INTRODUCTION

Neonatal sepsis is a major problem across the globe. Infections are a major contributor to newborn deaths in developing countries. Majority of these deaths occur at home without coming to medical attention. The child survival cannot be achieved without substantial reductions in infection-specific neonatal mortality **(Thaver et al., 2009).**

Neonatal sepsis may be categorized as early-onset or late-onset. Of newborns with early-onset sepsis, 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 **(Dagan et al., 1985).**

The gut of a neonate is colonized by bacteria immediately after birth. Among the hundreds of bacteria that colonize the gut, there are some potential pathogens **(Guarner&Malagelada, 2003; Sharma et al., 2009).** Not all colonization leads to infection, the pathogenicity of aerobic Gram-negative bacilli (GNB) may predispose neonates towards infection **(Graham et al., 2007; Pierro et al., 1998; vanSaene et al., 2003).**

The vulnerability of the immune system and the gut barrier in neonates, particularly in those who are premature and of low birth weight, make the neonate especially prone to colonization with aerobic GNB **(parijat et al., 2011).**

Studies have shown that GNB in the gut may predispose neonates to septicaemia **(Pierro et al., 1998; van Saene et al., 2003).** Evidence from surgical neonates shows that gut overgrowth, particularly with GNB, causes depression of the mucosal and systemic immunity leading to the development of sepsis **(Donnell et al., 2002)** However, in developing countries such as Egypt, neonatal sepsis occurs in large numbers of neonates without any surgical intervention **(Parijat et al., 2011).**

AIM OF THE WORK

To detect the pattern of colonization of the neonatal gut with gram negative bacilli in a tertiary care hospital (Obstetrics & Gynecology Hospital,ASU) and the possible association between this colonization and the subsequent development of neonatal sepsis.

Chapter 1

NEONATAL SEPSIS

Introduction:

Sepsis is characterized by systemic manifestations resulting from bacterial invasion and multiplication in the blood stream, and can lead to high neonatal mortality and morbidity **(Miura et al., 1999).** There is evidence that perinatal and neonatal infections are associated with neurodevelopmental impairment in preterm infants **(Stoll et al., 2004).**

Neonatal sepsis or septicaemia is a clinical syndrome characterized by systemic signs of circulatory compromise (e. g. lethargy, temperature instability, poor peripheral perfusion, pallor, hypotonia, tachypnea, tachycardia, poor responsiveness, abdominal distension) caused by invasion of the bloodstream by bacteria in the first month of life. In the pre-antibiotic era neonatal sepsis was usually fatal **(Thaver and Zaidi, 2009).**

Suspected sepsis" is one of the most common diagnoses made in the NICU**(Escobar, 1999).** However, the signs of sepsis are nonspecific, and inflammatory syndromes of noninfectious origin mimic those of neonatal sepsis. Most infants with suspected sepsis recover with supportive care (with or without initiation of antimicrobial therapy). The challenges for clinicians are threefold: (1) identifying neonates with a high likelihood of sepsis promptly and initiating antimicrobial

therapy; (2) distinguishing "high-risk" healthy-appearing infants or infants with clinical signs who do not require treatment; and (3) discontinuing antimicrobial therapy once sepsis is deemed unlikely. The purpose of this clinical report is to provide a practical and, when possible, evidence-based approach to the diagnosis and management of early-onset sepsis, defined by the National Institute of Child Health and Human Development and Vermont Oxford Networks to sepsis with onset at ≤3 days of age.

A positive-septic screen was defined as the presence of any two of the following four parameters: (i) total leukocyte count TLC using a Coulter cell counter. Values <5000/cmm or ≥20, 000/cmm (ii) absolute neutrophil count, 1800 cells cmm; Neutropenia /Neutrophilia (age adjusted count, described by **Rodwell et al.,1993**) (iii) CRP levels ≥6 mg/L and with 1 in 4 dilution of serum a positive reaction indicated serum CRP con-centration of 24 mg/L **(Srivastava et al., 1993)** and (iv)micro-erythrocyte sedimentation rate. 10 mm in the first hour **(Chiesa et al., 2004; NNPD, 2005).**

Neonates with one or more of the aforementioned signs and a positive-septic screen, without or with a positive-blood culture, were considered'clinical sepsis only' or 'clinical sepsis and culture-positive sepsis', respectively **(Chiesa et al., 2004; NNPD, 2005).**

Classification of neonatal sepsis:

A) Early onset sepsis (EOS):

In many reports the sepsis has been classified as early –onset sepsis (EOS), if the infection starts before 72 hours of life **(Mahkoul et al., 2005).**

The infections with 'early onset'originate from intrauterine colonization, but may also be acquired during delivery by contact with pathogens in the birth canal **(Jiang et al., 2004).** In addition, they use 'very early-onset' disease, if it starts less than 24 hrs of life, when infection probably occurred in utero, justifying the classification of this group as a single entity **(Haque et al., 2004).**

B) Late-Onset Sepsis (LOS):

The late onset sepsis defined if it occurred after 3 days of life. It is propably the result of nosocomial infection or community acquired and neonates usually present with septicemia, pneumonia or meningitis.

