

Neonatal sepsis

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Definition

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life. When pathogenic bacteria gain access into the blood stream, they may cause overwhelming infection without much localization (septicemia) or may get predominantly localized to the lung (pneumonia) or the meninges (meningitis).

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Importance

Neonatal sepsis is the single most important cause of neonatal deaths in the community, accounting for over half of them. If diagnosed early and treated aggressively with antibiotics and good supportive care, it is possible to save most cases of neonatal sepsis.

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Etiology

Most cases of neonatal sepsis in the community are caused by *Escherichia coli* and *Staphylococcus aureus*. In hospitals, *Klebsiella pneumoniae* is also a common organism.

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Early vs. late sepsis

Neonatal sepsis can be classified into two sub-types depending upon whether the onset of symptoms is before 72 hours of life (early onset) or later (late onset).

Early-onset infections are caused by organisms prevalent in the maternal genital tract or in the delivery area. The associated factors for early-onset sepsis include low birth weight, prolonged rupture of membranes, foul smelling liquor, multiple per vaginum examinations, maternal fever,

difficult or prolonged labour and aspiration of meconium. Early onset sepsis manifests frequently as pneumonia and less commonly as septicemia or meningitis.

Late-onset septicemia is caused by the organisms thriving in the external environment of the home or the hospital. The infection is often transmitted through the hands of the care-providers. The onset of symptoms is usually delayed beyond 72 hours after birth and the presentation is that of septicemia, pneumonia or meningitis. The associated factors of late-onset sepsis include: low birth weight, lack of breastfeeding, superficial infections (pyoderma, umbilical sepsis), aspiration of feeds, disruption of skin integrity with needle pricks and use of intravenous fluids. These factors enhance the chances of entry of organisms into the blood stream of the neonates whose immune defences are poor as compared to older children and adults.

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Clinical features

The manifestations of neonatal septicemia are often vague and therefore demand a high index of suspicion for early diagnosis (Table I). The most common and characteristic manifestation is an alteration in the established feeding behavior in late onset sepsis and respiratory distress in early onset sepsis. The baby, who had been active and sucking well, gradually or suddenly, becomes lethargic, inactive or unresponsive and refuses to suckle. Hypothermia is a common manifestation of sepsis, whilst fever is infrequent. Diarrhea, vomiting and abdominal distension may occur. Episodes of apneic spells or gasping may be the only manifestation of septicemia. In sick neonates, the skin may become tight giving a hide-bound feel (sclerema) and the perfusion becomes poor (capillary refill time of over 3 seconds). Cyanosis may appear. A critical neonate may develop shock, bleeding and renal failure.

TABLE 1: Clinical manifestations of neonatal sepsis

Lethargy	Cyanosis*
Refusal to suckle	Tachypnea*
Poor cry	Chest retractions*
Not arousable, comatosed	Grunt*
Abdominal distension	Apnea/gasping*
Diarrhea	Fever ⁺
Vomiting	Seizures ⁺
Hypothermia	Blank look ⁺
Poor perfusion	High pitched cry ⁺
Sclerema	Excessive crying/irritability ⁺
Poor weight gain	Neck retraction ⁺
Shock	Bulging fontanel ⁺
Bleeding	
Renal failure	

* Particularly suggestive of pneumonia

⁺ Particularly suggestive of meningitis

The additional features of pneumonia or meningitis may be present depending upon the localization of infection in different systems and organs of the body. The evidence of pneumonia includes tachypnea, chest retractions, grunting, early cyanosis and apneic spells in addition to inactivity and poor feeding. Cough is unusual. Findings on auscultation of the chest are non-specific and non-contributory. Meningitis is often silent, the clinical picture being dominated by manifestations of associated septicemia. However, the appearance of excessive or high-pitched crying, fever, seizures, blank look, neck retraction or bulging anterior fontanel are highly suggestive of meningitis.

A large WHO study published in 2003 identified nine clinical features which predict severe bacterial illness in young infants

1. Feeding ability reduced
2. No spontaneous movement
3. Temperature >38 C
4. Prolonged capillary refill time
5. Lower chest wall in drawing
6. Resp rate > 60/minute
7. Grunting

8. Cyanosis
9. H/o of convulsions

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Diagnosis

Direct method

Isolation of microorganisms from blood, CSF, urine, pleural fluid or pus is diagnostic.

Indirect method

There are a variety of tests which are helpful for screening of neonates with sepsis. The most useful and widely used is the white blood cell count and differential count. An absolute neutrophil count of < 1800 per cmm is an indicator of infection. Neutropenia is more predictive of neonatal sepsis than neutrophilia but it may be present in maternal hypertension, birth asphyxia and periventricular hemorrhage. Immature neutrophils (Band cells + myelocytes + metamyelocytes) to total neutrophils ratio (I/T) > 0.20 means that immature neutrophils are over 20 percent of the total neutrophils because bone marrow pushes even the premature cells into circulation, to fight infection. Platelet count of less than 100,000 per cmm, toxic granules on peripheral smear and gastric aspirate smears showing more than 5 leucocytes per high power field are also useful indirect evidences of infection. The micro-ESR may be elevated with sepsis and fall of > 15 mm during first hour indicates infection.

