INTRODUCTION

Sepsis is clinical syndrome characterized by the presence ofboth infection and a systemic inflammatoryresponse. Clinicalmanifestationinclude hemodynamic instability, hypoxemia and various signs of an acute inflammatory state**(Levy, 2003).**

Sepsis remainsthe most common cause of morbidity and mortality in neonates**(Camacho 2013),**Although advances in neonatal care have improved survival and reduced complication in pre term infant sepsis still contributes significantly to mortality and morbidity among low birth weight in NICUS **(Bizzaro MJ 2005).**

Since sepsis is a systemic inflammatory response to infection isolation of bacteria from the blood is consider the gold standard for the diagnosis of sepsis **(Goldstein, 2005).**

However it takes24-48h for culture results.inoculation of only 0.5 to 1.0 ml of blood decrease its sensitivity as 60% to 70% of infants have low level of bacteremia**(Hornik, 2012).**

Sepsis cannot be excluded even when blood cultures are found to be negative.conversely isolation of bacteria in blood culture may reflect asymptomatic bacteremia or contamination other supplemental diagnostic test based on evaluation of

immune system are being evaluated to help resolve ambiguities in these situations **(Brozanski BS, 2006).**

In the acute phase responseto a variety of insults arise in the level of the acute phase protein, including alpha one acid glycoprotein occurs.the physiological role of α1AGP is unknown, however the time course of its production in acute phase response together with its strong affinity for basic compounds suggests that α1AGP may function as an immune modulator to bind both exogenous and endogenous inflammatory mediators**(Hochepied T 2003).**

α1AGP is an acute phase serum protein that is produced in the liver in response to inflammation and infection.its 183 amino acid protein with five N-linked glycans comprise 45% of its 43 kda mass.Alternation of N-glycosylation is associated with certain pathophysiologicalstates.

α1AGP is belongs to lipocalin family and binds numerous basic and neutral lipophilic drugs and steroid hormones**(Zsilla, 2009).**

AIM OF THE WORK

Thisstudy designed to evaluate the diagnostic value of α1 acid glycoprotein and its relation to CRPin early diagnosis of neonatal sepsis

NEONATAL SEPSIS

Definition:

Neonatalsepsis, sepsis neonatorum and neonatal septicemia are terms that are used todescribe the systemic response to infection in the newborn infant.the criteria for neonatal sepsis should include documentation of infection in a newborn infant with a serious systemic illness in which non infectious explanations for the abnormal pathophysiology state are excluded or unlikely**(Garcia et al., 2007).**

Severe inflammatory response syndrome used to describe a clinical syndrome characterizedby two or more of the following: (1) fever (2) hypothermia (3) tachycardia (4) tachypnea, (5) abnormal white blood cell or increaseof immature forms. Severe inflammatory response syndrome may be result of many conditions. When it is a result of infection, it is termed sepsis**(Chiesa et al., 2004).**

Septicemia may be due to infection of specific organ system (such as meningitis or osteomyelitis) or occasionally may follow inadequately treated localized infection**(Bell et al., 2004).**

Incidence

Incidence of neonatal sepsis in the developed world is reported to be between 0.6 to 1.2% of all live births but in the

developing world it can be as high as 20 to 40 % of all live births**(Haque etal., 2003)**, in Egypt, incidence of neonatal sepsis in risk neonates was 59% in the study of**(Elwan et al., 2004),**while**(Badrawi et al., 2005)**found it to be 53%.twenty six percent of newborn death occur as a result of severe infections like sepsis an pneumonia**(WHO, 2006).**

Timing of the infection

During the gestational ages first trimester infection usual alters the embryogenesis, with result of congenital malformation, third trimester infection often result in active infection at the time of delivery or maybe delayed**(Anderson et al., 2014).**

The factor affecting the infection

The fate of the infection Depending on the age of the patient, the virulence and number of bacteria in the blood, the nutritional and immunologic status of the host, and the timing and nature of therapeutic intervention**(Chiesa et al., 2004).**

Causative organism

Neonatal sepsis syndrome can cause by infection with adenovirus, enterovirus, or coxsackievirus. also sexually transmitted diseases and viral diseases, such as gonorrhea, syphilis, herpes simplex virus (HSV), cytomegalovirus (CMV),

hepatitis, HIV, rubella, toxoplasmosis, Trichomonas vaginalis, and Candida species**(Bellig et al., 2004).**

Also corynebacterium, propionibacterium, penicillium, and diphtheroidshave been implicated in neonatal infection**(Stollet al., 2008).**Additional organisms, such as Chlamydia pneumoniae, Enterobacter aerogenes, and species of Bacteroides and Clostridium have also been identified in neonatal sepsis**(Anderson et al., 2014).**