Factors that might increase the risk of community acquired LOS include poor hygiene. Poor cord care and bottle-feeding. In contrast, breastfeeding helps in prevention of infections **(Sanker et al., 2008).**

C) Late-late onset sepsis:

Late, late-onset infections (onset after 1 month of life) occur particularly in VLBW preterm infants or term infants requiring prolonged neonatal intensive care for other chronic problems **(Stoll, 2008).**

These definitions has contributed greatly to diagnosis and treatment by identifying which micro organisms are likely to be responsible for sepsis during these periods and the expected outcomes of infection **(Jeong et al., 2006).**

The World Health Organization (WHO) estimates that 1 million deaths per year (10% of all under-five mortality) are due to neonatal sepsis and that 42% of these deaths occur in the first week of life **(Lawn JE et al., 2005).**

Table (1):Classification of neonatal infection:

Characteristics	Early onset	Late onset	Late, late (nosocomial) onset.
Age at onset	Birth to 7 days usually<72hrs	7 to30 days	>30 days
Maternal obstetric complications	Common	Uncommon	Varies
Prematurity	Frequent	Varies	Usual
Organism source	Maternal genital tract	Maternal genital tract/environment.	Environment/ Community
Manifestation	Multisystem	Multisystem or focal	Multisystem or focal
Site	Normal nursery, NICU, community	NICU, community	NICU, community

(Stoll, 2008)

Etiology:

A)Risk factors:

Distal risk factors for neonatal sepsis include poverty and poor environmental conditions. Proximate factors include prolonged rupture of membranes, preterm labour, maternal pyrexia, unhygienic intrapartum and postnatal care, low birth weight, and prelacteal feeding of contaminated foods and fluids. In high-income countries the major concern is the increasing numbers of extremely premature infants with high nosocomial infection rates

due to multiresistant organism intensive care units, while in low-income countries, the more pressing issues are the high proportion of home deliveries in unclean environments predisposing to sepsis **(Darmstadt et al., 2005; Bahl et al., 2009; Schuchat et al., 2000).**

Risk factors also can be classified into :

1)Maternal risk factors:

General condition and delivery:

Septic or traumatic delivery, maternal poverty, pre-eclampsia, cardiac disease and diabetes mellitus risk factors **(Haque., 2004).**

Prolonged premature rupture of membranes (PROM):

Maternal risk factors for infection include premature onset of labour and prolonged premature rupture of fetal membranes (PROM>18hrs) **(Chiesa et al., 2004).**

Maternal colonization with group B streptococci (GBS):

Neonatal exposure to GBS during birth is very common and results in the colonization of one in 10 infants. Most infants appear to successfully control GBS at the dermal and mucosal surfaces. Translocation of bacteria across mucosal surfaces can be assumed to occur frequently, usually leaving the immunological homeostasis of the host undisturbed. In most cases of GBS sepsis, newborn infant aspirate GBS that colonize the birth canal. GBS infections in

infants delivered by caesserian section with membranes intact rarely occur. Newborns with GBS sepsis have excessively high cord blood levels of proinflammatory cytokines, indicating that the infection and inflammatory process started prior to births **(Munfund and Pugin, 2001).**

Intraamniotic infection:

Intra amniotic infection (IAI) refers to infection of the amniotic fluid, membranes. placenta associated with 20% to 40% of early neonatal sepsis and pneumonia **(Cornette, 2004).**

The perinatal morbidities and mortality related to IAI in term and preterm neonates include pneumonia, meningitis and sepsis. Possible mechanisms include villous edema, fetal vascular inflammation, abruption placenta, increase in oxygen consumption related to hyperthermia and or a primary endotoxin effect on the fetu **(Aziz et al., 2009).**

Untreated 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).**

Procedures disturbing the integrity of uterine contents:

Aminocentesis, cervical cerclage and transcervical chorionics villus sampling or percutaneous blood sampling can permit entery of skin or vaginal organisms causing amnionitis and secondary fetal infection **(Chiesa et al., 2004).**

2)Neonatal risk factors:

Resuscitation at birth:

Infants who had fetal distress, were born by traumatic delivery or were severly depressed at birth and required intubation and resuscitation are more vulnerable to develop EOS **(Gomella et al., 2004).**

Birth weight and gestational age:

The incidence of neonatal sepsis is inversely proportional to gestational age and birthweight. In VLBW, culture proven early onset sepsis is seen in 2 % ; likewise late onset sepsis is reported to be approximately 25% **(stoll et al., 2005).**

Invasive procedures:

