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Original Research Article

A study on validity of C-reactive protein in deciding the duration of antibiotic therapy in suspected neonatal bacterial infection

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ABSTRACT

Background: Neonatal septicemia is defined as generalized bacterial infection of newborns documented by positive blood culture in first four weeks of life. Objective of present study was to determine whether C-Reactive protein can be used as a parameter to identify the time point when antibiotic treatment can safely be discontinued in a defined major subgroup of neonates treated for suspected bacterial infection.
Methods: A total of 50 neonates with birth weight more than 1500gms with suspected septicemia were enrolled in the prospective study. Serum CRP were determined 24-48 hours after the first dose of antibiotics. If CRP was less than 6mg/l, infants were considered unlikely to be infected and the antibiotic treatment was stopped. If CRP was more than 6mg/l, antibiotics were continued and CRP measured on alternative days in one subgroup (2a) and on seventh day in another subgroup (2b). CRP was the single decision criterion to stop the antibiotic therapy. Negative predictive value with respect to further treatment was determined.
Results: Duration of antibiotic therapy could be reduced to less than seven days in 54% cases and < 72 hours in 48% cases.
Conclusions: Negative predictive value of serial CRP is 100% in deciding the duration of antibiotic therapy in suspected neonatal septicemia.

Keywords: C-reactive protein, Neonate, Septicemia

INTRODUCTION

Neonatal septicemia is defined as generalized bacterial infection of newborns documented by positive blood culture in first four weeks of life. With better understanding of its etiology, pathophysiology, effects and outcome over decades, the concept of disease has changed. Now it is defined as a clinical syndrome resulting from pathophysiological effects of local or systemic bacterial infection during first month of life. Because of lack of specificity of many signs associated with this and limitation of laboratory criteria, the diagnosis continues to be difficult to establish. The incidence varies from 1-4 per 1000 live births. In India, neonatal septicemia incidence varies from 11-24.5 per 1000 live births.[1] Its clinical manifestations vary from being subtle to specific, testing the very skill of a pediatrician. The inability to be certain of an infection coupled with nonspecific signs of life threatening illness in neonates resulted in widespread use of antibiotics aggravating the problem of antibiotic resistance.

Current recommendations for the treatment of neonatal septicemia include end points of 48-72 hrs for clinically stable children with negative blood culture results and 7-14 days for blood culture positive or clinically probable infection.[2-4] However, the rationale and safety of these recommendations have never been formally evaluated.

The increasing problem of antibiotic resistance requires avoiding unnecessary administration of antibiotics.

Considering the varying spectrum of infectious agents and the variable interaction between the microbe and the immune system of the neonate, it seems most reasonable to individualize the duration of antibiotic therapy than to follow the concept of arbitrarily fixed "complete course.[5] The Acute phase C-reactive protein (CRP) is synthesized in the liver in response to inflammatory cytokines and may increase 1000 folds during an acute phase response.

Because of its short half-life of 19 hours CRP levels can be expected to fall quickly after efficient elimination of the microbial stimulus.[5] Thus CRP may sufficiently reflect the individual balance between the microbes and the immune system of the neonate for monitoring the effect of antibiotic treatment and for guiding the duration of antibiotic therapy.[6-8] The present prospective study is undertaken to determine whether C-reactive protein (CRP) can be used as a parameter to identify the time point when antibiotic therapy can safely be discontinued in suspected bacterial infection.

Objectives of present study were to determine whether C-reactive protein can be used as a parameter to identify the time point when antibiotic treatment can safely be discontinued in a defined major subgroup of neonates treated for suspected bacterial infection and to shorten the duration of hospital stay.

METHODS

This study was conducted in department of Pediatrics Cheluvamba Hospital Mysore. Fifty neonates (<28 days of life) with birth weight more than 1500grams with suspected septicemia as per the signs and symptoms mentioned in the proforma were included in this study. The following patients were excluded from the study because of the need of longer treatment regimen for the conditions.

Exclusion criteria

- Neonates who had undergone surgery because of risk of wound infection.
- Neonates with diagnosis of meningitis as they require longer duration of treatment with antibiotics.

After admission blood was drawn for culture and sensitivity and other relevant (Chest-Xray, urine culture sensitivity) investigations were sent and broad-spectrum antibiotics covering both Gram positive and gram-negative organisms were started (injection Ampicillin and Gentamicin).

CRP was estimated within 24-48 hours of admission. Then neonates were assigned to one of the 3 study groups according to their CRP serum levels.

Study groups

Group 1 Infection unlikely

This group included infants with CRP levels less than 6 mg% 24-48 hours after the initiation of antibiotic therapy.

Antibiotics were discontinued irrespective of other laboratory or clinical indices of infection unless decided by the attending consultant.

