INTRODUCTION

Sepsis refers to the presence of a serious infection that correlates with systemic and uncontrolled immune activation ***(Angus and van der Poll, 2013).*** Patients die as a result of organ failure as the disease elicits an exacerbated and damaging immune response with approximately 250,000 cases leading to fatalities in the USA annually ***(Martin et al., 2008).***

Owing to the broad and vague definition of sepsis along with its various manifestations and severity levels in different patient populations, a definitive biomarker that could aid in therapeutic strategies could be difficult to a scertain. More than 100 different molecules have been suggested as useful biomarkers of sepsis ***(Reinhart et al., 2012).***

The International Sepsis Forum Colloquium on Biomarkers of Sepsis was convened in 2005 to develop a systematic framework for the identification and validation of biomarkers of sepsis ***(Marshall and Reinhart, 2009).***

The diagnosis of sepsis is difficult, particularly in the ICU where signs of sepsis may be present in absence of a real infection ***(Abraham and Singer, 2007).***

The effort of many investigating groups has been to find a reliable marker to discriminate the inflammatory

response to infection from other types of inflammation. Gold standards for the diagnosis of infection do not exist; but procalcitonin is known to be among the most promising sepsis markers in critically ill patients, and is capable of complementing clinical signs and routine laboratory variables that are suggestive of sepsis ***(Shaaban et al., 2010).***

Several biomarkers, such as C-reactive protein and procalcitonin, have been used to indicate bacterial infection. These biomarkers could also provide prognostic information in distincting infectious processes and in patients with sepsis ***(Kim et al., 2011).***

A few studies have analyzed eosinophil count as a prognostic marker of outcome in patients with infection, but its utility as a marker of outcome in patients with bacteremia is unknown ***(Holland et al., 2010).***

Several studies have used eosinophil counts, specifically eosinopenia, as a marker of infection ***(Smithson et al., 2009),*** and as an indicator of bacteremia, but the results were controversial.

Eosinopenia would be an interesting biomarker because the eosinophil count is always measured in clinical practice and the additional costs would therefore be negligible ***(Wibrow et al., 2010).***

More recently, a study performed in an emergency department demonstrated that profound eosinopenia is very specific for sepsis, and it was suggested that it may become a helpful tool in daily practice ***(Lavoignet et al., 2016).***

The eosinophil count has been revisited in recent decades, especially eosinopenia, which some authors consider a criterion of SIRS. There is no precise cut-off value in the literature to define eosinopenia, with different authors reporting values ranging from <40/mm3 ***(Gil et al., 2003)*** to <50/mm3 ***(Abidi et al., 2008).***

Aim of the Work

The aim of this study was to test the value of Eosinopenia in the diagnosis of sepsis in critically ill patients admitted to ICUs.

Sepsis

Sepsis is a clinical syndrome that results from the dysregulated inflammatory response to infection that leads to organ dysfunction ***(Seymour et al., 2016).*** Sepsis is associated with high morbidity and mortality ***(Liu et al., 2014).*** Sepsis is among the most common reasons for admission to intensive care units (ICUs) throughout the world ***(Singer et al., 2004).***

The estimated mortality from sepsis is 20–30%, meaning that approximately 100.000 patients die after septic episode annually in the United States alone ***(Erickson et al., 2008).***

Definitions:

Systemic inflammatory response syndrome

Defined as two or more abnormalities in temperature, heart rate, respiration, or white blood cell count. Systemic inflammatory response syndrome may occur in several conditions related, or not, to infection. Noninfectious conditions classically associated with SIRS include autoimmune disorders, pancreatitis, vasculitis, thromboembolism, burns, or surgery ***(Levy et al., 2003).***

Sepsis

The new proposition defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection ***(Seymour et al., 2016).***

Severe sepsis

Is sepsis plus either dysfunction of an essential system in the body or inadequate blood flow to parts of the body due to an infection ***(Singer et al., 2004).***

Septic shock

Septic shock is a type of vasodilatory or distributive shock. Clinically, this includes patients who fulfill the criteria for sepsis who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg and have a lactate >2 mmol/L (>18 mg/dL) ***(Singer et al., 2004).***

Multiple organ dysfunction syndrome

Multiple organ dysfunction syndrome (MODS) refers to progressive organ dysfunction in an acutely ill patient, and can be classified as primary or secondary ***(Bellomo et al., 2000).***

- Primary MODS are the result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself (eg, renal failure due to rhabdomyolysis).

