Sepsis in the Newborn

Sepsis is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries.[1,2] It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes.[2] Sepsis related mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy and aggressive supportive care.

Epidemiology: Indian data

The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. The NNPD network comprising of 18 tertiary care neonatal units across India found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths[3].

Among intramural births, Klebsiella pneumoniae was the most frequently isolated pathogen (32.5%), followed by Staphylococcus aureus (13.6%). Among extramural neonates (referred from community/other hospitals), Klebsiella pneumoniae was again the commonest organism (27%), followed by Staphylococcus aureus (15%) and Pseudomonas (13%).[3]

Definition

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It encompasses various *systemic* infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections.

Superficial infections like conjunctivitis and oral thrush are not usually included under neonatal sepsis.

Classification of neonatal sepsis

Neonatal sepsis can be classified into two major categories depending up on the onset of symptoms:[4]

Early onset sepsis (EOS): It presents within the first 72 hours of life. In severe cases, the neonate may be symptomatic *at birth*. Infants with EOS usually present with respiratory distress and pneumonia. The source of infection is generally the maternal genital tract. Some maternal/ perinatal conditions have been associated with an increased risk of EOS. Knowledge about these potential risk factors would help in early diagnosis of sepsis.

Based on the studies from India, the following risk factors seem to be associated with an increased risk of early onset sepsis:[4, 5]

1. Low birth weight (<2500 grams) or prematurity
2. Febrile illness in the mother with evidence of bacterial infection within 2 weeks prior to delivery
3. Foul smelling and/or meconium stained liquor

4. Rupture of membranes >24 hours
5. Single unclean or > 3 sterile vaginal examination(s) during labor
6. Prolonged labor (sum of 1st and 2nd stage of labor $\geq$ 24 hrs)
7. Perinatal asphyxia (Apgar score <4 at 1 minute)

Presence of foul smelling liquor or three of the above mentioned risk factors warrant initiation of antibiotic treatment. Infants with two risk factors should be investigated and then treated accordingly.

Late onset sepsis (LOS): It usually presents after 72 hours of age. The source of infection in LOS is either nosocomial (hospital-acquired) or community-acquired and neonates usually present with septicemia, pneumonia or meningitis.[6,7] Various factors that predispose to an increased risk of nosocomial sepsis include low birth weight, prematurity, admission in intensive care unit, mechanical ventilation, invasive procedures, administration of parenteral fluids, and use of stock solutions.

Factors that might increase the risk of community-acquired LOS include poor hygiene, poor cord care, bottle-feeding, and prelacteal feeds. In contrast, breastfeeding helps in prevention of infections.

Clinical features

Non-specific features: The earliest signs of sepsis are often subtle and nonspecific; indeed, a high index of suspicion is needed for early diagnosis. Neonates with sepsis may present with one or more of the following symptoms and signs (a) Hypothermia or fever (former is more common in preterm low birth weight infants) (b) Lethargy, poor cry, refusal to suck (c) Poor perfusion, prolonged capillary refill time (d) Hypotonia, absent neonatal reflexes (e) Brady/tachycardia (f) Respiratory distress, apnea and gasping respiration (g) Hypo/hyperglycemia (h) Metabolic acidosis.

Specific features related to various systems:

Central nervous system (CNS):	Bulging anterior fontanelle, vacant stare, high-pitched cry, excess irritability, stupor/coma, seizures, neck retraction. Presence of these features should raise a clinical suspicion of meningitis
Cardiac:	Hypotension, poor perfusion, shock
Gastrointestinal:	Feed intolerance, vomiting, diarrhea, abdominal distension, paralytic ileus, necrotizing enterocolitis (NEC)
Hepatic:	Hepatomegaly, direct hyperbilirubinemia (especially with urinary tract infections)
Renal:	Acute renal failure
Hematological:	Bleeding, petechiae, purpura
Skin changes:	Multiple pustules, abscess, sclerema, mottling, umbilical redness and discharge.

Investigations

Since treatment should be initiated in a neonate suspected to have sepsis without any delay, only minimal and rapid investigations should be undertaken[8].

Blood culture: It is the gold standard for diagnosis of septicemia and should be performed in all cases of suspected sepsis prior to starting antibiotics. A positive blood culture with sensitivity of the isolated organism is the best guide to antimicrobial therapy. Therefore it is very important to follow the proper procedure for collecting a blood culture.