Group 2 Infection likely

If CRP was elevated >6 mg% after 24to48 hours of first dose of antibiotic, group was divided into two sub groups.

Group 2 CRP guided therapy

In this sub group, CRP was estimated on alternate day and as soon as CRP level was less than 6 mg% antibiotics were stopped

Group 2b 7-day therapy

In this sub group, antibiotics once started were continued for 7 days and CRP was estimated on seventh day. If CRP was <6 mg% and neonate was asymptomatic, antibiotics were stopped unless decided differently by the attending consultant.

Follow-up

Neonates were kept up to 48 hours after stopping the antibiotics to observe for recurrence of clinical feature of septicemia. The study group was divided into two groups.

No relapse

If no occurrence of symptoms of septicemia within four weeks of discharge or the baby required antibiotics for different diagnosis other than septicemia.

Relapse

If the baby needed another course of antibiotics for suspected/ proved septicemia within 4 weeks after discharge.

Outcome analysis

The primary outcome variable of this study was proportion of infectious relapses within 4 weeks after the end of therapy.

To estimate the value of CRP as a parameter for guiding the duration of antibiotic therapy, the negative predictive value with respect to further treatment was determined.

Statistical analysis

Contingency table analysis and chi square (x^2) were applied wherever statistical analysis was necessary.

RESULTS

Fifty cases of suspected neonatal septicemia were studied over a period of 1 year.

Patients characteristics

14 cases presented within 72 hours, 13 cases presented between 73 hours-7 days, 11 cases presented between 8-14 days and 12 cases between 15-28 days.

32 cases (64%) were male babies and 18 (36%) cases were female.

8 patients weighed between 1.5-2 kgs, 10 cases between 2.1-2.49 kgs, 25 cases between 2.5-2.9 kgs and 7 weighed more then 3 kgs. 5 patients (10%) were of pre-term gestation and the rest 45 (90%) were of term gestation.

11 cases presented within 72 hours after birth and constituted early onset septicemia and 39 cases presented after 72 hours of birth and constituted late onset septicemia.

Table 1: Risk factors.

	Clinical focuses	%
Vaginal delivery	44	88
Maternal fever >100.4°F	3	6
PROM >18 hrs	5	10

Table 2: Clinical features.

Clinical features	Cases	%
Refusal of feeds	22	44
Lethargy	19	38
Poor cry	11	22
Tachypnea	11	22
Jaundice	6	12
Conjunctivitis	7	14
Vomiting	6	12
Excessive cry	3	6
Pyoderma	2	4
Abdominal distension	2	4
Hypothermia	2	4
Fever	1	2
Diarrhea	1	2
Umbilical Sepsis	1	

Refusal of feeds (44%), lethargy (38%) were main presenting complaints followed by poor cry (22%) tachypnea (22%) and jaundice (12%).

Blood culture results

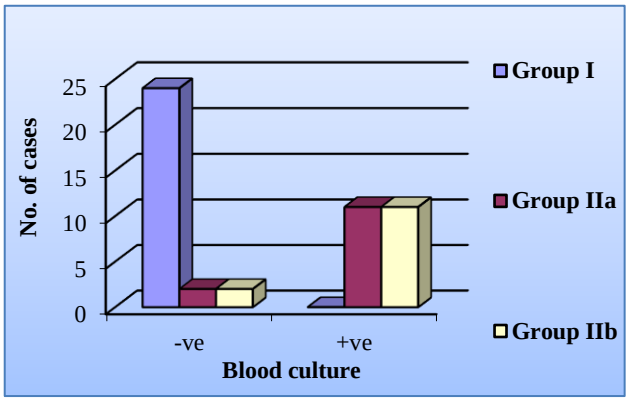

Figure 1: Blood culture results in various groups.

Out of 50 cases of clinically suspected neonatal septicemia cases 22 were blood culture positive. 28 cases were culture negative.

Table 3: Etiological agents.

Etiology	Organism	Cases	%
Gram negative (n=17)	*Klebsiella*	06	28.57
	E Coli	05	23.81
	Pseudomonas	04	19.04
	Acinetobacter	02	9.5
Gram positive (n=5)	*Staphylococcus aureus*	03	13.6
	CONS	01	4.76
	α Hemolytic streptococci	01	4.76

Out of 22 cases, 17 cases culture grew Gram positive organisms and in 5 cases culture showed Gram negative organism.

Among gram negative organisms *Klebsiella* was the Commonest organism isolated (28.57%) followed by *E-coli* and *pseudomonas* and *Staphylococcus aureus* (13.6% cases) was commonest among Gram positive organisms.

Table 4: Correlation of probable septicemia with CRP, BNR and Blood culture positivity.

