Paediatrica Indonesiana

VOLUME 42 September - October • 2002 NUMBER 9-10

Original Article

Diagnostic accuracy of clinical and blood examination for sepsis in potentially infected neonates

Ari Mulyani, MD; D Setyowireni, MD; Achmad Surjono, MD, PhD

ABSTRACT

Background Neonatal sepsis remains a diagnostic challenge due to its nonspesific symptoms and signs. Blood culture as the gold standard is still a problem because it takes time, is expensive, and not every health facility is able to perform.

Objective To evaluate the diagnostic accuracy of clinical symptoms, hematologic findings, and C-reactive protein (CRP) in neonatal sepsis.

Design Samples were taken from potentially infected neonates admitted to the Maternal-Perinatal Unit of Sardjito Hospital, between December 1st, 2000 and March 31st, 2001 using at least one of the criteria: prematurity, very low birth weight infants, maternal pyrexia during delivery, premature membrane rupture, or thick, cloudy amniotic fluid. Clinical symptoms, total leukocyte, neutrophil, platelet count, CRP, and blood culture as the gold standard were examined.

Results Among 99 neonates enrolled, the sensitivity, specificity, positive and negative predictive value of clinical symptoms were 79.3%, 75.7%, 57.5%, and 89.9%, respectively; leukopenia/ leukocytosis were 27.6%, 85.7%, 44.4%, and 74.1%; neutropenia/ neutrophilia were 41.4%, 71.4%, 37.5%, and 74.6%; thrombocytopenia were 79.3%, 51.8%, 40.4%, and 85.7%; positive CRP were 58.6%, 78.6%, 53.1%, and 82.1%. Parallel tests increased the sensitivity up to 89.7%. Specificity, positive and negative predictive value, and likelihood ratio were 44.3%, 40%, 91.2%, and 1.6, respectively. Serial tests increased the specificity up to 88.6%. Sensitivity, positive and negative predictive value, and likelihood ratio were 58.6%, 68%, 83.8%, and 5.1, respectively.

Conclusion Clinical sepsis, thrombocytopenia, and CRP are sufficiently accurate as diagnostic tests for sepsis in potentially infected neonates. Parallel tests will increase the sensitivity, while serial tests increase the specificity **[Paediatr Indones 2002;42:220-224].**

Keywords: *clinical symptoms, C-reactive protein, neonatal sepsis, leukopenia, leukocytosis, neutropenia, neutrophilia, thrombocytopenia.*

Neonatal infection is still a big problem, also in Indonesia, due to its high morbidity and mortality rates.[1] The major problems are to identify the infected infant for administering appropriate therapy as early as possible, and to discontinue therapy if it is not indicated because the symptoms and signs are usually not specific.[2] Besides the clinical manifestations, various patterns of hematologic changes associated with sepsis include total white blood count, total neutrophil count, platelet count and increased C-reactive protein (CRP).

Almost 60% of neonatal infection can be proven by blood culture, but obtaining the result requires several days[3] and not every health facility can perform the procedure and the cost is expensive. Although a positive blood culture is generally considered to be the gold standard for diagnosis of septicemia, spurious results from contaminated samples are not infrequent. We need clinical manifestations, hematologic, and CRP examination in attempt to support the diagnosis of infection.[4]. This study was conducted to evaluate the diagnostic value of clinical symptoms, white

From the Department of Child Health, Medical School, University of Gadjah Mada–-Sardjito Hospital, Yogyakarta, Indonesia.

Reprint requests to: Ari Mulyani, MD, Department of Child Health, Medical School, Gadjah Mada University/RS Sardjito, Yogyakarta, Indonesia. Tel. 62-274-561616; Fax. 62-274-583745

blood cell count, neutrophil count, platelet count, and CRP in neonatal sepsis.

