C-Reactive Protein as a Single Useful Parameter for Discontinuation of Antibiotic Treatment in Thai Neonates with Clinical Sepsis

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Background: *Clinical sepsis is a common diagnosis in neonate and is usually treated with antibiotic. The duration of treatment is usually more than five days or until all cultures from the patient's samples reveal negative.*
Objective: *To determine whether quantitative C-reactive protein (CRP) level less than 10 mg/L could be used as a reliable index for discontinuation of antibiotic treatment in Thai neonates with clinical sepsis.*
Material and Method: *All neonates with birth weight greater than 1,500 grams, diagnosed as clinical sepsis, were enrolled to the study. Serum CRP was measured at 24 to 48 hours after the first dose of antibiotics. If CRP level was less than 10 mg/L, infants were randomly divided to groups Ia and Ib. If CRP level was 10 mg/L or more, infants were randomly divided to groups IIa and IIb. Antibiotics were discontinued promptly after the CRP level was reported in group Ia, while CRP level was measured daily and antibiotics were discontinued after it returned to less than 10 mg/L in group IIa. In controlled groups (Ib and IIb), antibiotics were continued until all bacterial cultures were negative. The outcome measurements were the number of patients who required retreatment for clinical sepsis within three days and 28 days after discontinuing antibiotics.*
Results: *Of 98 neonates with clinical sepsis, 76 (77.6%) were in group I. The duration of antibiotic treatment in group Ia was shorter than group Ib significantly, 1.68 vs. 5.47 days ($p<0.01$). One neonate in group Ia was retreated on the third day after discontinuing antibiotics due to positive blood and urine cultures. The negative predictive value of CRP for discontinuation of antibiotics in group I was 97.4%. The durations of antibiotic treatments were 5.27 and 7.09 days in group IIa and IIb, respectively. One neonate in group IIa was retreated on the second day after discontinuing antibiotics since the patient's clinical and laboratory results suggested severe sepsis although all bacterial cultures were negative. No patient was readmitted for treatment of sepsis within 28 days after discontinuing antibiotics.*
Conclusion: *CRP levels were less than 10 mg/L in the majority of neonates with clinical sepsis. The negative predictive value for using this level as a guide for antibiotic discontinuation was 97.4%.*

Keywords: *Antibiotics, C-reactive protein, Neonatal sepsis*

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Neonatal clinical sepsis occurred in 2:100 live births at Phramongkutklao hospital. The diagnosis has usually been made based on the risks and/or clinical manifestations. The significant risks[1,2] are maternal fever and infection, fetal distress in utero, premature ruptured of membranes and premature birth of the infants. Signs and symptoms of neonatal sepsis include lethargy, irritability, poor feeding, core temperature higher than 37.5°C, tachycardia or bradycardia, respiratory distress, apnea, vomiting, hepatosplenomegaly, hypotonia, convulsion, poor skin color and prolonged capillary refill. As soon as the diagnosis of neonatal sepsis was made, patients were treated with antibiotics until all bacterial cultures were reported as negative[3]. The duration of this conventional treatment was at least five days. Treatment with antibiotics is recommended in neonate who had either positive hemoculture or clinical sign of sepsis[2,4]. Nevertheless, signs and symptoms of neonatal sepsis are not specific and can be found in other conditions including birth asphyxia, respiratory distress, polycythemia, and electrolyte disturbance, consequently, leading to over-prescription of antibiotics and unnecessary hospitalization. Although several studies have been reported the efficacy of laboratory indices including erythrocyte sedimentation rate (ESR), prealbumin protein and C-reactive protein

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(CRP) as confirming evidence of bacterial infection[5-7]. ESR seemed to be the most disappointing evidence since it is positive in non-inflammatory condition, Coombs' positive hemolytic anemia. On the other hand, it is negative in disseminated intravascular coagulopathy, and some inflammatory condition.

CRP, an acute phase reactant protein, which is synthesized in the liver[8], increases in response to inflammation[9,10]. The normal serum concentration of CRP ranges from 1 to 1.6 mg/L[11-13]. CRP level can reach up to 1,000-fold of normal serum concentration during bacterial infection and rapidly decline to normal level when the infection is eliminated[12]. The clinical cutoff point was evaluated in various studies regarding on the study population, laboratory technique, and time of measurement. The level of 10 mg/L is usually used for CRP measured by nephelometric method[5,7]. The half-life time has been reported to be 19 hours in any of the diseases studied[14], being the fractional catabolic rate independent of the plasma CRP concentration. Therefore, the synthetic rate of CRP appears as the only significant determinant of its plasma level, supporting the clinical use of CRP measurements to monitor disease activity[15]. In addition, CRP is not transferred through placenta[16,17]. CRP was retrospectively studied and reported as the best parameter for antibiotic assessment, antibiotic duration adjustment, and recurrent infection indicator determination[18]. A prospective randomized study reported that CRP could be used as a single reliable index for antibiotic discontinuation[7]. However, that study has been performed in temperate country[7] which the causative organisms of neonatal clinical sepsis were not the same as those found in the tropical countries.

