INTRODUCTION

Sepsis is a clinical syndrome characterized by systemic inflammation and widespread tissue injury due to infection. There is a degrees of illness severity ranging from sepsis to severe sepsis and septic shock ***(Gaurav et al., 2010).***

Severe sepsis and septic shock develop when infectious agents or induced inflammatory mediators lead to circulatory abnormalities including peripheral vasodilatation, reduced mean arterial pressure, myocardial depression, and intravascular volume depletion .Despite adequate fluid resuscitation, maldistribution of blood flow may cause an imbalance between oxygen delivery and demand, leading to global tissue hypoxia, shock, and, if not reversed, death ***(Levy et al., 2010).***

The timely administration of appropriate I.V. antimicrobial therapy is a crucial step in the care of patients with severe sepsis who may require surgery to control the source of sepsis. preopertive resuscitation, aimed at optimizing major organ perfusion, is based on judicious use of fluids, vasopressors and inotropes. Intraopertive anesthesia management requires careful induction and maintenance of anesthesia, optimizing intravascular volume status, avoidance of lung injury during mechanical ventilation and ongoing monitoring of artial blood gases, lactate concentration, hematological and renal indices, and electrolyte levels ***(Russell et al., 2009).***

Postoperative care overlaps with ongoing management of severe sepsis syndrome for patient in intensive care unit .These patients are by definition, high risk, already requiring multiple supports, and require experience and skillful decision-making to optimize their chances of a favorable outcome ***(Sharma, 2007).***

Similar to acute myocardial infarction, stroke, or acute trauma, the initial hours (golden hours) of clinical management of severe sepsis represent an important opportunity to reduce morbidity and mortality. Rapid clinical assessment, resuscitation and surgical management by a focused multidisciplinary team, and early effective antimicrobial therapy are the key components to improved patient outcome ***(Kumar, 2009).***

AIM OF THE WORK

In this study, we aim to delineate the updates in anesthetic management in septic shock to face the difficulties in patients suffering from septic shock and undergoing surgical interference .

EPIDEMIOLOGY OF SEPSIS & SEPTIC SHOCK

Sepsis is a systemic inflammatory response to infection. If the systemic inflammatory response is not caused by an infection (i.e. pancreatitis, ischemia or trauma), it is referred to as systemic inflammatory response syndrome SIRS. Two or more of the following are present in sepsis and SIRS:

- Temperature > 38 OR <36 degrees Celsius
- Heart rate > 90 bpm
- Respiratory rate > 20 breaths/minute OR PaCO2 < 32 mm Hg
- White blood cell count > 12,000/mm3 OR < 4,000/mm3 OR > 10% immature (band) form ***(Dillinger and Carlet, 2004).***

Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Sepsis induced hypotension is defined as a systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure <70 mm Hg or a SBP decrease >40 mm Hg in the absence of other causes of hypotension. Severe sepsis is a complex and often life-threatening condition. It can affect anyone but often develops in patients with pneumonia, trauma, surgery, burns or cancer. Severe sepsis results in the hospitalization of more than 750,000 patients each year in the United States ***(Marsh et al., 2006).***

Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, requiring vasopressor administration. Septic shock patients are very ill and need rapid emergency admission to the hospital intensive care unit ("ICU"). Despite active treatment in the ICU, the death rate is around 50%.Sepsis has risen to the 10th leading cause of death in United State ***(Martin et al., 2003).***

Causes of SIRS

SIRS may have infective and non-infective causes (Table1). However the word sepsis is commonly used in place of SIRS and both terms are considered interchangeable. Infections are common and amenable to treatment; therefore, in patients presenting with clinical signs of systemic inflammation (SIRS), an infective cause should be actively thought. Community-acquired infections in previously well patients are easier to recognize than nosocomial infections in debilitated hospitalized patients. Infections leading to sepsis include central nervous system (CNS) infections, for example, meningitis or encephalitis, cardiovascular infections (e.g. infective endocarditis), respiratory infections (e.g. pneumonia), gastrointestinal infections (e.g. peritonitis), or urinary tract infections (e.g. pyelonephritis). Although bacterial infections are the most common infective cause, viruses and fungi can also cause septic shock. Non-infective causes include; severe trauma or haemorrhage and acute systemic disease, pulmonary embolus, and acute pancreatitis ***(Rivers et al., 2001).***

