

Review Article

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Shuveksha Rawat*, **Kumar Neeraj**

Division of Pharmacy, Shri Guru Ram Rai (SGRR) Institute of Technology & Sciences, Uttarakhand Technical University, India

Dr. Kothiyal Preeti, Mathur Prashant

Division of Pharmacy, Shri Guru Ram Rai (SGRR) Institute of Technology & Sciences, Uttarakhand Technical University, India

Correspondence:

Shuveksha Rawat
M. Pharma (Clinical Pharmacy)
Division of Pharmacy, SGRR
Institute of Technology &
Sciences, Uttarakhand Technical
University, Dehradun, India-
248001
Tel: +91-94589779360
E-mail:
neetupharma.rawat792@gmail.com

A Review on Type, Etiological Factors, Definition, Clinical Features, Diagnosis Management and Prevention of Neonatal Sepsis

Shuveksha Rawat, Kumar Neeraj, Dr. Kothiyal Preeti, Mathur Prashant

Abstract

Neonatal sepsis is a clinical syndrome of bacterial infection characterized by signs and symptoms of systemic involvement during the first month of life. Sepsis is the most common cause of neonatal mortality. As per National Neonatal Perinatal Database (NNPD) 2002-2003, the incidence of neonatal sepsis in India was 30 per 1000 live birth. There are no specific signs and symptoms of neonatal sepsis and the onset and course of progression are much faster than in older children. Neonatal sepsis has been classified as either early onset sepsis (0-7 day of age) or late onset sepsis (7-28 days of age). Clinical features of sepsis are nonspecific in neonates and a high index of suspicion is required for the timely diagnosis of sepsis. The diagnosis of neonatal sepsis on the basis of the clinical symptoms is not possible. Although isolation of the causative microorganisms by using blood culture has been the golden standard method for its diagnosis, the result is ready only 24-72 hrs after the sampling and during this period, it is necessary to treat the suspicious infants for sepsis with antibiotics on the basis of reports. Various hematological indices had been utilized to screen for sepsis, most were neither highly sensitive nor specific and were commonly affected by perinatal factors like maternal hypertension, asphyxia and hemolytic disease. C-reactive protein (CRP) has been used as an acute phase reactant to diagnose and follow the course of infection in neonates. Treatment is most often started before a definitive causative agent is identified. An antibiotic therapy is commenced soon after the onset of the symptoms before the diagnosis is confirmed by blood culture.

Keywords: Neonatal sepsis, C-reactive protein, Gram-positive bacteria, Gram-negative bacteria.

Introduction

Neonatal sepsis is systemic infection of including septicemia, pneumonia, meningitis, arthritis, and urinary tract infection. Sepsis is more common in extramural admissions.¹ Neonatal sepsis is more common in developing countries in comparison of developed countries, it is a disseminated disease with the positive blood culture during the first month of life after birth.^{3, 4} Neonatal sepsis is an important cause of morbidity and mortality among neonates in developing countries accounting for 30-50% of total deaths each year.⁵ Clinical symptoms of sepsis are caused by the micro-organism and their toxic product. Sepsis is mostly characterized by bacteraemia.⁶ Neonatal sepsis is an invasive infection occurring in the first twenty eight (28) days of life. It could be bacterial, viral, or fungal. Early signs are frequently nonspecific and do not distinguish among organisms.

