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# Antibiotic Therapy in Neonatal Sepsis

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**Original Research Article**

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**Abstract:** A lot of bias exists in the management of suspected sepsis owing to the non-specific manifestations of sepsis in neonates resulting in injudicious use of antibiotics thereby increasing the risk of emergence of antibiotic resistance. Sepsis markers can help in detecting and managing sepsis more accurately. This study was conducted from June 2016 to June 2017 in the department of paediatrics in Gandhi Hospital, to determine whether normalization of CRP correlates with recovery from sepsis aiding the decision about the duration of antibiotic therapy .110 neonates with sepsis were studied prospectively. .A value of > 6 mg/L of CRP was taken as indicative of sepsis. If it was < 6mg/L antibiotics were stopped and patients were assigned to group 1.Neonates with CRP > 6mg/L were assigned to group 2 and are randomized into group 2A in which antibiotics were discontinued after 7 days if the CRP was negative and 2 B in which antibiotics were stopped as soon as CRP turned negative. All the babies were followed up for relapse for four weeks. CRP was negative on first estimation in 26 cases (23.6%) and antibiotics were stopped (Group 1). No relapse was observed. In the remaining 84(76.4%) cases, Group2, all the cases with positive blood culture were given standard therapy and were not followed up with serial CRP measurements. Fifteen babies from group 2 received antibiotics for seven days and antibiotics were stopped when CRP was found to be negative on 7th day (2A).Therapy was stopped based on negative CRP value on or before 7 days in 18 cases in group 2B. In group 2B, mean duration of treatment was 5.3 ± 1.1 days when compared to group 2A where it was 7 ± 1 days. No relapses were noted in both the groups. There is 100% negative predictive value of serial CRP measurement. This has implication in reducing the cost of therapy, duration of hospitalization and reducing the emergence of antimicrobial resistance.
**Key words:** Neonates, sepsis, CRP, duration of antibiotics, negative predictive value.

## INTRODUCTION

Sepsis in neonates is a leading cause of mortality contributing to around 5.3 lakh deaths per year globally [1]. Any clinical deterioration in a neonate compels the physician to start antibiotic therapy. Ideally this should follow a protocol. However wide variation in patterns of antibiotic usage has been reported [2].It is stated that almost 50% of prescribed antibiotics are either unnecessary or sub-optimally effective as prescribed [3]. Further, the choice of antibiotic or duration of empirical treatment is often not associated with risk factors for sepsis or indicators of illness severity but rather with centre [4]. Such conditions are highly conducive for proliferation of drug resistant bacteria in neonatal care units. Judicious use of antibiotics required to prevent antibiotic resistance is often not possible in neonates owing to their subtle and non-specific presentation with consequent subjective variation among physicians in the assessment. Accurate identification of sepsis or ruling out of sepsis can be aided by sepsis markers. Since we cannot wait for blood culture reports to start antibiotics, a number of sepsis markers like total leukocyte count, absolute neutrophil count, band cell count, ESR, C reactive protein (CRP), procalcitonin etc. are used to improve accuracy of diagnosis. CRP is the most commonly used sepsis marker in the management of sepsis in neonates. Several studies have highlighted its utility in the diagnosis of sepsis and also its negative predictive value (NPV) in ruling out the possibility of sepsis [5,6]. This study aims to find out if CRP can help in determining when to discontinue antibiotic therapy in neonates with sepsis.

## AIM AND OBJECTIVES

The primary aim was to estimate the value of CRP as a parameter for guiding the duration of antibiotic therapy with the negative predictive value determining the duration of therapy. The primary outcome variable of this study is duration of antibiotic therapy. Secondary outcome variable is the number of infectious relapses.

## METHODOLOGY

This study is conducted from June 2016 to June 2017 in the department of Pediatrics, Gandhi Hospital, Hyderabad. 110 neonates (<28 days of life) with birth weight more than 1500g with suspected sepsis were included in the study. Neonates with site specific infections like meningitis, osteomyelitis etc. warranting long duration of therapy, mechanically ventilated babies, severe birth asphyxia and postoperative cases were excluded. After admission, blood was drawn for culture and sensitivity, complete blood count and other relevant investigations (chest X ray, urine culture) were sent and broad-spectrum antibiotics covering both gram positive and gram-negative organisms were started. CRP was estimated 24-48 hours after admission. The subjects were assigned to one of the 3 study groups according to their CRP levels( Fig 1).