The aim of the present study was to determine whether CRP level less than 10 mg/L could be used as a single decision-making parameter to identify the time point when antibiotic treatment could be safely discontinued in the majority of Thai neonates with clinical sepsis.

Material and Method

All Thai neonates with birth weight greater than 1,500 gram, who were diagnosed as clinical sepsis and hospitalized to Neonatal Intensive Care Unit, Phramongkutklao Hospital between April 1998 and August 1999, were enrolled to the study. Neonates who were intubated, have umbilical or central line catheterization, or diagnosed as conditions requiring prolonged antibiotic treatment such as meningitis, arthritis, and osteomyelitis were excluded. Written informed consents were obtained from their parents.

Neonatal clinical sepsis was defined as a neonate who had at least one of the following conditions: 1) maternal fever that required antibiotic treatment; 2) maternal prolonged rupture of membranes >24 hours; 3) purulent gastric content that contained more than 10 white blood cells per high power field; 4) fetal distress in utero; 5) clinical manifestation of sepsis including lethargy, irritability, poor feeding, core temperature higher than 37.5°C, tachycardia or bradycardia, respiratory distress, apnea, vomiting, hepatosplenomegaly, hypotonia, convulsion, poor skin color and prolonged capillary refill.

After the diagnosis of neonatal clinical sepsis was made, complete blood count including evaluation of band to total neutrophil ratio, toxic granulation and vacuolization of neutrophil, urinary analysis, cerebrospinal fluid examination, blood, and body fluid culture were obtained. Antibiotics including ampicillin or cloxacillin plus gentamicin were given as indicated. Serum concentration of CRP was measured at 24 to 48 hours after the initiation of antibiotics.

Serum concentration of CRP was measured using a liquid-phase immunoprecipitation assay with nephelometric end-point detection. The level of CRP at 10 mg/L or greater was defined as suspected bacterial infection, while the level less than 10 mg/L was defined as normal.

If the level of CRP was less than 10 mg/L, infants were randomly divided into two groups (Ia and Ib). Antibiotics were immediately discontinued for those in group Ia, while those in group Ib received antibiotics treatment until all bacterial cultures were reported as negative. Patients in group Ia were observed in the hospital for three days after discontinuation of antibiotics to determine the acute retreatment rate.

If the level of CRP was 10 mg/L or greater, infants were also randomly divided into two groups (IIa and IIb). CRP level was measured daily and antibiotics were discontinued as soon as it returned to less than 10 mg/L in group IIa, while antibiotics were continued for at least five days until all bacterial cultures were negative in group IIb.

All infants were followed for 28 days. If they developed one of the following criteria, they were prescribed the second course of antibiotics treatment by one of the two neonatologists in our research team and their CRP results were considered as false negative. These criteria were 1) septic shock, 2) blood and body fluid cultures revealed bacterial infection,

3) symptoms and signs revealed progression of the illness such as drowsiness, sclerema, unstable vital signs, or 4) mechanical ventilator needed. The number of patients who required retreatment for clinical sepsis within three days and 28 days after antibiotic cessation were the primary outcome measurement in this study.

Statistical analysis

The retreatment rate and the duration of antibiotic treatment in group Ia and Ib were compared by using Student t-test. To estimate the value of CRP as a guide for discontinuation of antibiotic treatment, the negative predictive value with respect to the numbers of retreatment case were calculated. The enrollment of 2,000 cases were needed to determine CRP as a parameter for guiding the duration of antibiotic treatment in group IIa and IIb, therefore, these two groups were conceived as a pilot study.

