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NEONATAL SEPSIS

Microbiology

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ABSTRACT

Septicemia in neonates refers to generalized bacterial infection documented by positive blood culture in the first four weeks of life and is one of the four leading causes of neonatal mortality and morbidity in India. Although it is a global problem in developing countries is enormous because of the lack of clear guidelines for organizing the condition, the lack of standard laboratory procedures, and the impulsiveness of the physician to switch to antibiotics for any minor deterioration. The source of infection in the baby can be from the mother called early-onset sepsis or from the community or hospital called late-onset sepsis. Appropriate identification and knowledge of the causative microorganism can help in deciding the correct antibiotic and causative microorganisms in one area or hospital will be different from another area and therefore it is prudent to try to identify the disease-causing organism. Treatment requires well judged use of antibiotics with appropriate dosage and duration along with proper choice of antibiotics. Overuse of antibiotics should be discouraged because of the risk of complications and resistance development.

KEYWORDS

INTRODUCTION:

Septicemia in neonates refers to generalized bacterial infection documented by positive blood culture in the first four weeks of life and is one of the four leading causes of neonatal mortality and morbidity in India. The immature immune system is the major contributing factor for increased neonatal susceptibility to sepsis. [1-4]

Neonatal infections are unique in many ways. Infectious agents can be transmitted from mother to fetus or newborn in a variety of ways. Newborns are less able to respond to infection because of one or more immunological deficiencies. Clinical manifestations of neonatal infections vary and include subclinical infection, mild to severe manifestations of focal or systemic infection, and, rarely, congenital syndromes resulting from uterine infection. Time of exposure, size of inoculums, immune status, and virulence of the etiology agent affect disease manifestation. Maternal infection that is the source of trans-placental fetal infection is often not diagnosed during pregnancy because the mother was either asymptomatic or had non-specific signs and symptoms at the time of acute infection. A variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa and mycoplasma. Preterm, very low birth weight newborns have improved survival, but have prolonged hospital stays in an environment that puts them at constant risk for acquired infections. [5-6]

Epidemiology and Public Health Issue

Recently, the Global Burden of Disease (GBD) Study 2016/2017 estimated 1.3 million annual incident cases of neonatal sepsis worldwide,[7] resulting in 203000 sepsis-attributable deaths.[8] Neonates are disproportionately affected in low-income and middle-income countries (LMICs) with a high prevalence of infectious diseases[9] and poor access to adequately equipped and staffed healthcare facilities.[10]In sub-Saharan Africa alone, an estimated 5.3–8.7 million disability-adjusted life-years have been lost in 2014 due to neonatal sepsis and consecutive long-term morbidity.[11] Neonatal sepsis has resulted in an estimated economic burden of up to US$469 billion in this region (2014 data).[11]

The incidence of neonatal sepsis declined from 111 per 1000 live births in 1998 to 2001 to 19 per 1000 live births in 2016 to 2019, an 82.9% decrease , mean 4% decrease per year.[12] The current infant mortality rate for India in 2022 is 27.695 deaths per 1000 live births, a 3.74% decline from 2021. The infant mortality rate for India in 2021 was 28.771 deaths per 1000 live births, a 3.61% decline from 2020.[13] The major causes of neonatal deaths are infections. (*33*%) such as Pneumonia, Septicemia and Umbilical Cord infection; Prematurity (35%) i.e. birth of newborn.[14]

Etiology:

Neonatal sepsis can be classified based on the time of onset of the disease: early onset (EOS) and late onset (LOS). EOS disease is mainly due to bacteria acquired before and during delivery. Bacterial pathogens for EOS include Group B streptococcus (GBS), Escherichia coli, coagulase-negative Staphylococcus, *Staphylococcus aureus*, Enterococcus *spp*, gram-negative bacilli (*Enterobacter spp*, Haemophilus influenza, and Listeria monocytogenes. Maternal factors that increase the risk of neonatal sepsis include chorioamnionitis, GBS colonization, and delivery before 37 weeks, and prolonged rupture of membranes greater than 18 hours. LOS disease to bacteria acquired after delivery (nosocomial or community sources). [15-17]

