Guideline for Evaluation and Management of Neonatal Sepsis

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Introduction

Sepsis is an important cause of morbidity and mortality among newborn infants. Globally, It is the number one cause of death in Newborn. It is responsible for about 30-50% of the total neonatal deaths in developing countries. More than 40% of under-five deaths globally occur in the neonatal period, resulting in 3.1 million newborn deaths each year. The overall incidence of neonatal sepsis ranges from one to five cases per 1000 live births. In Maldives it is one of the leading cause of death in newborn. A proper systematic approach for the evaluation and management of Neonatal sepsis is needed to decrease the burden and impact of the disease.

This guideline is intended for the evaluation and management of an infant 28 days of life or younger with suspected or proven sepsis in Maldives.

Case definition:

Neonatal sepsis is a clinical syndrome in an infant 28 days of life or younger, manifested by systemic signs of infection and/or isolation of a bacterial pathogen from the blood stream. It includes various systemic infections of the newborn such as septicemia, meningitis, pneumonia, septic arthritis, osteomyelitis, and urinary tract infections.

Classification of Neonatal sepsis

Neonatal Sepsis is classified according to the infant's age at the onset of symptoms.

Early onset sepsis: It presents within the first 72 hours of life.

Late onset sepsis: It presents after 72 hours of life.

Early onset sepsis:

Presents within 72 hours of life. Respiratory distress is the most common presenting symptom. Most of Newborns are symptomatic by 24 hours of age. The source of infection is generally the maternal genital tract.

Risk factors for infection:

1. Prematurity (< 37 week)
2. Low birth weight (<2500 grams)
3. intrapartum fever (>38°C).

4. Foul smelling liquor.
5. Prolonged rupture of membranes >18 hours.
6. documented maternal colonization with group B Streptococcus (GBS)

Late onset sepsis:

Presents after 72 hours of age.

- Infection source in late onset sepsis is usually nosocomial (hospital-acquired) or community-acquired. Prematurity, Low birth weight, mechanical ventilation, Central venous access, parenteral nutrition is associsated with increased risk of nosocomial sepsis.

Etiologic Agents:

- Group B streptococcus (GBS)
- Gram negative bacteria (E. coli, Klebsiella, Enterobacter, Citrobacter, Pseudomonas)
- Enterococcus
- Coagulase negative staphylococcus
- Staphylococcus aureus
- Listeria monocytogenes

Clinical Manifestations

Because the signs and symptoms of sepsis are subtle and nonspecific, identification of risk factors and any deviation from an infant's usual pattern of activity or feeding should be regarded as a possible indication of systemic bacterial infection.

- Respiratory:
  - Respiratory distress (tachypnea, grunting, flaring of the nasal alae, retraction), apnea, cyanosis.
  - Respiratory distress starting >4 hour after birth.
- Central nervous system:
  lethargy, bulging anterior fontanelle, vacant stare, high-pitched cry, excess irritability, drowsy or unconscious, seizures, altered tone,
- Cardiac: Hypotension, poor perfusion, shock, mottling, tachycardia, bradycardia
- Gastrointestinal: Feed intolerance, vomiting, diarrhea, abdominal distension.
- Hepatic: Hepatomegaly, direct hyperbilirubinemia (especially with urinary tract infections)

- Renal: decrease urine output, Acute renal failure
- Hematological: Bleeding, petechiae, purpura, abnormal Coagulation.
- Metabolic: hypoglycemia, Hyperglycemia, Metabolic acidosis
- Temperature instability (fever, hypothermia)
- Skin changes: pustules, abscess, sclerema, mottling, umbilical discharge
- Musculoskeletal: edema or erythema overlying bones or joints

Evaluation

Asymptomatic infant with risk factor:

Each neonate should be evaluated for the presence of the following maternal and neonatal factors that are associated with an increased risk of sepsis.

Risk factor

- Intrapartum maternal temperature ≥38ºC (100.4ºF)
- Chorioamnionitis.
- Maternal group B streptococcal colonization, bacteriuria or infection in the current pregnancy.
- Invasive group B streptococcal infection in a previous baby.
- Membrane rupture ≥18 hours.

Consult Algorithm 1 for Protocol for asymptomatic infant with risk factor.