Acute phase reactants are also frequently used in predicting neonatal sepsis. The most widely used is C-reactive protein (CRP) which has a high degree of sensitivity for neonatal sepsis. The CRP can be affected by asphyxia, shock, meconium aspiration and prolonged rupture of membranes.

There are a variety of other tests which can be used to predict sepsis but it may be difficult to perform them at all places and hence the clinical acumen remains crucial. A practical positive "sepsis screen" takes into account two

or more positive tests as given below:

1. Leukopenia (TLC <5000/cmm)
2. Neutropenia (ANC <1800/cmm)
3. Immature neutrophil to total neutrophil (I/T) ratio (> 0.2)
4. Micro ESR (> 15mm 1st hour)
5. CRP +ve

If possible, lumbar puncture should be done in all cases of late onset (>72 hours) and symptomatic early onset sepsis because 10-15 percent of them may have associated meningitis. At a small hospital, one may only depend on the CSF cells. The implications of detecting meningitis in the setting of septicemia include: the need for using antibiotics with a high CSF penetration and provision of antibiotic treatment for at least 3 weeks, administered parenterally throughout.

Treatment

No investigation is required as a prerequisite to start treatment in a clinically obvious case. Early treatment is crucial. Institution of prompt treatment is essential for ensuring optimum outcome of neonates with sepsis who often reach the health care facilities late and in a critical condition. Supportive care and antibiotics are two equally important components of the treatment. It should be realized that antibiotics take at least 12 to 24 hours to show any effect and it is the supportive care that makes the difference between life and death early in the hospital course.

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Supportive care

The purpose of supportive care is to normalize the temperature, stabilize the cardiopulmonary status, correct hypoglycemia and prevent bleeding tendency (Table-II). The septic neonate should be nursed in a thermo neutral environment. If hypothermic, the temperature should be raised using a heat source. An intravenous line should be established. If perfusion is poor as indicated by a capillary refill time of more than 3 seconds, normal saline bolus should be infused immediately. A dextrose bolus will help correct hypoglycemia which is often present in septic infants. Vitamin K should be given to prevent bleeding. Oxygen should be provided if the

infant is having retractions, grunt or cyanosis. Apneic neonates should be given physical stimulation and bag-mask ventilation, if required. Enteral feeds are avoided if infant is very sick or has abdominal distension. Appropriate maintenance intravenous fluids are administered. In neonates with sclerema, exchange transfusion with fresh whole blood may be contemplated. There is no role of intravenous immunoglobulin therapy in neonatal sepsis.

TABLE -II: Supportive care of a septic neonate

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1. Provide warmth, ensure consistently normal temperature
 2. Start intravenous line.
 3. Infuse normal saline 10 ml/kg over 5-10 minutes, if perfusion is poor as evidenced by capillary refill time (CRT) of more than 3 seconds. Repeat the same dose 1-2 times over the next 30-45 minutes, if perfusion continues to be poor.
 4. Infuse glucose (10 percent) 2 ml/kg stat.
 5. Inject Vitamin K 1 mg intramuscularly.
 6. Start oxygen by hood or mask, if cyanosed or grunting.
 7. Provide gentle physical stimulation, if apneic.
 8. Provide bag and mask ventilation with oxygen if breathing is inadequate.
 9. Avoid enteral feed if very sick, give maintenance fluids intravenously
 10. Consider use of dopamine if perfusion is persistently poor.
 11. Consider exchange transfusion if there is sclerema.
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Antibiotic therapy

Antibiotic therapy should cover the common causative bacteria, namely, *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumoniae*. A combination of ampicillin and gentamicin is recommended for treatment of sepsis and pneumonia. In cases of suspected meningitis, cefotaxime should be used along with an aminoglycoside. Table III shows detailed guidelines about antibiotic therapy.

TABLE III: Antibiotic therapy of neonatal sepsis

I. Septicemia or Pneumonia

Antibiotic	Each dose	Frequency		Route	Duration
		<7 days age	> 7 days age		
Inj Ampicillin or	50 mg/kg/dose	12 hrly	8 hrly	IV,IM	7-10 days
Inj cloxacillin	50 mg/kg/ dose	12 hrly	8 hrly	IV	7-10 days
AND Inj Gentamicin or	2.5 mg/kg/dose	12 hrly	8 hrly	IV, IM	7-10 days
Inj Amikacin	7.5 mg/kg/dose	12 hrly	8 hrly	IV, IM	7-10 days

II. Meningitis

	Antibiotic	Each dose	Frequency		Route	Duration
			<7 days age	> 7 days age		
(1)	Inj Ampicillin	100 mg/kg/ dose	12 hrly	8 hrly	IV	3 weeks
	and Inj Gentamicin	2.5 mg/ kg/dose	12 hrly	8 hrly	IV	3 weeks
	OR					
(2)	Inj Cefotaxime and	50 mg/kg/ dose	12 hrly	8 hrly	IV	3 weeks
	Inj Gentamicin	2.5 mg/kg/ dose	12 hrly	8 hrly	IV	3 weeks

In late-onset sepsis to cover nosocomial staphylococcal infection, first line of antibiotics may comprise of cloxacillin 100 mg per kg per day and an aminoglycoside (gentamicin or amikacin). In nosocomial sepsis, antibiotic sensitivity pattern of organisms responsible for nursery infection should be known and the antibiotic therapy should be started accordingly. Usually staphylococci and Gram negative bacilli (Pseudomonas, Klebsiella) should be covered using aminoglycoside (gentamicin or amikacin) and a third

generation cephalosporin (cefotaxime). For resistant staphylococcal infection, vancomycin (30 mg per kg per day) should be used.

