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APPROPRIATE USE OF ANTIBIOTICS FOR THE MANAGEMENT OF SEPSIS IN NEONATES

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ABSTRACT

Neonatal sepsis is associated with increased mortality and morbidity including neurodevelopmental impairment and prolongation of hospital stay. Clinical features of sepsis are non-specific in neonates and a high index of suspicion is required for timely diagnosis. Antibiotics are a very important group of drugs for the sick neonate and have undoubtedly played a role in their improved survival. But they come with a set of risks like other drugs used in critical care which must be carefully considered and weighed against the benefits in any decision to commence antibiotics. Prophylactic antibiotics are not indicated in almost all situations in neonatology. There is high level of evidence to show that they are not useful for the prevention of infection following umbilical vessel or central venous catheterization. Traditionally, the selection of antibiotics for empirical therapy is based on the local policy, and the duration of therapy is decided by the treating physician based on clinical symptoms and blood culture results. In this paper, we discuss briefly about the causative organisms of neonatal sepsis in both the developed and developing countries; with a special focus on antibiotic therapy in neonates with suspected sepsis, culture proven sepsis, and meningitis.

INTRODUCTION: Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life [1]. it is responsible for about 30-50% of the total neonatal deaths in developing countries [2]. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes [3]. Sepsis related mortality is largely preventable with rational antimicrobial therapy and aggressive supportive care.

Virtually all extremely low birth weight infants too are treated with antibiotics [4]. High antibiotic exposure rates (75%–94%) have been reported in neonates and are most probably based on the common practice of administering antibiotics, pending bacterial culture results, to sick neonates and to neonates with risk factors for developing infectious diseases [5].

However among those who receive antibiotics only a small number eventually have culture proven infection. Clark et al reported that 98% of preterm infants who received empiric antibiotics were culture negative [6].

The neonatologist needs the skills and knowledge to weigh the benefits and harms of antibiotics. This would best be done on each individual baby. Selection of appropriate anti-infective therapy can be challenging to the Neonatologist.

It is not sufficient to know the likely pathogens causing the infection and which antibiotics have been successful in the past. It is well recognized that the total amount of antibiotic use as well as the number of patients treated with antibiotics are risk factors for the selection of resistant bacteria [7].

Microbiology of Neonatal sepsis: 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). Sepsis occurring in the first 72 hours of life is defined as early-onset sepsis (EOS) and that occurring beyond 72 hours as late-onset sepsis (LOS). Usually EOS is due to vertical transmission of pathogens and LOS is due to horizontal transmission of the pathogens from care givers.

The pattern of bacterial pathogen responsible for neonatal sepsis has changed with time and varies from place to place. There is a difference in the causative organisms for neonatal sepsis between the developed and developing countries [8]. In United States, the National Institute of Child Health and Development (NICHD) reported that the common pathogens causing EOS are group B *Streptococcus* (GBS) and *Escherichia coli*. GBS remains the most frequent pathogen in term infants, and *E. coli* the most significant pathogen in preterm infants with EOS [9].

In the developed countries, Gram-positive organisms account for about 70% of all LOS. The common pathogens causing LOS in very low birth weight (VLBW) infants include Coagulase Negative Staphylococci (CoNS) followed by *Staphylococcus aureus*, *Enterococcus* spp., and GBS [10]. About 18–20% of late-onset sepsis is caused by Gram-negative organisms especially *Enterobacteriaceae* spp. and *E. coli*. About 12% of LOS sepsis is caused by fungi especially *Candida* species [11].

In the developing world, *E. coli, Klebsiella species*, and *S. aureus* are the most common pathogens of EOS, whereas *S. aureus*, *Streptococcus pneumonia*, and *Streptococcus pyogenes* are the most commonly reported organisms in LOS. According to the National Neonatal Perinatal Database of India, *Klebsiella pneumonia*, *Staphylococcus aureus*, and *E. coli* are the three most common organisms causing neonatal sepsis both in hospital and community [12]. Moreover, the causative organisms of EOS and LOS sepsis are similar especially in hospital setting in developing country.