These signs could be multiple and include diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distention, jitteriness, seizures and jaundice.⁷ Increasing number of premature or low birth weight babies are mostly die within the first 14 days of life.⁸ Neonatal sepsis has been classified according to the time of onset as either early onset sepsis (0-7 day of age) or late onset sepsis (7-28 days of age).^{9, 10} Early onset sepsis is mainly due to bacteria acquired before and during delivery, and late onset sepsis acquired after delivery (nosocomial or community sources) but it may occur via vertical transmission at birth, and later to infection.¹¹ There are various sign & symptoms of sepsis like reluctance to feed, lethargy, fever, Jaundice, tachypnea, chest retraction, hypothermia, septic umbilicus, pallor, diarrhea, seizure, cyanosis & abdominal distension.¹² The highest rate of sepsis occur in low birth weight infants those who have the symptoms of depressed respiratory function and maternal or perinatal risk factors like premature rupture of membrane, maternal bleeding, maternal infection.^{13,14} Gram-negative bacteria is the major cause of neonatal sepsis in most of the developing countries.^{15,16} Prelabor rupture of membranes (PROM) is defined as rupture of the amniotic membrane before the onset of labor irrespective of gestational age.¹⁷

Premature rupture of chorioamniotic membrane is associated with increased incidence of neonatal sepsis.^{18- 22} There are many etiological factors for PROM. History of PROM in previous multifetal pregnancy, vaginal bleeding, cervical parameters, poor obstetric history, preexisting maternal hypertension, diabetes, genital tract infection, low socioeconomic level and smoking etc these are several predisposing factors of PROM.^{23, 24} Nutritional deficiencies and deficiency of vitamin C, copper, zinc have been associated with increased rate of PPRM.²⁵ puerperal sepsis is also a type of septic infection, puerperal sepsis is a common pregnancy related problem, puerperal sepsis is defined as an infection of the genital tract.^{26,27} According to World Health Organization²⁸ puerperal sepsis is defined as infection of the genital tract occurring at any time between the rupture of membranes or labor and the 42nd day post partum in which 2 or more of the following are present: pelvic pains, fever (that is oral temperature 38.5°C or higher on any occasion, abnormal vaginal discharge (example presence of pus), abnormal smell or foul odour of discharge, delay in the rate of reduction of the size of the uterus (less than 2 cm per day during the first 8 days). Neonatal sepsis is mainly caused by gram-positive bacteria²⁹ because these microbial species are infrequently

associated with infections in adults. Their occurrence may be explained by the immature immune system in newborns.³⁰ Gram negative bacteria remain the major cause of neonatal sepsis in developing countries.^{31, 32} Group B streptococcus is a most frequent causative agent of neonatal sepsis in developed countries which is responsible for high morbidity and mortality rates.³³ There are mostly five bacteria causing early onset sepsis *Escherichia coli* (*E.coli*), *Haemophilus influenza* (*H. flu*), *Listeria monocytogenes* and *Streptococcus pneumoniae* as well as GBS also contributes 20-50% mortality rate in newborn with sepsis.³⁴ Coagulase-negative staphylococcus, *Pseudomonas areuginosa*, Klebsiella, and methicillin-resistant *Staphylococcus aureus* these are the bacteria responsible for late onset infection in NICU35. Ampicillin-resistant *E. coli* and *Streptococcus pneumonia* are other etiological agent causing sepsis.³⁶ The diagnosis of neonatal sepsis is difficult, because clinical signs of sepsis often overlap with other noninfectious causes of systemic inflammation.³⁷ Although, microbiological culture can be used to distinguish sepsis from non-infectious conditions.³⁸ The initial diagnosis of sepsis is usually on the basis of clinical symptoms like temperature irregularity, change in the behavior, skin changes, feeding or cardiopulmonary or metabolic problems. It is useful to begin treatment before the results of cultures.³⁹ No single laboratory test has been enough to specificity and sensitivity and therefore laboratory confirmation must be used in conjunction with risk factors and clinical signs.⁴⁰ Culture of blood, urine and cerebrospinal fluid, leukocyte profile, platelet count, acute phase reactants (ESR, C-reactive protein), latex agglutination tests, or counter immune electrophoreses, and polymerase chain reaction (PCR) test are including for the diagnosis of sepsis.^{41- 44}

