Introduction

Septic shock and the ensuing multiple organ dysfunction is one of the leading causes of death of patients admitted to intensive care units. Despite advances in the diagnosis and management of disease, the frequency of sepsis and septic shock continues to increase. Conventional therapy has been unable to reduce the high mortality rate (approximately 40% to 60%) observed in patients with septic shock ***(Jacobs et al, 2003).***

Aggressive fluid challenge and administration of catecholamines still play a vital role in the current treatment regimen of patients with septic shock. However, development of adrenergic hyposensitivity with loss of catecholamine pressor effects, resulting in refractory hypotension, is a well known clinical dilemma ***(Dunser et al., 2003).***

Prompted by the desperate situation of patients with refractory septic shock, alternative or complementary vasoconstrictors have been used. Among these novel vasopressors is terlipressin, the synthetic, long-acting analogue of vasopressin. It has comparable pharmacodynamic but different pharmacokinetic properties than vasopressin ***(Delmas et al., 2004).***

During the last years, terlipressin has been identified as a useful adjunct vasopressor in the treatment of catecholamine-dependent septic shock. Nevertheless, concerns have been raised about the associated reduction in cardiac output and oxygen delivery ***(Morelli et al., 2008).***

Aim of the Work

The aim of this study is to compare between the effects of terlipressin used alone and the effects of dobutamine combined with terlipressin on central venous oxygen saturation in catecholamine dependent septic shock patients.

Sepsis

For nearly a century, sepsis has been defined as the systemic response to an infection. In the past few decades, the discovery of endogenous mediators of the host response has led to the recognition that the clinical syndrome of sepsis is the result of excessive activation of host defense mechanisms rather than the direct effect of microorganisms. Sepsis and its sequelae represent a continuum of clinical and pathophysiologic severity ***(Levy et al., 2003).***

Definitions of Sepsis

Standardized definitions for sepsis were produced by The American College of Chest Physicians and the Society for Critical Care Medicine Consensus Conference in 1992 ***(Bone et al., 1992):***

Systemic inflammatory Response Syndrome (SIRS): Patient present with two or more of the following criteria:

(1) Temperature >38 degrees or <36 degrees

(2) Heart rate >90 beats/min

(3) Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg

(4) White blood cell count >12000/microliter, <4000/microliter or >10% immature (band) forms ***(Bone et al., 1992).***

Sepsis Presence or presumed presence of an infection accompanied by evidence of SIRS ***(Bone et al., 1992).***

Severe sepsis*:** Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status ***(Bone et al., 1992).

Sepsis induced hypotension*:** A systolic blood pressure <90 mm Hg or a reduction of ≥ 40 mm Hg from baseline in the absence of other causes of hypotension ***(Bone et al., 1992).

Septic shock: A subset of severe sepsis and defined as sepsis-induced hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic shock ***(Bone et al., 1992).***

Multiple organ dysfunction syndrome (MODS) is the presence of altered organ function in a patient who is acutely ill and in whom homeostasis cannot be maintained without intervention ***(Bone et al., 1992).***

Although the previous criteria have provided a framework for communication and investigation of sepsis and its sequelae, they have been criticized as being overly sensitive and not specific. The 2001 International Sepsis Definition Conference attempted to improve on the specificity of these definitions by elaborating common clinical and laboratory manifestations of the disorder ***(Levy et al., 2003).***

Table (1): Extended criteria for diagnosis of sepsis ***(Levy et al., 2003).***

Infection (documented or suspected) and some of the following:
General variables
• Fever (core temperature >38.3°C)
• Hypothermia (core temperature <36°C)
• Heart rate >90 /min or >2 SD above the normal value for age
• Tachypnea
• Altered mental status
• Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
• Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
• Leukocytosis (WBC count >12,000/µL)
• Leukopenia (WBC count <4000/µL)
• Normal WBC count with >10% immature forms
• Plasma C-reactive protein >2 SD above the normal value
• Plasma procalcitonin>2 SD above the normal value
Hemodynamic variables
• Arterial hypotension(Systolic BP <90 mm Hg, MAP <70, or a Systolic BP decrease >40 mm Hg in adults or less than 2 SD below normal for age)
Organ dysfunction variables
• Arterial hypoxemia (PaO2/FIO2 <300)
• Acute oliguria (urine output <0.5 ml/kg/h for at least 2 hrs)
• Creatinine increase >0.5 mg/dL
• Coagulation abnormalities (INR >1.5 or PTT >60 seconds)
• Ileus (absent bowel sounds)
• Thrombocytopenia (platelet count <100,000 /µL)
• Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Tissue perfusion variables
• Hyperlactatemia (>1 mmol/L)
• Decreased capillary refill or mottling

