INTRODUCTION

Septic shock is a frequently occurring disease that is associated with high mortality and morbidity, Although extensive research and clinical efforts are continually being made to reduce the morbidity and mortality associated with severe pediatric sepsis, no published information exists about the potential variation that might occur in outcomes and resource utilization across different acute care settings ***(Folafoluwa et al., 2007).***

Shock is an acute complex state of circulatory dysfunction resulting in failure to deliver oxygen and nutrients to meet the metabolic demands which are usually increased during shock. If left untreated, multiple organ failure and ultimately death will occur ***(Smith et al., 2006).***

Septic shock is actually a combination of distributive shock (i.e. a decreased total vascular resistance and maldistribution of blood flow in the microcirculation) and relative as well as absolute hypovolaemia. Furthermore, impairment of myocardial fuction may occur with symptoms of cardiogenic shock ***(Martin, 2012).***

The ultimate goals of hemodynamic therapy in shock are to restore effective tissue perfusion and to normalize cellular

metabolism. In patients with sepsis, both global and regional perfusion must be considered ***(Steve, 2009).***

The significant economic and mortality impact of severe sepsis and septic shock has often resulted in some controversy concerning optimum management strategies, particularly as regards to the choice of vasopressor support ***(Annane et al., 2007).***

AIM OF THE WORK

To evaluate and compare the efficacy of norepinephrine, dopamine and milrinone in reversing the haemodynamic abnormalities in critically ill pediatric patient with septic shock.

SEPSIS AND SEPTIC SHOCK

The word`` sepsis'' comes from the Greek word "sepo" meaning decay or putrefaction, which describes the decomposition of organic matter in a manner that results in decay and death (***Geroulanos et al., 2006)***.

It is the systemic maladaptive response of the body to the invasion of normally sterile tissue by pathogenic or potentially pathogenic microorganisms ***(Kumar et al., 2008).***

According to the International Consensus which was held for defining pediatric sepsis and organ dysfunction in 2005, sepsis is defined as systemic inflammatory response syndrome (SIRS) resulting from a suspected or proven infectious etiology. The clinical spectrum of sepsis begins when a systemic (e.g. bacteremia, rickettsial disease, fungemia, viremia) or localized (e.g. meningitis, pneumonia, pyelonephritis) infection that can progress from sepsis to severe sepsis (sepsis combined with organ dysfunction). Further deterioration leads to septic shock (severe sepsis plus the persistence of hypoperfusion despite adequate fluid resuscitation or requirement of vasoactive agents) ***(Goldstein et al., 2005).***

Table (1) demonstrates the various definitions related to sepsis and the suggested criteria for their diagnosises according to the International Consensus for definition of pediatric sepsis and organ dysfunction.

The severity of illness and the inherent mortality risk escalate from SIRS, through sepsis, severe sepsis and septic shock to multi-organ failure. Mortality estimates vary, but severe sepsis and septic shock carry high potential mortality rates, possibly up to 46% ***(Dreiher et al., 2012).***

Table (1): Modified table showing the various definitions related to sepsis and the suggested criteria for their diagnosises

Definition	Criteria for diagnosis
Infection	A suspected or proven infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g.white blood cells in a normally sterile body fluid, perforated viscus, and chest radiograph consistent with pneumonia, petechial or purpuric rash or purpura fulminans).
SIRS	The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count ● Core temperature of ≥38.5°C or ≤36°C. ● Tachycardia, defined as a mean heart rate ≥ 2 SD above normal for age in the absence of external stimulus, chronic drugs or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period or for children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, B-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period. ● Mean respiratory rate ≥ 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuron-muscular disease or the receipt of general anesthesia. ● Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or ≥10% immature neutrophils
Sepsis	SIRS in the presence of or as a result of suspected or proven infection
Severe sepsis	Sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions.
Septic shock	Sepsis and cardiovascular organ dysfunction

(Goldstein et al., 2005)

Epidemiology of sepsis

Sepsis among children is a significant health problem. It is a leading cause of death in children worldwide and is associated with substantial resource use in industrialized countries. Incidence and mortality rates vary by age and the presence of underlying disease ***(Watson et al., 2005).***

In the developed countries, mortality from septic shock ranges between 10% and 50% in children ***(Wolfler et al., 2008).***

Age, sex, and race or ethnic group all influence the incidence of severe sepsis, which is higher in infants and elderly persons than in other age groups, higher in males than in females, and higher in blacks than in whites ***(Adhikar et al., 2010).***

In general, infants≤ 2 months are at risk for sepsis with organisms such as Group B streptococcus, Escherichia coli, Listeria, and herpes simplex virus. Children older than 1–2months are at risk for community acquired organisms (e.g., infection caused by invasive Streptococcus pneumonia or Neisseria meningitides) ***(Feigin et al., 2003).***

The types of the underlying disease vary with age. In infants, chronic lung disease and congenital heart disease are the most common, whereas neuromuscular diseases predominate

among children aged 1–9 yrs, and cancer is more common among adolescents. Site of infection also varies by age. Infants tend to have primary bacteremia, whereas almost half of older children have infections of the respiratory tract ***(Watson et al., 2005)***.