Classifications of neonatal sepsis

Neonatal sepsis may be classified according to the time of onset of the disease: early onset (EOS) and late onset (LOS).^{45, 46} Early onset sepsis is mainly due to bacteria acquired before and during delivery, and Late onset sepsis is bacteria acquired after delivery (nosocomial or community sources). A few papers distinguish between very early onset (within 24 hours), EOS (24 hours to six days), and LOS (more than six days) sepsis.^{47, 48}

a. Early onset sepsis (EOS)

Transplacental, hematogenous transmission of bacteria is an uncommon route of EOS and occurs primarily with *Listeria* (*L. monocytogenes*).⁴⁹ The most common route of

EOS in preterm and term infants are via an ascending amniotic infection. Members of the maternal genital flora, such as GBS and *Escherichia coli* (*E. coli*), the organisms responsible for the majority of cases of EOS, may ascend through the birth canal to the amniotic fluid either through intact amniotic membranes or, more commonly, after rupture of membranes.⁵⁰ Once infected amniotic fluid is aspirated or swallowed by the fetus, pathogens may penetrate through immature mucosal barriers, resulting in pneumonia or bacteremia, and may penetrate the blood-brain barrier, leading to meningitis. Bacteria have been implicated as a major cause of premature rupture of membranes and, consequently, of premature labor and delivery.^{51, 52}

b. Late onset sepsis (LOS)

LOS most commonly occurs via horizontal or nosocomial transmission, but it may occur via vertical transmission at birth, leading to colonization and, later, to infection.⁵³ Skin or mucosal colonization with potential pathogens may be acquired from the hands of health care workers or family members, from water used in incubator or ventilator humidification systems, or from contaminated fomites such as stethoscopes, which may carry organisms directly from one patient to another.⁵⁴ Colonizing organisms may enter the bloodstream through breaks in the skin or mucosa or by gastrointestinal translocation or may be introduced through invasive devices such as vascular catheters, endotracheal tubes, or feeding tubes. Alternately, nosocomial infection may result from infusion of contaminated intravenous solutions (especially lipid-based or high-glucose solutions) or from contaminated formula or breast milk. In LOS most common clinical manifestations are: meningitis (30-40%), bacteremia (40%), and septic arthritis (5-10%).^{55, 56}

Etiological factors causing sepsis

PROM: Premature rupture of membrane is one of the most common causes of neonatal sepsis. 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 (PPROM) is increases to 4%–6%. A 5-minute Apgar score <6 also raises the sepsis risk to 3%–4%.^{57, 58}

Chorioamnionitis/Maternal fever: The problem with chorioamnionitis is one of diagnostic definition in day-to-day clinical practice, with wide variability and

interpretation among clinicians. The generally accepted definition is presence of maternal fever >100.4°F with two or more of the following findings: fetal tachycardia, uterine tenderness, foul vaginal discharge, or maternal leukocytosis. The reported range of neonatal sepsis when chorioamnionitis is present is 3%–20%, with an odds ratio of 6:42 (2.32–17.8).⁵⁹ Maternal fever without signs of chorioamnionitis also raises the risk of sepsis, but may be confounded by noninfectious causes of maternal fever such as dehydration or epidural anesthesia.

Maternal colonization with group B Streptococcus (GBS): Maternal colonization with GBS without clinical complications and without antibiotic prophylaxis carries a neonatal sepsis risk of 1%; the risk rises to a best estimate of 4%–7% in the presence of clinical complications such as PROM, maternal fever, or prematurity; and as high as 20% in the presence of chorioamnionitis.⁶⁰⁻⁶²

Prematurity: Prematurity and neonatal sepsis increases the risk for premature infants. Preterm infants are more likely to require invasive procedures, such as umbilical catheterization and intubation. Prematurity is associated with infection from cytomegalovirus (CMV), herpes simplex virus (HSV), hepatitis B, toxoplasmosis, Mycobacterium tuberculosis, Campylobacter fetus, and Listeria species. Premature infants have less immunologic ability to resist and combat infection. This leads to infection with common organisms such as coagulase-negative staphylococci an organism usually not associated with severe sepsis.⁶³

