INTRODUCTION

Sepsis is one of the most common infectious conditions in the neonatal period, and remains a major source of morbidity and mortality despite extraordinary progress in the field of neonatology in recent years. According to the world health organization (WHO), approximately 5 million neonatal deaths occur each year worldwide, 98% of which in least developed and developing countries ***(Rio, 2010).***

The diagnosis of sepsis is sometimes very difficult because it is usually common for patients to show some sepsis criteria with no obvious source for the infection, especially in immune compromised patients. Also, the lack of sensitive diagnostic tests for sepsis highlights the role of early sepsis biomarkers. Various sepsis biomarkers have been proposed in the field of sepsis diagnosis ***(Pierrakos and Vince,2011).***

The acute phase reactant haptoglobin is a glycoprotein synthesized predominantly by the hebatocyts, Hp binds free hemoglobin during hemolysis preventing oxidative damage by reactive oxygen species and reducing iron loss through urinary excretion ***(Journal of Perinatology, 2011).***

The haptoglobin-hemoglobin complex is cleared after binding to the CD163 receptor on monocytes and macrophages.

The antioxidant and immunomodulatory effect of hemoglobin are relevant in hemolytic and infections diseases, diabetes mellitus and renal and coronary arteries diseases.

AIM OF THE WORK

THisstudy is designed to use radial immune diffusion to evaluate the diagnostic utility of cord blood haptoglobin, as a marker for early recognition of bacterial sepsis.

NEONATAL SEPSIS

Sepsis is a severe illness in which the bloodstream is overwhelmed by bacteria. Severe sepsis is the term used to describe the host response to infection when complicated by acute organ dysfunction ***(Derekc, 2011).***

The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) has defined sepsis as confirmed or suspected infection in the presence of the systemic inflammatory response syndrome (SIRS**)** ***(Levy et al., 2001).***

SIRS is primarily characterized by the presence of at least two of the following signs: Temperature >38.6ºC or <36ºC, Heart rate >90 beats/minute, Respiratory rate >30 breaths/minute, Leukocyte count >12,000 cells/mm^3 or <4, 000cells/mm^3 ***(Dellinger et al., 2008).***

Sepsis can progress to severe sepsis and/or septic shock. Progression is associated with a significant increase in morbidity and mortality. Septic shock is defined as severe sepsis and hypotension that does not respond to adequate fluid replacement ***(Levy et al., 2001).***

Neonatal sepsis is a blood infection that occurs in an infant younger than 90 days *old* ***(Verani et al., 2010).***

Classification:

1-Early onset sepsis:

Early-onset sepsis is a fulminant multisystem infection that most frequently presents in neonates within the first 72 hours of life but can occur as late as day 6 of life. Although the incidence is low (1.4%–3.2%, increasing with decreasing gestational age), newborns with early-onset infection, 85% present within 24 hours, 5% present at 24-48 hours, and a smaller percentage present within 48-72 hours. Onset is most rapid in premature neonates ***(Stoll et al., 2010).***

Early-onset sepsis syndrome is associated with acquisition of microorganisms from the mother. Transplacental infection or an ascending infection from the cervix may be caused by organisms that colonize in the mother's genitourinary tract, with acquisition of the microbe by passage through a colonized birth canal at delivery ***(Stoll et al., 2011).***

Early sepsis often manifests with pneumonia and/or septicemia, equal male and female incidence, predominantly due to organisms acquired from the birth canal, occasionally intrapartum hematogenous spread occurs e.g. Listeria. Over 80% of cases are due to GBS and gram negative bacteria ***(neonatal hand book, 2007).***

2-Late onset sepsis:

Late-onset sepsis syndrome occurs at 4-90 days of life and is acquired from the caregiving environment ***(Van den Hoogen et al., 2009).***

The pathogen causing late-onset sepsis (LOS) is generally acquired from the postnatal environment. LOS is most important as a nosocomially acquired infection in hospitalized babies ***(Gray, 2007)***.

It may occur via vertical transmission at birth, leading to colonization and, later, to infection ***(Jiang et al., 2004),*** or due to organisms acquired either around the time of birth or in hospital as Coagulase Negative Staphylococcus during hospitalization in the NICU. Candida is an important pathogen, particularly among extremely low birth weight infants, gram negatives and GBS predominate among infections acquired outside the NICU setting ***(Neonatal hand book, 2007)***.

