The role of plasma C-reactive protein in the evaluation of antibiotic treatment in suspected neonatal sepsis

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Abstrak

ABSTRAK Dilakukan analisis serial terhadap kadar C-reactive protein (CRP) untuk menguji perannya dalam tata laksana pasien yang tersangka menderita sepsis neonatal. Penelitian dilakukan pada 35 pasien tersangka sepsis neonatal yang dirawat di Bagian Ilmu Kesehatan Anak, Fakultas Kedokteran UI / RS Cipto Mangunkusumo, Jakarta, antara April sampai September 1999. Dari 35 pasien, 18 menunjukkan biakan darah positif, 10 di antaranya dengan kadar CRP meningkat pada saat diagnosis. Di antara 17 pasien dengan biakan darah negatif, 9 juga menunjukkan kadar CRP negatif. Pemeriksaan serial CRP pada kasus-kasus berat dengan CRP meningkat menunjukkan kadar CRP tetap tinggi, sedangkan pada kasus dengan CRP negatif kadarnya terus meningkat sampai hari ke-4. Pasien yang sembuh dan mempunyai kadar CRP awal yang rendah ternyata kadar CRP-nya tetap rendah pada hari ke-4. Penelitian ini menunjukkan keuntungan pemeriksaan CRP serial dalam evaluasi pemberian atibitotik pada pasien tersangka sepsis neonatal. ***(Med J Indones 2001; 10:16-21)***

Abstract

Analysis of serial C-reactive protein (CRP) levels was done to evaluate the effectiveness of antibiotic treatment in 35 suspected neonatal sepsis (SNS) patients who were hospitalized at Cipto Mangunkusumo Hospital, Jakarta. This cross sectional study was conducted from April to September 1999. Among 35 SNS patients, 18 had positive blood culture, 10 of which had positive CRP level at the time of diagnosis. Among 17 patients with negative blood culture, 9 had negative CRP level. Serial CRP in severe cases with positive CRP titer showed persistent high CRP level, and in those with negative CRP titer rose up to day 4 of treatment. On the other hand patients who were discharged and have negative blood culture demonstrated low CRP level in day 4. This study confirms the benefit of serial CRP examination in the evaluation of antibiotic treatment in SNS. ***(Med J Indones 2001; 10:16-21)***

Keywords: *neonatal sepsis, antibiotic treatment, serial CRP level measurements, prognosis.*

There have been significant improvements in the overall health of children during the past decade. Infant mortality has been decreasing steadily, but change in neonatal mortality has been much slower. Almost two thirds of newborn deaths occur in the first week of life. In developing countries almost 40% of death are due to infectious diseases such as sepsis, neonatal tetanus, pneumonia, and diarrhea. This problem occurs usually in low-birth weight infants and infants who have various perinatal risk factors such as deficiency of the immune system, factors relating with monitoring devices, and therapeutic procedures in the nursery.[1,2] Early identification of the infected newborn is essential but this effort is often difficult because symptoms and signs are usually non-specific and may resemble many other neonatal diseases, e.g., metabolic, hematological or central neural system disturbances.[3-6] Positive culture which is a 'gold standard' for confirming the diagnosis of infection usually takes time (at least 72 hours) and also with relatively low positive rates.[4-6] For those reasons, to gain good outcome, many clinics initiate antimicrobial therapy in neonatal infections on the basis of presumptive diagnosis.[5-7] On the other hand, the detrimental effects of antibiotic to the flora of individual infants and the rapid and widespread emergence of multidrug resistance among bacterial pathogens dictates the need for juducious use of antibiotic treatment. This condition becomes a dilemma in terms of which infants should receive antibiotic and how long it is needed.

To solve the problem, different strategies have been adopted in different institutions; these include determining serial C-reactive protein (CRP) level in every high risk newborn babies. CRP is a protein synthesized by hepatocyte cells and excreted into the

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blood; its level increases after systemic or local responses to infection.[8,9] CRP levels will elevate and can be detected at 6-18 hours after inflammatory responses, and reaches maximum level within 48-72 hours; the half life of CRP is 5-7 hours.[10-11] Some investigators also find that serial CRP levels decline as patient condition improves. This finding lead to the conclusion that serial CRP examination can be employed as a parameter in determining the duration of antibiotic administration in SNS.[11-14] Furthermore it is also suggested that antibiotic treatment should be discontinued if blood culture shows negative result, and serial CRP level shows similar results. The aim of this study was to evaluate serial plasma CRP level in SNS and to assess its levels before and after antibiotic treatment in patients with SNS.