Maternal urinary tract infection (UTI): As noted, GBS bacteremia is a risk factor for sepsis. Likewise, UTI of any cause raises the risk of sepsis in the neonate, in part due to raising the risk of prematurity and chorioamnionitis.⁶⁴

Other risk factors: NICU admission, Poor hygiene, Poor cord care, Bottle feeding, Invasive procedure, Superficial infection (pyoderma, umbilical sepsis) Low birth weight (<2500gms) or preterm baby.^{65, 66} Febrile illness in the mother within 2 weeks prior to delivery, Foul smelling and/or meconium stained liquor amni., Prolonged rupture of membrane (>24 hours), More than 3 vaginal examinations during labor, Prolonged and difficult delivery with instrumentation.^{67, 68}

Perinatal asphyxia in the presence of PROM and not readily explained by an obstetric cause such as placental abruption raises the risk of neonatal sepsis.⁶⁹ Male genders have also been implicated as a risk factor⁶⁹; the reasons for this finding are unknown. Another commonly accepted

risk factor is the presence of foul smell to the amniotic fluid, or “smelly baby.” It is thought that this sign may be due to the presence of anaerobic bacteria, but there is no evidence that this finding constitutes an independent risk factor for sepsis.

Definition

According to National Neonatal Forum of India sepsis has defined as follows:⁷⁰

Probable (Clinical) Sepsis: In an infant having clinical picture suggestive of septicemia, if there is the presence of any one of the following criteria:

- Existence of predisposing factors: maternal fever or foul smelling liquor or prolonged rupture of membranes (>24 hrs) or gastric polymorphs (>5 per high power field).
- Positive septic screen - presence of two of the four parameters namely, TLC (< 5000/mm), band to total polymorph nuclear cells ratio of >0.2, absolute neutrophil count < 1800/cumm, C-reactive protein (CRP) >1mg/dl and micro ESR > 10 mm-first hour.
- Radiological evidence of pneumonia.

Culture Positive Sepsis: In an infant having clinical picture suggestive of septicemia, Pneumonia or meningitis, if there is presence of either of the following:

- Isolation of pathogens from blood or CSF or urine
- Pathological evidence of sepsis on autopsy.

Pathogenesis

The pathophysiology of sepsis arises largely from the response of the host's innate immune system under the influence of genetic factors. Sepsis originates from a breach of integrity of the host barrier, either physical or immunological, and direct penetration of the pathogen into the bloodstream, creating the septic state.⁷¹ The fetus is protected by the membranes and placenta from bacterial exposure.⁷² It has also been shown that the amniotic fluid has inhibitory properties against bacterial growth.^{73, 74} Foetal bacteremia may occur in preterm labor⁷⁵, and term neonates may have bacteremia or present symptoms at birth⁷⁶ suggesting that bacterial colonization may take place before birth. Some bacteria (e.g. *Listeria monocytogenes*) cause transplacental infections via the mother's bloodstream. More commonly, however, bacterial exposure takes place in the amniotic cavity, or during the passage through the birth canal^{77, 78}. Some

studies show that neonatal GBS sepsis among 30000 newborn infants. Nearly all with sepsis and a birth weight less than 2000 gram presented with symptoms less than one hour after birth, whereas more than two-thirds of those with a higher birth weight developed symptoms later than four hours.⁷⁹ These findings suggest that preterm neonates may be exposed to GBS in utero, whereas term neonates often may be exposed during the passage through the birth canal. Foetal colonization is likely to take place by aspiration of contaminated amniotic fluid^{80, 81} or by bacteria penetrating through injured skin or natural body openings. In most cases this colonization proceeds without causing disease. The mechanism by which bacterial colonization converts to invasive disease is not fully understood, but it is likely to reflect bacterial virulence, maternal immunological factors, and the competence of the neonatal immune system.⁸²

