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Editorial

Duration of Antibiotics in Neonatal Infections and Antibiotic Stewardship in Neonatal Units

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Avoidance of inappropriate antibiotic use can avert the rising trends in antimicrobial resistance. Duration of antimicrobial therapy for different microbial diseases is a robust indicator of the impact of antibiotic stewardship program [1]. A shorter course of antibiotic therapy substantially reduces the duration of hospitalization and also reduces the cost of therapy [1,2]. Shorter course of antibiotic therapy can reduce the number of adverse events and healthcare costs and could conserve resources. Prolonged exposure to antibiotics tends to increase probability of emergence of resistant strains of bacteria. The problem of antibiotic resistance has spread all around the world and it is affecting the developing nations much harder than developed countries. Excessive over-utilization of antibiotics in hospitalized patients is one of the major risk factors for development of antibiotic resistance [3].

Excessive duration of antibiotics increases the potential for bacterial resistance and nosocomial infection and incurs higher hospital costs and may interfere with maternal-infant bonding. Prolonged use of antibiotics is also associated with increased risk of necrotizing enterocolitis and death in extremely low birth weight infants and also increased risk of fungal sepsis in neonates [4-6].

Early diagnosis and prompt use of antibiotics are probably more important in reducing the mortality and morbidity of infection than an extended antibiotic regimen. While the choice of antibiotics in neonatal infections has been evaluated over the years, the duration of antibiotic therapy still remains controversial. The duration of antimicrobial therapy in neonates with bacterial sepsis pneumonia and meningitis has often been based more on tradition than on evidence- based data. Neonatal sepsis is treated for 10 - 14 days. Group B Streptococcal meningitis is usually treated for 14 days, assuming prompt eradication of bacteria from the cerebrospinal fluid (CSF). For uncomplicated neonatal meningitis caused by Gram-negative bacteria, a minimum of 21 days is recommended. The recommended duration of treatment in children is 7 - 10 days for meningitis due to *H. influenza* type b, 10 - 14 days for *S. pneumoniae* meningitis, and 7 days for *N. meningitides* meningitis [7,8]. The duration of treatment of neonatal bacterial infection in general, and of meningitis and pneumonia specifically, is not based on solid evidence [9,10].

Neonatal pneumonia, sepsis and meningitis are often inappropriately bracketed together as sepsis inspite of inherent pathophysiologic differences. Neonatal sepsis has a wide spectrum of severity of the systemic inflammatory response syndrome and includes septic shock with multi organ dysfunction at the adverse end of the spectrum. The diagnosis of neonatal infections includes consideration of risk factors for infection, non-specific clinical presentation, haematological indicators and acute phase reactants which have variable sensitivity and specificity and isolation of organism from blood, (or cerebrospinal fluid or urine) which is the gold standard. Unfortunately, the gold standard takes at least 48 hours for the result to be available and it can be negative even in presence of histopathological evidence of infection. Moreover, delay in initiation of antibiotics in infected neonates can affect the outcome adversely. The clinician frequently faces the challenge of managing the sick neonate without the culture report. Culture negative sepsis is another controversial reality in the neonatal unit. There has been a felt need of data on the duration of antibiotics for meningitis, pneumonia and sepsis, particularly when the clinical response can be defined as prompt.

Mathur., *et al.* [11] compared 10 days duration of antibiotic therapy (study group) in neonatal bacterial meningitis versus 14 days (control group) if clinical remission was present, CSF had become normal and the cranial ultrasonography was not suggestive of infection by day 7 of antibiotic therapy. The above criteria were met in 54% of all neonates with meningitis. None of the babies in either group had recurrence of meningitis after discharge. However, 3 babies in the control group (14 days) were readmitted after discharge during follow up period with sepsis. None of the babies in the study group had occurrence of sepsis after discharge. Mortality in post discharge follow up was found to be 2.9% in study group and 5.7% in the control group. Considering all types of abnormal outcome including abnormal BERA, occurrence of sepsis after discharge and death, more babies were affected in the control group - 5.7% in the study group and 14.3% in the control group ($p = 0.43$). It was concluded that neonates with meningitis could be given shorter duration of antibiotic therapy (10 days) if clinical remission was present, CSF had become normal and the cranial ultrasonography was not suggestive of infection by day 7 of antibiotic therapy.