Abdominal surgery, use of umbilical and other central lines were associated with a significantly increased rate of infection. The rate of infection increased with an increasing duration of central venous catheter use **(Bizzaro et al., 2005).**

Therapy:

Exposure to more than two antibiotics, parentral nutrition for > 5 days, use of intravenous lipid emulsion for >7 days, exposure to H2 blocker, length of stay of >7 days and assisted ventilation are associated with increased risk of infection **(saiman et al, 2000).** Third generation cephalosporin exposures to systemic corticosteroids are associated with increased risk of fungal infection **(Benjamin et., 2006).**

Sex:

Generally, the male gender is significant factor to EOS **(Haque et al., 2004).**

Immune deficiency and metabolic disorders:

History of immune deficiency disorders such as severe combined immune deficiency syndrome and some inborn errors of metabolism such as galactosemia may present in the first week of life with Escherichia coli (E. COLI) sepsis **(Robinson et al., 2008).**

3)Nosocomial infection:

Nosocomial infection is defined as a localized or systemic condition that results from adverse reaction to the presence of an infectious agent (s) or its toxin (s) and that was not present or incubating at the time of admission to the hospital **(Srivastava and shetty, 2007).**

Nosocomial infections are one of the leading causes of mortality and morbidity in the neonatal intensive care unit (NICU). Neonatal nosocomial infections are late-onset infections (appearing after the first 72 h of life)in hospitalized infants. The incidence of infections varies widely among NICUS (7% to24.5%) depending on environmental factors and on differences in clinical practice **(Edwards et al., 2002).**

B)Causative organisms:

1)Infection with gram –ve organisms:

Gram negative organisms are less prevalent, but associated with greater mortality (19%-36%) **(Benjamin et al., 2004).** Risk factors for gram negative infections are: central venous catheters, catheterization for more than 10 days, nasal continous positive airway pressure, use of H2blockers and proton pump inhibitors. GIT tract serves as a reservoir for G-ve organisms and colonization in this important system predisposes neonates to infection **(Graham et al., 2007).**

Escherichia coli:

E. coli often presents at delivery and is characterized by bacteremia with or without meningitis **(Mahkoul et al., 2005).**

Enterobacter, Klebsiella, Serratia&Cirobacter spp:

Klebsiella spp. Infection in developing countries varies between 2.9 and 12.3 per 100 admissions, with case fatality rate of 18% to 68%. *Enterobacter* spp. is frequently isolated in neonatal and pediatric intensive care units, particularly in low birth weight and premature infants **(Zaidi et al., 2005).**

Pseudomonas spp:

Pseudomonas infection is rarely perinatally acquired:however it is among the most common gram –ve organisms causing

nosocomial infections. *P.saeruginosa* is commonly thought of as a" water bug", thriving in moist environments such as humidified incubators, sinks and ventilators. Hands of healthcare workers have also been identified as important reservoir **(Ladhani and Grandsen., 2002).**

Haemophilus influenza:

Haemophilus influenza may be vertically transferred from mother to infant at the time of delivery and occasionally causes EOS in preterm infants. Mortality has been reported as high as 90% **(Kristof et al., 2009).**

Anaerobic bacteremia:

The role of anaerobes (particularly *Bacteroides fragilis*) remains unclear, although deaths have been attributed to *bacteroides* bacteremia **(Kristof et al., 2009).**

2)Infection with gram positive organisms:

Gram-positive organisms accounts for 45-77%of infections. Of the gram negative organisms, coagulase-negative staphylococci are the most prevelant **(Perlman et al., 2007).**

Coagulase-negative staphylococci (coNs):

In many institutions CoNS are now the most common cause of all cases of neonatal bacteremia accounting for >50% of bloodstream infections **(Bindyana et al., 2006).**

The major species involved in neonatal infection is S. epidermidis. The majority of CoNS colonization is acquire nosocomically. Predominantly from the hands of health care workers. Risk factors are central vascular catheters which remain in place for prolonged periods, the use of parenteral nutrition and the administration of intravenous lipid infusions which provide a growth medium for the organism and frequent use of broad spectrum antibacterial (**Chapman and Faix, 2003).**

Streptococcus agalactiae, group B streptococcus (GBS):

Neonatal exposure to GBS during birth is very common and results in the colonization of one in 10 infants **(Jiang et al., 2004)**

In most cases of GBS sepsis, newborn infants aspirate GBS that colonize the birth canal. GBS infections delivered by caesarian section with membranes intact rarely occur **(Munford et al., 2001).**

Staphylococcus aureus:

The major reservoir of S. aureus in the neonate is the umbilical cord **(Cimolai, 2003).** Methicillin –resistant *S. Aureus* (MRSA) can be a special nosocomial pathogen in the NICUS. Overcrowding, limited space, inadequate cleaning of the equipment and initial lack of correct attitude to handwashing techniques appear to contribute to the spread of *MRSA* **(Usukara and Igarashi, 2003).**