NEONATAL SEPSIS

Dr S.Vidyaa Nayaki[(1),] Mr.Vignesh Kanna Balaji [(2)] , Mr PV Anto[(3)]

First author: Dr S Vidyaa Nayaki , Assistant Professor

Dept of Microbiology

Shri Satya Sai Medical College and Research Institute, Ammapettai, - Sri Balaji Vidyapeeth (Deemed to be university), Chennai, India

Second author: Mr Vignesh Kanna Balaji , Assistant Professor

Dept of Microbiology

Shri Satya Sai Medical College and Research Institute, Ammapettai, - Sri Balaji Vidyapeeth (Deemed to be university), Chennai, India

Third author: Mr PV Anto, Tutor

Dept of Microbiology

Shri Satya Sai Medical College and Research Institute, Ammapettai, - Sri Balaji Vidyapeeth (Deemed to be university), Chennai, India

ABSTRACT

Systemic bacterial infections are known by the generic term neonatal sepsis, which incorporates septicaemia, pneumonia and meningitis. *Escherichia coli, Staphylococcus aureus* and *Klebsiella* species are the predominant organism. Organism like *Acinetobacter, Pseudomonas* and *Coagulase Negative Staphylococci* are important pathogen in hospital acquired infections. Septic shock is usually a complication of gram-negative bacilli. Neonatal sepsis is associated with significant morbidity and mortality throughout the world. Septicaemia has been classified as Early Onset Neonatal Septicaemia (EONS) and Late Onset Neonatal Septicaemia (LONS). EONS defines the onset of sepsis before 72 hours after birth while LONS presents after 72 hours of life. Early and prompt diagnosis and antibiotic policy with adequate monitoring and supportive care would undoubtedly reduce the mortality and morbidity rates among newborn.

Keywords – Neonatal sepsis, Early onset neonatal sepsis, Late onset sepsis, Gram Negative bacteria , motality and morbidity

INTRODUCTION

Sepsis neonatorum or neonatal sepsis is defined as the systemic infection of the neonates. Septicaemia is defined as a condition in which the bacteria multiply leading to the release of toxins in blood, which triggers the production of cytokines, causing fever, chills, toxicity, tissue anoxia, reduced blood pressure and collapse, leading to a severe life-threatening condition. Septic shock is usually a complication of Gram-Negative bacilli. It is a

clinical syndrome characterized by systemic signs of infection and accompanied by bacteraemia. It is the most common cause of morbidity and mortality among neonates.

Septicaemia is classified into two types:

- Early Onset Neonatal Septicaemia
- Late Onset Neonatal Septicaemia

Early Onset Neonatal Septicaemia (EONS):

It is defined as sepsis which occurs within 72 hours of birth in neonates. It is caused by microorganism which is prevalent in maternal genital tract (ascending infection as the baby pass through the infected maternal genital tract), or in labour room or operation theatre (during resuscitation). Most common cause of EONS is *Group B Streptococci, E. coli, Coagulase negative Staphylococci (CONS), Haemophilus influenzae and Listeria monocytogenes.*

Late Onset Neonatal Septicaemia (LONS):

It is defined as sepsis which occurs after 72 hours of birth in neonates. It is acquired by nosocomial transmission. Most common time of presentation is around second week of gestation. It is caused by Gram Negative bacilli like *Klebsiella, Enterobacter, E. coli, Acinetobacter, Pseudomonas and anaerobes.*

EPIDEMIOLOGY

The incidence differs from place to place, based on various predisposing factors like low birth weight, prematurity, obstetric and nursery practices, nutritional status of the mother, environmental condition etc. Neonatal mortality rate in India is 28 per 1000 live birth, the second leading cause of mortality. 30 million newborns acquire infection every year, of which 1.2 million die of disease.

ETIOLOGY

The causative organism of neonatal sepsis differs according to geographical distribution. Majority of these organism are multi drug resistant. Compared to Gram positive organism, Gram negative organism is often associated with sepsis. Group B Streptococci is most frequent cause of sepsis in developed countries, whereas in India 85% of sepsis is mainly due to Gram negative bacteria.