Late-onset sepsis is caused by gram-positive bacteria but can also be attributed to gram-negative bacteria, fungi, and viruses. Gram-negative bacteria contribute to 20% to 42% of LOS cases and include *E coli*, *Klebsiella pneumonia,Serratia marcescens, Enterobacter spp.*, and *Pseudomonas aeruginosa*. *E coli* is the most common gram-negative species, and *P aeruginosa* the most fatal. The most common fungi are *Candida albicans*and *Candida parapsilosis*, which are becoming more prevalent in patients with central venous catheters. Herpes simplex viruses are the most common agents, with manifestation of symptoms between 5 and 28 days of life.[18-22]

Pathophysiology

The vascular compartment of the body is sterile. Microbes may enter the bloodstream from an infective focus with the help of phagocytic cell or form a surface with normal flora causing breakage of blood vessels or by introduction of contaminated material directly into the vascular system. Organisms that enter the bloodstream are quickly eliminated by various immune mechanisms. But when the immune system is overwhelmed or evaded, the microorganism persists in the blood and multiplies producing signs and symptoms of septicaemia. [23]

Risk factors

a) Risk factors of neonatal infection are as follows. [24]
b) Prematurity and low birth weight
c) Premature or prolonged rupture of membranes (>18 h)
d) Maternal peripartum fever (>100.4^0 F) or infection
e) Resuscitation at birth
f) Multiple gestations

g) Invasive procedures
h) Infants with galactosemia (predisposition to *E. coli* sepsis), immune defects.
i) Other factors: Male sex (four times more affected than females), bottle-feeding (as opposed to breast feeding), low socio-economic status, improper hand washing practice of NICU staff and family members etc.

Clinical manifestations

Initial signs and symptoms of infection in newborn infants. [25]

a) General: Fever, temperature instability, "not doing well", poor feeding, edema
b) Gastrointestinal system: Abdominal distension, vomiting, diarrhea, hepatomegaly
c) Respiratory system: Apnea, dyspnea, tachypnea, retractions, flaring, grunting, cyanosis
d) Renal system: Oliguria
e) Cardiovascular system: Pallor, mottling; cold, clammy skin, tachycardia, hypotension, bradycardia
f) Central nervous system: Irritability, lethargy, tremors, seizures, hyporeflexia, hypotonia, abnormal Moro reflex, irregular respirations, full fontanel, high-pitched cry
g) Hematologic system: Jaundice, splenomegaly,pallor, petechiae, purpura, bleeding

Laboratory Evaluations:

Various tests which aid the diagnosis of Neonatal Sepsis are listed below.

A. Specific laboratory tests

a) Blood Culture, cerebrospinal fluid and urine culture. (Conventional or Automated)
b) Direct visualization of bacteria (Gram stain)
c) Detection of bacterial antigens.
d) Polymerase chain reaction (amplification of bacterial DNA).

B. Hematological investigations

White blood cell counts, total and differential, platelet count.

C. Biochemical investigations

CRP, procalcitonin, ESR, serum amyloid, other acute phase reactants: haptoglobin, lactoferrin, neopterin, inter-inhibitor proteins (I Ips), lipopolysaccharide-binding protein (LBP), C5a, C5L2, immunoglobulins

D. Cytokines and receptors

IL-1, IL-6, IL-8, IL-10
IL-lra, IL-2rs
IP-10, RANTES, TNF-a, IFN-y
G-CSF, CSF1, SCF
MIP1-a
sCD14, sICAM-1, CD11b, CD64, CD69, CD25, CD45RO, CD19, CD33, Cd66b

The isolation of microorganisms from blood, CSF or urine. Blood culture is the gold standard for definitive diagnosis. Blood for culture should be obtained from a venous puncture or a peripheral arterial puncture. Indwelling catheters are usually colonized with microorganisms, and hence, culture results from these sites are difficult to interpret. If possible, lumbar puncture for extracting CSF should be done in all cases of late onset (> 72 hours) and symptomatic early onset sepsis because 10-15 percent of children may have associated meningitis. (20)

White blood cell count and differential count. Neutropenia is more predictive of neonatal sepsis than neutrophilia, but it may be present in maternal hypertension, birth asphyxia and periventricular hemorrhage. Total leukocyte count ,differential leukocyte count and morphology, total neutrophil count, total non segmented neutrophil count,neuotrophil ratios, platelet count are the indices most commonly used.