- Secondary MODS is organ failure that is not in direct response to the insult itself, but is a consequence of the host's response (eg, ARDS in patients with pancreatitis) ***(Colonna and DieTrich, 2000).***

Diagnostic Criteria for Sepsis (Infection, documented or suspected, and some of the following):

A. General variables:

- Fever (> 38.3°C).
- Hypothermia (core temperature < 36°C).
- Heart rate > 90/min or more than two sd above the normal value for age.
- Tachypnea.
- Altered mental status.
- Significant edema all over the body or positive fluid balance (>20 mL/kg over 24 hr.).
- Hyperglycemia (plasma glucose > 140 mg/dL) in the absence of diabetes.

B. Inflammatory variables:

- Leukocytosis (WBC count >12(10^3/mm^3) or Leukopenia (WBC count < 4[10^3/mm^3]) or Normal WBC count with greater than 10% immature forms.
- Elevated plasma C-reactive protein above the normal value (normal CRP level are below 3.0 mg/dL).

C. Hemodynamic variables:

Arterial hypotension; SBP < 90 mm Hg, MAP < 70 mm Hg, or SBP decrease> 40 mm Hg in adults.

D. Organ dysfunction variables:

- Arterial hypoxemia (paO2/FIO2 < 300)
- Acute oliguria (urine output < 0.5 mL/kg/hr. for at least 2 hrs. despite adequate fluid resuscitation)
- Creatinine increase > 0.5 mg/dL
- Coagulation abnormalities (INR >1.5 or aPTT >60s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count < 100 (10^3/mm^3)
- Hyperbilirubinemia (plasma total bilirubin >4mg/dL)

E. Tissue perfusion variables:

Any of the following thought to be due to the infection

- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal Urine output < 0.5mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation

- Acute lung injury with Pao2/Fio2 < 250 in the absence of pneumonia as infection source Acute lung injury with Pao2/Fio2 < 200 in the presence of pneumonia as infection source
- Creatinine> 2.0mg/dL (176.8 µmol/L)
- Bilirubin > 2mg/dL (34.2 µmol/L)
- Platelet count < 100,000 µL
- Coagulopathy (international normalized ratio > 1.5)

(Levy et al., 2003)

Etiology

Common causes

Gram-positive bacteria (e.g Staphylococcus, Streptococcus), *gram-negative bacteria* (e.g Escherichia coli, Proteus, Pseudomonas, Klebsiella) anaerobes (e.g Bacteroides, Clostridia, Fusobacteriumspp) fungi (e.g Candida spp, Mycobacteria, Rickettsia, Parasites and Viruses ***(Yende et al., 2007).***

Common sites of origin:

Genitourinary tract (e.g indwelling catheters) abdomen (e.g peritonitis, intra-abdominal abscess, appendicitis, pancreatitis) lungs (e.g pneumonia, empyema)

central nervous system (e.g meningitis) skin/soft tissue: (e.g cellulitis, trauma, catheters-related) ***(Yende et al., 2007).***

Risk Factors for Sepsis

1) Age

Advanced age (≥65 years): The incidence of sepsis is disproportionately increased in older adult patients and age is an independent predictor of mortality due to sepsis and aging patients account for 40-50% of all cases of bacteremia ***(Martin et al., 2006).***

2) Gender

Numerous reports show that female sex hormones are immune-enhancing, whereas male sex hormones are immunosuppressive. When the plasma female sex hormone levels are reduced by ovariectomy, mortality increased ***(Sands et al., 1997).***

3) Alcohol

Increases risk of aspiration, malnutrition, and alterations in the gut/ liver / lung and inflammatory axis are the mechanisms by which infections in alcoholics can lead to sepsis ***(de Wit et al., 2010).***

4) Race

In the US, the incidence of sepsis is significantly higher in African-Americans, Asians, Native Americans, and Pacific Islanders than in Caucasian populations ***(Yende et al., 2007).***

5) Genetic factors

Genetic defects have been identified that impair recognition of pathogens by the innate immune system, increasing susceptibility to specific classes of microorganisms ***(Netea and van der Meer, 2011).***

6) Geography

Geography has an effect on causative organisms. For example, sepsis from typhoid is more common in Southeast Asia and meningococcal sepsis is most common in sub-Saharan Africa ('the meningitis belt of Africa') ***(Dellinger et al., 2012).***

7) Other risk factors:

Acquired immunodeficiency syndrome, cytotoxic and immunosuppressant agents, diabetes, surgical invasive procedures, malnutrition and malignancy ***(Prescott et al., 2015).***

Pathophysiology

Host-Pathogen Relation

The host response to an infection is initiated when innate immune cells, particularly macrophages, recognize and bind to microbial components. This may occur by several pathways:

- Pattern recognition receptors (PRRs) on the surface of host immune cells may recognize and bind to the pathogen-associated molecular patterns (PAMPs) of microorganisms ***(Cinel and Dellinger, 2007).***
- The binding of immune cell surface receptors to microbial components has multiple effects ***(Dellinger et.al,2013):***

  I- The engagement of tool-like receptor (TLRs) elicits a signaling cascade resulting in activation of a large set of genes involved in the host inflammatory response, such as proinflammatory cytokines, chemokine, vascular cell adhesion molecule-1 [VCAM-1]), and nitric oxide.