Furthermore, the majority of pathogens associated with fulminant late onset sepsis (lethal within 48 hours) have been shown to be gram negative organisms with pseudomonas**.** Although CoNS are currently the most prevalent pathogens in late onset sepsis in neonatal intensive care units the associated mortality is low ***(Gordon and Isaacs, 2004).***

3-Nosocomial sepsis:

A hospital-acquired infection is an infection that first appears between 48 hours and four days after a patient is admitted to a hospital or other health- care facility ***(Rizzo and Culvent, 2005).***

However, some authors have found that the transition from maternal to nosocomial origin of infection may begin even earlier than this, and have proposed that only very early-onset infections presenting within the first 24 hr should be regarded as unequivocally of maternal origin ***(Gray, 2008).***

The risks for infection in VLBW infants after 72 hours of age primarily derive from the ongoing neonatal intensive care rather than from perinatal risk factors, the organisms causing infection after 72 hours of age among VLBW infants reflect the nosocomial flora of the NICU more than perinatally acquired maternal flora ***(Stoll et al., 2002).***

Epidemiology:

The early signs of sepsis in the newborn are nonspecific; therefore, many newborns undergo diagnostic studies and the initiation of treatment before the presence of sepsis has been proven. Additionally, because the American Academy of Pediatrics (AAP), American Academy of Obstetrics and Gynecology (AAOG), and Centers for Disease Control and

Prevention (CDC) all have recommended sepsis screening and/or treatment for various risk factors related to group B *Streptococcus* infections, many asymptomatic neonates now undergo evaluation ***(AAP, 2003).***

Because the mortality rate of untreated sepsis can be as high as 50%, most clinicians believe that the hazard of untreated sepsis is too great to wait for confirmation based on positive culture results. Therefore, most clinicians initiate treatment while awaiting culture results. The implementation of a prenatal screening and treatment protocol for GBS has resulted in a decreasing incidence of GBS sepsis. This has changed the epidemiology of early-onset sepsis as in **figure (1)** ***(Schrag et al., 2002).***

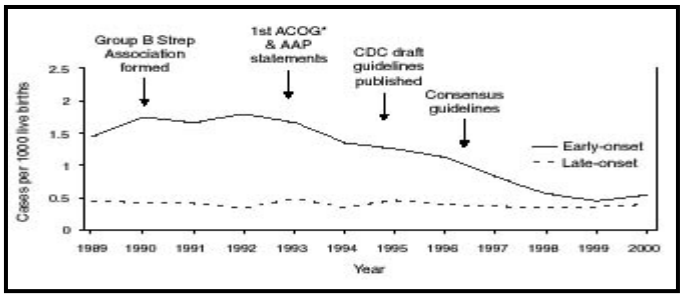

Fig. (1): Incidence of early – and late onset invasive group B streptococcal disease – selected Active Bacterial core surveillance areas, 1989-2000, and activities for prevention of group B streptococcal disease ***(ACOG, 2000).***

Trends in **late-onset** sepsis show an increase in coagulase-negative streptococcal sepsis; most of these isolates are susceptible to first-generation cephalosporins .The infant's

skin, respiratory tract, conjunctivae, GI tract, and umbilicus may become colonized from the environment, leading to the possibility of late-onset sepsis from invasive microorganisms ***(Lin et al., 2011).***

Pneumonia is more common in early-onset sepsis, whereas meningitis and bacteremia are more common in late-onset sepsis. Premature and ill infants have an increased susceptibility to sepsis and subtle nonspecific initial presentations; therefore, they require much vigilance so that sepsis can be effectively identified and treated ***(Van den Hoogen et al., 2009).***

Incidence of Nosocomial sepsis:

The incidence of nosocomial infections has been reported from 6.2 to 50.7 infections per 100 admissions or discharges, and from 4.8 to 62 infections per 1000 patient days ***(Buttery, 2002).***

First, there's a difference in the surveillance method for nosocomial infections. Many studies diagnosed neonatal infections based on the clinical and culture-proven evidence according to the CDC definition of neonatal infections; the incidence rate is very high but the incidence density is not so high, which may be related to the longer length of hospital stay of the subjects in this study. Length of stay can be related to the subjects' unique conditions. The mean hospital stay of was about 30 days, compared to more than 12.4 days ***(Evans, 2006).***

Race-,sex-, and age-related demographics

Black infants have an increased incidence of group B *Streptococcus* disease and late-onset sepsis. This is observed even after controlling for risk factors of low birth weight and decreased maternal age. In all races, the incidence of bacterial sepsis and meningitis, especially for gram-negative enteric bacilli, is higher in males than in females ***(Ann and Ted, 2011).***