Symptomatic Infant:

Perform investigations and start antibiotic in infants presenting with signs compatible with neonatal sepsis. Follow Algorithm 2 for evaluation and treatment of babies presenting with signs of infection.

Laboratory evaluation

Blood culture

A definitive diagnosis of neonatal sepsis is established by a positive blood culture. It should be performed in all cases of suspected sepsis prior to starting antibiotics. A minimum blood volume of 1 mL is desirable for optimal detection of bacteremia. Take blood sample from peripheral vein, using, aseptic technique.

Complete blood count

WBC < 5000/mm^3 is suggestive of sepsis.

Total Neutrophil count

The Absolute neutrophil count (ANC) varies considerably in the immediate neonatal period. A neutrophil count <1800/ mm^3 or > 15000/ mm^3 is supportive of sepsis .

C-reactive protein (CRP)

CRP is an acute phase reactant. A CRP value that is greater than 1.0 mg/dL or 10 mg/L is abnormal. CRP is not a sensitive test at birth because it requires an inflammatory response to increase its level. CRP concentration increases within 6 to 8 hours of an infectious episode in neonates and peaks at 24 hours.

As a result, a single measurement of CRP soon after birth is not a useful marker in the diagnosis of neonatal sepsis. However, sequential assessment of CRP values is useful in supporting a diagnosis of sepsis. If the CRP level remains persistently normal, neonatal bacterial sepsis is usually unlikely.

It is also helpful in guiding the duration of antibiotic therapy in suspected neonatal bacterial infection.

Platelet Counts

nonspecific, insensitive, and late indicator of sepsis.

Chest radiography

Obtain chest radiography in an infant with respiratory symptoms

Abdominal X-ray: If abdominal distension is noted.

Urine culture

Urine culture could be included in sepsis evaluation for infants >7 days of age.

Lumbar puncture (LP):

Is indicated in:

- A positive blood culture.
- Clinical findings that are highly suggestive of sepsis.
- Laboratory data strongly suggestive of sepsis.
- Worsening clinical status while on antibiotic therapy.
- Late onset sepsis.

When CSF is obtained, it should be sent for Gram stain, culture, cell count with differential and protein and glucose concentrations.

When an infant is critically ill or likely to have cardiovascular or pulmonary compromise from the procedure, defer LP until the patient's status has stabilized.

If LP is traumatic and there is strong suspicion of meningitis, repeat LP after 24–48hr.

Normal cerebrospinal fluid examination in neonates

CSF Components	Normal range
Cells/mm3	0-30 cells
Polymorphonuclear cells	60%
Proteins (mg/L)	100 (30-200)
CSF glucose	>2/3 of simultaneous blood glucose level

Septic screen

Send septic screen (CBC, CRP) at birth and /or at 6- 12 hour of life or at presentation if symptomatic.

Septic screen Components	Abnormal value
Total leukocyte count	< 5000/mm^3
C reactive protein (CRP)	>1 mg/dL or 10 mg/L

If septic screen is negative but clinical suspicion persists, repeat septic screen in 12- 24 hour.

Management

Supportive:

Adequate and proper supportive care is crucial in a sick neonate with sepsis.

Nurse in a thermo-neutral environment taking care to avoid hypo/hyperthermia.

Maintain oxygen saturation in the normal range, if needed with oxygen with nasal prongs, CPAP, mechanical ventilation as indicated.

Monitor fluids, electrolytes, and glucose levels with correction of hypovolemia, hyponatremia, hypocalcemia, and hypoglycemia/hyperglycemia.

Fluid resuscitation as needed.

Inotropic support as needed to maintain normal tissue perfusion and blood pressure.

Disseminated intravascular coagulation may complicate neonatal septicemia. Monitor Platelet counts, hemoglobin levels, and clotting times. Disseminated intravascular coagulation is treated by management of the underlying infection, but if bleeding occurs, may require fresh frozen plasma, platelet transfusions, or whole blood.

Antibiotic Therapy:

- The choice of antibiotics is dependent upon covering the most likely pathogens. If a pathogen is identified, antibiotic therapy should be modified depending upon the susceptibility of the isolate.
- The duration of therapy is dependent upon culture result, clinical course, and organism.