The resident doctor/staff should wear sterile gloves prior to the procedure and prepare a patch of skin approximately 5 cm in diameter over the proposed veni-puncture site. This area should be cleansed thoroughly with 70% isopropyl alcohol, followed by povidone-iodine, and followed again by alcohol. Povidone-iodine should be applied in concentric circles moving outward from the centre. The skin should be allowed to dry for at least 1 minute before the sample is collected.

One-mL sample of blood should be adequate for a blood culture bottle containing 5-10 mL of culture media. Since samples collected from indwelling lines and catheters are likely to be contaminated, cultures should be collected only from a fresh veni-puncture site. All blood cultures should be observed for at least 72 hours before they are reported as sterile. It is now possible to detect bacterial growth within 12-24 hours by using improved bacteriological techniques such as BACTEC and BACT/ALERT blood culture systems. These advanced techniques can detect bacteria at a concentration of 1-2 colony-forming unit (cfu) per mL.

Septic screen[9,10]: All neonates suspected to have sepsis should have a septic screen to corroborate the diagnosis. However, the decision to start antibiotics need not be conditional to the sepsis screen result, if there is a strong clinical suspicion of sepsis.

The various components of the septic screen include total leukocyte count (TLC), absolute neutrophil count (ANC), immature to total (IT) neutrophil ratio, micro-erythrocyte sedimentation rate and C reactive protein (CRP) *(Table 1)*.

Table 1: A practical sepsis screen

Components	Abnormal value
Total leukocyte count	<5000/mm^3
Absolute neutrophil count	Low counts as per Manroe chart[11] for term and Mouzinho's chart[12] for VLBW infants
Immature/total neutrophil	>0.2
Micro-ESR	>15 mm in 1st hour
C reactive protein (CRP)	>1 mg/dl

(ESR, erythrocyte sedimentation rate)

The ANC varies considerably in the immediate neonatal period and the normal reference ranges are available from Manroe's charts.[11] The lower limit for normal ANC begins at 1800/cmm at birth, rises to 7200/cmm at 12 hours of age and then declines and persists at 1800/cmm after 72 hours of age. For very low birth weight infants, the reference ranges are available from Mouzinho's charts.[12] The I/T ratio is ≤0.16 at birth and declines to a peak value of 0.12 after 72 hours of age.

Presence of two abnormal parameters in a screen is associated with a sensitivity of 93-100%, specificity of 83%, positive and negative predictive values of 27% and 100% respectively in detecting sepsis. Hence, if two (or more) parameters are abnormal, it should be considered as a positive screen and the neonate should be started on antibiotics. If the screen is negative but clinical suspicion persists, it should be repeated within 12 hours. If the screen is still negative, sepsis can be excluded with reasonable certainty.

Lumbar puncture (LP): The incidence of meningitis in neonatal sepsis has varied from 0.3-3% in various studies.[3,6] The clinical features of septicemia and meningitis often overlap; it is quite possible to have meningitis along with septicemia *without* any specific symptomatology. This justifies the extra precaution of performing LP in neonates suspected to have sepsis.

In EOS, lumbar puncture is indicated in the presence of a positive blood culture or if the clinical picture is consistent with septicemia. It is not indicated if antibiotics have been started solely due to the presence of risk factors. In situations of late onset sepsis, LP should be done in all infants prior to starting antibiotics.

Lumbar puncture could be postponed in a critically sick neonate. It should be performed once the clinical condition stabilizes. The cerebrospinal fluid characteristics are unique in the newborn period and normal values are given in *Table* 2.[13]

Table 2: Normal cerebrospinal fluid examination in neonates[13]

CSF Components	Normal range
Cells/mm^3	8 (0-30 cells)
PMN (%)	60%
CSF protein (mg/dL)	90 (20-170)
CSF glucose (mg/dL)	52 (34-119)
CSF/ blood glucose (%)	51 (44-248)

(PMN, polymorphonuclear cells; CSF, cerebrospinal fluid)

Radiology: 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 suggestive of necrotizing enterocolitis (NEC). Neurosonogram and computed tomography (CT scan) should be performed in all patients diagnosed to have meningitis.

Urine culture: urine cultures have a low yield and are not indicated routinely. However, neonates at risk for fungal sepsis, with urogenital malformation or vesicoureteral reflex or suspected of UTI (crying during micturition) should have a urine examination done to exclude urinary tract infection (UTI). Urine cultures obtained by suprapubic puncture, bladder catheterization or clean catch sample from midstream of urine.