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 database comprising 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 [13]. Septicemia was the commonest clinical category with an incidence of 23 per 1000 live births while the incidence of meningitis was reported to be 3 per 1000 live births. 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%) [14].

Factors affecting Antibiotic selection: When choosing an antibacterial agent, the following factors are the most important to consider.

1) **Microbiology**: What are the most common organisms causing the infection? What are the local antibiotic susceptibility patterns? Are resistance mechanisms likely already present in the pathogens; will additional mechanisms become apparent on exposure to the antibiotic?

2) **Pharmacodynamics**: Would treatment with the agent result in the type of exposure known to optimize the desired biologic effect on the pathogens?

3) **Pharmacokinetics**: Based on the expected absorption, metabolism, elimination, and distribution of the drug to the site of infection, what is the ideal route and dose of drug to prescribe?

4) **Host**: What host factors might affect drug selection and dosing?

5) **Antibiotic adverse reactions**: Are there potential side effects that might affect the relative risks and benefits of therapy? What toxicities should be anticipated, either directly or as a result of drug-drug interactions?

Defining Antibiotic treatment: It is convenient to classify the use of antibiotics into three main strategies,

1) Prophylaxis
2) Empirical treatment and
3) Definitive treatment

1. **Prophylactic treatment:** Prophylactic use of antibiotics implies that they are given to prevent infection. Prophylactic antibiotics are not indicated in almost all situations in neonatology. There is high level of evidence to show that they are not useful for the prevention of infection following umbilical vessel or central venous catheterization [15]. The only prophylactic use of antimicrobials that may be justified is the use of fungal prophylaxis in preterm infants on broad spectrum antibiotics, or with central arterial or venous lines. A Cochrane systematic review suggests oral or topical antifungals reduce the incidence of systemic fungal infections [16].

2. **Empirical treatment:** Empirical antibiotics are used when infection is suspected. Infection could be just one of several explanations for an infant's illness so we 'cover' with antibiotics. A common setting is to start antibiotics in all neonates with respiratory distress, in particular those who have risk factors for infection such as maternal chorioamnionitis and prlonged rupture of membranes.

3. **Definitive treatment:** Sometimes we are sure that an infant has clinical or proven infection and we make a decision to treat the infant with a full course of antibiotics.

Empirical Antibiotic therapy for Neonatal sepsis: The early and appropriate initiation of antimicrobial agents in high-risk neonates before the results of blood culture susceptibility is defined as "empirical antibiotic therapy."Most infants admitted to the neonatal intensive care units (NICUs) receive empirical antibiotics when in fact the incidence of culture-proven EOS is only between 1 and 4.6 cases per 1000 live births [17]. One study suggested that the ratio of non- infected to blood- culture- positive neonates treated with antibiotics was between 15: 1 and 28: 1 [18]. The risk factors for EOS include clinical chorioamnionitis, maternal intrapartum fever (>38.0 ^{o}C), delivery at <37 weeks, rupture of membranes (ROM) >18 hours before delivery, maternal GBS colonization, previous infant with GBS infection, GBS bacteriuria, and inadequate intrapartum antibiotic prophylaxis [19]. Among infants who are discharged home, new onset of fever, cough, fast or difficult breathing, poor feeding, lethargy, and convulsions are indicators of sepsis and warrant initiation of appropriate antibiotic therapy [20].

- **Antibiotic Regimen for Early onset sepsis:** Neonates with suspected sepsis or meningitis should be treated as soon as appropriate cultures and intravenous access can be obtained. The initial choice for empirical treatment is dependent on the knowledge of the probable pathogens based on the perinatal history, including any maternal symptoms, cultures, or instrumentation and susceptibility pattern of the organisms [21].