  II- Polymorphonuclear leukocytes (PMNs) become activated and express adhesion molecules that cause the cardinal signs of local inflammation: warmth and erythema. This process is regulated by proinflammatory and anti-inflammatory mediators ***(Wiaterek and Gray, 2010).***

Effects of microorganisms

Bacterial cell wall components (e.g endotoxin),and bacterial products (e.g staphylococcal enterotoxin B) may contribute to the progression of a local infection to sepsis such as endotoxins are associated with shock and multiple organ dysfunctions through activation of the complement, coagulation, and fibrinolytic systems ***(Christ-Crain et al ,. 2004).*** These effects may lead to microvascular thrombosis and the production of vasoactive products, such as bradykinin ***(Pugin et al., 1996).***

Complement activation

There is evidence that activation of the complement system plays an important role in decreasing the inflammation and improves mortality ***(Liu et al., 2007).***

Genetic susceptibility

The single nucleotide polymorphism (SNP) is the most common form of genetic variation. The total number of common SNPs in the human genome is estimated to be more than 10 million so SNPs can be used as genetic markers ***(Frantz et al., 2007).***

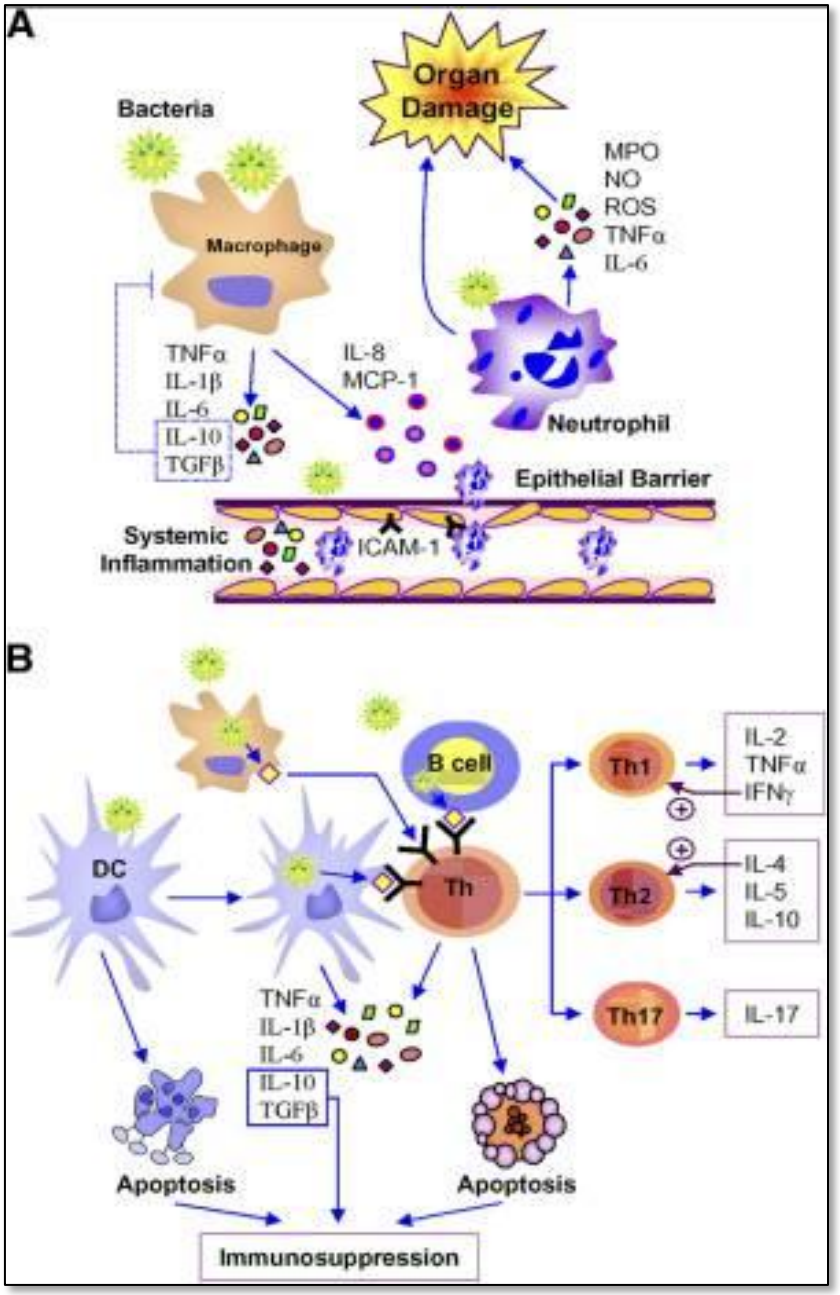

Fig. (1): Roles of innate and adaptive immune system in sepsis pathophysiology ***(Aziz et al., 2013)***

