in attempting to define an appropriate response versus a hyperactive response. Significant issue concerns inappropriate apoptosis of neutrophils in the septic patients. Neutrophils in the circulation typically have a very short lifespan of approximately 24 hours. However, patients with sepsis have a delay in their neutrophil apoptosis, causing them to persist longer in the bloodstream. This is due to prolonged activation of nuclear factor B and reduced caspase 3 levels. As a result, the septic patient has increased numbers of activated cells with the potential to cause organ injury.

However, it must be borne in mind that these activated neutrophils are also the precise defenders that are critical in the innate immune response to clear an infection ***(Brown et al., 2006)***.