  Based on the common antibiotic susceptibilities of the predominant organism causing EOS, the recommended initial empiric therapy for a neonate with suspected bacterial sepsis and/or meningitis includes Ampicillin and an Aminoglycoside [22]. The advantages of this combination are expansion of antimicrobial spectrum, synergistic bacterial killing, low cost and low rates of emergence of bacterial resistance.

  However, in developing countries where the causative organisms of EOS are different from the developed countries, the above combination of Ampicillin and Gentamicin may not be the best empirical antibiotic of choice. More than 99% of neonatal deaths occur in the developing world, and a quarter of these deaths are attributed to neonatal sepsis [23]. Due to the insufficient knowledge about the choice of appropriate antibiotic treatment and the emerging resistance to commonly prescribed antibiotics, it will be difficult to successfully treat this condition in the developing world.

- **Antibiotic Regimen for Late onset sepsis:** The empirical antimicrobial therapy for LOS should cover both Gram-positive and Gram-negative

organisms. In the developed countries, where CoNS is the predominant nosocomial pathogen and where resistance of these isolates to penicillin, semisynthetic penicillin, and gentamicin are common, experts recommend the use of vancomycin as empirical therapy [24]. Of the 18 participating NICUs in Australasian study group for neonatal infection, nine units used vancomycin and an aminoglycoside as the first-line empirical treatment for LOS [25].

In developing nations, LOS is complicated by a higher percentage of Gram-negative bacteria and greater antimicrobial resistance among the organisms. Zaidi *et al*., reported that the rates of neonatal sepsis were 3–20 times higher among hospitalized infants in developing countries compared to developed nations.[26] Empiric antifungal therapy should be considered if the infants have central vascular access, an endotracheal tube, thrombocytopenia (<100,000/mm3), exposure to broad spectrum cephalosporins or carbapenem, and gestational age less than 28 weeks [27]. Amphotericin B should be chosen for empiric therapy, and fluconazole should be reserved for prophylaxis.

An acceptable approach would be to start with cloxacillin and gentamicin as initial antibiotics for LOS in a stable neonate. Vancomycin and third-generation cephalosporin (e.g., cefotaxime) should be considered for LOS in a neonate presenting with cardiorespiratory instability and in areas where MRSA is prevalent. The dangers of starting vancomycin as the initial therapy in all infants include the risk of emergence of vancomycin-resistant *enterococci* and its overuse in cases where CoNS isolates represent mere contaminants.

- **Antibiotic therapy for Bacterial proven sepsis with Meningitis:** When bacterial meningitis is suspected as part of EOS, ampicillin with either an aminoglycoside or cefotaxime is commonly recommended as initial empirical therapy to cover GBS, *E.coli*, *Listeria monocytogenes*, and *Klebsiella* species.[28] For neonates with late-onset meningitis, a regimen containing an antistaphylococcal antibiotic, such as nafcillin or vancomycin,plus cefotaxime or ceftazidime with or without an aminoglycoside is recommended [29].

- **Duration of Antibiotic therapy:** C-reactive protein (CRP) is an excellent marker for established neonatal bacterial infections. However, it is not useful for early diagnosis because levels are elevated only in 35% to 65% of neonates at the onset of illness. Several studies have evaluated the role of serial CRP measurement as a guide to the duration of antibiotic therapy both in developed and developing countries.

  Normalization of CRP levels can be considered as a criterion for the discontinuation of antibiotic therapy to minimize antibiotic exposure and shorten hospital stay. However, previous studies that showed CRP as a good guide excluded high-risk infants with central lines, mechanical ventilation, post surgery, meningitis, birth asphyxia, and those with positive initial CRP [30]. Hence, the usefulness of CRP in guiding decisions regarding the duration of antibiotics might be valid only in selected subset of neonates.

