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A study on validity of c-Reactive protein in deciding the duration of antibiotic therapy in suspected neonatal sepsis.

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ABSTRACT

Introduction: Neonatal septicemia is defined as a clinical syndrome resulting from patho-physiologicaleffects of local or systemic bacterial infection during first month of life.InIndia,neonatalsepticemiaincidence varies from 11-24.5 per 1000 live births[1]. Because oflackofspecificityofmanyofthesignsassociatedwith thisandlimitationoflaboratorycriteria,thediagnosisco ntinuestobe difficulttoestablish.

Aim: TodeterminewhetherC-Reactiveproteincanbeusedasaparametertoidentifyth e time point when antibiotic treatment can safely be discontinued in a definedmajorsubgroupofneonatestreatedforsuspecte dbacterial infection.

Materials and methods:A total of50neonateswithbirthweight morethan1500gmswithsuspectedsepticemiawereenr olledintheprospectivestudy.SerumCRPwasdetermin ed24– 48 hours after the first dose of antibiotics. If CRP was less than 6mg/l, infantswereconsideredunlikelytobeinfectedandthea ntibiotictreatmentwasstopped.If CRP was more than 6mg/l, antibiotics were continued and CRP measured onalternative days in one subgroup (2a) and on seventh day in another subgroup (2b).CRP was the single decision criterion to stop the antibiotic therapy. Negativepredictivevaluewithrespect tofurthertreatmentwasdetermined.

Results: Durationofantibiotictherapycouldbereduce dtolessthansevendaysin54%casesand<72hoursin48 %cases.

Conclusion: NegativepredictivevalueofserialCRPis 100% indecidingthedurationofantibiotictherapyinsuspecte dneonatalsepticemia.

Keywords:C - reactive protein,Neonate,Septicemia.

I. INTRODUCTION

Neonatalsepticemiawhichwasknownasseps isneonatorumearlierwasdefined as generalized bacterial infection of newborns documented by positive bloodcultureinfirstfourweeksoflife.Withbetterunder standingofitsetiology,pathophysiology,effectsand outcome overdecades,theconceptofdiseasehaschanged. Now it is defined as a clinical syndrome resulting from patho-physiologicaleffects of local or systemic bacterial infection during first month of life. Because oflackofspecificityofmanyofthesignsassociatedwith thisandlimitationoflaboratorycriteria,thediagnosisco ntinuestobe difficulttoestablish.

The prevalence rate of neonatal sepsis variesfrom 10-15 per 1000 livebirthsin developed world and 15-25 in south Asia.Neonatal sepsis accounts for 30-40% oftotalneonatalmortalitiesindevelopingcountries.InI ndia,neonatalsepticemiaincidence varies from 11-24.5 per 1000 live births[1]. Its clinical manifestations varyfrom being subtle to specific, testing thevery skill of a pediatrician. Theinability tobe certain of an infection coupled with nonspecific signs of life threatening illness inneonatesresultedinwidespreaduseofantibioticsagg ravatingtheproblemofantibiotic resistance.Currentrecommendationsfor the treatment of neonatal septicemiaincludeend points of 48-72 hrsforclinically stable children with negativeblood cultureresults and 7-14 days for

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blood culture positive or clinically probable infection.[2,3,4]However the rationale and safety of these recommendations have never beenformallyevaluated.Theincreasingproblemofantibioticresistancerequiresavoidingunnecessaryadministrationofantibiotics.
Consideringthevaryingspectrumofinfectiousagentsandthevariableinteraction between the microbe and the immune system of the neonate, it seems mostreasonable to individualize the duration of antibiotic therapy than follow the conceptofarbitrarilyfixed"completecourse"[5].TheAcutephaseC-reactiveprotein(CRP)issynthesizedintheliverinresponse to inflammatory cytokines andmay increase 1000folds during an acutephaseresponse.Synthesisstartsveryrapidlyafterasinglestimuluswithserumconcentrationraisingabove5-6mg/lbyabout6hoursandpeakingby48hrs87.Because of its short half life of 19 hours[5] CRP levels canbe expected to fall quicklyafterefficienteliminationofthemicrobial stimulus.ThusCRPmaysufficientlyreflect the individual balance between the microbes and the immune system of theneonate for monitoring the effect of antibiotic treatment andfor guiding the durationofantibiotictherapy.[6,7,8]The present prospective study is undertaken to determine whether C-reactiveprotein (CRP) can be used as a parameter to identify the time point when antibiotictherapycansafelybe discontinuedinsuspectedbacterialinfection.