Pathophysiology: The Sepsis Cascade

Sepsis disturbs the harmonious balance that exists in healthy state between pro and anti inflammatory cytokines, coagulant and anti-coagulant elements, and between endothelial integrity and circulating cells. Infection by a pathogen disturbs this balance. Body deals with infection by activating many of host defense systems simultaneously to regain the balance. If the balance is regained then outcome is recovery, but if this balance is either not restored or accentuated then the outcome is poor. During the inflammatory process, cells of the haemopoietic system and immune modulating mediators are activated to move towards the affected site for destroying the pathogen. Activation of the inflammatory response is initiated by release of endotoxin (LPS) from Gram-negative or exotoxins (peptoglycans) from Gram-positive organism and other cellular antigenic components of the pathogen/s. From then on initiation and maintenance of inflammatory cascade result from a complex array of interactions between pathogen and host defence systems.^{83,84} Leukocyte activation in particular that of macrophage and mononuclear cells brings about transcriptional changes related to immune activation and signal transduction dependent on genetic predisposition and bacterial characteristics.⁸⁵ Transcription factors up-regulate the production of pro-inflammatory cytokines such as TNF- α , INF α , IL-6 and anti-inflammatory cytokines IL-10, IL-18.⁸⁶ Substances released from pathogens and damaged tissues up regulate adhesion molecules on the vascular endothelium arresting and activating rolling neutrophils on to the vascular wall. Activated neutrophils change shape to pass through the vessel wall and move to the site of

infection where they phagocytose C3b coated organisms. Mediators like complement, chemokines, products of prostaglandin metabolism, and leukotrienes all contribute towards recruitment of inflammatory cells to the site of infection. Preterm VLBW infants are either deficient or inefficient in generating these responses in an adequate manner. In particular, poor transmigration of neutrophils and chemotaxis results in lack of localization of infection hence the neonate is prone to more frequent generalised blood stream infections. The process of activated inflammatory cells producing range of pro-inflammatory mediators like TNF- α , IL-1, IL-6, and IL-8, platelet activating factor (PAF), leukotrienes and thromboxane A2 accentuate endothelial damage.⁸⁷ Leak of granulocytes and other mediators through the injured endothelium cause the clinical effects seen in sepsis which can be enumerated by the synonym CHAOS;

C = Cardiovascular; changes in the micro and macro-circulation, decrease vascular tone, poor tissue perfusion, hypotension and organ failure.

H = Haemopoetic; anaemia, neutropenia, disseminated intra-vascular coagulation (DIC).

A = Apoptosis; increase in planned cell death.

O = Organ dysfunction; renal, hepatic and cardiovascular system failure.

S = Suppression of the immune system; immune paralysis (usually transitory).

The process of CHAOS take place with varying degree of severity in every infant with sepsis and correction of CHAOS, the imbalance between pro-inflammatory and anti-inflammatory cytokines, hypercoagulation and fibrinolysis apart from killing the pathogen is required for adequate management of sepsis.⁸⁸

Clinical Features

There are various clinical features. Feeding behavior is common and early, but is a nonspecific symptom. Other features are hypothermia or fever (former is more common in LBW babies), lethargy, poor cry, poor perfusion i.e. prolonged capillary refill time (>2 seconds), hypotonic or absent neonatal reflexes, bradycardia or tachycardia, respiratory distress i.e. apnea or gasping respiration, hypoglycemia or hyperglycemia and metabolic acidosis. System wise specific features are:

- **General:** Fever, temperature instability, “not doing well”, poor feeding, edema.⁸⁹
- **Central nervous system:** Bulging Anterior Fontanel, Blank Look, High-Pitched Cry, Excessive Irritability, Coma, Seizures, and Neck Retraction.
- **Cardiac:** Hypotension and Poor Perfusion.
- **Gastrointestinal:** Feed Intolerance, Vomiting, Diarrhea, Abdominal Distension, Paralytic Ileus, and Necrotising Enterocolitis.
- **Hepatic:** Hepatomegaly and Direct Hyperbilirubinemia
- (Infants with the onset of jaundice after 8 days of age or with direct hyperbilirubinemia were more likely to have urinary tract infection.)⁹⁰
- **Renal:** Acute renal failure.
- **Hematological:** Bleeding and Petechiae, Purpura.
- **Skin:** Pustules, Sclerema, Mottling, Umbilical Redness and Discharge.