Results

Of 98 neonates with clinical sepsis, 76 (77.6%) had CRP level less than 10 mg/L (group I). Half of them were allocated in group Ia, while the rest were in group Ib. The general characteristics of group Ia and Ib were shown in Table 1. The mean age at diagnosis of clinical sepsis in groups Ia were not different from those in group Ib (21.79 vs. 21.74 hours, respectively (p>0.05). No significant differences of hematological indices were found between both groups (Table 2). One neonate in group Ia was retreated on the third day after discontinuing antibiotics because both blood and urine cultures revealed *Staphylococcus* coagulase negative. The duration of antibiotic treatment in group Ia was significantly less than group Ib, 1.68±0.21 vs. 5.47±0.26 days, respectively (p<0.01). The negative predictive value of CRP for discontinuation of antibiotics treatment in group I was 97.4%. Of 22 neonates (22.4%) who had CRP level of 10 mg/L or greater (group II), half were allocated in group IIa and the rest were in group IIb. The mean age at diagnosis of clinical sepsis in groups IIa and IIb were 18.55 and 17.73 hours, respectively. One neonate in group IIa was retreated on the second day after discontinuing antibiotics because the platelet count revealed 35x10^9/L. Severe sepsis was a differential diagnosis at the time of retreatment; however, all bacterial cultures were reported as negative later. The durations of antibiotic treatment were 5.27±0.78 and 7.09±0.91 days in groups IIa and IIb, respectively. No patient was re-hospitalized within 28 days after discontinuing antibiotics for treatment of clinical sepsis.

Discussion

This randomized controlled study demonstrated that CRP level less than 10 mg/L during

Table 1. Characteristics of neonates in each group

Group	n	Sex M:F (cases)	Mean BW (gm) (cases)	Apgar score				HBsAg positive (cases)	Anti HIV positive (cases)	Mean DX time (hours)
				1 minute		5 minutes				
				<3 (cases)	Mean (score)	<6 (cases)	Mean (score)			
Ia*	38	15:23	2908.8	0	7.8	2	9.0	0	1	21.8
Ib*	38	21:17	2964.2	0	8.0	2	9.2	2	1	21.7
IIa	11	8:3	2886.4	0	7.4	0	9.2	1	0	18.6
IIb	11	8:3	2596.4	3	6.8	1	8.8	0	0	17.7

M:F = male:female; BW = body weight; HBsAg = hepatitis B surface antigen; Anti HIV = antibody to human immunodeficiency virus; DX time = time at diagnosis; NS = not significant
* p = NS

Table 2. Hematological indicies and polymorphonuclear cell morphology in each group

Group	Hct (%)	WBC (x10^9/L)	Platelet count (x10^9/L)	PMN (%)	B:T	Toxic granulation (%)	Vacuolization (%)
Ia*	50.0	19.9	252.3	65.8	0.19	23.5	5.8
Ib*	49.3	18.3	276.4	61.7	0.15	25.8	6.5
IIa	53.7	21.6	273.2	73.4	0.24	27.3	11.3
IIb	50.4	18.9	240.8	71.4	0.22	20.0	7.5

Hct = hematrocrit; WBC = white blood cell count; PMN = polymorphonuclear cell, B:T = band-form:total neutrophil
* p = NS

Table 3. Number of cases required re-treatment and duration of antibiotic treatment

Group	Number of case required re-treatment			Duration of antibiotic mean ± SD (days)
	Within 3 days	Within 28 days	Total re-treatment	
Ia	1	0	1/38	1.68±0.21
Ib	0	0	0/38	5.47±0.26
p-value	NS	NS	NS	<0.001
IIa	1	0	1/11	5.27±0.78
IIb	0	0	0/11	7.09±0.91

24 to 48 hours after the first dose of antibiotic treatment could be used as a single decision-making parameter to identify the time point when antibiotic treatment could be safely discontinued in the majority of Thai neonates with clinical sepsis. This finding is similar to previous reports studied in temperate countries[7,19]. Ehl et al[7] demonstrated that 120 out of 121 neonates were successfully discontinued antibiotics by using CRP at the level less than 10 mg/L as the only parameter for determination. Although the bacterial infection of patients receiving a second course of antibiotic treatment in that study[7] were those with facial skin lacerations and Group B *Streptococcus* meningitis, the common causative bacterial sepsis in our hospital were gram negative bacilli especially *Esherichia coli*, followed by *Staphylococcus* species and rarely by *Streptococcus* group B. This finding indicates that CRP is a part of unspecified immune response of host and pathogen interaction, not interfering by different species of causative organisms.