II. MATERIALS AND METHODS:

Study Design: Prospective observational study
Total sample: 50 neonates
Study Center: Department of Paediatrics**,** Chalmeda Anand Rao Institute of medical sciences
Duration of the study:2019 December to June 2021.

Inclusioncriteria:
Newborns with birth weight>1500gms.Neonates withnocomorbiditiesBothinbornandoutbornbabies with neonatalsepsis.

ExclusionCriteria:
1)Neonateswhohad undergonesurgerybecauseofriskofwoundinfection.
2)Neonateswithdiagnosisofmeningitisasthey requirelongerduration oftreatmentwith antibiotics.
3)Noconsentfromparents.
4)Birthweight <1500gms.

After admission blood was drawn for culture and sensitivity and other relevant(Chest-Xray, urine culture sensitivity) investigations were sent and broad spectrumantibioticscoveringbothGrampositiveandgramnegativeorganismswerestarted(injectionAmpicillinandGentamicin)
CRP was estimated within 24 –48 hours of admission. Then neonates wereassignedtoone ofthe 3studygroupsaccordingtotheirCRPserumlevels.

Study Groups:
Group1:-Infection unlikely: This group included infants with CRP levels less than 6 mg% 24-48 hoursafterthe initiationofantibiotictherapy.Antibiotics werediscontinuedirrespective of other laboratory or clinical indices of infection unless decided by the attending consultant.
Group2: Infection likely: IfCRP was elevated >6mg % after 24 to 48 hours of first dose of antibiotic,group was divided in to two subgroups.
Group2a: CRP guided therapy: In this sub group, CRP was estimated on alternate day and as soon asCRPlevelwaslessthan6mg%antibioticswere stopped
Group2b:7daytherapy: 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**.**
Norelapse: If no occurrence of symptoms of septicemia within four weeks of discharge orthebabyrequired antibioticsfordifferentdiagnosisotherthansepticemia**.**
Relapse: If the baby needed another course of antibiotics for suspected /proved septicemia within 4weeks after discharge.
Outcome assessment: 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.
Statistic Analysis: Contingency table analysis and chi square(x^2) were applied wherever statistical analysis was necessary.

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CRP Estimation:

Collectionofblood:

1-2 cc of venous blood was drawn and kept in the test tube till complete clotting. Serum was separated for testing. One drop of serum was taken by dropper provided in CRP kit which was serially diluted with normal saline(l:2,l:4,1:8,1:16,1:32,1:64,1:128) , as per the instructions given in the manual supplied by the manufacturers. CRP kits were supplied by SPAN Diagnostic Ltd. to the Department of Microbiology.All the CRP reagents, which were stored at 4 to 8° C was brought to room temperature before use.After shaking the CRP reagent gently, one drop of CRP reagent was mixed with serially diluted serum.MixingofseriallydilutedserumandCRPreagentwasdonefortwominutesbyrotatingtheslidesmanually.The macroscopic clumping was observed as positive reaction.Qualitycontrolwasobservedafterregularintervalswithpositivecontrolandnegative control serum.Resultswereinterpretedbymultiplyingthehighestdilutionofpositiveresultby6mg%=6Xdilutionvalue.6mg%was normal value in this study.

Institute ethical approval: study was reviewed and approved by the institute Ethical committee, Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar.

III. RESULTS

Fifty cases of suspected neonatal septicemia were studied fromDecember2019–June2021. Out of them, males were 32 cases(64%) and females were 18(36%). 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 than 3 kgs.5 were preterm gestation(10%) and the rest were of tem gestation (90%). 14cases presented with in 72 hrs, 13 cases presented between 73 hours–7 days, 11 cases presented between 8-14 days and 12 cases between 15-28 days. Out of 22 cases, in 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.