Investigations

Sepsis screen

All newborns suspected to have neonatal sepsis should have a septic screen to corroborate the diagnosis of sepsis. However, if there is a strong clinical suspicion of sepsis, the decision to start antibiotics need not be conditional to a sepsis screen. Presence of any factor in neonates at risk of early onset sepsis should have a septic screen to decide antibiotic therapy. The various components of the septic screen include total leukocyte count, absolute neutrophil count, immature to total neutrophil ratio, micro-erythrocyte sedimentation rate and C reactive protein.⁹¹⁻⁹³

This is a panel of tests consisting of:^{94, 95}

| Component | Abnormal value |
|---------------------------|---|
| TLC | < 5000/mm ³ |
| ANC | < as per Manroe chart for term and Mouzinho’s chart for very LBL (VLBW) infants |
| Immature/Total neutrophil | > 0.2 |
| Micro-ESR | > 15mm in 1st hr |
| CRP | > 1mg/dl |

Blood culture

Blood culture is the gold standard for diagnosis of septicemia. It should be done in all cases before starting antibiotics. Blood from arterial or venous puncture can be used, as well as blood from newly inserted umbilical catheters.⁹⁶ One-mL sample of blood should be adequate for a blood culture bottle containing 5-10 mL of culture media. Blood culture should be observed for 72 hours before labeling it sterile. It is now possible to detect growth in 12-24 hours by BACTEC or BACT/ALERT culture system which can detect bacteria at a concentration of 1-2 cfu per ml. Blood samples collected from indwelling catheters or lines are likely to be contaminated.

Radiology: A chest x-ray should be considered in the presence of respiratory distress or apnea. An abdominal x-ray is indicated in the presence of abdominal signs and/ or suspicion of necrotizing enterocolitis (NEC). An ultrasound head and CT scan should be done in all patients diagnosed to have meningitis.⁹⁷

Urine culture: In early onset sepsis, urine cultures have a low yield and are not indicated. Although a suprapubic bladder punctures 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. We do not recommend a routine urine culture in babies with sepsis. However, patients at risk for fungal sepsis and very low birth weight babies with poor weight gain should have a urine examination to exclude urinary infection. Urinary tract infection may be diagnosed in presence of one of the following: (a) >10 WBC/mm³ in a 10 ml centrifuged sample (b) >10⁴ organisms /ml in urine obtained by catheterization and (c) Any organism in urine obtained by suprapubic aspiration.⁹⁸

Management

a. Supportive care: Attention should be given to basic supportive care in a sick child.⁹⁹

- **Thermal care:** Thermo-neutral environment should be ensured
- **Respiratory:** Adequate oxygenation with blood gas monitoring, and initial oxygen therapy or ventilator support (if needed) must be ensured.
- **Cardiovascular:** Blood pressure and perfusion must be supported to prevent shock. Volume expanders like normal saline, and inotropes such as dopamine or dobutamine may be needed. Intake and output of fluids should be monitored.

- **Hematologic:** DIC and neutropenia should be treated as per standard protocol.
- **CNS:** Seizures and SIADH should be addressed with proper attention.
- **Metabolic:** Hypoglycemia, hyperglycemia and metabolic acidosis should monitor and treated regularly.

b. Antimicrobial therapy: There cannot be single recommendations for the antibiotic regimen for neonatal sepsis in all settings. The choice of antibiotics depends on the prevailing flora responsible for sepsis in the given unit and their antimicrobial sensitivity. The initial choice of drugs for empirical treatment is dependent on knowledge of the probable pathogens based on the perinatal history, including any maternal symptoms, cultures, or instrumentation.¹⁰⁰ Decision to start antibiotics is based upon clinical features and/ or a positive septic screen. However duration of antibiotic therapy is dependent upon the presence of a positive blood culture.