Antibiotic therapy should be initiated for infants with suspected sepsis once the evaluation has been completed. If decision is made to give antibiotics, start within 1 hour.

Start ampicillin and amikacin as a first choice.

Repeat CRP after 24 hours of starting antibiotics.

Most infants with sepsis will improve clinically within 24 to 48 hours after appropriate antibiotic treatment is started.

Regularly reassess the clinical condition and results of investigations in babies receiving antibiotics. Consider whether to change the antibiotic regimen taking account of the baby's clinical condition (for example, if there is no improvement) and the results of investigations. If organism is isolated, change antibiotic according to sensitivity result.

Choice of antibiotics for treatment of Neonatal sepsis

FIRST LINE	Ampicillin and Amikacin
SECOND LINE	Cefotaxime and amikacin
THIRD LINE	Piperacillin-Tazobactam /ceftazidime and Vancomycin. If no improvement consider Meropenem.

- Soft tissue, skin, joint, or bone involvement: Add Vancomycin to cover S. aureus.
- Intravascular catheter-related infection: Add Vancomycin to provide empiric coverage for coagulase-negative staphylococci, S. aureus. Remove indewelling catheters.

- Gastrointestinal tract related infection: Add metronidazole to cover anaerobic bacteria.
- Meningitis: Start Cefotaxime. If CSF gram stain or culture suggests Group B streptococcus (GBS), give Ampicillin.

Duration of Antibiotics:

Diagnosis	**Duration**
Blood culture positive	10 days
Meningitis	21 days
UTI	10 days
Blood Culture negative, Sepsis screen positive and clinical course compatible with sepsis.	5-7 days
Blood Culture negative, sepsis screen negative and clinical course compatible with sepsis.	5-7 days
Blood culture negative, sepsis screen negative, clinical course not compatible with sepsis, well appearing infant	Stop antibiotics after 48-72 hours.

Intravenous immunoglobulin:

There is no role of Intravenous immunoglobulin (IVIG) in neonatal sepsis, so should not be used.

Common Antibiotics: Dose

Antibiotics	**Weight (kg)**	**Postnatal Age (days)**	**Interval (hours)**
Ampicillin 50mg/kg/dose For meningitis: 100mg/kg/dose	-	≤7	12
	-	>7	8
Amikacin 15 mg/kg	<2	≤7	48
		>7	24 – 48
	>2	≤7	24
		>7	12 –24
Cefotaxime 50mg/kg/dose (For meningitis: same dose)	-	≤7	12
		>7	8
Ceftazidime 50mg/kg/dose (For meningitis: same dose)	-	≤7	12
		>7	8
Meropenem 20mg/kg/dose (Meningitis 40mg/kg/dose)	-	≤7	12
		>7	8
Metronidazole 7.5mg/kg/dose	<1.2	0-28	48
	1.2 – 2	≤7	24
		>7	12
	>2	≤7	12
		>7	12 (15mg/kg/dose)
Piperacillin -Tazobactam 50-100mg/kg/dose	-	≤7	12
		>7	8
Vancomycin	1.2	≤7	24

15mg/kg/dose		>7	24
	1.2 – 2	≤7	12-18
		>7	12
	>2	≤7	12
		>7	8
Fluconazole Loading dose: 12mg/kg	-		
Maintenance dose: 6-12 mg/kg/dose (72 hours after loading dose)	-	0-14	72
	-	>14	48
Fluconazole (prophylaxis) 3-6 mg/kg/dose	-		72

Prevention and Infection Control Practices

- Maternal prenatal care continues to be important for prevention of early-onset sepsis. Early recognition of chorioamnionitis, with appropriate antimicrobial therapy for the mother, decreases maternal fetal transmission.
- Appropriate hand washing, infection control, and proper techniques for placement and management of central catheters should be followed to reduce hospital acquired late onset infections.

Indication of Intrapartum Antibiotic Prophylaxis.

1. Positive antenatal cultures for GBS (except for women who have a cesarean delivery without labor or membrane rupture).
2. Rupture of membranes ≥18 hours, or temperature >100.4°F (>38°C).
3. GBS bacteriuria during the current pregnancy.
4. Previous infant with invasive GBS disease.