There is a considerable interest in the contribution of the host genetic characteristics to the incidence and outcome of sepsis, in part because of strong evidence of inherited risk factors ***(simon et al., 2013).***

Pathogenesis of sepsis and septic shock

The complex events that occur in septic shock can be broadly divided into microorganism-related components and host-related components. The broad categories are further subdivided into cellular and humoral components. Pathogen-related events in the pathophysiology of septic shock include the mechanisms by which the microbes evade host defenses and subvert aspects of the host immune response, resulting in significantly increased morbidity. Concerning the host-related events in septic shock, multiple derangements involving several biologic systems contribute by different degrees to the development of septic shock and it includes aspects of microbial pathogenicity, key cellular and humoral aspects of the maladaptive immunoinflammatory response, the interactions

between the immuno-inflammatory and coagulation systems, and their cardiocirculatory consequences, resulting in the clinical picture of septic shock ***(Nduka et al., 2009).***

A. Host factors

The normal immune response to bacterial infection is a complex inflammatory process that attempts to localize and limit the spread of infection and repair the tissue ***(Mossie, 2013).***

Figure (1) shows host response to infection and occurance of shock.

The nature of the interactions between the microbial pathogen and the host at the tissues is complex and, results in excessive inflammation or immuno-suppression, abnormal coagulation and blood flow, and micro-circulatory dysfunction leading to organ injury and cell death, So the key term that describes the pathophysiologic events in septic shock at any point in time is the ‘‘mismatch’’ of the host response to the intensity of the pathogenic stimuli ultimately leading to organ injury or dysfunction with or without hypotension ***(Nduka et al., 2009)***.

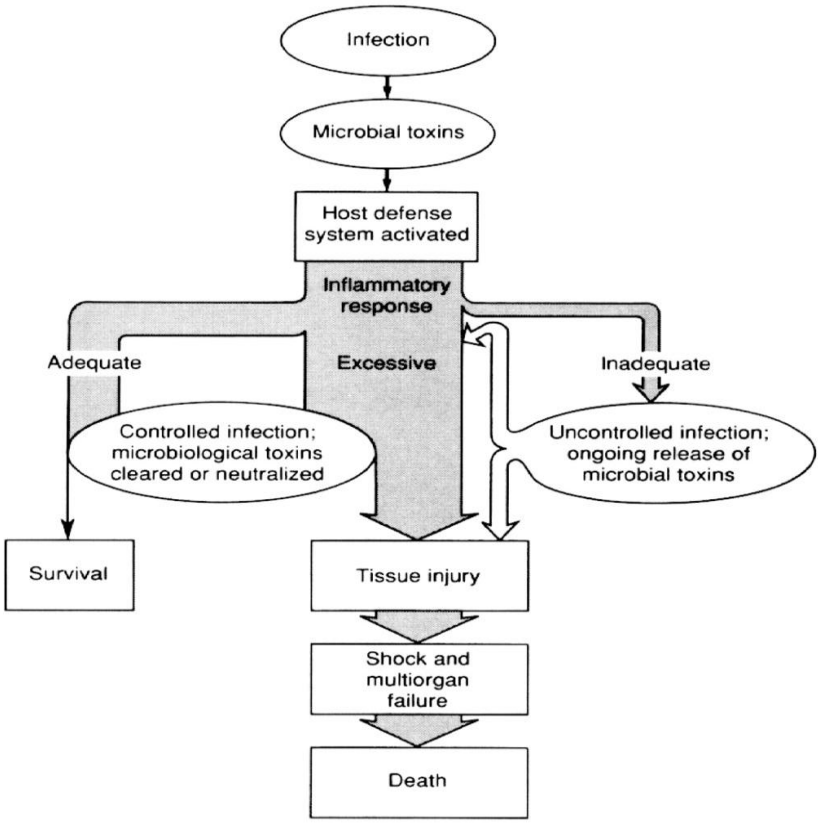

Figure (1): Host response to infection and occurance of shock ***(Charles et al., 1994).***

The composition and direction of the host response probably change over time in parallel with the clinical course. In general, proinflammatory reactions -directed at eliminating invading pathogens- are thought to be responsible for collateral tissue damage in severe sepsis, whereas anti-inflammatory responses -important for limiting local and systemic tissue injury- are implicated in the enhanced susceptibility to secondary infections ***(Derek et al., 2013).***

B. Pathogen factors

Bacteria and their products trigger cascades of cellular response in the host's body that involve several cell types (leukocyte, mast cells, endothelial cells and platelets), and several cellular pathways (proinflammatory, anti-inflammatory, coagulation cascades, complement activation, adhesion and apoptosis ***(Patel et al., 2003)***.