Indications for starting antibiotics: The indications for starting antibiotics in neonates at risk of early onset sepsis include the following: (a) presence of three risk factors for early onset sepsis (b) presence of foul smelling liquor (c) presence of 2 antenatal risk factor with a positive septic screen and (d) strong clinical suspicion of sepsis. The indications for starting antibiotics in late onset sepsis include (a) positive septic screen and/ or (b) strong clinical suspicion of sepsis.¹⁰¹

Prophylactic antibiotics: We do not recommend the use of prophylactic antibiotics for single exchange transfusions. An exchange transfusion conducted under strict asepsis (single use catheter, sterile gloves, removal of catheter after the procedure) does not increase the risk of sepsis and does not merit antibiotics. However a messy exchange or 3 exchange transfusions should be treated with prophylactic antibiotics. In our unit, ventilated neonates are treated with prophylactic antibiotics for 5-7 days.

Choice of antibiotics: The empirical choice of antibiotics is dependent upon the probable source of origin of infection. For infections that are likely to be community-acquired and where resistant strains are unlikely; a combination of ampicillin or penicillin with gentamicin may be a good choice for first line therapy. Chloramphenicol may be added to treat meningitis acquired from the community. For infections that are acquired during hospital stay, resistant pathogens are likely

and a combination of ampicillin or cloxacillin with gentamicin or amikacin may be instituted. Cefotaxime or Ceftriaxone should be added for treatment of meningitis where resistant strains are likely. In nurseries where this combination is ineffective due to the presence of multiple resistant strains of klebsiella and other gram-negative bacilli, a combination of a third generation cephalosporin (cefotaxime or ceftizoxime) with amikacin may be appropriate

Reserve antibiotics Third generation cephalosporins including cefotaxime, ceftriaxone and ceftazidime have excellent antimicrobial activity against gram negative organisms (including klebsiella) and have very good CSF penetration. Ceftazidime is particularly effective against pseudomonas infections. These antibiotics are an excellent choice for the treatment of nosocomial infections and meningitis. Newer antibiotics like aztreonam and imipenem are also now available in the market. Aztreonam has excellent activity against gram-negative organisms and imipenem is effective against most bacterial pathogens except methicillin resistant Staphylococcus aureus (MRSA) and Enterococcus.

The empirical use of the last two antibiotics is best avoided and should be reserved for situations where sensitivity of the isolate justifies its use. Ciprofloxacin is another antibiotic with excellent activity against gram-negative organisms although it does not have very good CSF penetration. Hence ciprofloxacin may be used for the treatment of resistant gram-negative bacteremia after excluding meningitis.

A combination of piperacillin or ceftazidime with amikacin should be considered if pseudomonas sepsis is suspected. Penicillin resistant Staphylococcus aureus should be treated with cloxacillin, nafcillin or methicillin. Addition of an aminoglycoside is useful in therapy against Staphylococcus. Methicillin resistant Staphylococcus aureus (MRSA) should be treated with a combination of either ciprofloxacin or vancomycin with amikacin. For sepsis due to Enterococcus, a combination of ampicillin and gentamicin is a good choice for initial therapy. Vancomycin should be used for the treatment of Enterococcus resistant to the first line of therapy.