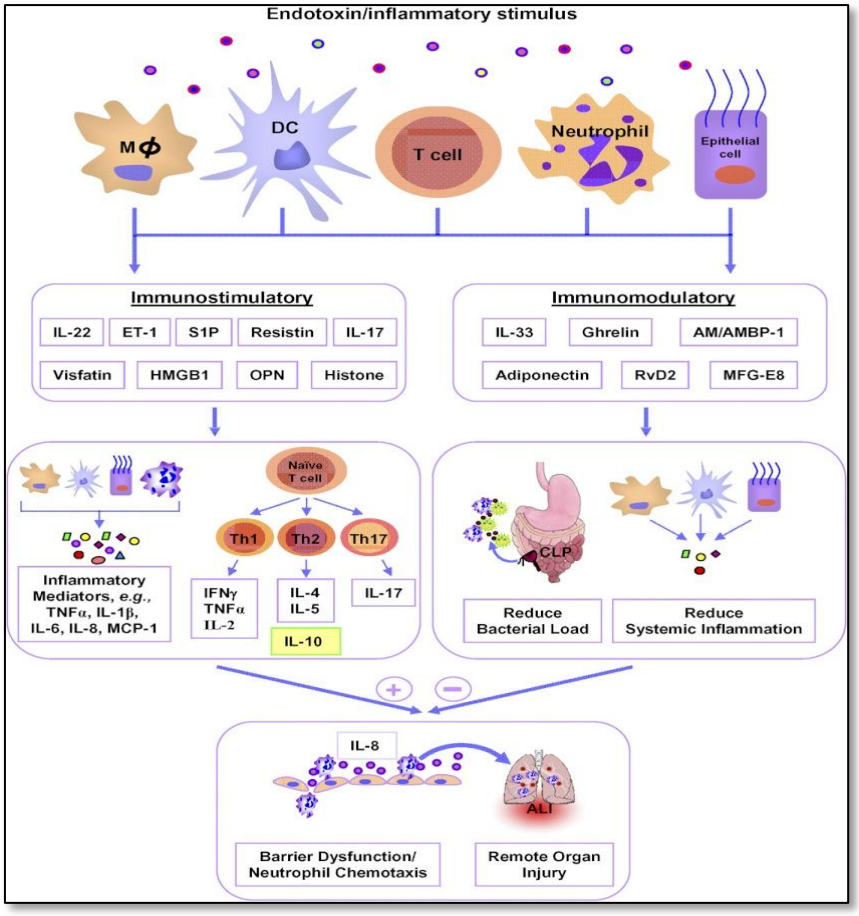

Fig. (2): Latest trends in sepsis mediators ***(Aziz et al., 2013).***

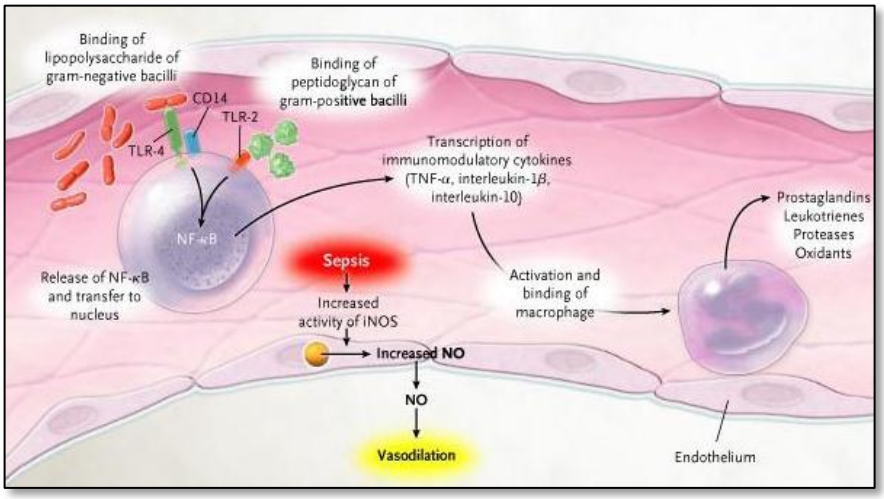

Fig. (3): Inflammatory mediators in sepsis ***(Bernhagen et al., 2013)***