**Study groups**

**Group 1: infection unlikely**

This group included infants with CRP levels < 6mg% 24-48 hours after the initiation of antibiotic therapy. Antibiotics were discontinued irrespective of other laboratory or clinical indices of infection unless decided against by the attending consultant.

**Group 2: infection likely**

This group contained babies whose CRP was elevated (>6mg%) after 24-48 hours of first dose of antibiotic. These were randomized into two sub groups – Group 2A and 2B

**Group 2A - 7day therapy**

In this subgroup, antibiotics once started were continued for a minimum of 7 days and CRP was estimated on 7th day. If CRP was <6mg% and neonate was asymptomatic, antibiotics were stopped.

**Group 2B – CRP guided therapy**

In this subgroup, CRP was estimated daily starting from day 4 and as soon as CRP was <6mg% antibiotics were stopped.

Follow up: Neonates were observed for 48 hours after stopping the antibiotics. After discharge all the neonates were followed up for relapse till four weeks after discharge.

This study group was divided into 2 groups: 1) No relapse 2) Relapse

No relapse: If no recurrence of symptoms of sepsis within 4 weeks of discharge.

Relapse: If the baby needed another course of antibiotics for suspected or proven sepsis within 4 weeks of discharge.

**STATISTICAL ANALYSIS**

Student 't' test and Crosstabs analysis were applied wherever statistical analysis was necessary.

**RESULTS**

Out of 125 neonates enrolled, 15 cases did not meet the inclusion criteria. Out of 110 eligible cases, 72(65.4%) cases had early onset sepsis (EOS).In the late onset sepsis (LOS) group, 25(22.7%) cases presented between 4-7 days; 8(7.2%) cases presented between 8-14 days and 5(4.5%) cases between 15-28 days. The sex distribution was 58(52.7%) were males and 52(47.3%) cases were females. Weight wise distribution showed Twenty babies(18.1%) between 1501-2000g , 42(38.1%) between 2001-2500 g, 40(36.3%)between 2501-3000g and 8(7.2%) babies more than 3000g .Analysis of gestational ages(GA) revealed 6(5.4%) babies with GA less than 32 weeks , 40(36.3%) between 32-36 weeks (36.3%), 62(56.3%) between 36-40 weeks (56.3%) and 4(3.6%) cases were > 40 weeks. Sixty five(59%) cases were delivered by normal vaginal delivery, 18(16.3%) by assisted vaginal delivery and the remaining 27(24.5%) by LSCS .

Analysis of clinical features revealed refusal of feeds to be the major presenting complaint (51%) followed by lethargy (40%) and respiratory distress (40%).Culture positive sepsis was documented in 29 (26.3%) cases with Klebsiella pneumoniae being the most common organism isolated contributing to 13(43%) followed by coagulase negative Staphylococci(18%), E.coli (14%) and Acitenobacter in 3(11%) of cases.

**Group wise results (Fig 1)**

GROUP 1: contained 26 babies in whom CRP was negative and antibiotics were stopped. Blood cultures were negative in all cases. All the cases were followed up for 4 weeks and no relapses were reported.

GROUP 2: contained 84 CRP positive cases that were randomly divided into two groups using web based randomization.

Group 2A: Out of 40 cases which were included in this group, 14(12.7%) cases were blood culture positive. Out of the remaining 26, 2 cases died before 1 week and 3 cases were lost to follow up. Among the 21 cases remained, 6 cases needed treatment beyond 7 days due to clinical requirement. In the remaining 15(13.6%) cases CRP became normal on day 7 and antibiotics were stopped. These 15 cases were followed up for 4 weeks and no relapses were found.

Group 2B: Out of 44 cases, 15 cases were blood culture positive (13.6%). Out of the remaining 29 cases, 3 cases died before 1 week and 2 cases were lost to follow up. Out of the remaining 24 cases 6 cases needed treatment beyond 7 days for there was no clinical improvement. Those 18 cases left were subjected to stoppage of antibiotics based on CRP

value. (In 5 cases antibiotics could be stopped at 4 days, in 6 cases at 5 days, in 4 cases at 6 days and in 3 cases at 7 days). All these 18 cases were followed up for 4 weeks where no relapses were reported.

