INTRODUCTION

Sepsis is a clinical syndrome characterized by systemic inflammation and widespread tissue injury due to infection. There is a continuum of illness severity ranging from sepsis to severe sepsis and septic shock. When infection is absent, the clinical syndrome is termed systemic inflammatory response syndrome (SIRS) **(Angus et al, 2001)**

Risk of septicemia in the nonwhite population is almost twice that of the white population, with the highest risk to black men**. (Laurie,2010)**

Epidemiologic data have shown that the age-adjusted incidence and mortality of septic shock is consistently greater in men. A strong correlation exists between advanced age and the incidence and mortality of septic shock, with a sharp increase in the number of cases in patients older than 50 years. (**Shapiro et al, 2006)**

Sepsis is a disease seen most frequently in elderly persons and in those with comorbid conditions that predispose to infection, such as diabetes or any immunocompromising disease. The latter are at particularly high risk, including those with cancer on chemotherapeutic agents, those with end-stage renal or liver disease, those with advanced HIV, or those on steroids for any other immunocompromising agent for chronic conditions. Patients with indwelling catheters or devices are also at high risk. The pathophysiology of septic shock involves a complex interaction between the pathogen and the host's immune system. As a result of these interactions, immune cellular activation occurs with the release of cytokine and noncytokine mediators.**(Michael, 2010)**

The following systems and mediators are activated in septic shock: Arachidonic acid metabolites (e.g., leukotrienes, prostaglandins, thromboxanes).Complement system,IL-1, IL-6, TNF-alpha - Released by mast cells; activate diffuse inflammatory response.Coagulation cascade - Contributes to micro thrombi and end-organ damage, Catecholamines - Stress hormones that counteract hypotension, Glucocorticoids - Stress hormones that augment vascular tone, Bradykinin - Contributes to vascular leak, Histamines - Released by mast cells; vasodilatory properties**. (Rivers et al ,2006)**

Procalcitonin, the precursor molecule of calcitonin is up regulated in severe bacterial infections and sepsis. Serial procalcitonin measurements have recently been shown to allow a safe reduction in the duration of antibiotic therapy in patients with severe sepsis and septic shock**. (Megan, 2009)**

The enzyme sphingosine kinase 1 (SphK1) is up-regulated in stimulated human phagocytes and in peritoneal phagocytes of patients with severe sepsis. Blockade of SphK1 inhibited phagocyte production of endotoxin-induced proinflammatory cytokines. Protection against sepsis in mice treated with a specific SphK1 inhibitor that was enhanced by treatment with a broad-spectrum antibiotic. These results demonstrated a critical role for SphK1 in endotoxin signaling and sepsis-induced inflammatory responses and suggest that inhibition of SphK1 is a potential therapy for septic shock. ***(Padmam et.al 2010)***

Acute respiratory distress syndrome (ARDS) is a major complication of sepsis and septic shock. The incidence of ARDS in septic shock is anywhere from 20-40%, occurring more frequently when a pulmonary source of infection exists.Other complications of septic shock include renal dysfunction, disseminated intravascular coagulation (DIC), mesenteric ischemia, myocardial ischemia and dysfunction, and other complications related to prolonged hypotension and organ dysfunction. The

mortality rate of sepsis varies widely based on factors such as severity of illness upon hospital presentation, patient's age and comorbid conditions, nature of infection, and infecting organism. The mortality rate for severe sepsis is quoted as anywhere between 30% and 50%. Resuscitation to correct hypoxia, hypotension and impaired tissue oxygenation. Identify source of infection and treat to include antimicrobials and/or surgery.Maintain organ system function and halt the development of multiorgan dysfunction. Studies have shown that appropriate antibiotic administration (i.e., antibiotics that are effective against the organism that is ultimately identified) has a significant influence on mortality. For this reason, initiating broad-spectrum coverage until the specific organism is cultured and antibiotic sensitivities are determined is important.**(Michael, 2010)**

Adult patients with severe sepsis or septic shock should receive (EGDT)-Early Goal Directed Therapy- or standard therapy upon presentation and for initial 6 hours.**(Emanuel,*2010)***

Aggressive fluid resuscitation the other areas of management addressed include:Antibiotic therapy and infection source control, Stress-dose and low dose corticosteroids, Glycemic control, Vasopressors and inotropes and Mechanical ventilation.**(Gregory et al 2010)**

Activated protein C (APC) is an endogenous protein that modulates inflammation and coagulation. Specifically, it inhibits TNF-alpha, IL-1, and IL-6, the mediators thought to play a major role in initiating the inflammatory response seen in sepsis. In addition, it inhibits monocyte and neutrophil adhesion to endothelial cells, and it inhibits thrombin and fibrin production, and thus prevents microvascular thrombi. APC levels have been shown to be low in sepsis, **(Henry et al, 2009)**

Polymyxin B hemoperfusion significantly improved hemodynamics and organ dysfunction, and reduced 28-day mortality rate in severe sepsis or septic shock when added to conventional therapy. This is an example of a novel therapy that targets the pathophysiology of septic shock, similar to APC, and which may become more widespread in the future. **(Cruz et al, 2009)**

Melatonin: in a number of animal models of septic shock, as well as in patients with septic disease, melatonin reportedly exerts beneficial effects to arrest cellular damage and multiorgan failure. (**Srinivasan et al, 2010)**

In the monoclonal immunoglobulin trials, anti-endotoxin antibodies showed no benefit while the anti-cytokines showed a very small reduction in deaths among adults with sepsis. The polyclonal immunoglobulin trials were small compared to the trials of monoclonal preparations. The reduction in deaths observed with polyclonal preparations needs to be confirmed in large studies that use high quality methods. (**Alejandria et al, 2010)**

Pilot Study of Bevacizumab (Avastin) in Patients with Septic Shock: a role for Bevacizumab in treating patients with severe sepsis. There are several advantages in employing Bevacizumab as a lead agent for inhibiting VEGF signaling in patients with severe sepsis. **(Nathan, 2010)**