INTRODUCTION

Sepsis is the commonest cause of neonatal mortality. Sepsis is a clinical syndrome characterized by symptoms and signs of neonatal infection with or without accompanying bacteremia in first month of life. It encompasses various systemic infection of newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection…etc ***(Nitin and Tanu, ٢٠٠٦).***

Neonatal sepsis can be divided into two categories early onset sepsis, occurring in the first seven days of life, and late onset sepsis occurring after the first seven days of life. Early onset sepsis is a severe infection affecting multi-organ systems and late onset sepsis is usually a slowly progressive illness often with focal infection ***(Cloherty et al., ٢٠٠٤)***.

Manifestations are mostly non-specific features including hypothermia, poor crying, lethargy, poor suckling, bradycardia or tachycardia. Specific features are related to various systems FOR example bulging anterior Fontanelle in central nervous system, hypotension in cardiovascular system affection, hematological system affection can present with bleeding tendency and petichae, Skin affection can present with mottling and pustules ***(Mathur, ٢٠٠٩).***

Inborn error of metabolism are group of disorders in which there is a block at some point in normal metabolic pathway caused by genetic defect of specific enzyme or a

coenzyme. It includes disturbances related to proteins, fats, carbohydrates, vitamins, trace elements….etc ***(Saundubray et al., ٢٠٠٦).***

Amino-acidopathy and organo-acidopathy are the most common acute life threatening inborn error of metabolism in neonatal period ***(Shulze et al., ٢٠٠٤).***

Many of the inborn errors of metabolism, including urea cycle defects tend to manifest with non-specific finding such as poor feeding, drowsiness, lethargy, hypotension which are manifestations simulating sepsis ***(Summar, ٢٠٠١).***

Examination findings may provide a clue to underlying inborn error of metabolism for example encephalopathy with or without metabolic acidosis in organic acidemia and urea cycle defects, jaundice in Gilbert and Criggler-najjar syndrome, liver failure in tyrosinemia and galactosemia, persistent and severe hypo-glycemia in galactosemia and fatty acid oxidation defect, dysmorphic features in peroxisomal disorders and pyruvate dehydrogenase deficiency ***(Cataltepe and Levy, ٢٠٠٨).***

Sepsis induces a catabolic state and metabolic disorders that includes loss of body weight, muscle wasting and acute phase protein synthesis in liver ***(Breuille et al., ١٩٩٣).***

Amino-acid extraction by liver is enhanced resulting in decreased plasma amino acid concentration. L-arginine is an essential amino-acid that plays an important role in immune and

vascular function in sepsis, its plasma concentration have been variably reported to be decreased in sepsis ***(Chiarla et al., ٢٠٠٥).***

Glutamine is an essential amino-acid which is important in mantaining the health of GIT (gastrointestinal tract) and immune system, also it has been shown to have beneficial effect on Hepatocyte metabolism during neonatal sepsis ***(Vemeulen et al., ٢٠٠٧).***

Inborn error of metabolism must be suspected whenever a patient presents with metabolic disturbances or neonatal sepsis. Prompt detection requires high index of suspicion and early measurement of biochemical markers such as ammonia and lactate together with performing screening test. Diagnosis is important not only for treatment but also for genetic counseling ***(Childs et al., ٢٠٠١).***

AIM OF THE WORK

To detect metabolic derangement in patient of neonatal sepsis, aiming to discover mild inborn error of metabolism exacerbated by sepsis and to study the reversible metabolic changes induced by sepsis.