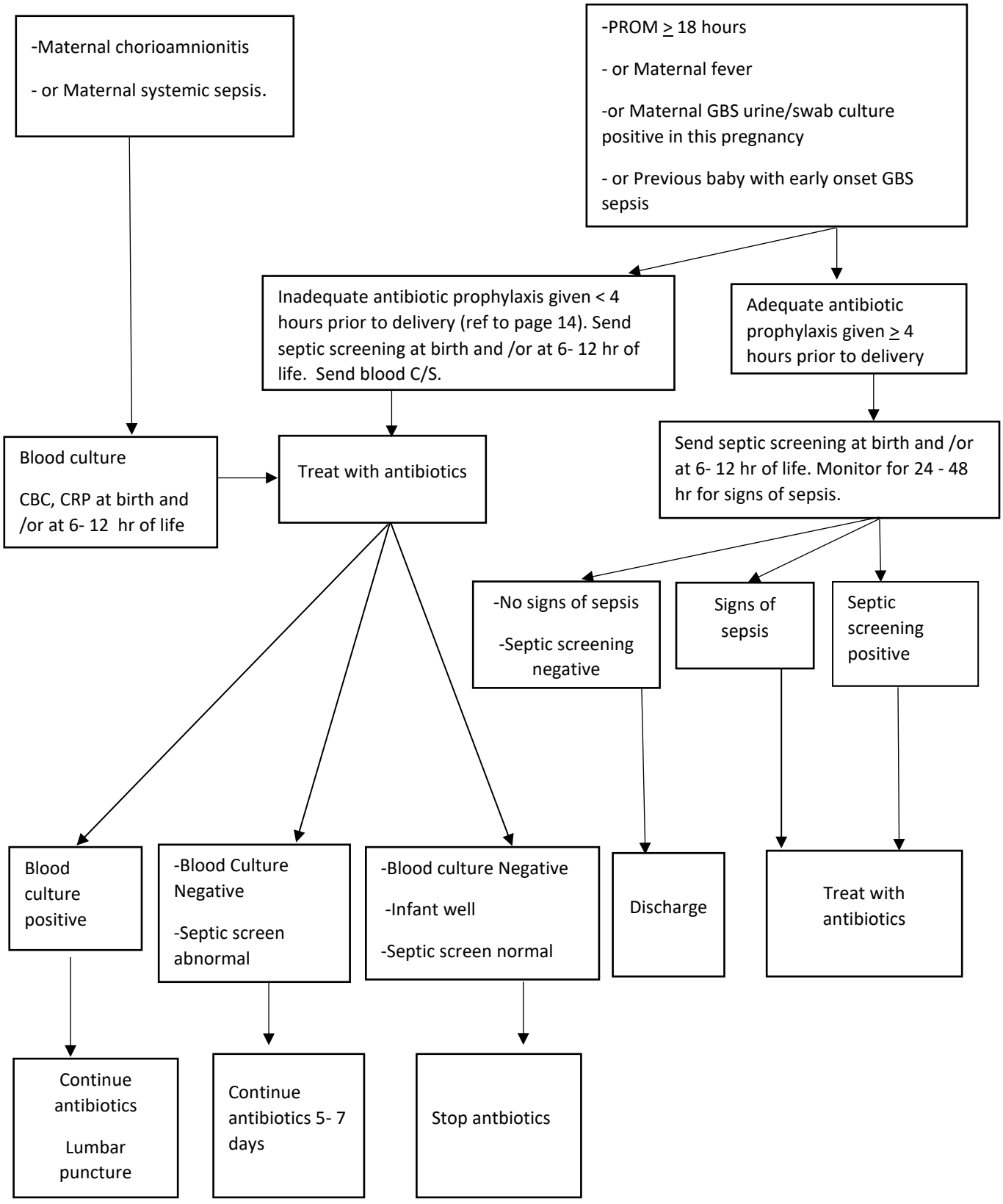
Adequate intrapartum prophylaxis: if mother received I.V Ampicillin or Cefazolin at least ≥ 4 hr prior to delivery.