The Neonate Immune System

The neonate is unable to respond effectively toinfectious hazards because of deficits in the physiological response to infectious agents**(Anderson et al., 2014).**

The neonatal neutrophil or polymorphonuclear

The neonatal neutrophil or polymorphonuclear (PMN) cell is defective in chemotaxis and killing capacity. Decreased adherence to the endothelial lining of blood vessels reduces their ability to marginate and leave the intravascular area to migrate into the tissues prematurely has less IgGdue to the shorter period of placental transmission of immunoglobulin**(Bellig et al., 2004).**

Additionally, if the mother is immune suppressed, it is possible that less IgG can be transmitted to the infant. The

neonate is capable of synthesizing immunoglobulin M (IgM) in utero at 10 weeks of gestation; however, IgM levels are generally low at birth, unless the infant was exposed to an infectious agent during the pregnancy anddelivery. The neonate may receive immunoglobulin A (IgA) from breastfeeding but does not secrete IgA until 2-5 weeks after birth. Response to bacterial polysaccharide antigen is diminished and remains so during the first 2 years of life**(Anderson et al., 2014).**

Natural killer (NK) cells

Natural killer (NK) cells are found in greater concentration in the peripheral blood of neonates than in that of adults; however, certain antigen expressivity by the cells' membranes is diminished, thereby reducing cytolytic activity. This decreased response has been observed with infection by herpes group viruses in the neonate**(Bellig et al., 2004).**

Complement protein. The fetus is capable of complement protein production as early as 6 weeks gestational age. Infants had comparable concentrations to adults. The terminal activity for complement that leads to killing of organisms, especially gram-negative bacteria, is inefficient. This deficiency is more marked in preterm infants. Mature complement activity is not reached until infants are aged 6-10 months. Fibronectin, a serum protein that assists with neutrophil

adherence and has opsonic properties, is found in lower concentrations in neonates. Therefore, neonatal sera have reduced opsonic efficiency against GBS, E coli, and S pneumonia**(Anderson et al., 2014).**

The physical and chemical barriers to infection

The physical and chemical barriers to infection in the human body are present in the newborn but are functionallydeficient. Skin and mucus membranes are broken down easily in the premature infant. Neonates who are ill and/or premature are additionally at risk because of the invasive procedures that breach their physical barriers to infection**(Bellig et al., 2004).**

Morbidity

Race:

Black infants have an increased incidence of GBS disease and late-onset sepsis. This is observed even after controlling for risk factors of low birth weight and decreased maternal age**(Bellig et al., 2004).**

Sex:

The incidence of bacterialsepsis and meningitis, especially for gram-negative enteric bacilli, is higher in males

than in females**(Bellig et al., 2004)**and the male-to-female ratio was 1.4**(Jiang et al., 2004).**

Age:

Premature infants have an increased incidence of sepsis**(Anderson et al., 2014).**The incidence of sepsis is higher in infants with very low birth weight (<1000 g) (75.9%) **(Jianget al., 2004),**at 26 per 1000 live births, than in infants with a birth weight of 1000 -2000 g, at 8-9 per 1000 live births and thepremature babies (76.7%) ofsepsis**(Jiang et al., 2004).**

Pathophysiology:

Neonatal sepsis is one of the major health problems throughout the world Every year an estimated 30 million newborns acquire infection and 1-2 million of these die**(Afroza, 2006).**

Neonatal infection classification according to age is classified

(A) Early onset sepsis

EOS is a low incidence disease**(Polin, 2003)**the incidence is between 1 and 4 cases per 1000 live births**(Marrekchi, 2007)**

EOS present in the first 5-7 days and is usually a multisystem fulminant illness withprominent respiratory symptoms**(Naglie, 2004).**

(B) Late onset sepsis

LOS is high incidence disease, it is defined by the presence of a positive blood culture performed after 5 days of life and not associated with culture –proven EOS**(Cordero and Ayers, 2003)**LOS is a significant cause of morbidity and mortality among LBW and premature infants**(Gordon and Isaacs, 2004).**

LOS may occur as early as 5 days of age, however it is more common after the first week of life.these infants usually have identifiable focus mostly meningitis in addition to sepsis**(Naglie, 2004).**

C) Nosocomial sepsis)

The center for Disease Control and prevention (CDC) defines a nosocomial infection as any infection occurring after admission to the NICU that was not tarnsplacentally acquired**(Stoll, 2008).**

This form of sepsis occurs in high risk newborn infants.its pathogenesis is related to the underlying illness and debilitation of the infant, the flora in the NICU environment, and invasive monitoring and other techniques used in neonatal intensive care**(Naglie, 2004).**

Coagulase –negative staphylococci are the most frequent neonatal nosocomial pathogens. The emergency of nosocomial bacterial pathogens resistant to multiple antibiotics is agrowing concern.Among NICU patients methicillin-resistant staph aureus, vancomycin-resistant enterococci, and multi drug resistant gram negative pathogens are particularly alarming**(Stoll, 2008).**

(D) Late, late onset sepsis

Late, late onset sepsis onset after one month of life occur particularly in VLBW preterm infant or term infants requiring prolonged neonatal intensive care for other chronic problems**(Stoll, 2008).**

Table (1): Neonatal infection by age of onset (Stoll, 2008).