CorrelationofprobablesepticemiawithCRP,BNRandBloodculturepositivity

Table1. Correlation ofprobablesepticemiawithCRP,BNRandBloodculture positivity.

Tests	Cases		Total(50)	Percentage	PValue
	EOS (11)	L05(39)			
PositiveBNR*	05	24	29	58	<0.05
Positive Bloodculture**	03	19	22	44	<0.05
Positive CRPonday5***	03	09	12	24	>0.05
PositiveCRP on day_7****	01	10	11	22	<0.05

*StatisticalanalysisbyChi-squaretestx^2=12.448, P=<0.05 Significant.**StatisticalanalysisbyChi-squaretestx^2=11.636,P=<0.05-Significant.***Statisticalanalysisbycontingencycoefficientmethod CC=0.333P>0.05****Statisticalanalysisbycontingencycoefficientmethod CC=0.614 P<0.05significant

Out of 50 cases of suspected neonatal septicemia, 22 cases were blood culture positive.22%cases for positive for CRP on day7 and 58% showed BNR>0.2.

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CRP Guided Distribution of Cases:

Table 2: CRPguided distribution of treatment, relapse rate in various groups and correlation with blood culture results

CRP Value	Groups(Case)		Durationoftherapy (No.ofcases)	Bloodculture Positive cases	Relapse	Negativepredictivevalue(%)
<6 mg %	Group1(24)		<3days(24)	Nil	Nil	100
>6 mg %	Group2	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 1: In 24 cases (48%) out of 50 cases of suspected neonatal septicemiaCRPwasNegativeafter48hoursandantibioticswerestopped.Bloodculturesshowed nogrowth.There wasnorelapseinthefollowingfourweeks.

Group2a: Thisgroupcomprisedof13(26%)casesoutofwhichCRPreturned to normal in one case on 5th day and antibiotics were stopped. Blood culturecame out to be normal and there was no relapse. In rest of 12 patients antibiotics werecontinuedbeyond7daysasCRPwasraised.Blood culturewaspositivein11cases.

Group2b:Thisgroupcomprisedof13(26%cases)outofwhichCRPreturned 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 asCRPwaspositive on7th dayoftreatment.Allwerebloodculture positive.

Overallduration of Treatment:

Table 3. Shows overall treatmentduration 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 >7days.

IV. 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[9]. who reported incidence as30%and70%respectively.

The incidence of EOS was reported 52.4% and LOS 44.3% by Namdeo et al[10].Higher incidence of EOS in this study was due to inclusion of EOS upto 7 days. The incidence of EOS (44%) as reported by Mishra et al[11] was higher as compared topresent study. The higher incidence was probably due to inclusion of only hospitaldeliveredbabiesinwhomsymptomsandsigns wererecognizedattheearliest.Whereasinthe presentstudyoutbornneonates were alsoincluded.

SexDistribution:

In the present study, males outnumbered females. The incidence of septicemiainmaleswas 64% andinfemalesitwas 36% which issimilar to thatreported bySomuetal[12].Whoreportedmaleandfemaleincidenceof54.6%and45.4%respectively.Similarweretheobservationsof Kuruveillaetal[9]andSinha et al[13].WithNo specificreasonsofPredispositionofmalesforsepticem

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ia;allstudies;Somuetal[12],Kuruveillaetal[9]andSinhaeta l[13]havereportedhigherincidenceofsepticemiainmales .Thepresentstudyisinconcordancewiththese observations.Guha et al[14]have also observed the similar result. Abdominal distention wasthecommonestsymptom(68.4%)followedbyDiar rheaandrefusaloffeedsasreportedbySomuetal[12]. The higher incidence of abdominal symptom in the study of Somu et al[12] wasmainly due to inclusion of more Preterm babies who are more prone to Necrotizingenterocolitis. Fever was not a prominent feature in this study where as Guha et al[14] andBhakooetal[15]havereportedtheincidenceoffeverto be20-26%assuchfeverisnota common feature of neonatal septicemia as compared to hypothermia, of which thereisnomentionis thesestudies.

