INTRODUCTION

Neonatal sepsis is a significant cause of morbidity and mortality particularly in preterm and low birth weight infants ***(Stoll, 2011)***. Mortality rate in neonatal sepsis is about 20%-50%. It differs according to the type of organism involved. Gram negative bacteria and enterococci cause the highest mortality rate in neonatal sepsis ***(Karunakaran et al., 2007).***

Spectrum of organisms which cause neonatal sepsis varies in different countries and sometimes changes from one center to another within the same country ***(Desinor et al., 2004).*** This is due to the changing pattern of antibiotic use and changes in life style ***(Darmstadt et al., 2000).*** The spectrum of organisms most commonly implicated in neonatal sepsis are quite different in industrialized countries compared with middle and low income countries ***(Sundaram, 2009).***

The most common pathogens of bacterial sepsis and antibiotic sensitivity patterns vary in different parts of the world, different hospitals and even in the same hospital at different time ***(Shrestha et al., 2010).***

The most common causes of neonatal sepsis are group B streptococci (GBS) Escherichia coli (E. coli) and Listeria monocytogenes in developed countries and gram negative bacteria and coagulase-negative staphylococci in developing countries ***(Palazzi et al., 2006).***

Gram negative bacteria are the predominant causes of neonatal sepsis and among them Klebsiella is the most common pathogen, especially in developing countries ***(Kaistha, 2009).***

An increase in sepsis caused by Gram-negative organisms has been reported in recent years ***(Kristóf et al., 2009).*** Neonatal sepsis caused by Gram-negative microorganisms is responsible for 18%-78% of all neonatal sepsis ***(Macharashvili et al., 2009).***

The inadvertent use of broad-spectrum antibiotics has led to the emergence of multidrug resistant Gram-negative bacteria ***(Koksal, 2001)***. Klebsiella species are of significant importance in this regard ***(Roilides et al., 2000)***.

Due to different pathogens involved in neonatal sepsis of onset, appropriate management and care depends on our knowledge about the causative organisms and their sensitivity to antibiotics. So results of the studies in other parts of the world are not suitable for the management of neonatal sepsis in the regions that no study has been done ***(Al-Zwaini, 2002).***

AIM OF THE WORK

The aim of this study is to:

1- Evaluate the changing pattern of the most common causes of the neonatal sepsis.

2- Identify the predisposing factors of neonatal sepsis due to gram negative bacteria.

3- Study the antibiotic sensitivity and resistance patterns of gram negative isolates.

4- Know the outcome of neonatal sepsis due to gram negative bacteria.

NEONATAL SEPSIS

Neonatal sepsis is one of the major causes of morbidity and mortality among the newborns in the developing countries. It is a life-threatening clinical emergency that demands urgent diagnosis and treatment. High rate of antibiotic resistance against commonest bacterial pathogen has further worsened the situation ***(Mahmood et al., 2002).***

Definition:

Neonatal sepsis, sepsis neonatorum and neonatal septicemia are terms refer to a constellation of clinical and laboratory findings associated with invasive infection during the first 30 days of life. Traditionally, the neonatal sepsis syndrome has been associated with bacteremia, but it may be caused by a variety of pathogens, including bacteria, viruses and fungi ***(McMillan et al., 2006)***.

Neonatal sepsis is a clinical syndrome characterized by systemic signs of circulatory compromise (e.g., poor peripheral perfusion, pallor, hypotonia, poor responsiveness) caused by invasion of the bloodstream by bacteria in the first month of life ***(Thaver and Zaidi, 2009).***

Short (2004) stated that sepsis is defined as a phenomenon related to the hosts response to infection and is considered an uncontrolled, unregulating and self sustaining intravascular inflammatory reaction and excessive anti- inflammatory response.