NEONATAL SEPSIS

Definition:

Neonatal sepsis is an invasive infection occurring within first ٢٨ days of life ***(Shim et al., ٢٠١١).*** It encompasses various systemic infections of the newborn such as septicaemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection ***(Kaftan and Kenney, ١٩٩٨).***

Incidence:

It occurs in a range of ١-١٠/١٠٠٠ live births and despite advances in perinatal care, neonatal sepsis is still a significant cause of morbidity and mortality ***(Shim et al., ٢٠١١).*** It is estimated that up to ٢٠٪ of neonates develop sepsis and approximately ١٪ die of sepsis related causes٢. Sepsis related mortality is largely preventable with rational antimicrobial therapy and aggressive supportive care ***(Stoll et al., ١٩٩٩).***

Aetiology:

A number of pathogens have been associated with sepsis in the neonatal period. The predominant agents are bacterial, but viruses including herpes simplex and enteroviruses have been associated fulminant neonatal sepsis with high mortality ***(Verboon et al., ٢٠٠٥ and Verboon et al., ٢٠٠٨ and Kawada et al., ٢٠٠٤).***

Gram-positive etiologies of sepsis are dominated by GBS and coagulase-negative staphylococcus (CoNS) ***(Stoll et al., ٢٠٠٢ and Hyde et al., ٢٠٠٤).*** While lethality and shock from GBS have been well described, mortality associated with CoNS is extremely low and septic shock is rare ***(Karlowicz et al., ٢٠٠٠; Stoll et al., ٢٠٠٢ and Stoll et al., ٢٠٠٥).***

Gram-negative infection accounted for ٣٨٪ of cases of septic shock and ٦٢.٥٪ of sepsis mortality ***(Kermovant et al., ٢٠٠٨)***

Fungi (primarily Candida albicans) may also lead to fulminant neonatal sepsis and predominantly affect ELBW infants ***(Benjamin et al., ٢٠٠٤ and Benjamin et al., ٢٠٠٦ and Stoll et al., ٢٠٠٢).***

It is important to note that studies of neonatal sepsis are confounded by the limitations of sensitivity of the current diagnostic "gold standard" blood culture. Sample volume constraints in newborns may undermine the identification of organisms causing shock, particularly in preterm infants ***(Schelonka et al., ١٩٩٦).***

Pathophysiology:

The systemic inflammatory response depends on the host's ability to recognize foreign substances. Although this response facilitates microbial clearance, the host essentially pays the price of some tissue damage to achieve this goal. Figure ١ depicts a

schematic outline of the putative pathophysiologic events in the septic process.