Tests	Cases		Total (50)	%	P value
	EOS (11)	L05 (39)			
Positive BNR	05	24	29	58	<0.05
Positive blood culture	03	19	22	44	<0.05
Positive CRP on day 5	03	09	12	24	>0.05
Positive CRP on day 7	01	10	11	22	<0.05

Out of 50 cases of suspected neonatal septicemia, 22 cases were blood culture positive. 22% cases for positive for CRP on day 7 and 58% showed BNR>0.2.

Group 1: In 24 cases (48%) out of 50 cases of suspected neonatal septicemia CRP was Negative after 48 hours and antibiotics were stopped. Blood cultures showed no growth. There was no relapse in the following four weeks.

Table 5: CRP guided distribution of treatment, relapse rate in various groups and correlation with blood culture results.

CRP value	Groups (Case)		Duration of therapy (No. of cases)	Blood culture positive cases	Relapse	Negative predictive value (%)
<6 mg%	Group 1 (24)		< 3 days (24)	Nil	Nil	100
>6 mg%	Group 2	2a (13)	5 days (1)	Nil	Nil	100
			7 days (12)	11	Nil	100
		2b (13)	7 days (2)	Nil	Nil	100
			> days (11)	11	Nil	100

Group 2a: This group comprised of 13 (26%) cases out of which CRP returned to normal in one case on 5th day and antibiotics were stopped. Blood culture came out to be normal and there was no relapse. In rest of 12 patient's antibiotics were continued beyond 7 days as CRP was raised. Blood culture were positive in 11 cases.

Group 2b: This group comprised of 13 (26% cases) out of which CRP returned to normal on 7th day of treatment in 2 cases and antibiotics were stopped. None had relapse. In rest of 11 cases. Antibiotics were continued beyond 7 days as CRP was positive on 7th day of treatment. All were blood culture positive.

Table 6: Overall durations treatment with CRP guided treatment.

Groups		Duration of treatment	
		<7 days (cases)	>7 days (cases)
1 (24)		24	Nil
2	2a	1	12
	2b	2	11
Total		27	23

Out of 50 cases of suspected neonatal septicemia antibiotics were stopped in <7 days in 27 cases (54%). In 24 out of 27 cases (48%) it was stopped after 48 hours of initiation of antibiotics. In 23 cases (46%) where CRP was more than 6 mg% after 48 hours of treatment, Antibiotics was required for >7 days.

DISCUSSION

The present study was designed to evaluate the role of CRP in deciding the duration of antibiotic therapy in suspected neonatal bacterial infection and to determine whether CRP can be used as a parameter to identity the time point at which antibiotics can be safely discontinued in suspected bacterial infection. During the study period of August 2004 to August 2005, 50 cases of suspected neonatal septicemia were studied.

Incidence of EOS was 22% and LOS was 78 in present study, which is in concordance with study conducted by Kuruveilla et al who reported incidence as 30% and 70% respectively.[9] The incidence of EOS was reported 52.4% and LOS 44.3% by Namdeo et al Higher incidence of EOS in this study was due to inclusion of EOS upto 7 days.[10] The incidence of EOS. (44%) as reported by Mishra et al was higher as compared to present study.[11] The higher incidence was probably due to inclusion of only hospital delivered babies in whom symptoms and signs were recognized at the earliest. Whereas in the present study out born neonates were also included.

In the present study, males outnumbered females. The incidence of septicemia in males was 64% and in females it was 36% which is similar to that reported by Somu et al.[12] Who reported male and female incidence of 54.6% and 45.4% respectively. Similar were the observations of Kuruveilla et al and Sinha et al.[9,13]

Table 7: Comparison of clinical features.

Clinical features	Present study (n=50) in %	Somu et a (n=725)17 in %	Guha et al (n=400)16 in %
Refusal of feeds	44	46.30	66.25
Lethargy	38	38.50	61.25
Poor cry	22	26.90	-
Tachypnea	22	-	27.50
Jaundice	12	-	42.50
Conjunctivitis	14	-	-
Vomiting	12	37.60	-
Excessive cry	6	-	-
Pyoderma	4	-	-
Abdominal distension	4	68.40	43.11
Hypothermia	4	-	-
Fever	2	20.70	30.00
Diarrhea	2	47.20	48.70
Umbilical sepsis	-	-	-

With No specific reasons of Predisposition of males for septicemia; all studies; Somu et al, Kuruveilla et al and have reported higher incidence of septicemia in males.[9,12] The present study is in concordance with these observations.

