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REVIEW ARTICLE

ANTIBIOTIC USAGE AND RATIONAL GUIDELINE PRACTICES IN NEONATAL SEPSIS

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Abstract - Antibiotics are being extensively used in India today leading to emergence of multi-drug resistant pathogens, and increased incidence of fungal sepsis. A rational antibiotic policy needs to be in place to prevent the emergence of drug resistant strains. This review covers the common organisms causing neonatal sepsis in India, rationale for selection of antimicrobial agents, duration of therapy and the suggested steps to prevent antimicrobial resistance.

Key Words - Early Onset Sepsis (EOS); Late Onset Sepsis (LOS); Extended Spectrum Beta Lactamase.

Introduction - India has an enormous and growing problem of antibiotic use and abuse. Between 11 and 23 non-infected newborns are treated with antibiotics for every one infant with proven sepsis [1] Appropriate usage of antibiotics helps, undoubtedly, in reducing the risk of deaths secondary to sepsis, but their indiscriminate use can have serious repercussions, including multidrug resistant bacterial pathogens, and increased incidence of fungal sepsis. There is, hence, a need to have a rational antimicrobial policy that minimizes the use of antibiotics in non-infected neonates, without denying it to an infant with sepsis. The aim of this article is to enable those involved in the care of newborns to devise a rational antibiotic policy for their respective units, based on the available information and evidence.

The reported incidence of neonatal sepsis in the western world varies from < 1 to 8.1 cases per 1000 live births. [2] In developing countries, sepsis is the commonest cause of mortality responsible for 30-50 % of the 5 million total neonatal deaths each year. [3] It is estimated that almost 20% of all neonates develop infection, and approximately 1% die of the serious systemic infection. [3] The reported incidence of neonatal sepsis varies from 7.1 to 38 per 1000 live births in Asia. [4,5]

The National Neonatal Perinatal Database (2002-2003) reports an incidence varying from 0.1 to 4.5% from 18 hospitals across India [6]. However, authentic community figures are lacking. Most of the reports from community often include all cases of "Suspect Sepsis". Bang et al [7] reported an incidence of 6.5%, based on clinical diagnosis from the community. By comparison, the reported incidence is 1 to 10 per 1000 live births in developed countries (1.5 - 3.5 / 1000 for early onset, and up to 6 / 1000 for late onset sepsis [8]

The incidence of bacterial meningitis in the West is 0.2-1.0 per 1000 live births. In Indian nurseries, the incidence of meningitis was estimated as 3 per 1000 live births. [6]

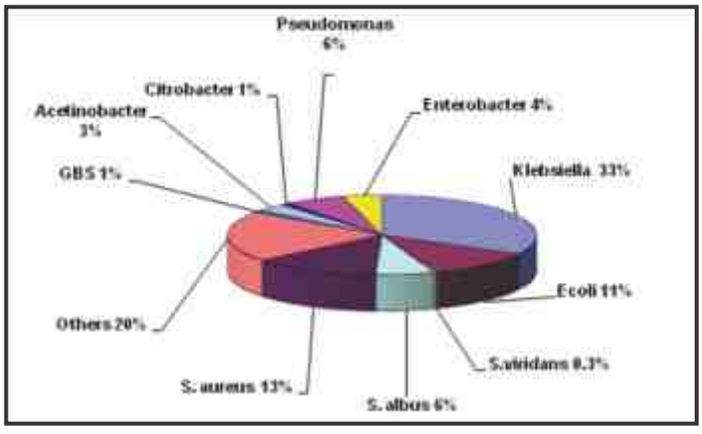
Organisms Causing Sepsis - Organisms causing infection would vary from place to place and time of onset of infection. Early Onset Sepsis (EOS) would be mostly vertically-acquired from mothers, where maternal flora would be the predominant organisms causing bacterial sepsis. E.Coli, Enterobacter, Enterococcus, H influenzae and Listeria monocytogens are most commonly associated with early onset infection. [9]