- **Empirical antibiotic therapy**: The standard practice is to discontinue antibiotics as soon as blood cultures are confirmed negative (48–72 hours) and there are no clinical or hematologic signs of infection [31]. A symptomatic baby can have a false-negative blood culture if antibiotics are given prenatally to the mother or if the blood sample is collected improperly. Hence, antibiotics should be continued for symptomatic infants and those with positive blood culture.

- **Proven Bacterial sepsis without meningitis**: it is reasonable to treat for 10–14 days with appropriate antimicrobial agents in infants with blood-culture-proven sepsis. However, in selected situations (neonates ≥32 weeks gestation and ≥1500 grams, who become asymptomatic within 5 days of appropriate therapy), we can consider stopping antibiotics at 7–10 days, provided appropriate follow up can be ensured [32].

- **Neonatal meningitis:** Repeat lumbar puncture to document CSF sterilization and improvement of CSF parameters is not indicated routinely.

However, it should be done in all patients who have not responded clinically after 48 hours of appropriate antimicrobial therapy. Neonates with meningitis due to Gram-negative bacilli should undergo repeated lumbar punctures to document CSF sterilization, because the duration of antimicrobial therapy is determined, in part, by the result. The duration of antimicrobial therapy for neonatal meningitis should be 14 to 21 days for GBS, ≥21 days for *L. monocytogenes* meningitis, and minimum of 21 days for Gram-negative meningitis [33].

TABLE 1: RECOMMENDED DOSAGES OF SELECTED PARENTERAL ANTIBIOTICS IN NEONATES

Name of Drug	Recommended Dose & Dosing Interval
Amikacin	PMA ≤ 29 Weeks PN : 0-7 days 18mg/Kg 48th hourly, 8-28 days 15mg/Kg 36th hourly, ≥ 29 days 15 mg/ Kg 24th hourly PM A :30- 34 Weeks PN : 0-7 days 18mg/Kg 36th hourly, ≥ 8 days 15mg/Kg 24th hourly PMA ≥ 35 Weeks, 15mg/Kg 24th hourly
Ampicillin	DOSE : 25-50 mg/Kg per dose by slow IV push/IM PMA ≤ 29 Weeks PN: 0-28 days 12th hourly, > 28 days 8th hourly. PMA: 30-36 Weeks PN: 0-14 days 12th hourly, >14 days 8th hourly. PMA: 37-44 Weeks PN: 0-7 days 12th hourly, >7 days 8th hourly PMA ≥45 Weeks 6th hourly.
Cefazolin	DOSE: 25 mg/Kg per dose IV slow push or IM PMA ≤ 29 Weeks PN: 0-28 days 12th hourly, > 28 days 8th hourly PMA: 30-36 Weeks PN: 0-14 days 12th hourly, >14 days 8th hourly PMA: 37-44 Weeks PN: 0-7 days 12th hourly, >7 days 8th hourly PMA ≥45 Weeks 6th hourly
Cefepime	Term/ Preterm; ≤ 28 days 30mg/Kg per dose every 12 hours. ≥ 28 days 50mg/Kg per dose every 12 hours Meningitis/ severe infections: 50 mg/kg 12th hourly.
Cefotaxime	50 mg/ Kg per dose IV infusion by syringe pump over 30 minutes, or IM. PMA ≤ 29 Weeks PN: 0-28 days 12th hourly, > 28 days 8th hourly PMA: 30-36 Weeks PN: 0-14 days 12th hourly, >14 days 8th hourly PMA: 37-44 Weeks PN: 0-7 days 12th hourly, >7 days 8th hourly PMA ≥45 Weeks 6th hourly
Ceftazidime	30 mg/ Kg per dose IV infusion by syringe pump over 30 minutes, or IM. PMA ≤ 29 Weeks PN: 0-28 days 12th hourly, > 28 days 8th hourly PMA: 30-36 Weeks PN: 0-14 days 12th hourly, >14 days 8th hourly PMA: 37-44 Weeks PN: 0-7 days 12th hourly.: >7 days 8th hourly PMA ≥45 Weeks 8th hourly
Clindamycin	5 - 7.5 mg/ Kg per dose IV infusion by syringe pump over 30 minutes. PMA ≤ 29 Weeks PN: 0-28 days 12th hourly, > 28 days 8th hourly PMA: 30-36 Weeks PN: 0-14 days 12th hourly, >14 days 8th hourly PMA: 37-44 Weeks PN: 0-7 days 12th hourly, >7 days 8th hourly PMA ≥45 Weeks 6th hourly
Gentamicin	PMA ≤ 29 Weeks PN : 0-7 days 5mg/Kg 48th hourly, 8-28 days 4mg/Kg 36th hourly, ≥ 29 days 4mg/ Kg 24th hourly PMA :30- 34 Weeks PN : 0-7 days 4.5mg/Kg 36th hourly, ≥ 8 days 4mg/Kg 24th hourly PMA ≥ 35 Weeks, 4mg/Kg 24th hourly
Imipenem/Cilastatin	20- 25 mg/Kg per dose every 12 hours IV infusion over 30 minutes
Meropenem	Sepsis: 20mg/Kg per dose IV.