METHODS

This was a prevalence study with cross-sectional design to assess serial plasma CRP levels in 35 patients with SNS. All subjects were patients admitted to the neonatal ward and neonatal intensive care unit of the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, from April until September 1999 who were diagnosed as having SNS. Subjects were included to the study if the birth weight was > 1000 g, did not suffer from fatal congenital malformation, and did not receive previous antibiotic treatment. Informed consent was obtained from parents. The samples size was calculated based on sample formula for single proportion estimation.[15]

The patients were divided into 2 groups, i.e., infants with early sepsis (age less than 72 hours), and those with late sepsis (age more than 72 hours). The diagnostic criteria of early sepsis depended upon the risk factors and clinical manifestations. The risk factors included premature rupture of the membrane of more than 18 hours, maternal temperature of more than 38°C, prematurity (gestational age less than 37 completed weeks), and unpleasant odor of amniotic fluid. The clinical mainfestations were respiratory rate >60/minute, unstable temperature (temperature <36°C or > 37.5°C), lethargy or irritability, dyspnea/cyanosis, poor sucking reflex, vomiting, apnea. An infant was suspected to have neonatal sepsis if he or she had 2 risk factors or had one risk factor and one clinical manifestation.[5]

In late sepsis the diagnosis was established if one or more of the following clinical signs were found: lethargy, unexplained low Apgar scores, unstable temperature, apneic attacks, unexplained cyanosis, gastrointestinal disturbances, respiratory disorder, hepatomegaly, diarrhea, vomiting, skin lesions and unexplained abnormal hematological parameter.[4,13]

Blood culture, CRP, and peripheral blood examination were done upon the inclusion into the study. CRP level was re-examined on day 2, 4, and if the patient died or discharged from hospital. The assessment of CRP was done semi-quantitaively with the cut-off point of 12 mg/dl. In babies with early sepsis amoxicillin and gentamicin were given, while those of late sepsis the antibiotic given were cefotaxime and amikacin. Important clinical findings which were relevant to sign of sepsis was also recorded every day until the patient died or discharged. All data were recorded in the case report form, performed by Epi info program.

RESULTS

During the study period, 35 cases of SNS were enrolled. Among the 35 cases, 18 showed positive culture (Table 1).

Table 1. Etiology of 18 cases positive blood culture*

Microorganism	n
Citrobacter freundii	5
Staphilococcus epidermidis	4
Serratia marcescens	2
Klebsiella pneumoniae	2
Staphilococcus sitreus	1
Acinobacter anitreus	1
Escherichia coli	1
Enterobacter aerogenes	1
Pseudomonas sp	1
Total	18

* = n = 35 cases

At the time of diagnosis, only 19 showed positive CRP level (CRP> 12 mg/dl), in which 10 were babies with positive blood culture and 9 were those with negative culture. The remaining 16 patients showed CRP level of less than 12 mg/dl, and they come from 8 babies with positive blood culture and 8 from negative blood culture.

Assessment of serial CRP levels in patients who were then died showed that either in positive or negative blood culture the level of CRP was persistent or increased up to day 4 (Tables 2 and 3).

Table 2. Patterns of serial CRP levels in death cases with positive blood culture

No	No case	Age	CRP (day of examination)				Microorganism in blood culture	Therapy & Recistency test	Note
			D0	D2	D4	D†			
1	12	22 days	24	24		96	*Pseudomonas aeroginase*	C*G*	† days-3
2	15	0 hours	12	12	48	48	*Serratia marcescens*	A**G**	† days-4
3	18	0 hours	< 12	48	96	96	*Klebsiella peneumonia*	A**G**	† days-6

Note: A= Amoxillin; G=Gentamicin; C= Cefotaxim; Am=Amikacin; T= Tienam; F=Flagyl; * = sensitive; ** = resistant
D0 = day null, D2 = day-2, D4 = day-4, D† = day of death