In contrast, Late Onset Sepsis (LOS) occurs at 6-90 days of life and would generally be acquired from the hospital surroundings, & hence the organism would be determined by prevailing micro flora. Organisms that are associated with LOS are Staphylococci, Coagulase negative Staphylococcus (CONS), E Coli, klebiella, Pseudomonas, Enterobacter, Candida, Serratia, acinetobacter & anaerobes. [9]

In developing countries, Gram negative organisms are more common and are mainly represented by Klebsiella, E. coli and Pseudomonas. (Fig. 1) [6]. Among Gram positive organisms Staphylococcus aureus, coagulase-negative staphylococcus (CONS) and Streptococcus pneumoniae are most common. Due to unknown reasons, Group B Streptococcus (GBS) is rare or not seen in India.

Figure - 1

Organisms causing neonatal sepsis in Intramural neonates (n= 1248) [6]



In a survey to evaluate the current practices of antibiotic usage in major level II / III units across the country (n = 19)[9], it was noted that 94.1% units employed a "Sepsis Screen" to screen neonates with risk factors and/ or non-specific symptoms; while 75% use prophylactic antibiotics for neonates requiring ventilation for respiratory distress syndrome (RDS) .About two-third (70.6%) of the surveyed units would wait for 48-72 hours before changing to the next line of antibiotics in case of non-response to the first line.

Antibiotic Resistance -

It is now well known that excessive antibiotic use selects for antibiotic resistant bacteria. . Broad spectrum antibiotics are more potent selectors of antibiotic resistance than narrow spectrum antibiotics. Reports of multi-resistant bacteria causing neonatal sepsis in developing countries are increasing.[10,11]Gram negative bacteria like Klebsiella & Enterobacter species are often found to be resistant. Klebsiella & E Coli can produce plasmid-mediated extended spectrum beta lactamases (ESBL) which render the Klebsiella resistant to almost all antibiotics, not just beta lactams. [12,13] Gram positive bacteria can carry genes conferring vancomycin resistance, such as vancomycin resistant enterococci (VRE), and genes coding for methicillin resistance, such as methicillin resistant Staphylococcus aureus (MRSA) & methicillin resistant Staphylococcus epidermidis (MRSE) [12,13].

Microbes and resistance pattern -

From the available data, the incidence of resistant bacteria in our country is higher than that reported from neighboring countries and also from resource-rich nations. Most of the Klebsiella isolates are resistant to Ampicillin (97.2%), Gentamicin (88.6%) and Cefotaxime (60.6%). However the organism is sensitive to Amikacin (64.4%) and Ciprofloxacin (73.3%) (12). Similarly E.Coli isolates were resistant to Ampicillin (86.3%), Gentamicin (60%) and Cefotaxime (52.3%). 90% of the Staphylococcus isolates were resistant to Penicillin and 10% to Vancomycin. [12]

In a study from North India, [14] among the 75 cases with Gram-negative septicemia, the common isolates were Klebsiella, E.Coli, Acinetobacter, Proteus and Enterobacter species. Overall 61.5% of Gram-negative isolates and 52.2% of Klebsiella isolates were ESBL producers. Most of the isolates were resistant to Gentamicin (57.2%) and Cefotaxime (68.3%). However, majority were sensitive to Amikacin (55.6%), Piperacillin-tazobactum (92.1%) and Meropenem (96.8%). In a study done by Lee J. et al. on pediatric patients, the incidence of ESBL producing Gram-negative bacteria decreased from 39.8% to 22.3% with Cephalosporin restriction.[15] A similar study done by Rasaily [9] revealed nearly 80% of Klebsiella isolates and 66% of S. aureus isolates were resistant to Gentamicin. 70% of Klebsiella and 60% of S. aureus were resistant to Amikacin; however 76% of all isolates of E.Coli were sensitive to Amikacin.