Characteristics	Early onset	Late onset	Late, late onset
Age at onset	Birth to 7 days usually <72h	7 to 30 days	>30 days
Maternal obstetric complication	Common	Un common	Varies
Prematurity	frequent	varies	Usual
Organism source	Maternal genital tract	Maternal genital tract/ environment	Environment/ community
Manifestation	multisystem	Multisystem/ focal	Multisystem/focal
Site	NICU/ community	NICU/ community	NICU/community

Mode of infection

Prenatal infection Throughout pregnancy and until the membrane rupture, thefetus is relatively protected from the microbial flora of the mother by chorioamniotic membranes, the placenta and poorly understood antibacterial factors in the amniotic fluid**(Klein and Remington, 2001).**

However there are many ways that infectious agents can reach the fetus to cause infection**(Chiesa et al., 2004)**in addition

some microbial species cause intrauterine infection that present as congenital infections in the newborn**(Gordon and Isaacs, 2004)**

Intrauterine infection is a result of clinical or subclinical maternal infection with a variety of agents (cytomegalo virus CMV, treponema pallidum, toxoplasma gondii, Rubella virus, parvovirus B19and varicella virus) by hematogenous trasplacental transmission to the fetus**(Stoll 2008).**

Transplacental infection may occur at any time during gestation.and signs and symptoms may be present at birth or be delayed for months or years. Infection may result in early spontaneous abortion, congenital malformation, intrauterineretardation, premature birth, still. birth, acute or delayed diseases in neonatal period, asymptomatic persistent infection with sequelae later in life.some cases no apparent effects are seen in the newborn infant the timing of infection during gestation effects the outcome.first trimester infection may alter embryogenesis, with resulting congenital malformation**(Stoll, 2008).**

Natal infection

The human birth canal is colonized with aerobic an anaerobic organisms.vaginal delivery results in contamination and the beginning of colonization of skin and gut of the

newborn**(Badrawi et al., 2001)**the commonest causative organisms are group B streptococci (GBS), gram negative enteric organismsStaphylococcus Aureus, and Streptococcus fecalis**(Naglie, 2004).**

Aspiration or ingestion of bacteria in amniotic fluid mayled to congenital pneumonia or systemic infection with manifestation becoming apparent before delivery (fetaldistress), at delivery (prenatal asphyxia) or after a latentperiod of few hours (respiratory distress, shock) resuscitation at birth, particularly if it involves endotracheal intubation, insertion of umbilical or both is associated with increased risk of infection**(Sotll, 2008).**

Postnatal infection

Microorganisms can be introduced after birth from environment surrounding the newborn, either in the nursery or at home**(Chiesa et al., 2004)**

Postnatal infections may be transmitted by direct contact with hospital personnel, the mother, or other family members, from the breast milk, or from contaminated equipment.the most common source of the postnatal infection in hospitalized newborn is hand contamination of health care personnel**(Stoll, 2008).**

Pathogenesis

Risk factors for neonatal infection

Maternal, environmental, and host factors determine which infants exposed to potentially pathogenic organisms will develop invasive bacterial infection**(puopolo, 2008).**

I-Risk factor of early onset sepsis

Obstetric risk factors

At least oneofthe obstetricriskfactors was present in 79%of early-onset cases caused by other organisms**(Schuchat et al., 2000).**Rupture of the membranes more than 18 hours before delivery, rupture of the membranes before the onset of labour is associated with increase the incidence to1%for proven and 2%for suspected sepsis**(Gerdes, 2004).**

1-Chorioamnionitis and maternal fever

The definition of chorioamnionitis is the presence of fever (.>37) with two or more of the following findings;fetal tachycardia, uterine tenderness, foul vaginal discharge or maternal leukocytosis**(stoll, 2008)**maternal fever without chorioamnionitis also raises the risk of sepsis**(Gerdes, 2004).**

2-Amniotic fluid problems

Meconium-stained, foul smelling or cloudy amniotic fluid**(Naglie, 2004).**