C-Reactive Protein (CRP) is a globulin that forms a precipitate when combined with the C-polysaccharide of *Streptococcus pneumoniae*. It is the most extensively acute phase reactant studied so far. The sensitivity is low for early diagnosis of sepsis.

Very high serum procalcitonin levels are present in neonates with proven or clinically diagnosed bacterial infection; early decrease of these concentrations reflects appropriate antibiotic therapy (23). Compared with CRP, procalcitonin has the advantage that increases more rapidly.

Several cytokines and receptors have been evaluated for the early diagnosis of infection in neonates (27–32). In most cases of neonatal sepsis, interleukin-6 (IL-6) increases rapidly several hours before an increase in the concentration of CRP, and decreases to undetectable levels within 24 hours. IL-6 has good sensitivity and good specificity when used as a very early marker. One study showed that IL-6 and interleukin-1 receptor antagonists (IL-1ra) increased significantly two days before a clinical diagnosis of sepsis (27). Unlike CRP, IL-6 is a very early marker but levels may return to normal as the infection continues. When used in combination with CRP, susceptibility to infected infants is higher at any postnatal age.

Management

A. Antibiotic Policies in Sepsis

Newborns may be exposed to antibiotics before birth in the form of GBS IAP (intrapartum prophylaxis), maternal surgical prophylaxis in cesarean delivery, intra-amniotic infection or other maternal infections. Previous data have shown that newborns associate with antibiotic use in the neonatal period with increased risks of childhood medical issues such as wheezing, asthma, food allergies, inflammatory bowel disease, childhood obesity and alterations of the developing gut micro biome..[26] Therefore, the use of antibiotics should be rationalized. Until recently, most premature neonates have been empirically treated with antibiotics, often for a long period of time, even in the absence of a culture-confirmed infection. Empirical antibiotics given to the very premature neonate in the first days after birth are associated with an increased likelihood of death, necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD). [27]

Principles of antibiotic Policies:

a. Prescribing antibiotics when they are truly needed and appropriate doses.
b. Maintain duration of antibiotics based on evidence.
c. Reviewing the treatment /diagnosis once the culture and other laboratory test is available.
d. Surveillance of antimicrobial resistance and audit of antibiotic usage.

B. Empirical Therapy of Antibiotics in initial stage:

The initial choice of antimicrobials for suspected neonatal sepsis is based on the age, pathogens, and the susceptibility patterns of organisms and the presence of an evident source of infection. Recently Antibiotic policy based on the blood culture and drug sensitivity report of last year. The first-line antibiotic chosen should be able to cover approximately 70% of the prevalent organisms in the preceding year. Second-line antibiotic should cover approximately 90% of the prevailing organism and third-line antibiotics should be able to cover for 95–100% of the organisms. In India the organisms responsible for EOS/ LOS are similar and therefore empirical antibiotics in both situations should be similar.

C. Special conditions for uses of antibiotics

a. Suspected meningitis—in neonates with LOS with meningitis (e.g., CSF pleocytosis), cefotaxime, or ceftazidime is added because of better CNS penetration of these drugs. Meropenem is chosen if there is a concern for infection due to multidrug resistant gram-negative organisms.
b. Suspected pneumonia—ampicillin, gentamicin or ampicillin, Linezolid cefotaxime or vancomycin, and gentamicin to covet for *Listeria*.
c. Skin, soft tissue, bone, and joint infections— Linezolid, vancomycin or nafcillin to cover for *Staphylococcus*.
d. Catheter-related infection—vancomycin and gentamycin.
e. Suspected intestinal source—clindamycin or metronidazole to account for anaerobes.