Table 1 : The etiology of neonatal sepsis is classified into following groups

Gram Positive Bacteria	Gram Negative Bacteria	Anaerobes (less common)
Staphylococcus aureus	*Escherichia coli*	*Bacteriodiaceae*
Coagulase negative Staphylococci	*Klebsiella pnemoniae*	*Peptococcus and Peptostreptococcus*
Group B Streptococci	*Citrobacter species*	*Clostriduim tetani and Clostridium welchi*
Streptococcus pneumonia	*Proteus species*	*Veillonella species*
Enterococcus species	*Enterobacter species*	
Listeria monocytogenes	*Salmonella species*	
	Pseudomonas aeruginosa	
	Acinetobacter species	
	Haemophilus influenzae	

PATHOGENESIS

The protective barrier (placenta and amniotic sac) protects the fetus from any infection. Infection results due to discontinuity or breech of this protective barrier.

Routes of Infection

i. Transplacental
ii. Ascending Infection
iii. Infection from environment

Transplacental Route:

Hematogenous dissemination of bacteria through placenta in utero results in infection of the fetus. Maternal bacteraemia can also cause infection in fetus by transplacental route. The microorganism reaches the intervillous space of placenta by maternal circulation, from where they are carried to fetal blood stream.

Ascending Infection:

Infected amniotic fluid is the main important cause of infection. Amniotic fluid gets contaminated during prolonged labour and excessive manipulation. Systemin infection in neonates is more common if the amniotic fluid gets contaminated. Other risk factors include Urinary tract infection, coitus before two weeks of delivery, premature delivery, gestation age less than 34 weeks, prolonged rupture of membrane i.e., >24 hours. The incidence of neonatal septicaemia in infected amniotic fluid is around 1-5%. *E. coli, Streptococcus faecalis and Staphylococcus aureus* are the most common organism found in amniotic fluid and vagina. Before birth or during passage through birth canal, the fetal gastrointestinal tract and respiratory tract gets colonized with contaminated amniotic fluid and vaginal secretions either by swallowing or aspiration. Infection results due to alteration in the mucosal barrier or exposure to large inoculum.

From environment:

Infection after birth is acquired from the environment resulting in nosocomial infection of the neonates. Gastrointestinal tract and respiratory tract is the main portal of entry. Resuscitation with contaminated equipment is the main cause of infection. Improperly sterilized suction catheters and contaminated waters of isolators and humidifiers also contribute to infection.

Following birth, skin and umbilical cord become the main portal of entry for infections to reach systemic circulation. The most common site of cutaneous infection is umbilical cord stump, which can lead to septicaemia. Congenital abnormalities of central nervous system or urinary tract can also predispose to infections in few cases. Umbilical venous and arterial catheters also aid in entry of bacteria. The various risk factors of neonatal sepsis include:

Table 2 : RISK FACTORS OF NEONATAL SEPSIS

MATERNAL RISK FACTORS	NEONATAL RISK FACTORS	NOSOCOMIAL RISK FACTORS	OTHER FACTORS
Premature rupture of membranes (PROM)	Low birth weight (LBW)	Prolonged hospital stay	Geographical factors
Prolonged rupture of membranes	Birth asphyxia	Overcrowding in NICU	Socio economic status
Maternal fever	Meconium staining	Invasive procedures	
Recurrent abortions	Prematurity	Lack of hand washing	
More than 3 vaginal examinations done during delivery	Central venous catheterization > 10 days	Indiscriminate use of antibiotics	
Foul smelling vaginal discharge	Poor cord care		
Gestational age	Birth order		
Mode of delivery	Gender (males > females)		

Other factors which make the neonates more susceptible to infections are immature immune system, which includes impaired humoral defence mechanism, impaired phagocytosis, deficiencies of the complement, reduced T cell production etc.