The pathophysiology of sepsis can be initiated by the outer membrane component of Gram-negative organisms (e.g., lipopolysaccharide [LPS], lipid A, endotoxin) or Gram-positive organisms (e.g. lipoteichoic acid, peptidoglycan), as well as fungal, viral, and parasitic components ***(Deborah et al., 2011)***.

Pathogenic molecules derived from microbial infectious agents that can bind with specific receptors on the immune cells to activate the production of cytokines and chemokines are collectively called pathogen associated molecular pattern (PAMP). The common PAMPs are surface molecules such as, lipopolysaccharide (LPS), peptidoglycan (PGN), lipoteichoic acid (LTA), unmethylated bacterial DNA (CpG DNA), lipoarabinomannan (LAM) of mycobacterium, viral double stranded RNA, flagellin, lipopeptides, mannans and zymosan of yeast and choline-containing phosphoglycolipids and internal

motifs released during bacterial lysis such as heat shock proteins and DNA fragments ***(Denk et al., 2012).***

Immune cells recognize microbes through pattern recognition receptors (PRRs) on the cells. Toll-like receptors (TLRs) are among the PRRs that can activate immune cells to produce pro-inflammatory cytokines and chemokines ***(Lewis et al., 2012).***

In the initial phase of infection, TLRs activate the innate immune system; as a result the invading pathogens are destroyed by macrophages, natural killer cells and the complement system. In the second phase, TLRs form an important link between the innate immunity and the adaptive immunity, by activating the T and B lymphocytes to produce cytokines ***(Modlin et al., 2000).***

Signalling by these mediators which occurs via TLRs within the monocytes, results in their activation which leads to the production of pro-inflammatory cytokines, TNF-α, and IL-1β. TNF-α and IL-1β lead to the production of toxic downstream mediators, including prostaglandins, leukotrienes, platelet-activating factor, and phospholipase A2 ***(Cinel et al., 2009)***.

Figure (2) shows the sequence of events leading to established infection in human hosts.

C. Anti-inflammatory mechanisms and immune system

The balance between the pro-inflammatory and the anti-inflammatory mediators derived from the innate immune system defines the progression and severity of infection. If unbalanced, an overproduction of endogenous pro-inflammatory mediators-including cytokines, platelet activating factor, oxygen radicals and nitric oxide- synergistically interact to mediate hypotension, multiple organ failure and death ***(Mossie, 2013).***

CD4 lymphocytes play a key role in the inflammatory response during sepsis. Early in the process of sepsis, these cells assume a T-helper-1 (TH1) phenotype where they produce large amounts of the pro-inflammatory mediators including IF-γ, TNF-α, and IL-2 ***(Hotchkiss et al., 2001).***

T-lymphocytes may evolve over time to a T-helper-2 (TH2) phenotype, whereby the CD4 lymphocytes produce anti-inflammatory cytokines including IL-10, IL-4, and IL-13.These cytokines dampen the immune response and can lead to deactivation of monocytes. Additionally, TNF-α released early can cause apoptosis of lymphocytes in the gut, leading to further immune suppression (***Lyn et al., 2008)***.

Progression from sepsis to septic shock coincides with an increase in the circulating levels of the pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1β, and IL-6**.** These

mediators damage the endothelial lining, leading to increased capillary leakage. Finally, activated macrophages and neutrophils release nitric oxide, a potent vasodilator that leads to septic shock ***(LaRosa, 2002).***