	<32 weeks GA: ≤ 14 days PNA, every 12 hours, > 14 days PNA every 8 hours. 32 weeks and older: ≤7 days PNA, every 12 hours, > 7days PNA every 8 hours
Piperacillin-Tazobactam	50-100 mg/Kg per dose IV infusion by syringe pump over 30 minutes PMA ≤ 29 Weeks PN: 0-28 days 12th hourly, > 28 days 8th hourly PMA: 30-36 Weeks PN: 0-14 days 12th hourly, >14 days 8th hourly PMA: 37-44 Weeks PN: 0-7 days 12th hourly, >7 days 8th hourly PMA ≥45 Weeks 8th hourly
Vancomycin	Meningitis: 15mg/Kg per dose. Bacteremia: 10 mg/Kg per dose IV infusion by syringe pump over 60 minutes. PMA ≤ 29 Weeks PN: 0-14 days 18th hourly, > 14 days 12th hourly PMA: 30-36 Weeks PN: 0-14 days 12th hourly, >14 days 8th hourly PMA: 37-44 Weeks PN: 0-7 days 12th hourly, >7 days 8th hourly PMA ≥45 Weeks 6th hourly

***PMA: Post menstrual age *PN: Post natal**

TABLE 2: THE TEN POINT PLAN ON ANTIBIOTIC USE

1. Always take cultures of blood (and perhaps CSF and/ or urine) before starting antibiotics.
2. Use the narrowest spectrum antibiotics possible, almost always a pencillin and an aminoglycoside
3. Do not start treatment, as a general rule, with third generation cephalosporin (eg: cefotaxime, ceftazidime) or a carbapenem (e.g., imipenem, meropenem)
4. Develop local and national antibiotic policies to restrict the use of expensive, broad spectrum antibiotics for emergency treatment
5. Trust the microbiology and rely on the blood culture results.
6. Stop believing that a raised CRP means the baby is definitely septic
7. If blood cultures are negative at 2-3 days, it is almost always safe and appropriate to stop antibiotics.
8. Try not to use antibiotics for long periods.
9. Treat sepsis but not colonization.
10. Do your best to prevent noscomial infection, by reinforcing infection control, particularly hand washing.

CONCLUSION: The optimal selection, dosage, appropriate administration and duration of the antimicrobial treatment are the important factors for achieving the best clinical outcomes for the treatment or prevention of infection with minimal toxicity to the patient and minimal impact on subsequent resistance. The choice of antibiotics should be based on the causative organisms and the patterns of antibiotic susceptibility.

The manifestations of neonatal sepsis are non-specific so 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. Above all a disciplined approach consisting of a thorough physical examination and evaluation of clinical response to treatment are important in tailoring appropriate dose and duration of antibiotics in neonates with suspected or proven sepsis.

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