It is interesting to note that almost all of the neonates diagnosed as clinical sepsis in our study were not able to find the causative bacterial infection, even though bacterial cultures were obtained in blood, urine, cerebrospinal fluid, and any suspected sources of each patient. Although it might be wondered whether it is a true bacterial sepsis, the neonate was routinely admitted in the hospital and received antibiotic treatment until all bacterial cultures were negative. Despite the poor immunity comparing to adult[2,3], neonates usually recovered fast even sometimes only a short time after receiving the first dose of antibiotic. Using the CRP level of less than 10 mg/L as a single decision-making parameter in discontinuation of antibiotic treatment, the treatment duration was significantly decreased from 5.5 to 1.7 days in 38 neonates with unlikely infection and 7.1 to 5.3 days in 11 neonates with likely infection. Neonates with birth weight less than 1,500 gram and those with central or umbilical catheter or endotracheal intubation were excluded from the study since they were at increased risk of secondary bacterial infection and therefore might interfered with the CRP level and the duration of antibiotic treatment.

The present study demonstrated that the majority of neonates who were diagnosed as clinical sepsis had CRP level less than 10 mg/L and these were supposed to be unlikely bacterial infection. Antibiotics could be stopped despite persisting symptoms or neutrophil abnormalities including band form to total neutrophil ratio greater than 0.2, toxic granulation or vacuolization greater than 25% which were found in 18 of 38 (47.4%) neonates in group Ia. One neonate in group I received the second course of antibiotic treatment because of the positive results from bacterial cultures of urine and blood samples. However, it was hard to determine whether it was a true infection because the patient had no symptom. On the other hand, this data showed that CRP measured during 24 to 48 hours after the initiation of antibiotics could be used as a guide for discontinuation antibiotics with the risk of 2.6% false negative. This risk was demonstrated to be safe if the patient was observed three days longer in the hospital. The shorter duration of hospital stay and reduced antibiotic usage were pleasant results.

Our study had some limitations that need careful consideration. 1) The results of this study were valid in non-intubated neonates with BW greater than 1,500 grams without central or umbilical catheterization who were treated within the first week of life. 2) The probably different causative organisms and treatment regimen between our institution, and others. 3) According to a large numbers of neonates with CRP level at10 mg/L or greater were required to get the correctly statistical analysis, the results of this group were reported as a pilot study.

In conclusion, the majority of neonates with clinical sepsis had quantitative CRP during 24 to 48 hours after the first dose of antibiotics less than 10 mg/L. The negative predictive value for using this level as a single guide for antibiotic discontinuation was 97.4%. Another three days observation after

discontinuation of antibiotics would increase the precision and safety.

What is already known on this topic?

Clinical sepsis in neonate has usually been made based on the risks and/or non-specific sign and symptoms. Once the diagnosis is made, patient is usually treated with antibiotics until all microbial cultures from clinical specimens reveal negative results. To decrease unnecessary hospitalization, several lab parameters have been studied to be used as reliable indices for discontinuing antibiotic. Several retrospective and observational studies reported that CRP was one of the best parameters for determination of antibiotic duration and assessment of recurrent infection during follow-up. However, a few prospective randomized studies in temperate countries have demonstrated that CRP at the level less than 10 mg/L could be used as a safe parameter for antibiotic discontinuation.

What this study adds?

This present randomized controlled study conducted in a tropical country showed that CRP level of less than 10 mg/L measured during 24 to 48 hours after the first dose of antibiotic treatment could be used as a single decision-making parameter to identify the time point when antibiotic treatment was safely discontinued in the majority of Thai neonates with clinical sepsis. Using CRP level of less than 10 mg/L as a cut point, the length of hospitalization was shorten for three to four days in neonate with unlikely infection and for two days in neonate with likely infection. Moreover, CRP is a part of unspecified immune response of host and pathogen interaction, not interfering by different species of causative organisms.

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Potential of conflicts of interest

None.

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การใช้ C-reactive protein ในการพิจารณาหยุดการรักษาด้วยยาปฏิชีวนะในทารกแรกเกิดชาวไทยที่มีอาการของภาวะติดเชื้อ

นวพร นำเบญจพล, แสงแข ชำนาญวนกิจ, ปรียาพันธ์ แสงอรุณ, ศรีลักขณ์ สิมะเสถียร, วีระชัย วัฒนวีรเดช

ภูมิหลัง: *ทารกแรกเกิดได้รับการวินิจฉัยได้บ่อยว่ามีอาการของภาวะติดเชื้อและได้รับการรักษาด้วยยาปฏิชีวนะ ระยะเวลาในการให้ยามักเกิน 5 วัน หรือ จนกระทั่งผลการเพาะเชื้อจากสิ่งส่งตรวจของผู้ป่วยไม่พบเชื้อใด ๆ*