Table (1): Causes of SIRS ***(Rivers et al., 2001).***

Infective causes	Non infective causes
CNS infections	Severe trauma
CVS infections	Haemorrhage
Respiratory infections	Complication of surgery
Renal infections	Complicated aortic aneurysm
GIT infections	Pulmonary embolism
Skin and soft tissue infections	Subarachnoid haemorrhage
Bone and joint infections	Burns
	Acute pancreatitis
	Drug overdose/toxicity

Causative organisms

Gram-negative organisms account for most adult cases of septic shock. In the hospitalized patient, the most common gram-negative organisms are E. Coli, Klebsiella, Enterobacter and Pseudomonas aeruginosa ***(Khwannimit and Bhurayanontachai, 2009)***

Gram-positive organisms are becoming increasingly associated with sepsis due to the use of intravenous catheters and invasive devices. The most common gram-positive organisms seen are the Staphylococcus and Streptococcus species as well as Pneumococcus and Enterococcus fecalis. Viruses, protozoa, parasites, fungi (i.e. Candida albicans) and anerobic organisms (i.e. Clostridium, Bacteroidesfragilis) are also known to be associated with sepsis ***(levi et al., 2003).***

Predisposing factors for developing sepsis and septic shock include: extremes of age,granulocytopenia, prior antibiotic therapy, severe burn injury, recent trauma, recent surgery and/or invasive procedures ,immunosuppression, malnutrition and total parenteral nutrition ,alcohol and drugs of abuse, prolonged ICU stay, *especially* endotracheal intubation > 48 hours and ventilator-associated pneumonia ***(Dombrovskiy et al., 2007).***

Epidemiology

- Severe sepsis and septic shock are major healthcare problems with a reported incidence of 66–132 per 100 000 population in the USA and UK, respectively ***(Harrison et al., 2006).***

- Severe sepsis occurs in 1–2% of all hospital patients and accounts for as much as 25% of intensive care unit (ICU) bed utilization. It is common in elderly, immune compromised, and critically ill patients and is a major cause of death in ICUs worldwide. Sepsis is the second leading cause of death in non-coronary ICU patients. Mortality rate remains high at 30–50% despite improved care the past 10–15 years ***(Martin et al, 2003).***

- Sepsis is the tenth leading cause of death in the United States and accounts for more than 17 billion dollars in direct healthcare expenditures ***(Angus et al, 2001).***

- A primary site of infection cannot be established in 10% of patients with severe sepsis ***(Harrison et al., 2006).***

PATHOPHYSIOLOGICAL CONSIDERATIONS

The pathophysiology of septic shock is not precisely understood but is considered to involve a complex interaction between the pathogen and the host's immune system(figure1) . The normal physiologic response to localized infection includes activation of host defense mechanisms that result in the influx of activated neutrophils and monocytes, release of inflammatory mediators, local vasodilation, increased endothelial permeability, and activation of coagulation pathways ***(Crea and Biasucci, 2012).***

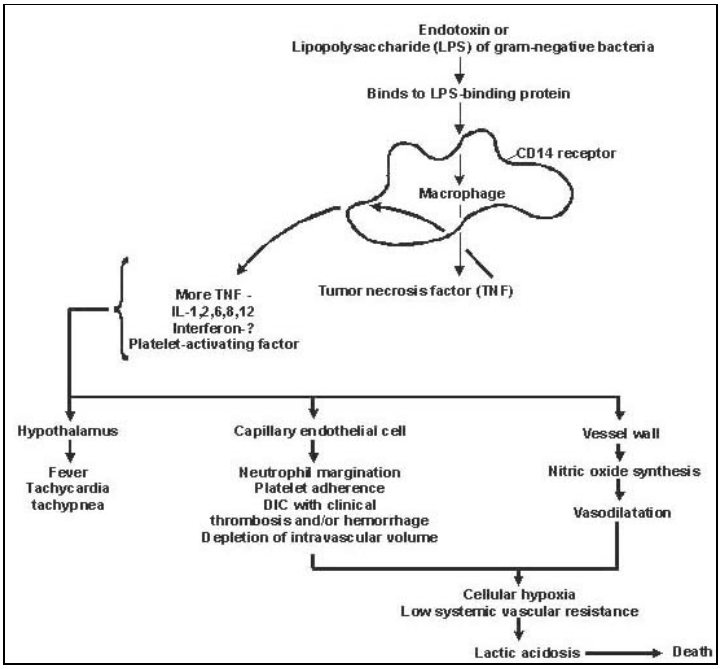

Figure (1): Diagram depicting the pathogenesis of sepsis and multiorgan failure ***(Crea and Biasucci, 2012).***