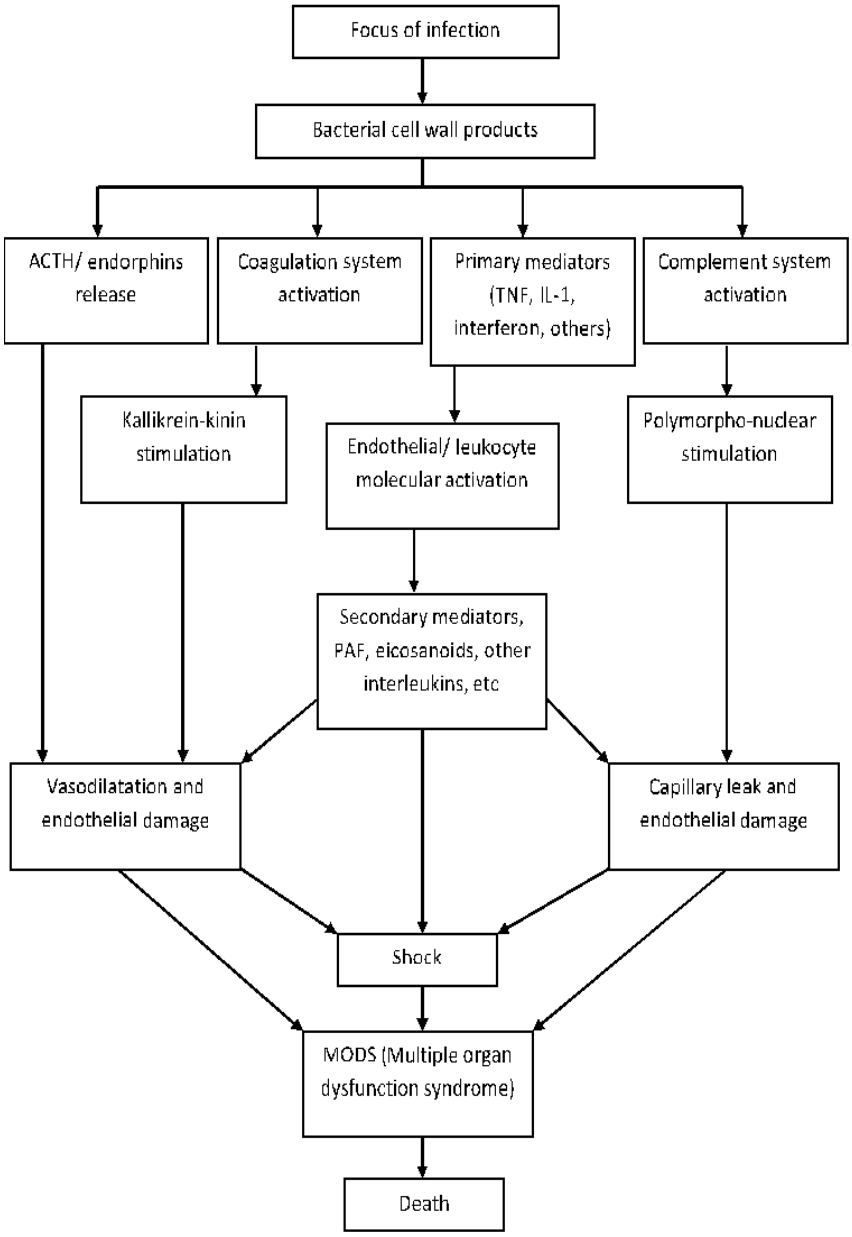

Figure (١): Hypothetical pathophysiology of the septic shock
(Bang et al., ١٩٩٩)

Risk factors for neonatal sepsis

A-Maternal factors:

Rectovaginal colonization with group B streptococcus (GBS), prolonged rupture of membranes, maternal intrapartum fever, and chorioamnionitis ***(Stoll et al., ٢٠٠٢, Shah et al., ٢٠٠٦ and Salem et al., ٢٠٠٦).***

B-Fetal Factors:

Male gender, birth weight <١٠٠٠ grams, hypogamma-globulinemia, intravenous alimentation, central venous catheters, use of steroids or drugs that decrease gastric acid acidity, prolonged duration of mechanical ventilation and development of severe necrotizing enterocolitis (NEC) were associated with severe sepsis, shock, multi-organ system failure and death ***(Sonntag et al., ١٩٩٨ and Sharma et al., ٢٠٠٧).***

In children and adults a number of polymorphisms in cytokines and their receptors as well as other host defense proteins that may either increase or decrease risk for sepsis or poor outcome from sepsis ***(Kumpf and Schumann, ٢٠٠٨ and Sutherland and Walley, ٢٠٠٩)***.

Yet, gene polymorphism studies in neonates have not yielded consistent results due to relatively small sample sizes and a general lack of formal prospective validation ***studies (Chauhan and McGuire, ٢٠٠٨ and Dzwonek et al., ٢٠٠٨)***

Classification of Neonatal Sepsis

Neonatal sepsis can be classified into two major categories depending up on the onset of symptoms

A-Early onset sepsis (EOS):

Early onset sepsis usually presents within the first ٧٢ hrs of life. In severe cases the neonate may be symptomatic in utero. (fetal tachycardia, poor beat to beat variability) or within few hours after birth. The source of infection is generally the maternal genital tract. Clinically neonates usually present with respiratory distress and pneumonia. Presence of some perinatal risk factors has been associated with an increased risk of early onset sepsis. Recommendations from developed countries suggest that presence of more than ٢ risk factors should be considered an indication for starting antibiotics.

Presence of the following high risk factors has been associated with an increased risk of early onset sepsis:

١- Low birth weight (less than ٢٥٠٠ gram) or preterm baby.

٢- Febrile illness in the mother within ٢ weeks prior to delivery.