D. Up gradation of Empirical Antibiotics

Antibiotics therapy should be done in case the expected clinical improvement does not occur in 48–72 hours or any new sign appears. Recurrent and very early changes are probable to result in antibiotic resistance development. In the case of the incredibly sick neonate or deteriorating very rapidly, the first line of antibiotics should be bypassed and one can directly start with the 2nd line of antibiotics. Once the blood culture test report is available, narrower spectrum and

lower cost pathogen-specific monotherapy should be used.

E. Special consideration for use of Antibiotics

a) If sensitive to empirical antibiotics has been reported, but the neonate has worsened on these antibiotics, it may be a case of in vitro resistance. Antibiotics can be converted into an alternative sensitive antibiotic with the shortest spectrum and lowest cost.
b) If reported to be resistant to empirical antibiotics, but clinically improved in the newborn, it may or may not be a case of in vivo susceptibility. In such cases, careful evaluation should be made before deciding to continue with empiric antibiotics.
c) Antibiotics with in vitro resistance should not be continued in cases of Pseudomonas, Klebsiella, and methicillin-resistant Staphylococcus aureus (MRSA), and central nervous system (CNS) infections and deep-seated infections.
d) If no antibiotic has been reported as sensitive, but one or more has been reported as "moderately sensitive", treatment should be switched to such antibiotics at the highest permissible dose. It is better to use a combination of the two.

F. Duration of Antibiotics therapy

a. Blood culture positive: 10–14 days.
b. Meningitis, culture positive: GBS or gram-positive organisms, such as *L. monocytogenes* or *Enterococcus*, 14 days. *E. coli* or other gram-negative enteric pathogens, 21 days.
c. For neonates with CSF pleocytosis and bacteremia, but negative CSF cultures continue meningeal doses of antimicrobial therapy for 10 days for gram-positive bacteremia and 14 days for gram-negative bacteria.
d. Bone and joint infection, ventriculitis: 6 weeks
e. Urinary Tract Infection: 7–14 days

Prognosis

Mortality rates are associated with gestational age, preterm or younger neonates, sociodemographic status have higher mortality rates. *E. coli, Klebsiella spp.* has also been found to be associated with a higher mortality rate when compared with GBS. As mentioned above, the introduction of GBS intrapartum antibiotic prophylaxis has reduced mortality due to GBS. The treatment of clinically suspected neonates with negative cultures has also significantly reduced mortality. Premature infants with sepsis may develop impaired neurodevelopment. In addition, others may have vision loss. Infants who have been pretreated with aminoglycosides may also develop ototoxicity and nephrotoxicity.

CONCLUSION

Neonatal sepsis is one of the most important causes of morbidity and mortality early in life. Educating the neonate's family about the disease process and keeping them updated throughout the treatment process is an integral part of management. There is a need for a systematic approach to the evaluation of the disease, including a risk-based approach and appropriate use of diagnostic tests, both to diagnose this condition and to rule out an under diagnosis. Antibiotics can be used to treat this condition in the appropriate dose and for the appropriate duration. Overuse can lead to complications, and resistance and early elimination where it is not needed to continue should be the goal. Any changes in antibiotics or the treatment plan must be communicated to the parents. Upon hospital discharge, caregivers of all infants, including healthy newborns, should be educated to watch for signs of illness or sepsis.

Efforts to prevent the development or progression of sepsis have been a driving factor for many quality improvement projects in newborn nurseries and NICUs. Management of such infants is complex and requires a multidisciplinary care approach (therapists, nurses, pharmacies, lactation consultants, and social workers) supported by medical decisions made during the family-based care phase. Obstetricians are important in ensuring that GBS screening for infection and all other prenatal screenings are performed and adequately treated before and during delivery. Nursery nurses are also important in preventing and managing neonatal sepsis because they can pick up on and detect early signs of sepsis.

Research Priority and future prospective

There are several important gaps in our knowledge, and further studies are urgently needed considering simple and permanent interventions to reduce the burden of neonatal infection. Longitudinal monitoring is important to describe the different pathogens causing neonatal sepsis, as well as their changing antibiotic susceptibility patterns.

Research should continue to block some of the body's inflammatory mediators that result in significant tissue injury, as well as endotoxin inhibitors, cytokine inhibitors, nitric oxide synthetase inhibitors, and neutrophil adhesion inhibitors.

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