Table 3. Patterns of serial CRP levels in death case with negative blood culture

No	No Case	Age	CRP (day of examination)				Note
			D0	D2	D4	D†	
1	7	4 hours	< 12			12	† first day
2	9	5 hours	24	24	96	96	† days- 27
3	16	4 days	< 12	48	48	48	† days-4
4	19	18 hours	< 12	48	96	96	† days-8
5	29	2 days	96	96		96	† days-2
6	31	10 hours	96	96	96	96	† days-23

Note: D0 = day null, D2 = day-2, D4 = day-4, D† = day of death

Table 4. Patterns of serial CRP levels in survive cases with positive blood culture

No	No case	Age	CRP (days of examination)				Microorganism in blood culture	Therapy & Resistency test	Length of hospitalization
			D0	D2	D4	DD			
1	2	11 hours	<12	48	96	<12	*Citrobacter freundii*	A**G*	60
2	3	14 hours	48	48	96	<12	*Staphylococcus citreus*	A**G*	29
3	5	25 days	<12	12	96	48	*Staphilococcus epidermidis*	C*Am*	7
4	10	20 hours	12	48	48	<12	*Serratia marcescens*	A**G*	25
5	11	19 hours	48	48	24	24	*Citrobacter freundii*	A**G*	10
6	13	1 days	96	96	96	48	*Citrobacter freundii*	A**G*	7
7	14	17 hours	48	48	48	<12	*Citrobacter freundii*	A**G*	15
8	17	0 hours	<12	24	24	12	*Klebsiella pneumonia*	C*Am*	14
9	20	0 hours	<12	24	24	12	*Citrobacter freundii*	C*A**G*	42
10	21	0 hours	<12	<12	<12	<12	*Staphylococcus epidermidis*	A**G**	4
11	22	3 days	24	48	48	<12	*Staphylococcus epidermidis*	A*G*C*	23
12	26	19 days	<12	96	96	48	*Acinebacter anitratus*	C*Am**	8
13	28	7 days	96	96	48	12	*Enterobacter aerogenes*	A**G*	17
14	32	6 days	48	48	48	48	*Escherichia colli*	C***Am*A***	45
15	34	3 days	<12	<12	-	<12	*Staphylococcus epidermidis*	A**G**	2

Note: A=Amoxillin; G=Gentamicin; C= Cefotaxim; Am=Amikacin; * = sensitive; ** = resistent; *** = intermediate
D0 = day nol, D2 = day-2, D4 = day-4, DD = day of discharged

In survivors with positive blood culture, CRP levels remained high until day 4 of treatment (Table 4). In contrary, in patients who were discharged from hospital with negative blood culture, the serial level of CRP examination tended to decline until day 4 of treatment (Table 5).

DISCUSSION

As mentioned before, bacterial sepsis is one of the most common diagnostic challenges in neonatal medicine. The ability to make a definitive diagnosis by blood cultured not only complicated by delayed in having positive results, but also due to the difficulties in obtaining large samples to detect positive blood cultures, the increasing use of prenatal antibiotics administered to the mother and relatively low positive results. In our series of 35 cases with suspected sepsis, only 18 cases were found to have positive blood culture. The Coliform bacteria (i.e Citrobacter spp; Klebsiela spp, E. coli etc) seem to play a role in bacteremia found in our clinic. Klebsiella and *E. coli* are usually common bacteria find in the newborn sepsis. The finding of *Citrobacter freundii* as a cause of neonatal sepsis should be done a further studies, since it is very rare reported in the literature.

As already mentioned before, it is now generally acknowledged that in neonatal sepsis there is a rise of CRP values as a response of inflammation or tissue necrosis. This will be seen especially if a serial CRP determination are done. In this study, at the time of suspected neonatal sepsis was diagnosed, in 18 cases with positive blood culture babies only 10 cases indicated increase in CRP finding. In the other 8 babies, the CRP begin rising at day two when serial CRP examination were done except in one case with *S epidermidis*. This common skin bacteria may have been a contaminant to the blood culture and this can explain the normal CRP finding in that particular case. In this study, the increase of CRP finding was also seen in babies with negative blood culture. There were 9 babies with increased CRP values at the time of diagnosis and 8 babies were normal. From this series, a serial determinations of CRP indicate an increasing values except on 3 cases in which one baby died in the first day and the other 2 cases were normal until discharge.