Methods

Babies admitted to the Maternal-Perinatal Unit of Sardjito Hospital, Yogyakarta during the period of December 1st, 2000 to March 31st, 2001 with high risk for infections were included in the study. We defined high risk for infection if there was at least one of the criteria: prematurity (<37 weeks gestational age); very low birth weight (<1,500 g); maternal pyrexia during delivery (>38°C or white blood cell count >15,000/μL); premature rupture of the membrane (> 24 hours), thick and cloudy amniotic fluid. Subjects were tested for having infection.[4,5,6] Neonates with congenital anomaly or blood disorder not caused by sepsis were excluded from this study.

All infants were evaluated for clinical manifestations by a pediatrician. The patient was considered clinically sepsis if he met at least 1 sign in 4 out of 6 group categories: (1) general condition (not doing well, poor feeding, fever, hypothermia, sclerema); (2) gastrointestinal system (abdominal distention, vomiting, diarrhea, hepatomegaly); (3) respiratory system (apnea, dyspnea, tachypnea, retraction, flaring, grunting, cyanosis); (4) cardiovascular system (tachycardia, bradycardia); (5) central nervous system (irritability, lethargy, tremor, seizure); (6) hematologic system (jaundice, splenomegaly, pallor, petechiae, purpura, and bleeding).[4,7-9]

White blood cell, neutrophil and platelet counts were calculated using standard procedures by our central laboratory. We defined abnormal white blood cell count when there was leukopenia/leukocytosis (<7 days old: <9,000/μL or >30,000/μL; ≥7 days old: <5,000/μL or >21,000/μL) ; neutropenia/neutrophilia (<7 days old: <6,000/μL or >26,000/μL; ≥7 day old: <1,500/μL or >10,000/μL).[10] Thrombocytopenia was defined as a platelet count of <150,000/μL.[1] CRP measurement was done semi-quantitatively using latex agglutination method. CRP is positive if >6 mg/L[1]. Blood cultures were performed to all the high risk infants by our central laboratory and 4-6 days were required for the results. Blinding was obtained by the difference between test and gold standard result. The protocol was approved by the Ethics Committee of Sardjito Hospital.

Accuracy of diagnostic test was analysed with sensitivity, specificity, predictive values, and likelihood ratio. Sensitivity, specificity and predictive values of clinical manifestation, white blood cell count, neutrophil count, platelet count and CRP were determined using the usual 2 x 2 tables. Results of blood culture were used as the gold standard.

Results

Between December 2000 and March 2001, a total of 278 neonates were admitted to Maternal-Perinatal Unit, Sardjito Hospital. One hundred and fifty three (55%) met one of the criteria and were grouped as potentially infected baby. However, only 99 cases fulfilled the criteria.

The characteristics of the subjects are shown in **Table 1**. Blood cultures were positive in 29 neonates (29%). Clinical sepsis was found in 40 neonates (40%), leukopenia/leukocytosis was positive in 32 neonates (32%), while thrombocytopenia was positive in 57 neonates (58%). CRP >6 mg/L was positive in 32 neonates (32%).

Table 1. Characteristics of the subjects

Variables	n (99)	%
Age		
<7 days	86	87
≥7 days	13	13
Sex		
Male	60	61
Female	39	39
Birth weight		
4000g	2	2
2500-4000g	65	66
1500-2499g	27	27
<1500g	5	5
Gestational age		
<37 weeks	21	21
37-41 weeks	77	78
≥42 weeks	1	1
Maternal pyrexia/leukocytosis	21	21
Premature rupture of the membrane	18	18
Thick and cloudy amnion fluid	40	40

TABLE 2. SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES OF CLINICAL SEPSIS IN THE DIAGNOSIS OF NEONATAL SEPSIS

Indicator	+ Blood culture	- Blood culture	Total
+ Clinical sepsis	23	17	40
- Clinical sepsis	6	53	59
Total	29	70	99

Sensitivity:	79.3%	(95% CI: 59.7;91.3)
Specificity:	75.7%	(95% CI: 63.7;91.3)
Positive predictive value:	57.5%	(95% CI: 41.0;72.6)
Negative predictive value:	89.8%	(95% CI: 78.5;95.8)

The sensitivity and specificity of clinical sepsis were 79.3% and 75.7%, respectively **(Table 2).** Meanwhile, the sensitivity and specificity of the other parameters are shown in **Table 3.** It can be seen that clinical manifestation, platelet count, and CRP can be considered as a diagnostic tool for neonatal sepsis.