Premature infants have an increased incidence of sepsis. The incidence of sepsis is significantly higher in infants with very low birth weight (<1000 g), at 26 per 1000 live births, than in infants with a birth weight of 1000-2000 g, at 8-9 per 1000 live births. The risk of death or meningitis from sepsis is higher in infants with low birth weight than in full-term neonates ***(AAP, 2003).***

Pathophysiology:

Sepsis results when an infectious insult triggers a localized inflammatory reaction that then spills over to cause systemic symptoms. These clinical symptoms are called the systemic inflammatory response syndrome. The inflammatory reaction is mediated by the release of cytokines, including tumor necrosis factor-alpha, interleukins, and prostaglandins, from neutrophils and macrophages ***(Jacobi, 2002)***. The

cytokines activate the extrinsic coagulation cascade and inhibit fibrinolysis as in **figur 2**.

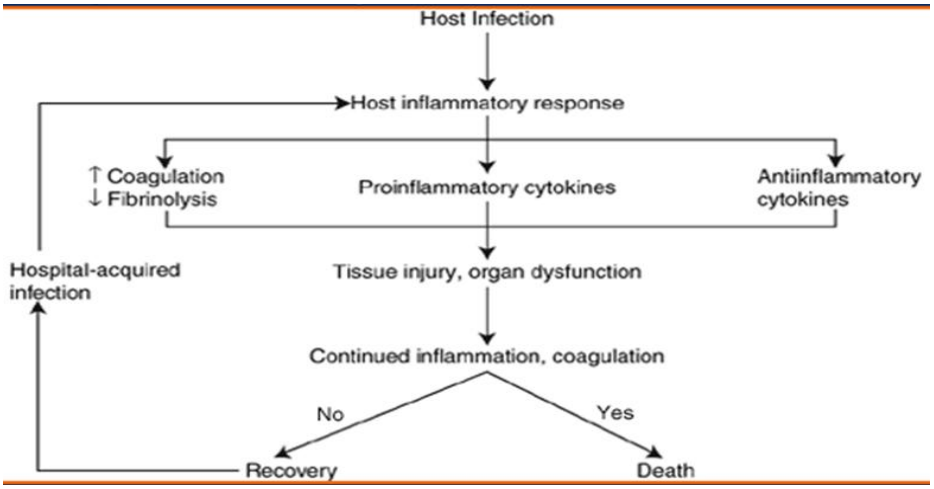

Fig. (2): Cascade of inflammatory response to sepsis ***(Micek , 2003).***

These overlapping processes result in microvascular thrombosis; thrombosis is one potential factor producing organ dysfunction. Activation of the coagulation system leads to consumption of endogenous anticoagulants (e.g., protein C and antithrombin); this may be an important factor in the development of microvascular coagulation. Anti-inflammatory mediators as well as inflammatory mediators have a role in sepsis, and an excess of either can result in poor patient outcomes. Sepsis is a complex syndrome involving activation of a variety of systems ***(Jacobi, 2002).***

In late-onset disease, pathologic changes consistent with the particular focal infection can be demonstrated, including meningitis, pneumonia, hepatic abscesses, and arthritis or

osteomyelitis ***(Edwards, 2011)***. Another viewpoint would argue that septic patients failed to control the bacterial infection and died as a result of immunosuppression rather than immuno-stimulation ***(Remick, 2007).***