In the present study refusal of feeds (44%) was the commonest symptom followed by lethargy. Guha et al have also observed the similar result.[14] Abdominal distention was the commonest symptom (68.4%) followed by diarrhea and refusal of feeds as reported by Somu et al.[12] The higher incidence of abdominal symptom in the study of Somu et al was mainly due to inclusion of more Preterm babies who are more prone to Necrotizing enterocolitis.[12] Fever was not a prominent feature in this study whereas Guha et al and Bhakoo et al have reported the incidence of fever to be 20-26% as such fever is not a common feature of neonatal septicemia as compared to hypothermia, of which there is no mention is these studies.[14,15] The incidence of culture positivity in the present study is 44% which is in concordance with the studies conducted by Bharatiya D et al and Singh, which have shown its incidence to be 40% and 36.8% respectively.[16,17] Although incidence ranging from 20% to 85% has been reported by Sharma A et al and Somu N et al respectively.[12,18]

The incidence of gram negative organism is (77.2%) and gram positive organism is (22.7%). Guha and Kuruveilla have reported much higher incidence of gram negative organism.[9,14] There cannot be universal pattern of such studies because pattern of Organism varies from nursery to nursery and place to place. The prevalence of Klebsiella in the present study was consistent with other studies by Kuruveilla et al (33.8%), pooled data from different part of country by NNF 30% and Sharma A 38%.[4,9,18]

Table 8: Comparison of etiological agents.

Organism	Present study (n = 50) in %	NNF[4] (n = 837) in %
Klebsiella	28.57	29.7
Ecoli	23.81	13.9
Pseudomonas	19.04	9.2
Acinetobacter	9.5	2.4
Staphylococcus aureus	13.6	-
CONS	4.76	-
α hemolytic streptococci	4.76	-

In the present study CRP was positive beyond 7 days in 22%, blood culture in 44 % and BNR < 0.2% in 58% of cases. A study conducted by Bharatiya D revealed positive CRP is 52.5% of Suspected neonatal septicemia cases and positive blood culture in 40% of cases.[16] CRP was positive in all blood culture. In a study conducted by Jaswal et al, CRP was positive in 56% and blood culture in 42% cases.[19]

Comparison of CRP guided therapy groups

Group 1

In the present study, antibiotics were discontinued in 48% of neonates within 3 days after starting treatment and there was no relapse over the next 4 weeks. Similar results have been claimed by Stephan et al in which antibiotics were discontinued in 47.7% and Jaswal RS et al in which antibiotics were stopped in 44% of presented within 3 days after starting a treatment.[12,19] The authors have reported the negative predictive value of CRP guided therapy to be 99% and 100% which is comparable with the figure of 100% in the present study.

Table 9: Comparison of negative predictive values.

Groups	Present study (n=50)	Ehl S et al[21] (n=176)	Jaswal RS[19] (n = 50)
2a	100 %	99%	100%
2b	100%	95%	100%

In another study conducted by Philips AG et al antibiotics was stopped in 162 cases out of 425 (38%) within 48 hours based on CRP value. No relapse was reported in the study with negative predictive value of 100% which is similar to the present study.[20]

Group 2

- Group 2a**:** in this group 1 case out of 13 antibiotics could be stopped on 5th day whereas in 12 cases CRP levels were still raised even on 7th day. Since there was no relapse in any of these sub groups, the negative predictive value is 100% which is comparable to the study conducted by Ehls et al.[21] In which 38 out of 39 cases, guided by CRP within 6 days respectively with a negative predictive value of 99%. However, there was only 1 case in sub group 2 a in which antibiotics were stopped on 5th day to be of any statistical significance.
- Group 2b: in this group antibiotics could be stopped on 7th day in 2 out of 13 cases assigned to this group with a negative predictive value of 100%. In 11 cases treatment was continued beyond 7 days as CRP levels were still raised.

Since there was no relapse in this sub group, negative predictive value is 100% which is comparable with Ehl et al in their study Serum CRP continued to be raised in 6% of patients after 5th day of therapy.[21] 2 out of 42 patients had likely relapse and needed second course of antibiotics within 4 weeks giving negative predictive value of 95%. Hundred percent negative predictive value of CRP in guiding duration of antibiotic therapy is similar to the report by Phillips AG, Mills PC, who studied 425 neonates with clinical manifestations suggesting possible infection out of 8299 live births.[20] 100% negative predictive value of CRP is also similar to the study

reported by Jaswal et al.[19] Antibiotics were stopped within 7 days in 3 out of 14 cases in this study.

CONCLUSION

Negative predictive value of serial serum CRP is 100% in deciding the duration of antibiotic therapy in neonatal septicemia upto 7 days.

Duration of antibiotic therapy could be reduced to <7 days in 54% cases and <72 hours in 48% cases in the present study. This has implication in reducing the cost of therapy, duration of hospitalization and preventing over use of antibiotics.

New borns with suspected septicemia having raised serum CRP levels and positive blood culture need longer duration of antibiotic therapy (more than 7 days).

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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