The optimal duration of antibiotic therapy for neonatal pneumonia is unclear [12]. Pneumonia caused by gram-negative enteric bacilli or Group B *Streptococcus* has been treated for 10 days; while disease caused by *Staphylococcus aureus* is treated for 3 to 6 weeks. Empyema and lung abscess require longer courses of therapy [12,13]. There has been paucity of studies evaluating the duration of treatment in neonatal pneumonia. Mathur., *et al.* [14] compared the effect of 4 day course (study group) with 7 day course (control group) of antibiotic treatment in term and near term neonates (> 34 weeks) with neonatal pneumonia if clinical remission was present at 48 hours of treatment and neonates were asymptomatic, with respiratory rate < 60, no grunting, chest retractions, or nasal flaring and no need for oxygen therapy. Neonates born to mothers with meconium stained liquor, neonates with blood culture positive sepsis, associated meningitis, and neonates who had received prior antibiotics were excluded. The success rate of 4-day course of antibiotic therapy was 100%, which was the same as that of 7-day group. There was a significant reduction of 2.1 days (29%) in the duration of hospital stay in 4-day group ($p = < 0.001$). There was a significant reduction in antibiotic usage (43%) in 4-day group by 300 mg/Kg for Ceftriaxone ($p = < 0.001$) and 45 mg/Kg for Amikacin compared to 7-day group ($p = < 0.001$). There was a significant reduction in the cost of antibiotic therapy in 4-day group compared to 7-day group ($p = < 0.001$).

Recent studies in adults with sepsis have suggested the utility of procalcitonin (PCT) for deciding the duration of antibiotic therapy by observing time to normalization of PCT levels. Serial estimation of PCT levels in neonatal sepsis have been done in few studies, but the time to normalization of PCT levels in neonatal sepsis has not been evaluated. As time to normalization of PCT following clinical resolution is useful to decide the optimum duration of antibiotics, its implication in antibiotic stewardship is remarkable. Mathur., *et al.* in a recent study determined time to normalization of PCT levels following clinical resolution of symptoms to decide the duration of antibiotics in neonatal sepsis with special reference to blood culture positivity and presence of septic shock [15]. Sick neonates > 34 weeks of gestation with clinical features of sepsis plus positive bedside markers of sepsis were enrolled. Clinical assessment of SIRS and its severity and progression was based on definitions suggested by Saez-Llorens and Mc Cracken [16]. Neonates with life threatening congenital malformations, meningitis and prior exposure to antibiotics in past seventy two hours were excluded from the study. PCT levels were repeated at clinical resolution and if not normalized, then every 48 hours till normalization. PCT levels were known to the treating physicians and antibiotics were stopped when the neonate was asymptomatic and subsequent PCT levels normalized. After discharge the neonates were followed up weekly for up to 4 weeks of enrollment, to look for recurrence of symptoms or any morbidity. Mean duration of antibiotics was 7.2 ± 3.4 days. All surviving neonates with sepsis showed fall in procalcitonin values at the time of clinical resolution after antibiotic therapy, indicating response to therapy. Based on the time to normalization of PCT values in our study, the optimum duration of antibiotics in neonatal sepsis was 9.6 ± 3.1 days in culture positive neonates, 6.4 ± 3.1 days in culture negative neonates, 9.6 ± 4.2 days in neonates with shock, 6.2 ± 2.5 days in neonates without shock. There was no recurrence of symptoms or any other morbidity among the survivors up to 4 weeks after discharge [15]. The duration of antibiotic therapy and hospitalization in neonatal sepsis can be rationalized and optimized by PCT estimation. PCT levels were repeated at clinical resolution of symptoms and if not normalized, then every 48 hours till normalization. This strategy was followed to minimize the frequency of PCT estimation. To conclude, the antibiotic therapy can be optimally stopped at the time of normalization of PCT levels following resolution of symptoms. There was no recurrence of symptoms, morbidity or mortality during four week follow up. Larger multicentric studies on duration of antibiotics need to be conducted to validate these findings.

Antibiotic stewardship program is extremely important in the neonatal units. Robust work up of sick neonates is important to suspect infection early, while ruling out other causes of sickness. Appropriate duration of antibiotics is an effective strategy for antibiotic stewardship in neonatal units.

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