Management -

NEONATES WITH PRESUMED SEPSIS MAY PRESENT IN THE FOLLOWING WAYS-

A. Asymptomatic neonate with Risk factors, with/ without septic screen

B. Asymptomatic neonate with Risk factors, mother given intrapartum antibiotics

C. Symptomatic Neonate- Presumed Sepsis

D. Treatment of Neonate where bacterial cultures are negative

E. Management if neonate with catheter associated infections

F. Management of Neonatal Meningitis

A. Asymptomatic neonate with Risk factors

Most of these infants are asymptomatic at birth, but may manifest symptoms usually by 24 (~90%) to 48 hours (~ 100%).[16] These may be managed by observation alone; or active screening with or without antibiotics. Though the first seems more rational, there is a danger of missing an occasional neonate who progresses to develop a fulminant disease within hours of presentation.

In a study involving about 1300 neonates with risk factors for sepsis, Escobar et al [17] found that an asymptomatic status was found to reduce the probability of sepsis by about 75%, however 1% of these infants were found to be infected. Some authors have, therefore, suggested a middle path –observation alone for asymptomatic neonates born at >35 weeks of gestation; and antibiotic therapy with or without screening for those born at lesser gestations. [18]

Most sepsis screen panels combine 4-5 tests, usually a combination of WBC counts and C Reactive Protein levels. Timing of the sepsis screen is important – it is suggested that an initial screen should not be obtained immediately, but at least 2 - 12 hours after birth.[19] A screen done at 2 hours and found to be negative should be repeated at 12 hours of age. If both are negative, sepsis is virtually ruled out. The predictive accuracy of a positive screen is low (about 30-40%)[20]. Therefore, many non-infected infants with positive screen are also likely to be treated with antibiotics. On the other hand, the screen with its high negative predictive value has almost 100% ability to rule-out sepsis in at-risk neonates. [19]

Table 1. THE SPECTRUM OF NEONATAL SEPSIS [16]

	Normal Newborn	Suspect or at-risk for sepsis	Suspect or at risk for sepsis	Definite Sepsis	Definite Sepsis
Condition	Asymptomatic No risk factor	Asymptomatic; Risk factor+; Received IP antibiotics	Asymptomatic Risk factor+; Not received Intrapartum antibiotics	Symptomatic Low suspicion	Symptomatic High suspicion
Examples		Mother with PPROM for >7 days on antibiotics	Prematurity and prolonged labor	Respiratory distress; apnea lethargy	Bulging fontanel with seizures s clerema, shock,
Typical Presentation		Some cases of EOS	Most cases of EOS	LOS in preterm VLBW infants; Occasional cases of EOS	Community acquired LOS

B. Neonate with Risk factors, mother given intrapartum antibiotics - Antimicrobial agents commonly are administered to women in labor who have risk factors associated with sepsis in the fetus, including premature delivery, prolonged rupture of membranes, fever, or other signs of chorioamnionitis. However, since the antibiotic prophylaxis could affect the blood culture results, the decision to stop antibiotic therapy in these infants should be based more on the clinical course than on the negative culture report.

Guidelines include-[2]

1. Infants who have signs of sepsis should have a full diagnostic evaluation and should be treated, with Ampicillin and Gentamicin, until laboratory studies are available.

2. Infants born at 35 or more weeks' gestation, who appear healthy and whose mothers received intrapartum prophylaxis for 4 or more hours before delivery do not have to be evaluated or treated, but should be observed in the hospital for 48 hours.

3. Infants who are less than 35 weeks' gestation who appear healthy, and whose mothers received antibiotics for less than 4 hours before delivery should receive a limited evaluation, including a blood culture and a complete blood cell count with a differential count, and be observed for 48 hours in the hospital.

C. Symptomatic Neonate - Any neonate with clinical features suggestive of sepsis should be promptly evaluated. When clinical suspicion is low, e.g. Preterm VLBW neonate developing 'vague' symptoms like lethargy, tachycardia or even apnea in the second week of life – it is prudent to wait until the results of a septic screen and/or blood culture reports are available.[16] When the clinical suspicion is high – as in neonates with community acquired sepsis (pneumonia / meningitis) – antibiotic therapy should be initiated without any delay.