٣- Foul smelling and / or meconium stained liquor aminii.

٤- Prolonged rupture of membranes more than ٢٤ hrs.

٥- Prolonged and difficult delivery with instrumentation.

٦- More than ٣ vaginal examination during labour.

٧- Perinatal asphyxia (Apgar score less than ٤ at ١ minute of age) or difficult resuscitation.

(Kaftan and Kenny, ١٩٩٨)

B- Late Onset Sepsis: (LOS)

Late onset sepsis usually presents after ٧٢ hours of age.The source of infection is either nosocomial or community acquired and neonates usually Present with septicemia, pneumonia or meningitis ***(Blatimore, ١٩٩٨)***.

Various factors that predispose to an increased risk of nosocomial sepsis Include NICU admissions, low birth weight, prematurity, invasive Procedures, parentral fluid therapy, ventilation and use of stock solutions. Factors that may increase risk of community- acquired late onset sepsis, include poor hygiene, poor cord care, bottle feeding and prelacteal feeds.Breast feeding on the other hand, prevents infection in neonates. ***(Wolach, ١٩٩٧).***

Clinical features:

A-Non-specific features:

Are often associated with characteristics of response to the pathogens. These non- specific signs and symptoms are also either common to or associated with other neonatal conditions like respiratory distress syndrome, metabolic disorders, and intracranial bleeding. Signs and symptoms like temperature

instability, changes in heart rate or its variability, apnoea, prolonged capillary refill time, hypotension and or decreased urine output, persistent metabolic acidosis, hypo or hyperglycaemia individually have low sensitivity and specificity with none exceeding the likelihood ratio of ١٥٪. ***(Goldstein, ٢٠٠٥).***

Added to this, are the ever changing metabolic changes due to sepsis that are reflected in the constantly changing signs and symptoms in sepsis. These changes vary from initial phase of hypo-metabolism (temperature and heart rate variability), decreased energy expenditure (lethargy), decreased cardiac output (hypotension, prolonged capillary refill time), lower oxygen consumption and vasoconstriction (peripheral cyanosis, apnoea) to the later phase of hyper- metabolism, increased energy expenditure (irritability, increased oxygen requirement), increased cardiac output (tachycardia) and high oxygen consumption (cyanotic episodes) ***(Orr et al., ٢٠٠٢)***.

B-Specific Features Related to Various systems:

Central nervous system (CNS): Bulging anterior fontanelle, blank look, high pitched cry, excess irritability, not arousable, comatose, seizures, neck retraction. Presence of these features should raise a clinical suspicion of meningitis.

Cardiac: Hypotension, poor perfusion, shock.

Gastrointestinal: food intolerance, vomiting, dirrhea, abdominal distension, paralytic ileus, necrotizing enterocolitis (NEC).

Hepatic: Hepatomegaly, direct hyperbilirubinemia (especially with urinary tract infection).

Renal: Acute renal failure.

Hematological: Bleeding, petichae, purpura.

Skin changes: Multiple Pustules, abscess, sclerema, mottling, umbilical redness and discharge.

(Orr et al., ٢٠٠٢)

Investigations:

It is important that the supportive and antimicrobial therapy of a neonate with sepsis is instituted quickly ***(Gerdes and Polin, ١٩٩٨).*** Hence minimum and rapid investigations should be undertaken.

A-Conventional investigaions

I-Laboratory

١-Septic screen

The various components of the septic screen include total leukocyte count, absolute netrophil count, immature to total neutrophil ratio, micro-erythrocyte sedimentation rate and C reactive protein ***(Polinski, ١٩٩٦ and Dasilva et al., ١٩٩٥)***.