c. Adjunctive therapy

Intravenous Immune Globulin (IVIG): According to Cochrane database systemic review there is insufficient evidence to support the routine administration of IVIG preparations investigated to date to prevent mortality in

infants with suspected or subsequently proved neonatal infection.¹⁰² Immunotherapy used as an adjuvant for the prevention and treatment of neonatal sepsis holds promise. However clinical trials specifically designed toward the neonatal population and appropriately powered to detect treatment differences are necessary prior to universal recommendation of these therapies in the nursery.¹⁰³ In a recent paper, the authors have reviewed immunotherapies that modulate the immune system of the neonate, including intravenous immunoglobulins and myeloid haematopoietic growth factors. Future studies should focus on investigating other abnormalities of neonatal host defence and/or combined immunotherapy approaches in an attempt to circumvent the immaturity of host defense and potentially reduce both the incidence and severity of neonatal sepsis.¹⁰⁴

Granulocyte colony stimulating factor (G-CSF): Carr and colleagues reported a randomized trial (PROGRAMS) of GM-CSF for the prevention of sepsis in small for gestational age preterm neonates.¹⁰⁴ This increased the neutrophil count, but had no effect on the primary end point of sepsis free survival to 14 days from trial entry.¹⁰⁵ According to the Cochrane database systemic review there is currently insufficient evidence to support the introduction of either G-CSF or Granulocyte monocyte colony stimulating factor (GM-CSF) into neonatal practice, either as treatment of established systemic infection to reduce resulting mortality, or as prophylaxis to prevent systemic infection in high risk neonates. The limited data suggesting that G-CSF treatment may reduce mortality when systemic infection is accompanied by severe neutropenia should be investigated further in adequately powered trials which recruit sufficient infants infected with organisms associated with a significant mortality risk.¹⁰⁶

Exchange transfusion: Exchange transfusion in neonatal sepsis has not been extensively studied. It may be used with caution in neonatal sepsis associated with neutropenia, sclerema, earliest evidence of disseminated intravascular coagulation and metabolic acidosis (pH <7.2).¹⁰⁷

Pentoxifylline: Pentoxifylline is a methylxanthine that has been postulated to improve outcomes in sepsis through modulating the activity of the reticuloendothelial system and decreasing the neutrophil activation that contributes to acute tissue injury. Large scale clinical trials have not yet been performed.¹⁰⁸

Prevention

Possible preventive strategies to be considered might include:¹⁰⁹

- ❖ Intrapartum antibiotic prophylaxis
- ❖ Use of antiseptic solution to disinfect the birth canal, and Implementation of simple infection control methods of proven efficacy such as -
 - Hand washing, and barrier nursing
 - Promotion of clean deliveries
 - Exclusive breast feeding
 - Restriction of antibiotic use, and
 - Rationalization of admissions to and discharges from neonatal units

Principles for the prevention of nosocomial infection in the NICU:¹¹⁰

- Universal precautions with all patient contact: Gloves, gowns, mask, and isolation as needed
- Nursery design engineering: Appropriate nursing: patient ratio, avoid overcrowding and Excessive workload, readily accessible sinks, antiseptic solutions, soap, and paper towels
- Handwashing
- Minimizing central venous catheter contamination
- Meticulous skin care
- Encourage early and appropriate advancement of enteral feeding
- Education and feedback for nursery personnel
- Continuous monitoring and surveillance of nosocomial infection rates in the NICU

Conclusion

In most developing countries, gram negative bacteria remain the major cause of neonatal sepsis. Neonatal sepsis may be categorized as early or late onset. Clinical diagnosis of sepsis in new born infants is not easy because symptoms and signs are nonspecific. There is no laboratory test with 100% specificity and sensitivity, and hence, the search has continued for a reliable test. Blood culture has been the gold standard for confirmation of diagnosis but the results of the test are available only after 48-72 hours. The neonates with "riskfactors" for neonatal sepsis are thus treated with broad-spectrum antibiotics and require prolonged hospitalization. The choice of antibiotics should be based on the causative organisms and the patterns of antibiotic susceptibility. The combination of ampicillin and gentamicin is an appropriate choice for empirical therapy

of neonatal EOS in developed countries where GBS and *E. coli* continue to be the predominant organisms.

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