D. Treatment of Neonate where bacterial cultures are negative[2] **-** If the neonate seems to be well and there is reason to believe that infection was unlikely, treatment can be discontinued at 48 hours. If suspicion of an infectious process remains, therapy should be continued as outlined for documented bacterial sepsis, unless another diagnosis becomes apparent. Significant bacterial infection can occur without bacteremia. Squire and colleagues [21] found that results of premortem blood cultures were negative in 7 (18%) of 39 infants with unequivocal infection at autopsy. If treatment for infection is deemed necessary, parenteral administration for 10 days is recommended.

E. Management of an infant with catheter-associated infection

Multiple catheters, low birth weight, low gestational age at birth, and low Apgar scores were significant risk factors for late-onset sepsis[22]. Infants bacteremic with S. aureus or a gram-negative rod who have their catheter retained beyond 24 hours have a 10-fold higher rate of infection-related complications than infants in whom the central catheter is removed promptly. In neonates with infection associated with a central venous catheter, prompt removal of the device is advised.

F. Management of Neonatal Meningitis

The pathogens responsible for neonatal meningitis are largely the same as the pathogens that cause neonatal sepsis; initial therapy and subsequent therapy are similar. Cefotaxime has excellent in vitro and in vivo bactericidal activity against many microorganisms responsible for neonatal meningitis. The rapid development of resistance of gram-negative enteric bacilli when cefotaxime is used extensively for presumptive therapy for neonatal sepsis suggests that extensive use of third-generation or fourth-generation cephalosporins can lead to rapid emergence of drug-resistant bacteria in nurseries [23]. Studies have identified a principal risk factor for development of invasive infection with Candida and other fungi in preterm neonates to be extended therapy with third-generation cephalosporins [24] Empirical use of cefotaxime in neonates should be restricted to infants with evidence of meningitis or with gram-negative sepsis.

Choice of Antibiotics:

The initial choice of antibiotics for sepsis is almost always empirical, because the culture reports would be available after only 48-72 hours. Knowing the sensitivity pattern of the prevalent of flora of the Unit will assist in choice of antibiotics pending culture reports Treatment of the infant who becomes septic while in the nursery after age 6 days (late-onset disease) must include therapy for hospital-acquired organisms.

Table 2. Suggested regimen for first line antibiotic therapy (WHO recommendations)

▪ Early and late onset sepsis	Ampicillin plus Gentamicin
▪ Early onset meningitis	Ampicillin plus Gentamicin
▪ Late onset meningitis	Ampicillin, Gentamicin (or Amikacin),and /or Cefotaxime
▪ Suspected staphylococcal sepsis, focal skin, bone, joint infections, omphalitis -	Methicillin/Nafcillin plus Gentamicin
▪ For sepsis of suspected GI origin -	Ampicillin, Gentamicin/Amikacin, plus clindamycin or piperacillin
▪ Nosocomial infection in setting with MRSA -	Vancomycin plus Gentamicin (and/or ceftazidime, if high prevalence of pseudomonas)

Source: From the report of WHO meeting to "Explore simplified antimicrobial regimens for the treatment of neonatal sepsis", 2002. (WHO Ref. No. WHO/FCH/CAH/04.1)

Table 3. Suggested empirical regime for neonatal sepsis in different settings [16]

Examples	Septicemia & Pneumonia	Meningitis
Situations where resistant strains are unlikely (e.g. community-acquired pneumonia)	Penicillin or Ampicillin plus Gentamicin	Same as for septicemia/ Pneumonia Plus Cefotaxime
Situations where a few strains are likely to be resistant to common antibiotics (e.g. nosocomial infections in intermediate care units that cater to stable preterm infants; also in units that adhere to rational antibiotic therapy and avoid indiscriminate use of broad-spectrum antibiotics)	Ampicillin or Cloxacillin Plus Gentamicin or Amikacin	Same as for septicemia/ pneumonia plus Cefotaxime
Situations where most of the strains are or likely to be resistant (e.g. nosocomial infections in intensive care units that cater to high-risk, sick infants; also in units that use broad-spectrum antibiotics indiscriminately)	Cefotaxime or Piperacillin-tazobactam or Ciprofloxacin Plus Amikacin (Consider Vancomycin if MRSA is suspected.)	Same as for septicemia/ pneumonia (but avoid ciprofloxacin)
Special situations No improvement / worsening of clinical condition despite 'appropriate' first-line antibiotics Sudden outbreak of infections	Consider reserve antibiotics (e.g. meropenem, aztreonam, cefoperazone- sulbactum) Based on the source of outbreak and the suspected/ isolated organism (e.g. if due to MRSA, then use vancomycin)	