The use of parallel test (clinical finding, platelet count and CRP) resulted in a sensitivity of 89.6%, specificity of 44.2%, positive likelihood ratio (LR) of 1.6, and negative LR of 0.23. The use of serial test started from the higher specificity (CRP, clinical manifestation and thrombocytopenia) resulted in sensitivity of 58.6%, specificity of 88.5%, positive LR of 5.1, and negative LR of 0.46. In parallel test, with the prevalence 29.3%, pre-test odds was 0.41, post-test odds 0.65, post-test probability 0.39. In serial test, pre-test odds was 0.41, post-test odds 2.09, the post-test probability 0.67.

Discussion

The purpose of this study was to compare the diagnostic value of clinical findings, hematologic findings and CRP in neonatal sepsis with blood culture examination as the gold standard. Our study showed that the sensitivity and specificity of clinical sepsis were 79.3% and 75.7%, respectively. It has been known that total white blood cell counts are of limited value in the diagnosis of septicemia of the newborn. Among neonates evaluated for suspected sepsis, less than half of those with decreased (<5,000/μL) or elevated (>20,000/μL) cell counts are ultimately identified as being infected[11], while Oski *et al*[10] defined leukopenia if white blood cell count <9,000/mL (<7 days old) or < 5,000/mL (≥7 days old) and leukocytosis if white blood cell count >30,000/mL (<7 days old) or >21,000/mL (≥7 days old). Leukopenia/leukocytosis had a 27.6% sensitivity and a 85.7% specificity, while in the Kosim study[1] had 16.7% and 66.7 %, respectively. Anwer & Mustafa (2000) had a specificity of 93% but a sensitivity of 14%[13]. Total neutrophil counts decreased or elevated in only one quarter to one third of infant with bacteremia, particularly when counts were obtained early in the course of illness.[12] Neutropenia/neutrophilia had a sensitivity and a specificity of 41.4% and 71.4%, while Anwer & Mustafa (2000) found over 60% and 50%, respectively[13].

Thrombocytopenia accompanying bacterial infection is thought to be due to a direct effect of bacteria or bacterial products on platelets and vas-

TABLE 3. SENSITIVITY, SPECIFICITY, PREDICTIVE VALUES, AND LIKELIHOOD RATIO IN DIAGNOSIS OF NEONATALSEPSIS

Indicator of sepsis	sensitivity %	specificity %	PPV* %	NPV** %	PLR†	NLR‡
Clinical	79.3	75.7	57.5	89.8		
Leukopenia/leukocytosis	27.6	85.7	44.4	74.1		
Neutropenia/neutrophilia	41.4	71.4	39.5	74.6		
Thrombocytopenia	79.3	51.8	40.4	85.7		
CRP +	58.6	78.6	53.1	82.1		
Parallel test	89.7	44.3	40.0	91.2	1.6	0.23
Serial test	58.6	88.6	68.0	83.8	5.1	0.48

* Positive predictive value, ** Negative predictive value, † Positive likelihood ratio
‡ Negative likelihood ratio

cular endothelium leading to increased aggregation and adhesion, or due to increased platelet destruction caused by immune mechanisms.[12,14] Thrombocytopenia (<150,000/μL) had a 79.3% sensitivity and a 51.8% specificity, while Kosim *et al* (1993) found 11.1% and 66.7%, respectively[1].