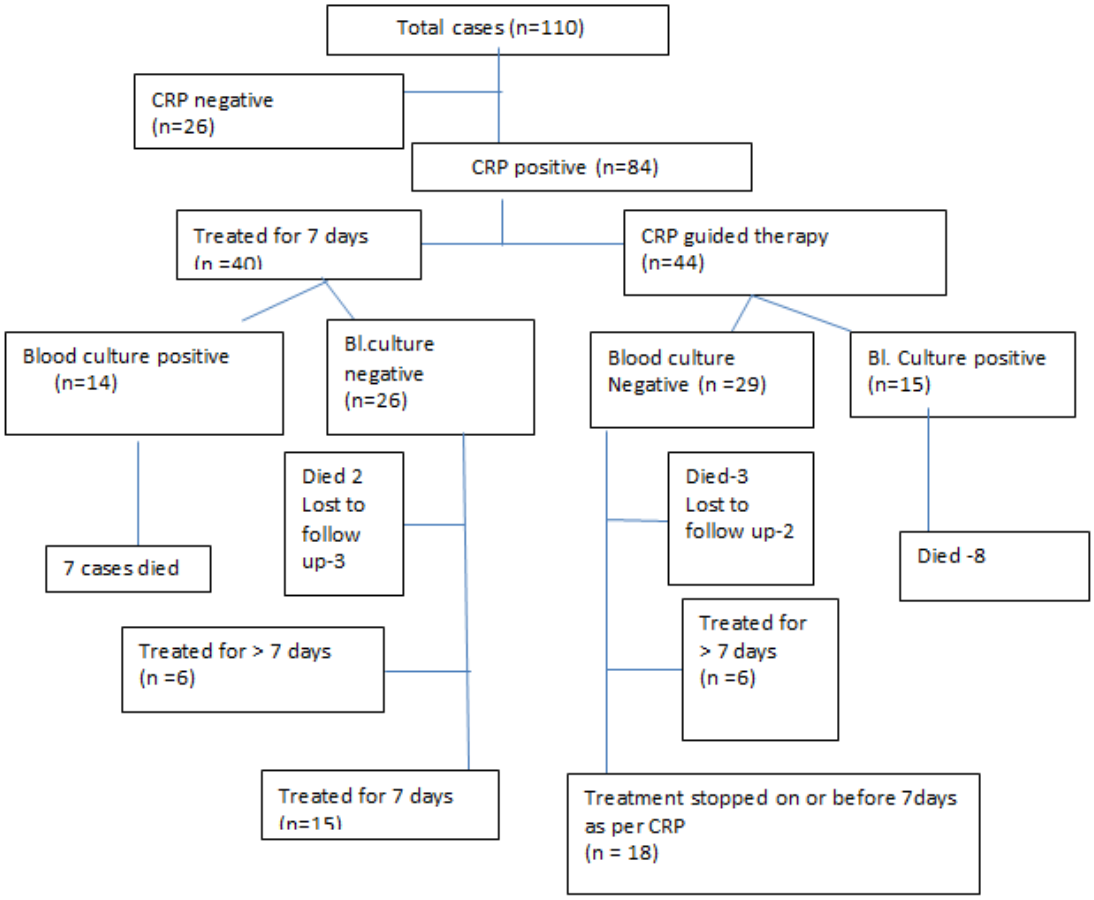


**Fig-1: Flow chart of results**

Comparative analysis of groups 2A and 2B showed similar incidence of patient characteristics like sex, birth weight, GA and clinical features. No relapses were noted in both groups. In group 2A, 5 deaths occurred in culture positive cases and 2 deaths in culture negative cases. In group 2B, 5 deaths occurred in culture positive and 3 in culture negative cases. The duration of antibiotic therapy was significantly low in group 2B (p value <0.05) (Table 1).

**Table-1: Data comparison between groups 2A and 2B**

| No | Character | 2A | 2B | p value |
|---|---|---|---|---|
| 1 | NO. of cases | 40 | 44 | |
| 2 | Males | 23 | 23 | 0.23 |
| 3 | Preterm | 17 | 20 | 0.07 |
| 4 | Weight<br>1.5-2.5 kg<br>>2.5 kg | <br>25<br>15 | <br>28<br>16 | 0.45 |
| 5 | Risk factors | 28 | 30 | 0.42 |
| 6 | Blood culture positive | 14 | 15 | 0.46 |
| 7 | Mean CRP value | 24 | 30 | 0.08 |
| 8 | Mean duration of treatment(days) | 7±1 | 5.3±1.1 | <0.05 |
| 9 | No.of relapses | 0 | 0 | |

## DISCUSSION

C reactive protein is an acute phase reactant synthesized in liver in response to inflammatory cytokines. Following the onset of sepsis it starts to rise within 6-12 hours. Because of the short half–life, it rapidly declines after the elimination of microbial source. The present study is designed to evaluate the role of CRP in deciding the duration of antibiotic therapy in neonatal sepsis and to determine if antibiotics can be stopped when baby becomes asymptomatic and CRP becomes negative.