CulturePositivity:

The incidence of culture positivity in the present study is 44% which is inconcordance with the studies conducted by Bharatiya Deepa et al[16] and Singh[8], whichhave shown its incidence to be 40% and 36.8% respectively. Although incidenceranging from 20% to 85% has been reported by Sharma Anita et al[16]and N. Somu etal[12]respectively.

BacterialIsolates:

Theincidenceofgramnegativeorganismis(7 7.2%)andgrampositiveorganism is (22.7%). Guha[14]and Kuruveilla[9] have reported much higher incidence ofgram negative organism. There cannot be universal pattern of such studies becausepatternof organismvariesfromnurserytonurseryandplacetopla ce.The prevalence of Klebsiella in the present study was consistent with otherstudies by Kuruveilla et al[9] (33.8%), pooled data from different part of country byNNF[4]30%andSharmaAnita[17] 38%.

CRP, BNRandBloodculturePositivity:

In the present study CRP was positive beyond 7 days in 22%, blood culture in44 % and BNR < 0.2% in 58% of cases – A study conducted by Bharatiya Deepa[16]revealed positive CRP is 52.5% of suspected neonatal septicemia cases and positive blood culture in 40% of cases. CRP was positive in all blood culture. In a studyconductedbyJaswaletal[18], CRP was positive in 56% and blood culture in 42% cases.

ComparisonofCRPguidedtherapygroups:

Group– 1: In the present study, antibiotics were discontinued in 48% of neonates within 3days after starting treatment and there were no relapse over the next 4 weeks. Similarresults have been claimed by Stephan et al[19]in which antibiotics were discontinued in47.7% and Jaswal R.S. et al[18] in which antibiotics were stopped in 44% of presentedwithin3daysafterstartingatreatment.Theau thorshavereportedthenegativepredictive value of CRP guided therapy to be 99% and 100% which is comparablewiththefigure of100%inthepresentstudy.

In another study – conducted by Philips Ag et al [20] antibiotics was stopped in162 cases out of 425 (38%) within 48 hours based on CRP value. No relapse wasreported in the study with Negative Predictive value of 100% which is similar to thepresentstudy.

Group– 2:

Group 2 a :- In this group 1 case out of 13 antibiotics could be stopped on 5th day whereasin 12 cases CRPlevels were still raised even on 7th day.Since therewas norelapsein any of these sub groups, the negative predictive valueis 100%which is comparable to the study conducted by Ehls, et al[19]. In which 38 out of 39cases, guided by CRP within 6 days respectively with a negative predictive value of99%. However there was only 1 case in sub group 2 a in which antibiotics werestoppedon5th daytobeofanystatisticalsignificance.

Group 2 b: - In this group antibiotics could be stopped on 7th day in 2 out of13 cases assigned to this group with a negative predictive value of 100%. In 11 casestreatmentwascontinuedbeyond7 daysasCRPlevelswere stillraised.

Since there was norelapsein this sub group, negative predictive valueis100% which is comparable with Ehl et al[18] in their study Serum CRP continued to beraised in 6% of patients after 5th day of therapy. 2 out of 42 patients had likely relapseand needed second course of antibiotics within 4 weeks giving negative predictivevalue of 95%. Hundred percent negative predictive value of CRP in guiding durationof antibiotic therapy is similar to the report by Phillips AG, Mills PC , who studied425 neonates with Clinical manifestations suggesting possible infection out of 8299livebirths[20].100%negativepredictivevalueofCR Pisalsosimilartothestudyreportedby Jaswaletal[18].Ant ibioticswerestopped within 7daysin3outof14casesinthis study.

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V. CONCLUSION

NegativepredictivevalueofserialserumCRPis100%indeciding thedurationofantibiotictherapyinneonatalsepticemia upto7days.Duration of antibiotic therapy could be reduced to < 7 days in 54% cases and <72hoursin48%cases inthepresentstudy. Thishas implicationinreducingthecost of therapy, duration of hospitalization and preventing over use ofantibiotics.Newborns with suspected septicemia having raised serum CRP levels andpositivebloodcultureneedlongerdurationofantibiotictherapy(morethan7days).

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