UTI may be diagnosed in the presence of one of the following: (a) >10 WBC/mm^3 in a 10 mL centrifuged sample (b) >10^4 organisms/mL in urine obtained by catheterization and (c) any organism in urine obtained by suprapubic aspiration

Management

***Supportive*:** Adequate and proper supportive care is crucial in a sick neonate with sepsis. He/she should be nursed in a thermo-neutral environment taking care to avoid hypo/hyperthermia. Oxygen saturation should be maintained in the normal range; mechanical ventilation may have to be initiated if necessary. If the infant is hemodynamically unstable, intravenous fluids should be administered and the infant is to be monitored for hypo/hyperglycemia. Volume expansion with crystalloids/colloids and judicious use of inotropes are essential to maintain normal tissue perfusion and blood pressure. Packed red cells and fresh frozen plasma might have to be used in the event of anemia or bleeding diathesis.

Antimicrobial therapy: There cannot be a single recommendation for the antibiotic regimen of neonatal sepsis for all settings. The choice of antibiotics depends on the prevailing flora in the given unit and their antimicrobial sensitivity. This protocol does not aim to provide a universal recommendation for all settings but lays down broad guidelines for the providers to make a rational choice of antibiotic combination. 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 and meningitis *(Table 3).*

Table 3. Duration of antibiotic therapy in neonatal sepsis

Diagnosis	Duration
Meningitis *(with or without positive blood/CSF culture)*	21 days
Blood ***culture positive*** *but* ***no meningitis***	14 days
Culture ***negative*** *sepsis* ***(screen positive*** *and clinical course* ***consistent with sepsis)***	5-7 days

Indications for starting antibiotics: The indications for starting antibiotics in neonates at risk of EOS include any one of the following:

(a) presence of ≥3 risk factors for early onset sepsis (*see above*)
(b) presence of foul smelling liquor
(c) presence of ≥2 antenatal risk factor(s) *and* a positive septic screen and
(d) strong clinical suspicion of sepsis.

The indications for starting antibiotics in LOS include:

(a) positive septic screen and/or
(b) strong clinical suspicion of sepsis.

Prophylactic antibiotics: We do not use prophylactic antibiotics in the following circumstances: infants on IV fluids/TPN, meconium aspiration syndrome, and after exchange transfusion(s). 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 hence does not merit antibiotics. However a messy exchange transfusion could be treated with prophylactic antibiotics. In our unit, ventilated neonates are treated with prophylactic amikacin for the period of ventilation.

Choice of antibiotics: Empirical antibiotic therapy should be unit-specific and determined by the prevalent spectrum of etiological agents and their antibiotic sensitivity pattern. Antibiotics once started should be modified according to the sensitivity reports. Guidelines for empirical antibiotic therapy have been provided in *Table 4*.

Table 4. Empirical choice of antibiotics for treatment of neonatal sepsis

Clinical situation	**Septicemia & Pneumonia**	**Meningitis**
FIRST LINE Community-acquired (Resistant strains unlikely)	Penicillin or Ampicillin and Gentamicin	Add Cefotaxime
SECOND LINE Hospital-acquired Some strains are likely to be resistant	Ampicillin or Cloxacillin and Gentamicin or Amikacin	Add Cefotaxime
THIRD LINE Hospital-acquired sepsis (Most strains are Likely to be resistant)	Cefotaxime or Piperacillin-Tazobactam or Ciprofloxacin and Amikacin;	Same (Avoid Cipro)

Consider Vancomycin if MRSA is suspected.

The empirical choice of antibiotics is dependent upon the probable source of infection. For infections that are likely to be community-acquired where resistant strains are unlikely, a combination of ampicillin or penicillin with gentamicin may be a good choice as a first line therapy.

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. 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 ceftazidime) with amikacin may be appropriate. 3rd generation cephalosporins have very good CSF penetration and are traditionally thought to have excellent antimicrobial activity against gram negative organisms. Hence they were considered to be a good choice for the treatment of nosocomial infections and meningitis. However, recent reports suggest that at least 60-70% of the Gram-ve organisms are resistant to them.[14-16] More over, routine use of these antibiotics might increase the risk of infections with ESBL (extended spectrum beta-lactamase) positive organisms. Therefore it is preferable to use antibiotics such as piperacillin-tazobactam or methicillin/vancomycin in units with high incidence of resistant strains.

A combination of piperacillin-tazobactam 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 ciprofloxacin or vancomycin with amikacin. Ciprofloxacin has excellent activity against gram-negative organisms also; however, it does not have good CSF penetration. It may be used for the treatment of resistant gram-negative bacteremia after excluding meningitis.

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.