These response mechanisms occur during septic shock, but on a systemic scale, leading to diffuse endothelial disruption, vascular permeability, vasodilation, and thrombosis of end-organ capillaries Endothelial damage itself can further activate inflammatory and coagulation cascades, creating, in effect, a positive feedback loop and leading to further endothelial and end-organ damage***(Moore et al., 2012).***

Mediator-induced cellular injury

The evidence that sepsis results from an exaggerated systemic inflammatory response induced by infecting organisms is compelling. Inflammatory mediators are the key players in the pathogenesis of sepsis ***(Cinel and Opal, 2009).***

Table (2): Mediators of Sepsis ***(Sharma, 2007).***

Type	Mediator	Activity
Cellular mediators	Lipopolysaccharie	Activation of macrophages, neutrophils, platelets, and endothelium releases various cytokines and other mediators
	Lipoteichoic acid	
	Peptidoglycan	
	Superantigens	
	Endotoxin	
Humoral mediators	Cytokines	Potent inflammatory effect
	TNF-alpha and IL1 IL-8 IL-6 IL-10	Neutrophil chemotactic factor
	G-CSF	Acts as pyrogen, stimulates B and T lymphocyte proliferation, inhibits cytokine production, induces immunosuppression
	Complement	Activation and degranulation of neutrophils
	Nitric oxide	Cytotoxic, augments vascular permeability, contributes to shock
	Lipid mediators PhospholipaseA2 Eicosanoids	Involved in hemodynamic alterations of septic shock Promote neutrophil and macrophage, platelet activation and chemotaxis, other proinflammatory effects
	Arachidonic acid metabolites	Enhance vascular permeability and contributes to lung injury
	Adhesion molecules Selectins Leukocyte integrins	Enhance neutrophil-endothelial cell interaction, regulate leukocyte migration and adhesion, and play a role in pathogenesis of sepsis

Immunologic abnormalities

The following 3 families of pattern recognition receptors are involved in the initiation of the sepsis response:

- Toll-like receptors (TLRs)
- Nucleotide-oligomerization domain leucine-rich repeat proteins
- Cytoplasmic caspase and recruiting domain helicases

These receptors trigger the innate immune response and modulate the adaptive immune response to infection ***(Cinel (Cinel and Opal, 2009).***

An initial step in the activation of innate immunity is the de novo synthesis of small polypeptides (cytokines) that induce variable manifestations on most cell types, from immune effector cells to vascular smooth muscle and parenchymal cells. Several cytokines are induced, including tumor necrosis factor (TNF) and interleukins (ILs), especially IL-1. These factors help keep infections localized; however, once the infection progresses, the effects can also be detrimental ***(Solomkin et al., 2010).***

Circulating levels of IL-6 have a strong realation with outcome. High levels of IL-6 are associated with mortality, but the role of this cytokine in pathogenesis is not clear. IL-8 is an important regulator of neutrophil function, synthesized and released in significant amounts during sepsis. IL-8 contributes to the lung injury and dysfunction of other organs ***(Ward.,2002).***

Chemokines (eg, monocyte chemoattractant protein [MCP]-1) orchestrate the migration of leukocytes during

endotoxemia and sepsis. Other cytokines thought to play a role in sepsis include the following:

- IL-10
- Interferon gamma
- IL-12
- Macrophage migration inhibition factor (MIF or MMIF)
- Granulocyte colony-stimulating factor (G-CSF)
- Granulocyte macrophage colony-stimulating factor (GM-CSF)

In addition, cytokines activate the coagulation pathway, resulting in capillary microthrombi and end-organ ischemia ***(Hotchkiss and Karl, 2003).***