Table 4 Duration of antibiotic therapy in neonatal sepsis [16]

Diagnosis	Duration
Meningitis (with or without positive blood/CSF culture)	21 days
Blood culture positive but no meningitis	14 days
Culture negative but definite clinical sepsis	10-14 days
Culture negative, sepsis screen positive and clinical course consistent with sepsis	7-10 days
Culture and sepsis screen negative, but clinical course compatible with sepsis	5 -7 days

Antibiotic therapy can be stopped after 48-72 hours in those infants who are started on antibiotics, for the presence of perinatal risk factors, if the clinical course is not compatible with sepsis and the cultures are sterile.

Route of Antibiotic Therapy -

Intravenous or intramuscular routes are usually preferred while treating neonatal sepsis. Oral antibiotic therapy is avoided because of the unpredictable absorption and bioavailability especially in seriously ill neonates.

Prophylactic Antibiotics -

The use of prophylactic antibiotics for infants on IV fluids/TPN, meconium aspiration syndrome, or after exchange transfusions is not recommended. 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. As for antibiotic prophylaxis in ventilated neonates is concerned, there is not enough evidence to either support or refute its use[25]

Steps To Reduce Microbial Resistance To Antibiotics [12,13]

1. Always take cultures of blood and/or CSF and/or urine before starting an antibiotic.
2. Use narrow spectrum antibiotics if possible, almost always a penicillin (e.g., piperacillin-tazobactam) and an amino glycoside (e.g. amikacin)
3. Do not start treatment with a third generation cephalosporin (e.g. cefotaxime, ceftazidime) or a carbapenem (e.g. imipenem, meropenem), unless meningitis is suspected.
4. Restrict use of broad-spectrum antibiotics.
5. Develop local and national antibiotic policies to restrict the use of expensive, broad-spectrum antibiotics like imipenem for emergency treatment. Empiric Vancomycin is not necessary unless MRSA is common.
6. Trust the microbiology laboratory: rely on the blood culture results.
7. Stop believing that a raised CRP means the baby is definitely septic
8. If blood cultures are negative at 2-3 days, it is almost always safe and appropriate to stop antibiotics.
9. Try not to use antibiotics for long periods, no role of prophylactic antibiotics.
10. Treat sepsis but not colonization
11. Prevent nosocomial infection, by reinforcing infection control, particularly hand washing.

    Early introduction of enteral feeds, preferably breast milk, allows intravenous access to be removed quicker, reducing the risk of sepsis.
12. Use of cephalosporins, quinolones and carbapenems should be restricted to microbes resistant to amino glycosides or penicillins. The incidence of ESBL producing Gram-negative bacteria decreases with cephalosporin restriction.

Conclusions -

Modern neonatal intensive care would be impossible without antibiotics. Their effectiveness can only be preserved if they are used rationally and with great care. Irresponsible use can quickly lead to the selective appearance of organisms that are resistant to most forms of treatment.

Key Messages -

- Excessive use of antibiotics leads to selection of antibiotic resistant strains.
- No role of prophylactic antibiotics
- Preferably use narrow spectrum antibiotics over broad-spectrum antibiotics.
- Empirical use of Cephalosporins should be restricted to meningitis and severe gram negative sepsis.
- Prevention of infections pays a key role in reducing use of antibiotics, and emergence of drug resistant strains.

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