The dosage, route, and frequency of commonly used antibiotics are given in Table 5.

Reserve antibiotics: Newer antibiotics like aztreonam, meropenem and imipenem are also now available in the market. Aztreonam has excellent activity against gram-negative organisms while meropenem is effective against most bacterial pathogens except methicillin resistant staphylococcus aureus (MRSA) and enterococcus. Imipenem is generally avoided in neonates because of the reported increase in the incidence of seizures following its use. Empirical use of these antibiotics should be avoided; they should be reserved for situations where sensitivity of the isolated organism warrants its use.

Adjunctive therapy

Exchange transfusion (ET): Sadana et al[17] have evaluated the role of double volume exchange transfusion in septic neonates with sclerema and demonstrated a 50% reduction in sepsis related mortality in the treated group. We perform double-volume exchange transfusion with cross-matched fresh whole blood as adjunctive therapy in septic neonates with sclerema.

Intravenous Immunoglobulin (IVIG): Non-specific pooled IVIG has not been found to be useful.[18]
Granulocyte-Macrophage colony stimulating factor (GM-CSF): This mode of treatment is still experimental.[19]

Table 5. Drugs, route of administration and doses of common antibiotics used.

Drug	Route	Birth Weight ≤2000g		Birth Weight >2000g	
		0-7 d	>7 days	0-7 days	>7 days
Amikacin	I/V, I/M	7.5 q12h	7.5 q8h	10 q12h	10 q8h
Ampicillin					
Meningitis	I/V	100 q12h	100 q8h	100 q 8h	100 q6h
Others	I/V, I/M	25 q12h	25 q8h	25 q8h	25 q6h
Cefotoxime					
Meningitis	I/V	50 q6h	50 q6h	50 q6h	50 q6h
Others	I/M, I/V	50 q12h	50 q8h	50 q12h	50 q8h
Piperacillin+ Tazobactam	I/V	50-100 q12h	50-100 q8h	50-100 q12h	50-100 q12h
Ceftriaxone	I/M, I/V	50 q24h	50 q24h	50 q24h	75 q24h
Ciprofloxacin	I/V, PO	10-20 q24h	10-20 q24h	10-20 q12h	10-20 q12h
Cloxacillin					
Meningitis	I/V	50 q12h	50 q8h	50 q8h	50 q6h
Others	I/V	25 q12h	25 q8h	25 q8h	25 q6h
Gentamicin					
Conventional	I/V, I/M	2.5 q12h	2.5 q8h	2.5 q12h	2.5 q8h
Single dose	I/M	4 q24 h	4 q24 hr	5 q24h	5 q24h
Netilmicin	I/V, I/M	2.5 q12h	2.5 q8h	2.5 q12h	2.5 q8h
Penicillin G		(units/kg/dose)			
Meningitis	I/V	75,000 q12h -100,000	75,000 q8h -1,00,000	75,000 q8h -1,00,000	75,000 q6h -1,00,000
Others	I/V, I/M	25,000 q12h	25,000 q8h	25,000 q8h	25,000 q6h
Vancomycin	I/V	15 q12h	15 q8h	15 q12h	15 q8h

All doses are in mg/kg/dose; (I/V, intravenous; I/M, intramuscular; PO, per-oral; h, hourly)

Table 7 : Research questions pertaining to neonatal sepsis

Research question	**Subjects**	**Study design**	**Intervention**	**Outcomes to be measured**
1. Does antimicrobial stewardship (AMS) reduce the rates of health care associated infections in NICU?	All babies admitted to NICU	Before and after study	Bundle of interventions to constitute AMS:	The incidence of health care associated infections, neonatal mortality
2.What is the rate of medication errors with regard to antibiotic prescripti-on in a level II NICU?	All babies admitted to NICU in the last two years	Retrospective study	None	Rates of medication errors and estimated additional costs due to it
3. What are the trends of de-escalating from broad-spectrum combination therapy to directed therapy and the rates of relapse of infection in those undergoing this de-escalation?	All babies admitted to NICU and receiving antibiotics	Descriptive study	None	The rates of de-escalation of therapy and incidence of infections/morbidities after antibiotic change
4. What is the culture positivity rates in babies previously exposed with antibiotics?	All babies born in the hospital to mothers with prior antibiotic exposure	Descriptive study (stratified by birth weight/gestational age)	None	The rate of blood, CSF and other fluids culture
5. What is the antimicro-bial expenditu-re(both out of pocket and hospital supply) and trends over time?	All babies receiving antibiotics in NICU	Descriptive	None	The costs of both out of pocket and hospital supply antibiotic per baby receiving antibiotics