Gram-positive and gram-negative bacteria induce a variety of proinflammatory mediators, including the cytokines mentioned above, which play an important role in initiating sepsis and shock. Various bacterial cell-wall components are known to release the cytokines, including lipopolysaccharide (LPS; gram-negative bacteria), peptidoglycan (gram-positive and gram-negative bacteria), and lipoteichoic acid (gram-positive bacteria) ***(Opal, 2003).***

Several of the harmful effects of bacteria are mediated by proinflammatory cytokines induced in host cells (macrophages/monocytes and neutrophils) by the bacterial cell-

wall component. The most toxic component of gram-negative bacteria is the lipid moiety of LPS, which leads to cytokine induction via lipoteichoic acid. Additionally, gram-positive bacteria may secrete superantigencytotoxins that bind directly to the major histocompatibility complex (MHC) molecules and T-cell receptors, leading to massive cytokine production ***(Hotchkiss and Karl, 2003).***

The complement system is activated and contributes to the clearance of the infecting microorganisms but probably also enhances the tissue damage. The contact systems become activated; consequently, bradykinin is generated ***(Nguyen et al., 2006).***

Hypotension, the cardinal manifestation of sepsis, occurs via induction of nitric oxide (NO). NO plays a major role in the hemodynamic alterations of septic shock, which is a hyperdynamic form of shock ***(Landry and Oliver et al., 2001).***

In a study that evaluated the role of active nitrogen molecules in the progression of septic shock, investigators found not only that patients with sepsis and septic shock had elevated mean levels of nitrite (NO_2)/nitrate (NO_3) (sepsis, 78.92 μmol/L; septic shock, 97.20 μmol/L) as well as TNF-α (sepsis, 213.50 pg/mL; septic shock, 227.38 pg/mL) but also that levels of these 3 mediators increased with the severity of the sepsis ***(Kothari et al., 2012).***

Another factor that contributes to the poor cellular oxygen utilization and tissue organ dysfunction during sepsis is mitochondrial dysfunction. This is associated with excessive generation of peroxynitrates and reactive oxygen species (ROS) in combination with glutathione depletion ***(Crouser, 2004).***

A dual role exists for neutrophils: They are necessary for defense against microorganisms, but they may also become toxic inflammatory mediators, thereby contributing to tissue damage and organ dysfunction. Lipid mediators—eicosanoids, platelet-activating factor (PAF), and phospholipase A2—are generated during sepsis, but their contributions to the sepsis syndrome remain to be established ***(Hotchkiss et al., 2013).***

Neutrophils are constitutively proapoptotic, a capacity that is essential for the resolution of inflammation and cell turnover. Poor apoptosis is associated with poor cell clearance and a proinflammatory state ***(Brown et al., 2006).***

There is a growing body of evidence regarding sepsis-induced immunosuppression, which may culminate in a worse prognosis and a greater predisposition to other nosocomial infections. In addition, there is evidence that patients with sepsis who have previously been infected with cytomegalovirus may have worse outcomes than those who have not. That cytomegalovirus infection can also cause immunomodulation which may be another factor contributing to sepsis-induced immunosuppression ***(Kalil and Florescu, 2009).***

Multiorgan dysfunction syndrome (MODS):

Sepsis is described as an auto destructive process that permits the extension of the normal pathophysiologic response to infection (involving otherwise normal tissues), resulting in MODS. Organ dysfunction or organ failure may be the first clinical sign of sepsis, and no organ system is immune to the consequences of the inflammatory excesses of sepsis ***(Marsh et al., 2006).***

The precise mechanisms of cell injury and resulting organ dysfunction in patients with sepsis are not fully understood. MODS is associated with widespread endothelial and parenchymal cell injury occurring via the following proposed mechanisms ***(Matsuda and Hattori, 2006).***

Hypoxic hypoxia – The septic circulatory lesion disrupts tissue oxygenation, alters the metabolic regulation of tissue oxygen delivery, and contributes to organ dysfunction; microvascular and endothelial abnormalities contribute to the septic microcirculatory defect in sepsis; ROS, lytic enzymes, vasoactive substances (e.g., NO), and endothelial growth factors lead to microcirculatory injury, which is compounded by the inability of the erythrocytes to navigate the septic microcirculation ***(Gustot, 2011).***

- **Apoptosis** (programmed cell death) – This is the principal mechanism by which dysfunctional cells are normally eliminated; the proinflammatory cytokines may delay