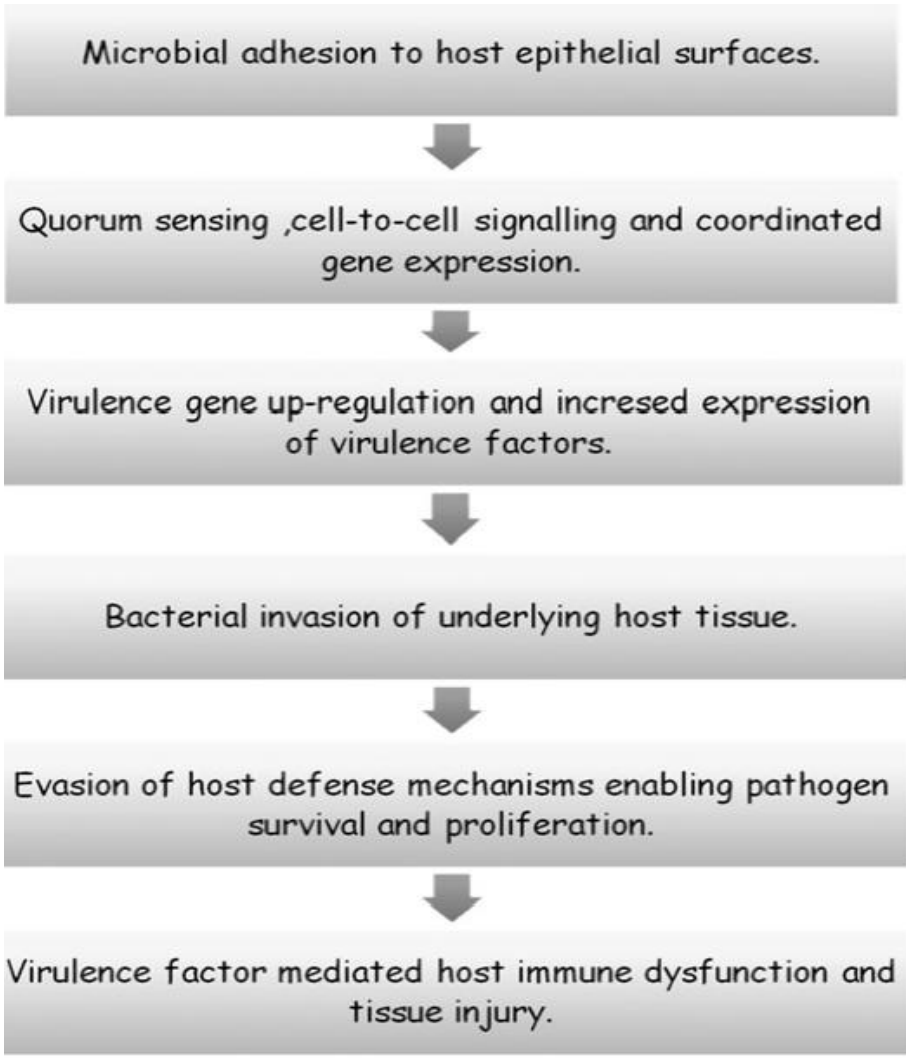

Figure (2): Sequence of events leading to established infection in human hosts ***(Nduka et al., 2009).***

D. Homeostasis

The inflammatory state found in septic animals and patients leads to numerous alterations in the coagulation system, shifting the normal hemostatic balance towards a procoagulant state. Virchow's triad of endothelial injury, hypercoagulability and abnormal blood flow can all occur in the septic patient, creating a predisposition to thrombus formation ***(Levi et al., 2003).***

The coagulation abnormalities observed in the septic patient range from slightly prolonged bleeding times and mildly decreased platelet counts to fulminant disseminated intravascular coagulation (DIC). The development of DIC in the septic patient has been shown to be an independent predictor of mortality and multiple studies have shown the severity of DIC to be directly related to increased mortality ***(Voves et al., 2006).***

Endothelial cells have an integral role in the vascular response of acute inflammation. This response is characterized by smooth muscle cell changes that result in vasodilation as well as endothelial cell contraction, which allows for leakage of proteins into the extravascular spaces and tissues, and an increased expression of adhesion molecules such as selectins that promotes migration of leukocytes from the microcirculation into the infected sites. These endothelial cell changes also lead to endothelial cell disruption, which disturbs their anticoagulant properties ***(Remick, 2007).***

The relationship between inflammation and disordered coagulation occurs via several inter-related mechanisms, mainly the release of pro-inflammatory cytokines (IL-1, IL-6, IL-12 and TNF-α) that induce the expression of tissue factor (TF), decreased levels of antithrombin, inhibition of the normal anti-coagulant protein C system and impaired fibrinolysis.These changes lead to systemic formation of intravascular microthrombi resulting in tissue hypoxia, infarction and multisystem organ failure ***(Petajia, 2011).***

E. Multiple organ dysfunction syndrome and possible complications in sepsis and septic shock

Multiple organ dysfunction syndromes (MODS) is characterized by organ injury and/or failure that is distant from the primary cause of illness or insult. It is an important cause of mortality in intensive care units (ICUs) globally ***(Dellinger et al., 2013).***

MODS is defined as a clinical syndrome characterized by the development of progressive and potentially reversible physiologic dysfunction in 2 or more organs or organ systems that is induced by a variety of acute insults, including (but not limited to) sepsis. It has conventionally been defined in terms of involvement of six organ systems, namely, pulmonary, renal, hepatic, central neurologic, cardiovascular, and haematologic systems. As per the current understanding, MODS also include