Information and support

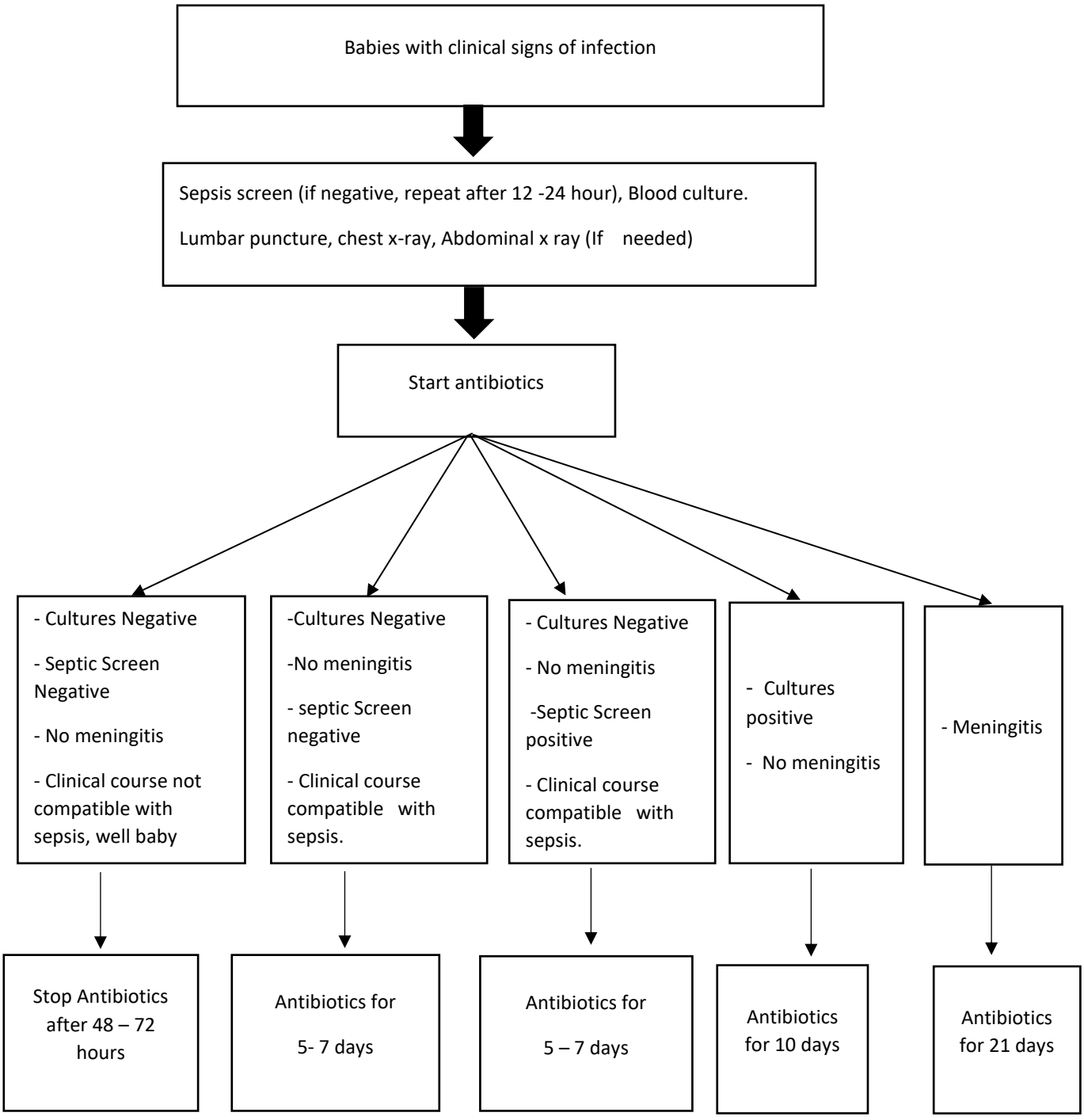
During discharge, advise the parents and care givers that they should seek medical attention if they are concerned that the baby:

- is showing abnormal behaviour (e.g inconsolable crying or listlessness, lethargy), or
- is unusually floppy, or
- has developed difficulties with feeding or not tolerating feeds, or
- has an abnormal temperature unexplained by environmental factors (lower than 36°C or higher than 38°C), or
- has rapid breathing, or
- has a change in skin colour

Algorithm 1: Evaluation of Asymptomatic infants with Risk factors for sepsis.



Algorithm 2: Neonatal Sepsis (symptomatic Neonate)



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