วัตถุประสงค์: *เพื่อศึกษาว่า ระดับ C-reactive protein (CRP) ที่น้อยกว่า 10 มิลลิกรัม/ลิตร จะสามารถนำมาใช้เป็นเกณฑ์ในการพิจารณาหยุดการรักษาด้วยยาปฏิชีวนะในทารกแรกเกิดชาวไทยที่มีอาการของภาวะติดเชื้อได้หรือไม่*

วัสดุและวิธีการ: *ทารกแรกเกิดทุกรายที่มีน้ำหนักแรกเกิดมากกว่า 1,500 กรัม และได้รับการวินิจฉัยว่ามีอาการของภาวะติดเชื้อจะได้รับการตรวจวัดระดับ CRP หลังจากที่ได้รับการรักษาด้วยยาปฏิชีวนะนาน 24 ถึง 48 ชั่วโมง หาก CRP ที่วัดได้มีค่าน้อยกว่า 10 มิลลิกรัม/ลิตร ทารกจะได้รับการสุ่มคัดเลือกออกเป็นกลุ่ม Ia และ Ib ส่วนทารกที่มีค่า CRP มากกว่าหรือเท่ากับ 10 มิลลิกรัม/ลิตร จะได้รับการสุ่มคัดเลือกออกเป็นกลุ่ม IIa และ IIb ในทารกกลุ่ม Ia จะพิจารณาหยุดยาปฏิชีวนะทันทีที่ทราบผลของ CRP ส่วนทารกในกลุ่ม IIa จะได้รับการตรวจวัดระดับ CRP ทุกวัน และจะพิจารณาหยุดยาปฏิชีวนะเมื่อระดับของ CRP ที่วัดได้น้อยกว่า 10 มิลลิกรัม/ลิตร กลุ่มควบคุมคือ กลุ่ม IIa และ IIb ทารกจะได้รับการรักษาด้วยยาปฏิชีวนะจนกว่าจะได้รับรายงานว่าไม่พบเชื้อแบคทีเรียจากการเพาะเชื้อ ผลการศึกษาที่ต้องการวัดคือ จำนวนผู้ป่วยที่จำเป็นต้องได้รับการรักษาภาวะติดเชื้ออีกครั้งภายใน 3 วัน และ 28 วัน หลังการหยุดยาปฏิชีวนะ*

ผลการศึกษา: *ทารก 98 ราย ที่ได้รับการวินิจฉัยว่ามีภาวะติดเชื้อ 76 ราย (ร้อยละ 77.6) มีค่า CRP น้อยกว่า 10 มิลลิกรัม/ลิตร ระยะเวลาในการใช้ยาปฏิชีวนะในกลุ่ม Ia สั้นกว่ากลุ่ม Ib อย่างมีนัยสำคัญทางสถิติ (1.68 และ 5.47 วัน, $p<0.01$) ทารก 1 ราย ในกลุ่ม Ia จำเป็นต้องได้รับการรักษาภาวะติดเชื้อ ในวันที่ 3 หลังหยุดยาปฏิชีวนะ เนื่องจากผลการเพาะเชื้อในการะแสเลือดและในปัสสาวะพบเชื้อแบคทีเรีย ค่า negative predictive value สำหรับการใช้ระดับ CRP ดังกล่าวเป็นเกณฑ์ในการพิจารณาหยุดยาปฏิชีวนะในกลุ่ม I เป็นร้อยละ 97.4 ระยะเวลาในการใช้ยาปฏิชีวนะในกลุ่ม IIa และ IIb คือ 5.27 และ 7.09 วัน ตามลำดับ ทารก 1 ราย ในกลุ่ม IIa ได้รับการรักษาในวันที่ 2 หลังหยุดยาปฏิชีวนะ เนื่องจากผู้ป่วยมีอาการและผลการตรวจทางห้องปฏิบัติการที่เข้าได้กับภาวะติดเชื้อ แม้ว่าจะไม่พบเชื้อแบคทีเรียจากการเพาะเชื้อก็ตาม ไม่พบว่ามีทารกในกลุ่มใดที่จำเป็นต้องได้รับการรักษาภาวะติดเชื้อหลังหยุดยาปฏิชีวนะ 28 วัน*

สรุป: *ทารกส่วนใหญ่ที่มีอาการของภาวะติดเชื้อมีค่า CRP น้อยกว่า 10 มิลลิกรัม/ลิตร ค่า negative predictive value สำหรับการใช้ระดับ CRP ดังกล่าวเป็นเกณฑ์ในการพิจารณาหยุดยาปฏิชีวนะเท่ากับร้อยละ 97.4*