Incidence of sepsis in our institute is 30% which is more than the national statistics (23%).In our study, 65.4% cases had early onset sepsis. Group 2A contained 27(24.5%) cases of early onset sepsis and group 2B contained 30(27.2%) cases of early onset sepsis (P value 0.47).Incidence of EOS as reported by other researchers is considerably variable due to differences in the proportion of inborn and out born cases [7, 8].The higher incidence in our study could be due to more number of inborn cases. In the present study 46 cases were preterm (41.8%) and 64 cases were term (58.2%). Among the comparison groups, Group 2A has 17 preterm cases (15.4%) and group 2B has 20 (18.1%) (p value 0.45).

In the present study, poor feeding was the most common presenting complaint (in 51% of cases). Jaswal *et al.* and Siddhaiah P *et al.* also reported poor feeding as the commonest presentation [7, 9]. In Fareena Ahamed's study fever was a predominant symptom (51.7%) but tachypnea was seen only in 25% of cases whereas in the present study fever was seen in 5.4% cases and respiratory distress was observed in 40% of the cases [10]. Incidence of culture positivity in the present study is 26.3% whereas in Dr. Fareena Ahamed's study the blood culture yield was 20.8% and in Jaswal *et al*. study, it was 42%.

**COMPARISON OF CRP GUIDED THERAPY GROUPS: (Table 2)**

**GROUP 1**

All the 26 cases in this group were followed up for 4 weeks through weekly reviews and also through telephonic contact. None of them developed relapse or received antibiotics for the same. Based on these results, the NPV of CRP is proved to be 100%. Jaswal *et al*. and Siddaiah *et al*. also reported a NPV of 100% [7, 9]. Khasabi *et al*. reported a NPV of 98.9% [11].

**GROUP 2**

Serial CRP estimation was not done if the cases were proved to be blood culture positive. All the culture positive groups (in both group 2A and 2B) were given treatment for 10-14 days. In the CRP positive and culture negative group, CRP was not estimated beyond 7 days in any of the cases. The decision to prolong antibiotic therapy beyond 7 days is based on clinical assessment of the baby irrespective of the CRP values (which happened with 6 cases in group 2A and 6 cases in group 2B).

**Group 2A**

In this group after excluding cases which needed treatment beyond 7 days (like blood culture positive or CRP positive on day 7), treatment was given for 7 days according to the standard protocol in 15 cases (13.6%). This group showed no relapses in the period of follow up for 4 weeks with a NPV of 100% which is consistent with other studies [7, 9].

**Group 2B**

Among the CRP positive blood culture negative cases enrolled in this group, 18 cases were intervened according to the CRP value. Antibiotics were given for 4 days in 5 cases, 5 days in 6 cases, 6 days in 4 cases and 7 days in 3 cases. Mean duration of antibiotic therapy was 5.3 days with a standard deviation of 1.1 days. Ehl S et al showed a shorter mean duration of treatment in CRP guided group compared to the group which received antibiotics for a fixed duration[12].These 18 cases of group 2B in the present study were followed up for 4 weeks. No relapse was reported. The NPV was calculated to be 100% which is consistent with other studies [7, 9]. In contrast Al-Zwaini reported a modest sensitivity and NPV (86%) for CRP [13].

**Table-2: Comparison of NPV among study groups**

| CRP value | Groups | Duration of therapy days | Blood culture positive | Relapse | Negative predictive value |
|---|---|---|---|---|---|
| < 6mg% | 1(26) | ≤ 3 | nil | Nil | 100% |
| >6mg% | 2A(40) | 7 ( 15 cases) | nil | Nil | 100% |
| | | ≥ 7( 20 cases) | 14 | Nil | 100% |
| | 2 B(44) | ≤7(18 cases) | nil | Nil | 100% |
| | | >7(21 cases) | 15 | Nil | 100% |

The limitations of this study are its limited number of cases; CRP estimation was done by semi quantitative method; other acute phase reactants were not considered in the study. It is recommended that a large multicentered trial needs to be done to study the value of CRP as an adjunct to the clinical judgement in deciding the duration of treatment.

## CONCLUSIONS

- Among the 55 cases of CRP positive and blood culture negative group, duration of antibiotic therapy was significantly less in CRP guided therapy group.
- NPV of serum CRP is 100% in ruling out the possibility of neonatal sepsis.(Table 2)
- CRP values can aid in detecting recovery from sepsis and deciding about antibiotic therapy in clinically stable babies.

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