CLINICAL PRESENTATION

Diagnosis of neonatal sepsis still remains as a challenge as the neonate presents with nonspecific signs and symptoms. History taking is an important clue in arriving at the diagnosis. The neonates presents with following symptoms like:

- Lethargy,
- Refusal or decreased feeding

- Failure to gain weight
- Meconium staining of skin
- Foul smelling amniotic fluid
- Premature rupture of membranes (>24 hours)
- Intubation or umbilical catheterization
- Congenital abnormalities
- Vomiting and diarrhoea

Clinical signs include

- Fever or hypothermia (> 38 C [100.4F) < 37 C [98.6F]
- Oliguria
- Apnea
- Tachypnea
- Pallor
- Cold clammy skin
- Hypotension
- Poor capillary filling
- Irritability
- Lethargy
- Coma
- Hypotonia
- Hyporeflexia
- Meningitis
- Otitis media

LABORATORY DIAGNOSIS

Laboratory diagnosis is very important to diagnose neonatal septicaemia as the clinical signs are nonspecific.

The various diagnostic methods are

I. Culture (culture of blood, CSF or body fluids)

II. Rapid screening method – Sepsis screen (Buffy coat smear examination, ESR, Acute phase reactants, WBC, Platelet count, Absolute neutrophil Count, immature to total neutrophil ratio Nitroblue tetrazolium dye reduction test, Limulus amoebocyte lysate assay, Measurement of cytokine levels in serum)

III. Molecular Assay (PCR, Nucleic acid Probe)

IV. Others (chest X-Ray, Abdominal X- ray, CT scan, MRI)

I. CULTURE

a. Blood culture: Most important tool to diagnose sepsis. It helps in diagnoses of patients presenting with or without localizing signs and symptoms. Factors such as volume of blood, frequency of culture and

duration of incubation determines the isolation of bacterial pathogens from blood. Misinterpretation of skin commensal as source of infection can happen if the blood culture bottles are contaminated with skin commensals, while collecting the blood sample. Hence proper sterile precaution has to be followed while drawing blood sample.

Sample collection

Two sets of blood samples are collected is collected from two different sites prior to administration of the antibiotics. The venepuncture site has to be cleaned with 70% isopropyl alcohol or ethyl alcohol and allow it to dry. At least 1 ml of blood sample is preferred for neonates. The following blood culture media is used for inoculation of blood sample for blood culture

i. Brain heart infusion (BHI) broth
ii. Trypticase soya broth
iii. Casteneda biphasic broth
iv. Thioglycolate broth
v. Glucose broth
vi. Bile broth

Culture media preferred for subcultures are:

i. Blood agar,
ii. MacConkey agar
iii. Chocolate agar

Methods of blood culture

A. Conventional method
B. Automated system

Conventional blood culture method:

Blood culture bottles after inoculation are incubated aerobically at 37°C for 7 days. After 24 hours, first subculture is done, second subculture on third day and final on seventh day. 7 days incubation of blood culture is required in conventional method to isolate the growth of any significant bacteria.

AUTOMATED SYSTEMS:

BACTEC : This system has evolved from a relatively simple manually operated device to a fully automated computerized assembly that can detect positive blood cultures. The original models monitored bacterial growth by detecting 14C labelled CO2 produced by bacterial metabolism of 14C labelled substrate in the liquid growth medium

Lysis centrifugation: This is a commercially available isolator where blood cells are lysed and centrifuged. The sediment is then plated to a solid agar medium, incubated and observed for growth.

b. **CSF culture:** CSF is collected aseptically by lumbar puncture and the deposits of centrifuges sample is used for culture and gram staining.

c. **Urine culture :** Common site of infection in late onset septicaemia. Has better yield of organism after 72 hours of life.