Table 5. Patterns of serial CRP levels in survived case with negative culture

No	No case	Age	CRP (days of examination)				Note Days of hospitalization
			D-0	D-2	D-4	DD	
1	1	0 hours	48	48	<12	<12	9 days
2	4	25 days	96	96	96	96	13 days
3	6	2 days	96	48	12	12	7 days
4	8	9 hours	24	96	48	12	30 days
5	23	0 hours	48	96		96	2 days
6	24	16 hours	<12	<12	<12	<12	Clinical condition was good 6 days
7	25	9 days	<12	48	48	12	Clinical condition was good 5 days
8	27	10 hours	<12	48	48	<12	28 days
9	30	16 hours	24	48	24	24	6 days
10	33	8 hours	<12	48	12	<12	7 days
11	35	4 days	<12	<12	<12	<12	Clinical condition was good 4 days

Note: D0 = day nol, D2 = day-2, D4 = day-4, DD = day discharged

Table 6. Diagnostic value of serial CRP in SNS cases

CRP value	D0	D2	D4
Proportion	19/35 (54 %)	31/35 (89 %)	27/31 (87 %)
Sensitivity	10/18 (56 %)	16/18 (89 %)	15/17 (88 %)
Positive predictive value	10/19 (53 %)	16/31 (52 %)	15/27 (56 %)
Negative predictive value	8/16 (50 %)	2/4 (50 %)	3/4 (75 %)

Note: D0 = day nol, D2 = day-2, D4 = day-4

It seems that in this study, a serial CRP determination play an important role and have some value in the diagnosis of neonatal sepsis not only in proven positive blood culture babies but also in suspected neonatal sepsis as also seen in the studies by others. It is also seen in this study at different finding in negative predictive value of the CRP examination in day 4 compared with at the time of diagnosis. The plasma CRP examination at the time of diagnosis and at day 4 were 50% and 75% respectively. In another study, on the day of diagnosis, Squire at al found negative predictive value of 82% where as Ng et al found 75% in their studied.[13,16] These different finding not only might be due to different in sample size, but the time of diagnosis of baby with suspected neonatal sepsis should also took into consideration. All the normal value of plasma CRP were found in babies where the diagnosis were done soon after birth (i.e. case 16, 20, 21 of Table 5). This early detection of sepsis before the infant respond by elevation of CRP level might be responsible for the different finding of predictive value at the time of diagnosis in our study. This different was not found on day 4 where there were already an increasing values of CRP level (Tables 4 and 5).

Determination of serial C-reactive protein, in cases with positive blood culture (Table 1 and Table 3), show that the pattern of the level was high till day four. This result differed with the finding of Ng et al or Hidoncha et al studies.[14,16] Ng et al found that the peak of serial plasma CRP levels was on day two. While Hindoncha et al in 12 neonates with septicemia treated by combined antibiotic found the plasma CRP levels reached maximum on day two then declined onwards. In our study, whether inadequate antibiotic treatment together with less optimal management might play a role in the different finding of the pattern of CRP level still need further elaboration.[17,18] The multiple problems seen in some cases (like in case number 19) in which the baby's clinical condition was worse, although the antibiotic treatment was adequate, there was a delay in response to therapy and this might be also the cause of the delay in lowering of C-reactive protein levels.

In the series of survivors with positive culture we also see an increasing tendency or persistent high level of the pattern of serial CRP level in day 4 (Table 4). But at the time of discharge, the level was decreasing or normal. In a series of cases with suspected neonatal sepsis, where as the concentration of CRP was analyzed in detail after the beginning of treatment, Ehl et al found that there was initial increase in the CRP level which occurred until 10-48 hours after the beginning of treatment and then decreasing there after.[19] This decreasing pattern of serial CRP level was used in other studies as a supportive criterion for discontinuing of antibiotic therapy.[12,16] This was due to the fact that in a series of cases using CRP as single criterion of suspected neonatal infection, Ehl et al[12] mentioned that there was a low relapse rates of the primary infection within 4 weeks after discontinuing antibiotic therapy.

As a conclusion, it seems that C-reactive protein levels can be used as a monitoring guide of antibiotic administration in sepsis. However, to prove either clinically or statistically result, more studies with greater sample size are needed.

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