Classification of Sepsis:

PIRO classification

The PIRO is a staging system that characterizes the disease based on *predisposition* (especially genetic factors), the insult *infection* (especially the type, source and location of infection), the *response* of the host system (as SIRS and septic shock), specific markers (as IL-6, protein C, TNF) and *organ dysfunction*.

This classification would take into account the clinical status of the patient in addition to biochemical analysis. This should ultimately permit more precise classification of sepsis-related disorders and might be particularly helpful in more closely defining entry criteria for clinical trials of sepsis therapies ***(Levy et al., 2003).***

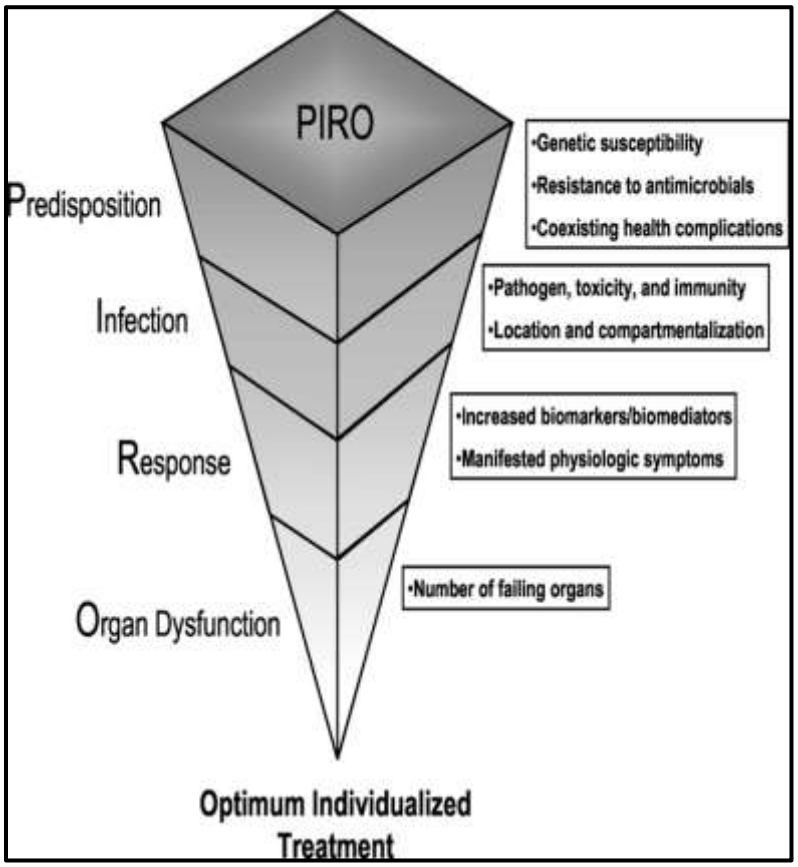

Fig.(1): PIRO-directed treatment selection based on patient characteristics ***(Shawn et al., 2004).***

Prevalence and Incidence of Sepsis

Sepsis is the leading cause of death in non-coronary intensive care units and the 13th leading cause of death in the United States overall. 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 ***(Dombrovskiy et al., 2007).***

The best data about the incidence of severe sepsis is given in the United States by Angus and colleagues. They determined that an estimated 751,000 cases of severe sepsis occur annually in the United States. More than 55% of these patients have underlying co-morbidity, and more than one half of the cases occur in those aged 65 years and older. When patients with human immunodeficiency virus are excluded, the incidence of sepsis in men and women is similar ***(Angus et al., 2001).***

The incidence of sepsis is expected to rise during the next decade owing to the aging population, a growing immunosuppressed population, the increased use of invasive catheters and prosthetic materials, and the growing problem of antimicrobial resistance. In the year 2020, it is estimated that there will be 1,100,000 new sepsis cases in the United States ***(Angus et al., 2001).***