Neonatal sepsis can be defined as "a clinical syndrome characterized by systemic signs and symptoms and bacteremia during the first month of life ***(Mahmood et al., 2002).***

The term systemic inflammatory response syndrome (SIRS) is used to describe a clinical syndrome characterized by two or more of the following: (a) fever or hypothermia, (b) tachycardia, (c) tachypnea or hyperventilation and (d) abnormal white blood cells or increase in immature forms. SIRS may be a result of a variety of immunologic, endocrinologic, traumatic, surgical, chemotherapeutic and infectious insults. Sepsis is considered when there is a systemic response to a possible infection. Evidence of bacteremia or an infectious focus is not required ***(Chiesa et al., 2004)***.

When sepsis is accompanied by organ dysfunction, hypoperfusion or hypotension, the sepsis is considered severe. Septic shock ensues when hypotension develops despite adequate fluid replacement. Finally, in the presence of altered organ function in an acutely ill patient, so severe that homeostasis cannot be maintained without intervention, multiple-organ dysfunction syndrome is diagnosed. The term systemic inflammatory response syndrome (SIRS) is most frequently used to describe this unique process of neonatal infection and the subsequent systemic response. Neonates with SIRS have a spectrum of clinical symptoms that represent progressive stages of the pathologic process ***(Stoll, 2011)***.

EPIDEMIOLOGY OF NEONATAL SEPSIS

Incidence:

The reported incidence of neonatal sepsis varies from 7.1 to 38 per 1000 live births in Asia, from 6.5 to 23 per 1000 live births in Africa, and from 3.5 to 8.9 per 1000 live births in South America. By comparison, rates reported in the United States and Australasia range from 1.5 to 3.5 per 1000 for EOS sepsis and up to 6 per 1000 live births for LOS sepsis, a total of 6–9 per 1000 for neonatal sepsis ***(Vergnano et al., 2005)***.

Neonatal sepsis has a fairly low incidence at birth (1–10/1000 live births) but may affect up to 16% of infants in the neonatal intensive care unit (NICU) with birth weight of 501–1500 gm ***(Kurt et al., 2007)***. The highest rates occur in low-birth-weight (LBW) infants, those with depressed respiratory function at birth, and those with maternal perinatal risk factors ***(Porter et al., 2005)***.

Race

Black infants have an increased incidence of group B streptococci (GBS) disease and late onset sepsis. This is observed even after controlling for risk factors of low birth weight and decreased maternal age ***(Anderson-Berry et al., 2014).***

Mortality and morbidity

Neonatal mortality accounts for more than one-third of deaths of children aged less than five years ***(Rajaratnam et al., 2010).*** Infection accounts for one-fourth of total neonatal deaths. About 99% of these neonatal deaths take place in low and middle-income countries ***(Lawn et al., 2004).*** Bacterial infection is a significant cause of neonatal and early childhood admissions to hospitals and probably of morbidity in the community but its burden is unclear ***(Rahman et al., 2002).*** Identification and treatment of newborns with infection are weak in many developing countries ***(Thaver and Zaidi, 2009).***

Classification of neonatal sepsis

Neonatal sepsis is categorized as early or late onset. Early onset sepsis occurs at <72 hours. Eighty-five percent of newborns with early-onset infection present within 24 hours, 5% present at 24-48 hours, and the rest present within 48-72 hours ***(Van den Hoogen et al., 2010)***.

Early onset sepsis 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 ***(Van den Hoogen et al., 2010).***

Late-onset sepsis occurs at > 72 hours of life and is acquired from the care giving environment. The infant's skin, respiratory tract, conjunctivae, gastrointestinal tract and umbilicus may become colonized from the environment, leading to the possibility of late-onset sepsis from invasive microorganisms. Vectors for such colonization may include vascular or urinary catheters, other indwelling lines or contact from caregivers with bacterial colonization ***(Van den Hoogen et al., 2010)***. Late, late onset infections occurs > 30 days, while very –late-onset neonatal sepsis defined as sepsis starts >60 days after birth ***(Kaufman and Fairchild, 2004).***

Pneumonia is more common in early onset sepsis, whereas meningitis and bacteremia are more common in late-onset sepsis ***(Anderson - Berry et al., 2014)***.