On confirmation of sensitivity pattern, appropriate antibiotics are used singly or in combination. In a baby in whom the antibiotics were started on low suspicion, these may be stopped after 3 days, if baby is clinically well and the culture is negative. However, if a baby appears ill even though the cultures are negative, antibiotic therapy should be continued for 7 to 10 days as bacterial infection can occur with negative cultures.

The duration of antibiotic therapy in sepsis depends upon the pathogen, site of infection and the clinical response of the baby. 7-10 days therapy is required for soft tissue infections or pneumonia. Deep-seated infections (osteomyelitis) and meningitis may require therapy for 3-6 weeks.

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Superficial infections

Superficial infections can be treated with local application of antimicrobial agents. Pustules can be punctured with sterile needles and cleaned with spirit or betadine. Purulent conjunctivitis can be treated with neosporin or chloramphenicol ophthalmic drops. Oral thrush responds to local application of clotrimazole or nystatin (200,000 units per ml) and hygienic precautions. Superficial infections must be adequately managed; if neglected they can lead to sepsis or even an epidemic.

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Prevention of infections

A good antenatal care goes a long way in decreasing the incidence, morbidity and mortality from neonatal sepsis. All mothers should be immunized against tetanus. All types of infections should be diagnosed early and treated vigorously in pregnant mothers. Babies should be fed early and exclusively with expressed breast milk (or breastfed) without any prelacteal feeds. Cord should be kept clean and dry. Unnecessary interventions should be avoided.

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Hand washing

This is the simplest and the most effective method for control of infection in the hospital. All persons taking care of the baby should strictly follow hand washing policies before touching any baby. The sleeves should be rolled above the elbows. Rings, watches and jewellery should be removed. Wash hands up to elbows with a thorough scrub for 2 minutes with soap and water taking care to cover all areas including the under surface of well trimmed nails. Rinse thoroughly with running water. Dry hands with sterile hand towel/paper towel. Wash hands up to the wrist for 20 seconds in between patients. Hands should be rewashed after touching contaminated material like one's face, hair, papers etc.

It is preferable to use bar soaps rather than liquid soaps as the latter tend to harbor organisms after storage. In emergency situations bactericidal and virucidal solutions like Sterillium can be used to clean hands before touching babies. Surgical, elbow- operated taps should be used in the hospitals for hand washing.

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Prevention of infection in hospital

The nursery environment should be clean and dry with 24 hour water supply and electricity. There should be adequate ventilation and lighting. The nursery temperature should be maintained between $30\pm 2^{\circ}\text{C}$. Overcrowding should be avoided.

All procedures should be performed after wearing mask and gloves. Unnecessary invasive interventions such as needle pricks and setting up of intravenous lines should be kept to the barest minimum. There should be no compromise in the use of disposables. Stock solutions for rinsing should be avoided.

Every baby must have separate thermometer and stethoscope and all barrier nursing measures must be followed.

Strict house-keeping routines for washing, disinfection, cleaning of cots and incubators should be ensured and these policy guidelines should be available in the form of a manual in the nursery.

The use of prophylactic antibiotics for prevention of nosocomial infections is strongly condemned. They are not only useless but also dangerous because of the potential risk of emergence of resistant strains of bacteria.

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Control of outbreak

General measures for the control of an outbreak include detailed epidemiological investigations, increased emphasis on hand washing, review of protocols, procedures and techniques, disinfection and sterilization of nursery and assessment of the need for additional measures. The nursery may be fumigated using formalin 40% and potassium permanganate (70 gms of KMNO₄ with 170 ml of formalin for 1000 cubic feet area). Alternatively, bacillocid spray for 1-2 hours may be used. Linen and cotton should be washed thoroughly, dried and autoclaved. Use of disposable items for invasive and non- invasive interventions (catheters, probes, cannulae, chest tubes etc.) though costly, reduces the risk of infection.

Depending upon the pathogen and type of outbreak, culture surveys of susceptible patients, cohorting of infants in nursery and a review of antibiotic policy may be necessary. Most of the times a scrupulous reinforcement of general control measures may be sufficient to stop the outbreak.

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Conclusion

In conclusion, manifestations of neonatal sepsis are non-specific. A high index of suspicion with or without lab evidences of infection is the key for early diagnosis. Prompt institution of antibiotic therapy and supportive care will save most of the cases of neonatal sepsis.