Outcome of sepsis

It is estimated that the overall hospital mortality rate for patients with severe sepsis was 28.6%. This figure would account for 215,000 deaths in the United States annually ***(Angus et al., 2001).***

Mortality in children is approximately 10%; this figure rises to more than 38.4% in those aged 85 years and older. The mortality rate for men is only slightly higher than the rate for

women (29.3% versus 27.9%). Despite the rising incidence of sepsis, some studies indicate falling mortality rates. Specifically, Martin et al. in 2001 demonstrated declining in hospital mortality rates, from 27.8% in 1979 through 1984 to17.9% in 1995 through 2000 ***(Martin et al., 2001).***

Factors that influence outcome:

Clinical characteristics that relate to the severity of sepsis include an abnormal host response to infection, the site and type of infection, the timing and type of antimicrobial therapy, and the development of shock.

Abnormal host response to infection:

Failure to develop fever (or the occurrence of hypothermia) is associated with increased fatality rates in patients with sepsis. Thus, failure to develop a febrile response and the presence of leucopoenia are characteristic of severe disease, and probably represent anomalies in the host's inflammatory response ***(Brun-Buisson et al., 2003).***

Underlying disease:

The presence of underlying diseases and the functional health status of the patient are important determinants of outcome in severe sepsis. Risk factors for mortality from sepsis include age above 40 years and comorbid conditions at the time of diagnosis of sepsis, such as AIDS, hepatic failure, cirrhosis,

hematological malignancies metastatic cancer, or immune suppression ***(Martins, 2003).***

Site of infection:

The site of infection in patients with sepsis may be an important determinant of outcome, with urosepsis being associated with lower mortality rates.

Blood culture positivity:

Approximately 50 percent of patients with severe sepsis demonstrate bacteremia at the time of diagnosis. However, the presence or absence of a positive blood culture does not appear to influence outcome, suggesting that the prognosis may be more related to the severity of sepsis rather than to the severity of any underlying infection ***(Brun-Buisson et al., 1996).***

Offending organism:

The type of microorganism may be an important variable determining the nature and severity of the septic process. Although severe infections due to gram-negative and gram positive bacteria appear to have a similar outcome, nosocomial bloodstream infections have a worse outcome than community-acquired infections ***(Brun-Buisson, 1996).***

Pathophysiology of Sepsis

The normal host response to infection is a complex process that serves to localize and control bacterial invasion and to initiate repair of injured tissue. This inflammatory process is normally accompanied by activation of circulating and fixed phagocytic cells and by generation of pro-inflammatory and anti-inflammatory mediators. Sepsis results when the inflammatory response to infection becomes generalized, and extends to involve normal tissue remote from the initial site of injury of infection ***(Richard and Irene, 2003).***

Normal inflammatory response

Inflammation is intended to be a local and contained response to infection, while initiating insults may be numerous, the inflammatory processes are qualitatively similar. At the site of injury, the endothelium expresses adherence molecules to attract leukocytes. At the same time, polymorph nuclear leukocytes (PMNs) are activated and express adhesion molecules that cause their aggregation and margination to the vascular endothelium. A prerequisite for subsequent phagocytosis of invading bacteria and debris from injured tissue is diapedesis and then migration of these PMNs to the site of injury ***(Abraham et al., 2000).***

The net effect is clearing of bacteria and debris, which is followed by tissue repair. The response to tissue trauma on any level is biphasic. The first phase appears to represent activation of mechanisms to ensure short-term survival which in turn

means preservation of substrate delivery to the heart and brain. As a result, blood flow to these two organs increases, while flow to all other systems decreases ***(Murray et al., 2002).***

In some cases, mediator release exceeds the boundaries of the local environment. This may lead to a more generalized response that affects otherwise normal tissue. This process is referred to as sepsis when it occurs in association with infection, and as SIRS when it is induced by noninfectious conditions ***(Cohen, 2002).***

Predisposing factors

Predisposing factors include individual characteristics, such as age, chronic diseases, prolonged immuno-depressant medications etc., that may influence a patient's response to infection and/or indicate which therapies are likely to be most effective in that patient ***(Waterer et al., 2003).***