Table (1): Neonatal infection by age of onset

Characteristics	Early onset	Late onset	Late, late onset
Age of onset	Birth to 7 days usually<72hour	7 to 30 days	>30 days
Maternal obstetric complications	Common	Uncommon	Varies
Prematurity	Frequent	Varies	Usual
Organism source	Maternal genital tract	Maternal genital tract/ environment	Environmental/ community
Manifestation	Multisystem	Multisystem or focal	Multisystem or focal
Site	Nursery, NICU, community	NICU, community	NICU, community

(Stoll, 2011)

ETIOLOGY OF NEONATAL SEPSIS

Early-onset neonatal sepsis

The most commonly microorganisms associated with early-onset neonatal sepsis include GBS, E coli, Coagulase-negative Staphylococcus, H influenzae and Listeria monocytogenes ***(Klinger et al., 2009)***.

Late-onset neonatal sepsis

Organisms that have been implicated in causing late-onset neonatal sepsis include Coagulase-negative staphylococci, S aureus, E coli, Klebsiella, Pseudomonas, Enterobacter, Candida, GBS, Serratia, Acinetobacter and Anaerobes ***(Anderson - Berry et al., 2014)***.

Risk factors

An awareness of the many risk factors associated with neonatal sepsis prepares the clinician for early identification and effective treatment, thereby reducing mortality and morbidity ***(Anderson-Berry et al., 2014).***

The most common risk factors associated with neonatal sepsis include:

I- Maternal risk factors:

A- Prolonged premature rupture of membranes (PROM):

Once the membranes have been ruptured for >18 hours, the risk of sepsis in the neonate increases approximately 10 fold over

baseline, to a rate of 1% for proven and 2% for suspected sepsis. The risk of proven sepsis with PROM in the preterm infant increases to 4%–6%. A 5-minute Apgar score <6 also raises the sepsis risk to 3%–4% ***(Gerdes, 2004).***

PROM may occur in response to an untreated infection of the urinary tract or birth canal and is also associated with previous preterm delivery, uterine bleeding in pregnancy, and heavy cigarette smoking during pregnancy ***(Bell et al., 1989).***

Rupture of membranes without other complications for more than 24 hours prior to delivery is associated with a 1% increase in the incidence of neonatal sepsis; however, when chorioamnionitis accompanies the rupture of membranes, the incidence of neonatal infection is quadrupled ***(MacDonald et al., 2005).***

B- Chorioamnionitis and maternal fever:

Maternal fever without signs of chorioamnionitis raises the risk of sepsis but may be confounded by non-infectious causes of maternal fever such as dehydration or epidural anesthesia. Another commonly accepted risk factor is the presence of foul smell of the amniotic fluid due to the presence of anaerobic bacteria ***(Gerdes, 2004).***

A recent multicenter study demonstrated that clinical chorioamnionitis and maternal colonization with GBS are the most

important predictors of subsequent neonatal infection following PROM ***(Anderson–Berry et al., 2014)***.

C- Maternal colonization with group B streptococci (GBS):

The most common etiology of neonatal bacterial sepsis is GBS. Nine serotypes exist and each is related to the polysaccharide capsule of the organism. Types I, II and III are commonly associated with neonatal GBS infection. The type III strain has been shown to be most highly associated with CNS involvement in early-onset infection, whereas types I and V have been associated with early-onset disease without CNS involvement ***(Anderson-Berry et al., 2014)***.

D- Procedures disturbing the integrity of uterine contents:

Procedures disturbing integrity of uterine contents as amniocentesis, cervical cerclage, transcervical chorionic villus sampling or percutaneous blood sampling permit entry of vaginal organisms to the skin causing amnionitis and secondary fetal infection ***(Chiesa et al., 2004).***

E- Urinary tract infection (UTI):

UTI of any cause raises the risk of sepsis in the neonate due to raising the risk of prematurity and chorioamnionitis ***(Gerdes, 2004).***

F- Traumatic or septic delivery:

Infection of skin abrasions after use of obstetric forceps or infection of cephalohematoma following fetal monitoring procedures increases the risk of infection in the neonates ***(Chiesa et al., 2004)***.