CRP is known to be produced by the fetus and has been found in high concentrations in the sera of newborn infants with a variety of infection. So, the increased CRP level may be used as a diagnostic procedure of neonatal infections.[1] CRP with cut off point of >6 mg/L had a sensitivity and specificity of 58,6% and 78.6%, respectively, while Kosim *et al* (1993) found a 83.3% sensitivity and a 58.3% specificity[1]. Anwer & Mustafa (2000) found a sensitivity of over 60% with a specificity 50%.[13]

Results from these analyses showed that both white blood cell count and neutrophil count had low sensitivity; on the other hand clinical manifestation, platelet count and CRP examination had higher sensitivity and specificity. The clinical manifestation, platelet count, and CRP were sufficiently accurate as diagnostic tests for potentially infected neonates. Parallel test increased the sensitivity up to 89.7%. The specificity, positive predictive value, negative predictive value, and likelihood ratio were 44.3%, 40%, 91.2%, and 1.6, respectively. Serial test started from the higher specificity examination (CRP, clinical manifestation and platelet count) increased the specificity up to 88.6%. Sensitivity, positive predictive value and negative predictive value were 58.6%, 68%, and 83.8%, respectively, likelihood ratio was 5,1. So this test was sufficiently accurate as diagnostic test for sepsis in potentially infected neonates. Parallel test is used in clinical practice. Results of this study are limited to neonates with potential infection. To generalise the results in large population, we need to conduct a study in all neonates.

In conclusion, clinical sepsis, thrombocytopenia, and CRP are sufficiently accurate as diagnostic tests for sepsis in potentially infected neonates. Parallel test increases sensitivity, while serial test increases specificity. There is high probability of having sepsis, if the results are positive.

References

1. Kosim MS, Arthana BNP, Mangunsong H. Diagnostic accuracy of CRP examination in neonatal infections. Paediatr Indones 1993;33:150-8.
2. Philip AGS, Hewitt JR. Early diagnosis of neonatal sepsis. Pediatrics 1980;65:1036-41.
3. Liu CH, Lehan C, Speer ME, Fernbach DJ, Rudolph AJ. Degenerative changes in neutrophils: an indicator of bacterial infection. Pediatrics 1984;74: 823-7.
4. Pourcyrons M, Bada HS, Korones SB, Baselski V, Wong SP. Significance of serial CRP responses in neonatal infection and other disorders. Pediatrics 1993;92:431-5.
5. Harris MC, Cortarino AT, Sulivan JS, Dulkerian S, Mc Cavky L, Corcoran L. Cytokine elevations in critically ill infants with sepsis and necrotizing enterocolitis. J Pediatr 1994;124:105-11.
6. Schuchat A, Zywichi SS, Dinsmoor M, Mercer B, Romaquera J, O'Sullivan MJ, *et al*. Risk factors and opportunities for prevention of early onset neonatal sepsis: a multicenter case control study. Pediatrics 2000;105:21-6.
7. Gotoff SP. Neonatal sepsis and meningitis. In: Behrman RE, Kliegman RM, Arvin AM, editors. Textbook of pediatrics. 15th ed. Philadelphia: WB Saunders Co; 1996. p. 528-37.
8. Roberton NRC. Bacterial infection in the newborn. In: A manual of neonatal intensive care. 3rd ed. London: Arnold; 1993. p. 196-204.
9. Yu VYH, Monintja HE. Infeksi sistemik pada neonatus. In: Beberapa masalah perawatan intensif neonatus. Jakarta: Balai Penerbit FKUI; 1997. p. 217-30.
10. Oski FA, Naiman JL. Hematologic problems in the newborn. In: Cloherty JP, Stark AN, editors. Manual of neonatal care. 3rd ed. Boston: Little Brown and Co; 1992. p. 727-8.
11. Ehl S, Getting B, Bartmann P, Hogel J, Pohlandt F. C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics 1997;99:216-21.
12. Klein JO, Marcy SM. Bacterial sepsis and meningitis. In: Klein JO, Remington JS, editors. Infectious diseases of the fetus and newborn infant. 3rd ed. Philadelphia: WB Saunders Co; 1990. p. 627-35.

13. Anwer SK, Mustafa S. Rapid identification of neonatal sepsis. J Pakistan Med Ass 2000;50:94-8.
14. Zipursky A, Palku J, Milnner R, Akenzua GI. The hematology of bacterial infections in premature infants. Pediatrics 1976;57:839-53.
15. Sackett DL, Strauss SE, Richarson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone; 2000. p. 35-54.