Table (2): Predisposing factors for sepsis ***(Waterer et al., 2003).***

Extremes of age: <1 year and >65 years
Surgical/invasive procedures
Malnutrition
Use of broad-spectrum antibiotics
Chronic illness
Diabetes mellitus
Chronic renal failure
Hepatitis
Immunodeficiency disorders /Compromised immune status
Acquired immunodeficiency syndrome
Use of cytotoxic and immunosuppressive agents
Alcoholism
Malignant neoplasms
Transplantation procedures
Increase in the number of drug-resistant microorganisms

Aberrant hyperinflammatory response

The pathophysiology of sepsis is initiated by the outer membrane components of both gram negative organisms (Lipopolysaccharide, lipid A and endotoxin) and gram positive organisms (lipoteichoic acid and peptidoglycan). These outer membrane components are able to bind to the CD14 receptor on the surface of monocytes. By virtue of the recently described toll-like receptors, a signal is then transmitted to the cell, leading to the eventual production of the pro-inflammatory cytokines, initiating a cascade ending in 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 ***(Wang and Ma, 2008).***

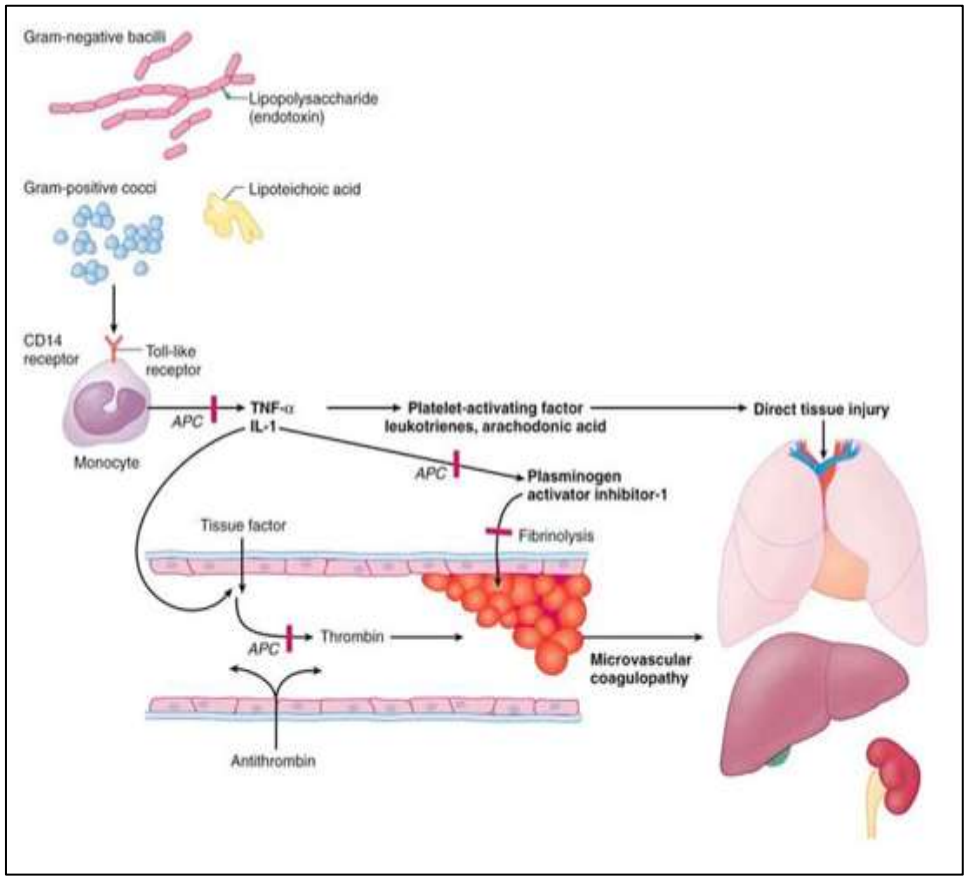

Fig. (2): Pathogenesis of severe sepsis ***(Vervloet et al., 1998).***

Link Between Inflammation and Coagulation

Complement products such as C5a, cytokines and oxidants activate the coagulation system through induction of tissue-factor from endothelial cells and monocytes. Plasminogen activator inhibitor 1 (PAI1) is produced by leukocytes, which inhibits fibrinolysis cascade. Altered coagulation/fibrinolysis system causes microvascular thrombosis by fibrin deposition, resulting in disseminated intravascular coagulation (DIC) ***(Okazaki and Matsukawa, 2008).***