II- Neonatal risk factors:

A- Prematurity and low birth weight (LBW):

The most important neonatal factor predisposing to infection is prematurity or LBW. Preterm infants have a 3- to 10-fold higher incidence of infection than full-term normal birth weight infants ***(Stoll, 2011).***

Premature infants are particularly vulnerable to sepsis because of their immature immune systems, poor skin integrity, repeated handling and exposure to multiple personnel and invasive procedures ***(Stoll et al., 2002a)***. Preterm infant has poor skin and mucosal barriers to infection. These anatomic barriers may be further compromised by trauma before, during or after delivery, such as those caused by fetal scalp electrode placement, fetal scalp blood sampling, abrasions during delivery and injury from obstetric forceps ***(McMillan et al., 2006)***.

As many as 65% of infants with birth weights less than 1,000 g have at least one infection during their initial hospitalization. Approximately 35% of preterm babies delivered at

less than 28 weeks will develop a hospital-acquired infection during their stay ***(Bartels et al., 2007)***.

B-Apgar score:

A 5-minute Apgar score <7 carries 56-fold risk of sepsis for infants delivered vaginally higher than infants with higher scores. Apgar score less than 5 at one minute may be due to sepsis, especially with the presence of risk factors for infection ***(Shah et al., 2006)***.

C- Sex:

The incidence of bacterial sepsis and meningitis, especially for gram-negative enteric bacilli is higher in males than females ***(Anderson-Berry et al., 2014).***

D- Underlying diseases.

Perinatal asphyxia, hyperbilirubinemia, galactosemia, malformations, patent ductus arteriosus and meconium aspiration syndrome increase the risk of infection ***(Stronati and Borghesi, 2012)***.

E- Immaturity of the immune system.

Neonates have lower IgA levels and lower serum levels of complement factors. Several studies have demonstrated an immaturity in chemotaxis, phagocytosis and cytotoxicity. Furthermore, maternal- to-fetal transplacental transfer of IgG

occurs mainly during the third trimester of pregnancy and neonates with gestational age < 32 weeks have lower IgG levels and an immature humoral immune response ***(Mussi-Pinhata and Rego, 2005).***

F- Resuscitation:

Infants, who had fetal distress, were born by traumatic delivery or were severely depressed at birth and required intubation and resuscitation have an increased risk of bacterial infection ***(Gomella et al., 2009).***

G- Drugs:

An association between systemic postnatal steroids for chronic lung disease and sepsis has been observed in several studies ***(Stronati and Borghesi, 2012).*** In a study on 371 VLBW neonates treated with dexamethasone at 14 days of life, showed that the incidence of infection was significantly higher in the treated than in the control group ***(Stoll et al., 1999).***

The use of H2-antagonists for stress gastritis and gastroesophageal reflux increases the risk of both sepsis and necrotizing enterocolitis in preterm neonates ***(Guillet et al., 2006).***

Frequent use of broad-spectrum antibiotics in the NICU interferes with colonization by normal flora and facilitates colonization of the infant skin, umbilicus, nasopharynx and

gastrointestinal tract by pathogenic bacteria or fungi ***(Judith et al., 2004)***.

H- Invasive procedures and nutritional history:

Invasive procedure which interrupt the normal barriers such as intravascular lines, endotracheal intubation, chest tubes, invasive monitoring of respiratory function, metabolic support as total parenteral nutrition (TPN), various drains and shunts for hydrocephalus all increase the risk of sepsis ***(Houseknecht et al., 1996)***.

Infants with prolonged duration of central catheters and TPN, those with delayed initiation of enteral feeding and those with a prolonged period to reach full enteral feedings or to regain their birth weight are all at substantially increased risk of LOS ***(Stoll, 2011)***.

I- Iron overload or therapy:

Iron overload or therapy increases the susceptibility of neonates to infection as it enhances the growth of certain organisms ***(Raghavendra and Georgieff, 2007).***

J- Nursery design and staffing:

Overcrowding and understaffing greatly affects the risk of bacteremia. Overcrowding and longer workloads decrease compliance with hand washing and raise the risk of nosocomial infection ***(Robert et al., 2000).***