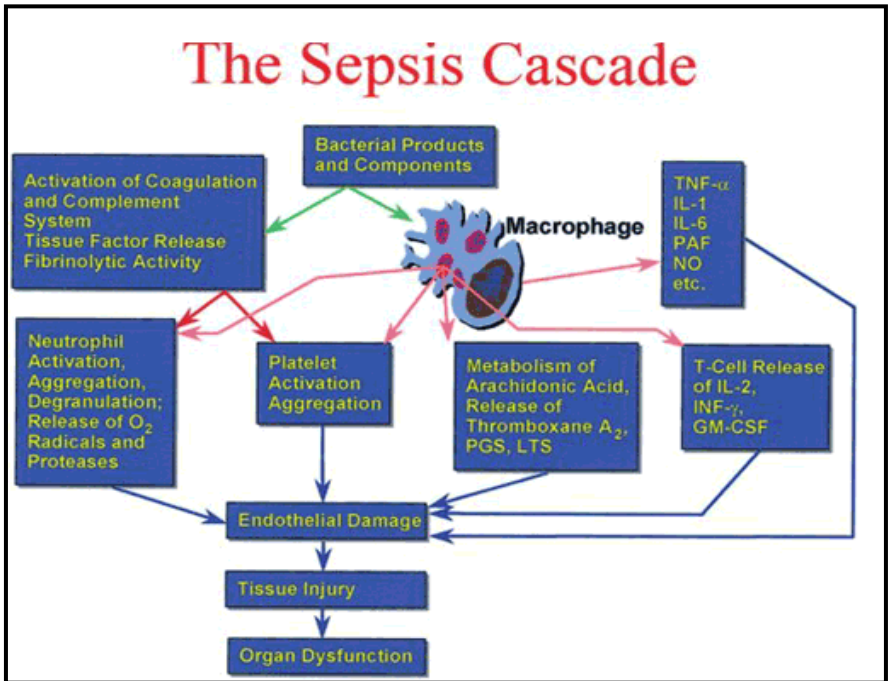

Fig. (3) The pathophysiology of the sepsis cascade. In response to microbial invasion, macrophages release primary inflammatory mediators that result in endothelial damage. The clinical result of the endothelial damage is capillary leak, vasodilation, and formation of microthrombi resulting in organ dysfunction ***(Saunders, 2004).***

Route of sepsis:

1-Hematogenous spread:

It leads to fetal infection in the absence of rupture of the membranes via the placenta after invasion of maternal blood stream ***(Gomella et al., 2010).***

2-Vertical transmission:

Most are acquired by the ascending route in utero or as the fetus passes through the colonized birth canal. Though the intensity of maternal colonization is directly related to risk of invasive disease in the neonate, many mothers with low-density colonization give birth to infants with high-density colonization who are therefore at risk. It is the predominant route of bacterial infection causing early-onset neonatal sepsis, and it occurs mostly by Group B streptococcus (GBS) and Gram-negative enteric bacteria **(*Platt and Brien, 2003*)**.

3- Nosocomial infection:

This type of infection is acquired in the hospital and usually develops 48-72 hours after birth resulting in considerable morbidity and mortality among neonates especially those in neonatal intensive care units ***(Tseng et al., 2002).***

4-Household-acquired infection:

The newborn infant is susceptible to many of the infectious agents that colonize other members of the household through the respiratory tract, gastrointestinal tract (GIT) and skin. In addition the umbilical cord stump and circumcision site represent sites for access of pathogenic organisms such as skin pathogens as Staphylococcus aureus ***(Tseng et al., 2002).***

Risk factors of neonatal sepsis

1. Maternal risk factors:

Presence of multiple maternal risk factors makes the child more susceptible to early onset neonatal sepsis ***(Javed and Memon, 2009)***.

1- Premature rupture of membranes (PROM):

The Public Health Laboratory Service's recommendations for best practice can be applied indifferent ways depending on the definitions used for prolonged rupture of the membranes and intrapartum fever (for example, counting 19 hours of rupture of the membranes as a risk factor**.** Known antecedents of early onset bacteremia include prelabor rupture of membranes (PROM) >18 hours **(PHLS, 2000)**.

2- Chorioamnionitis.

3- Maternal fever

4- Maternal vaginal or rectal colonization with group B

Streptococcus (GBS), maternal GBS bacteruria , foul smelling amniotic fluid.

5- Previous history of preterm labor ***(Shani et al., 2008).***

6- Maternal urinary tract infection.

7- Poor prenatal care

8- Poor maternal nutrition

9- History of recurrent abortion.

10- Difficult delivery.

11- Maternal substance abuse ***(Arnon and Litmanovitz, 2008).***

12- Gestational hypertension, chronic illness, maternal anemia.

2. Neonatal risk factors:

The most important risk factor in late-onset sepsis is preterm delivery. Factors that cannot be influenced, and relate to the patient's biological status. Some such risk factors are static, for example, birth weight, gestational age and condition at birth, whereas others, for example, postnatal age, vary daily.

1- **Birth weight:** It is universally agreed that the incidence of LOS is inversely proportional to birth weight and gestational age. In a recent study demonstrated both birth gestational age and birth weight to be risk factors for blood stream infection, but only a gestational age of less than 26 weeks was an independent risk factor ***(James, 2008).***

2- **Postnatal age:** Has also been shown to be a significant risk factor for LOS, although there are differences in experiences. The incidence of bloodstream infection was highest in the first 10 days of life ***(Roy et al., 2006)*** followed by between