II. RAPID SCREENING METHODS

a. **Buffy Coat Smear (BCS) Examination:** It is a easy and rapid technique to demonstrate microorganism in a stained preparation of the infants blood.

b. **Nitroblue Tetrazolium Dye (Nbt) Reduction Test :** It is a test of phagocytosis of white cells which is abnormal during infections. Large numbers of normal peripheral neutrophils reduce NBT dye to formazan during phagocytosis.

c. **Microerthyrocyte Sedimentation Rate:** It is a simple inexpensive test. Although not reliable, it helps in the diagnosis of sepsis.

d. **Acute phase reactant proteins (APR):** They are proteins synthesized by liver. During inflammation the synthesis of acute phase proteins either increase (Positive APR) or decrease (Negative APR). Eg: C-Reactive protein, Procalcitonin, Haptoglobulin, Fibrinogen, Pre albumin and transferrin. Estimation of CRP levels helps in the diagnosis of sepsis, as it is a more reliable marker. A value of >1.0mg/dl in neonates is considered abnormal.

Other test which can be performed includes Leucocyte count, band cell ratio, Platelet count, Absolute neutrophil count

III. MOLECULAR ASSAY

a. **Polymerase Chain Reaction (PCR):** Amplification of DNA by thermal cycles(10^6- 10^9times) such as a single target molecule can be detected.

TREATMENT:

Main strategies to improve the outcome includes early diagnosis, initiation of appropriate antibiotics and supportive management.

Supportive treatment includes :

- ✓ Intravenous fluid
- ✓ Correction of hypoglycemia
- ✓ Correction of metabolic acidosis
- ✓ Correction of anemia
- ✓ Maintenance of normal body temperature
- ✓ Correction of septic shock
- ✓ Correction of electrolyte ombalance
- ✓ Vitamin K administration

Antibiotic therapy includes :

Antibiotics has to be administered based on the most common organism causing sepsis in the current geographical location. Each NICU should maintain separate register of the organism causing neonatal sepsis. the first line drug should cover most of the common pathogens. Empirical therapy with ampicillin and gentamicin can be initiated.

Table 3 First and second line therapy based on clinical picture

Clinical picture	First line	Second line
Community acquired infections and where resistant strains are unlikely	Ampicillin and gentmicin or amikacin	Cefotaxime and gentamicin or amikacin
Hospital acquired infections where resistant strains are likely	Cefotaxime and amikacin	Ciprofloxacin and gentamicin or amikacin

Antibiotics like tobramycin, netilmicin, vancomycin, aztreonam should be kept in reserve for treatment of life-threatening situation. Meropenem and piperacillin tazobactum is effective against Extended spectrum beta lactamases positive organism.

PREVENTIVE MEASURES

Neonatal sepsis can be prevented if following measures are adopted during delivery and child birth

- Hand hygiene
- Conducting delivery in a clean environment
- Sterilization and disinfection of the equipment
- Following standard precautions
- Screening of high-risk patients and treating them according to risk strata.

REFERNCES

1. Meharban Singh, Medical Emergencies in Children. Revised 5th ed, CBS publishers 2012; 345-361.
2. Monica Cheesebrough, District Laboratory Practices in Tropical Countries. 2nd ed, Cambridge 2006; 124-130.
3. Karthikeyan G, Premkumar K, "Neonatal Sepsis: Staphylococcus aureus as the Predominant Pathogen". Indian J Pediatr 2011 Aug ; 68(8): 715-7
4. Gotoff SP, Behrman RE. Neonatal septicemia. J Pediatr 2012 Jan; 76 (1): 142- 153.
5. Sanskar MJ, Neogi SB, Sharma J, Chauhan M, Shrivastava R, Prabhakar PR et al. "State of Newborn Health in India". Journal of Perinatology 2016;36(3):3-8.
6. Afroze S, "Neonatal Sepsis – a Global Problem: an Overview". Mymensingh Med. 2006; 3.15 (1): 108-14.
7. Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. Indian JPediatr 2008 Mar, 75: 261-6
8. Collee JG, Fraser AG, Marmion BP, Simmons A. Mackie and McCartney Practical Medical Microbiology. 14th ed. Edinburg: Churchill Livingstone; 1996
9. Behrman Richard E. "Fetal and Neonatal Medicine". The Journal of Paediatrics. 2006; 76 (1): 143-153
10. Henry D Isenberg, Clinical Microbiological Procedures Handbook.2nd Edition 2007; Volume1 : 3.4.1.1 – 3.4.1.19.