6. Does the use of rifampin in cases of proven MRSA infection reduce the rates of colonization and incidence of MRSA?	All babies developing proven MRSA infection	RCT	Rifampin	Colony count of MRSA in colonized patients

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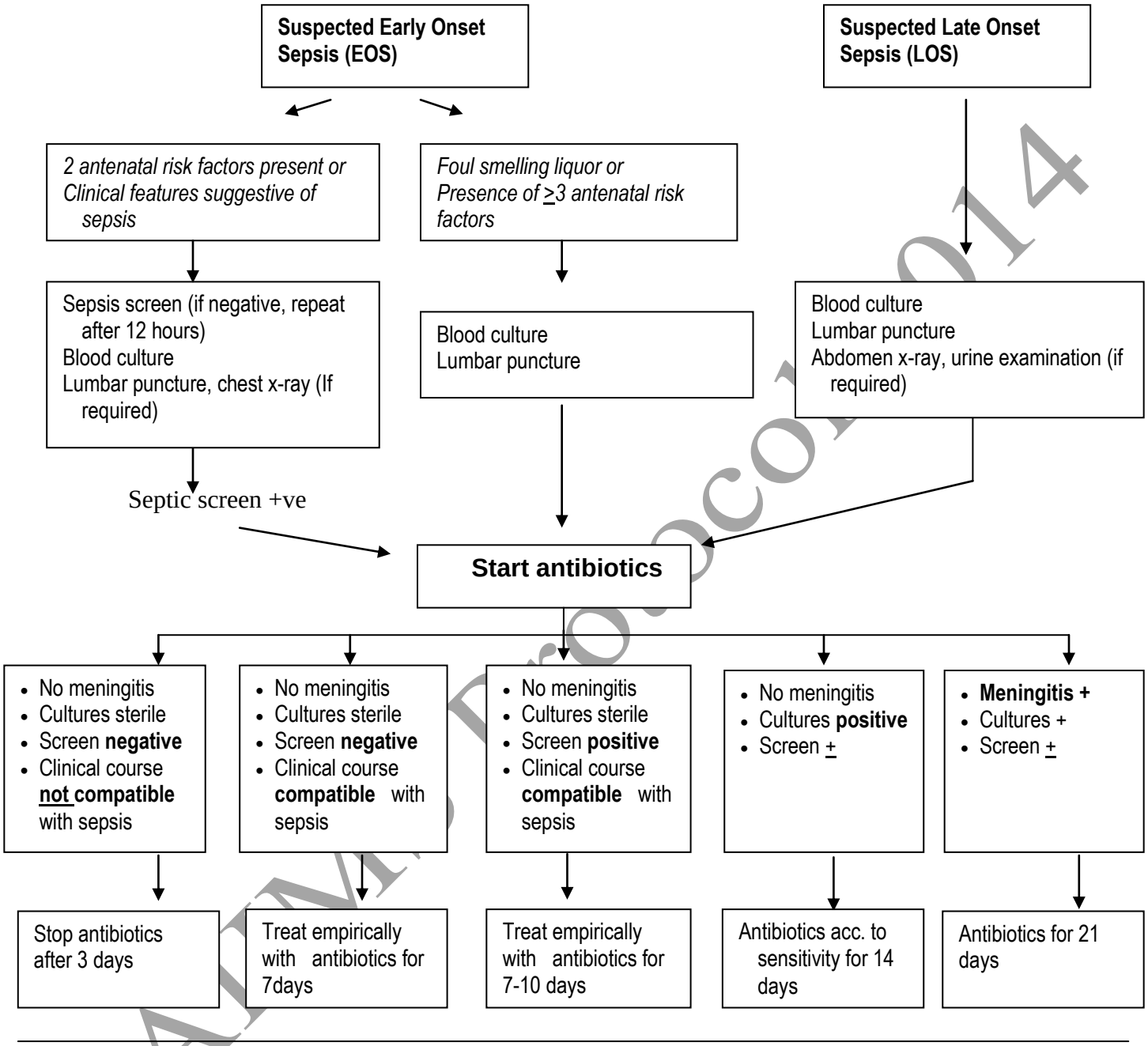
Protocol for sepsis



NB. If no response is seen within 48-72 hours of starting treatment, a repeat blood culture should be obtained to determine appropriate choice and duration of antibiotic therapy. A lumbar puncture should be repeated in gram negative meningitis to assess for response to therapy.