Leukocyte number, character and indices are most frequently utilised to diagnose or monitor sepsis. Total leukocyte counts below ٤٠٠٠ x ١٠ ٩ /l or above ٣٠, ٠٠٠ x ١٠ ٩ /l is considered abnormal with sensitivity between ١٧٪-٩٠٪, and specificity ٣١٪-١٠٠٪. **The absolute neutrophil count and** varies considerably in the immediate neonatal period and normal reference ranges are available from Manroes charts ***(Manroe et al., ١٩٧٩)*** The lower limit for normal **total neutrophil counts** in the newborn begins at ١٨٠٠/cmm, **rises** to٧٢٠٠/cmm at ١٢ hours of age the **declines** and persists at ١٨٠٠/cmm after ٧٢ hrs of age. For very low birth weight infants, the reference ranges are available from Mouzinhos charts ***(Mouzinho et al., ١٩٩٤)***.

The ratio of immature to total neutrophils (I/T) is less than or equal to ٠.١٦ at birth and declines to a peak value of ٠.١٢ after ٧٢ hrs of age.

If **platelet** count of less than ١٠٠, ٠٠٠/cu.mm is added to immature to total neutrophil ratio greater than ٠.٠٢ then the PPV increases to ٤٣٪ and NPV to ٩٦٪, of an important consideration in resource limited conditions ***(Dasilva et al., ١٩٩٥)***.

Presence of two abnormal parameters in a screen is associated with a sensitivity of ٩٣-١٠٠ %, specificity of ٨٣ % positive, and negative predictive values of ٢٧ % and ١٠٠ % respectively in detecting sepsis. Hence, if two or more parameters are abnormal, it should be considered as a positive screen and the neonate should be started on antibiotics. If the

screen is negative but clinical suspicion persists, it should be repeated within ١٢ hrs. If the screen is still negative, sepsis can be excluded with reasonable certainty. For early neonatal sepsis, documentation of polymorphs in the neonatal gastric aspirate at birth could serve as a marker of chorioamnionitis and it may be taken as one parameter of septic screen ***(Dasilva et al., ١٩٩٥)***.

٢-*Blood culture*

It is the gold standard for the diagnosis of septicemia and should be done in all cases of suspected sepsis prior to starting antibiotics. A positive blood culture and sensitivity of the isolate is the best guide to antimicrobial therapy. Therefore the procedure for collecting a blood culture should be strictly followed to avoid contamination.

Blood cultures should be collected from a fresh veni-puncture site because samples collected from indwelling lines and catheters are likely to be contaminated. All blood cultures should be observed for at least ٧٢ hrs before they are reported as sterile. It is now possible to detect bacterial growth within ١٢-٢٤ hrs by using improved bacteriological techniques such as **BACTEC** and **BACT /ALERT** blood culture systems. These advanced techniques can detect bacteria at a concentration of ١-٢ colony forming unit (**cfu**) per ml ***(Garges et al., ٢٠٠٦)***.

٣-Urine culture:

In early onset sepsis, urine cultures have a low yield and are not indicated. Although a supra pubic bladder puncture sample or bladder catheterization sample has been recommended in all cases of late onset sepsis, the procedure is painful and the yield is very poor. However patients, at risk for fungal sepsis and very low birth weight babies with poor weight gain, should have urine examination to exclude urinary infection. Urinary tract infection may be diagnosed in presence of one of the following: (a) more than ١٠wbc/mm^{٣} in a ١٠ ml centrifuged sample (b) more than ١٠^{٤} organisms / ml in urine obtained by catheterization and (c) any organism obtained in urine by supra pubic aspiration ***(Blatimore, ١٩٩٨).***

٤-Lumbar puncture:

The incidence of meningitis in neonatal sepsis has varied from ٠.٣-٣٪ in various studies, the clinical features of septicemia and meningitis often overlap; it is quite possible to have meningitis along with septicemia without any specific symptomatology. This justifies the extra precaution of performing LP in neonates suspected to have sepsis. Cerebrospinal Fluid (CSF) There is considerable difference of opinion amongst clinicians and in literature whether meningitis (١٪ of over ٩٠٠٠ blood culture positive infants ***(Garges et al., ٢٠٠٦)***.

In EOS, lumbar puncture is indicated in the presence of positive blood culture or if the clinical picture is consistent with