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Original Article

Diagnostic accuracy of septic markers for neonatal sepsis

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Abstract

Background Neonatal sepsis is a major cause of morbidity and mortality. A positive blood culture is the gold standard for diagnosis of neonatal sepsis. The signs and symptoms suggesting neonatal sepsis are non-specific. There is no rapid and reliable laboratory test findings for confirmation of etiologic diagnosis. Clinical signs, symptoms, and laboratory examinations are not perceived as sensitive or specific for diagnosis of sepsis.

Objective The purpose of this study was to evaluate the accuracy of the septic markers for diagnosis of neonatal sepsis.

Methods Blood culture was used as gold standard to compare septic markers to diagnose neonatal sepsis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio (LR), and accuracy were calculated.

Results We identified 130 cases suspected of neonatal sepsis during September 2005 until March 2006. Four patients were excluded because of major congenital anomalies. The mean age was 2.2 days and 51.6% were boys. We found fifty six (44.4%) neonates have positive blood culture. All of septic markers had sensitivity more than 80%. Immature to Total Neutrophil ratio (I/T) ratio had the highest sensitivity (96.4%) and C-Reactive Protein (CRP) had the lowest sensitivity (80.4%). Combination among leukocyte count, thrombocyte, and I/T ratio had the highest sensitivity (sensitivity was 85.7%, specificity was 97.1%, positive predictive value was 95.9%, negative predictive value was 89.5%, accuracy was 94.4%, and positive likelihood ratio was 30.0).

Conclusion Septic markers can be used in the diagnostic evaluation of neonates with suspected sepsis. **[Paediatr Indones 2008;48:299-305]**.

Keywords: *neonatal sepsis, septic markers, blood culture*

Neonatal sepsis is a disease in less than one month of age infants who are clinically ill and have positive blood cultures.[1] The incidence of neonatal sepsis in developing countries is approximately 10 cases per 1000 live births and as high as 13-27 per 1000 for premature live births. The mortality rate is high (13-50%), and the highest is seen in premature infants.[2-4] The prevalence rates of neonatal sepsis in Sanglah Hospital during the year of 2004 was 5.3% from all of neonates admitted.[5]

The gold standard for diagnosis of bacteremia in suspected neonatal sepsis is a positive blood culture.[6-8] However, the blood culture is an imperfect reference standard because of the required time to obtain result and more importantly, the low sensitivity of

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the culture methods. In one study, data prior to the use of intrapartum therapy indicated that premortem blood culture results were positive merely in 80% of infected infants. Furthermore, blood culture results were negative in up to 50% neonates with a congenital bacterial pneumonia.[8,9] In 1994, Mathur *et al* [10] reported a low positive blood culture (24.9%).

The signs and symptoms suggesting neonatal sepsis are non-specific.[7-9] Clinicians have not found reliable clinical signs for the neonatal sepsis diagnosis. Occasionally, the suspicion of neonatal sepsis is supported by laboratory parameters. However, there are no rapid and reliable laboratory test findings for confirmation of etiologic diagnosis.[11-17] Neonatology Unit of Sanglah Hospital is using septic markers (total leukocyte count, thrombocyte count, CRP, and I/T ratio) for evaluation of sepsis suspected neonates. The purpose of this study was to evaluate the accuracy of septic markers for diagnosis of neonatal sepsis.

Methods

This study analyzed septic markers against blood culture, as a gold standard, and was conducted in the Neonatology Unit of Sanglah Hospital during September 2005 to March 2006. Consecutive neonates diagnosed with suspected sepsis were included. Exclusion criteria were the presence of major congenital anomalies and refusal to participate in this study. Informed consent was obtained from the parents. The protocol of the study was approved by the Hospital Ethics Committee.

Clinical evaluation was performed by doctor on duty. Blood specimen to perform all the necessary laboratory tests were drawn at the time of the initial sepsis evaluation, before the first dose of antimicrobials. Blood culture and complete blood count tests were done at Clinical Laboratory of Sanglah Hospital. Plasma CRP concentration was measured in Quantum Laboratory. All study subjects were treated with appropriate standard treatment.

Age was defined days from birth until the diagnosis of suspected sepsis. Birth weight was measured at birth without clothes using DS Pediatric Examining Table (Atom Medical, Japan) with 10 gram accuracy. Low birth weight (LBW) was defined as birth weight less than 2500 grams. Neonatal sepsis was suspected if there were clinical signs and symptoms or asymptomatic but at least has one major risk factor or two minor risk factors and two abnormal septic marker evaluations.[18] The major factors were maternal prolonged rupture of membranes > 24 hours, intrapartum maternal fever > 38°C, chorioamnionitis, sustained fetal tachycardia > 160 beats/minute.[18] The minor risk factors were maternal prolonged rupture of membranes >12 hours, intrapartum maternal fever >37.5°C, premature infant (gestational age < 37 weeks), twin gestation, baby with very low birth weight (< 1500 gr), low Apgar score (<5 on the 1st minute, < 7 on the 7th minute), foul lochia, and maternal infection of the urinary tract or suspected urinary tract infection without treatment.[18]

Clinical sign of sepsis neonatorum based on:[9] (a) General condition: not doing well, poor fed, hyperthermia, hypothermia, sclerema, edema, (b) Central nervous system: hypotonia, lethargy, seizure, irritable, high pitched cry, (c) Respiratory system: apnea, tachypnea, dyspnea, cyanosis, irregular breathing, (d) Cardiovascular system: tachycardia, bradycardia, clammy, shock, (e) Gastrointestinal system: retention, hepatomegaly, diarrhea, vomiting, meteriomus, (f) Hematology system: icteric, splenomegaly, bleeding tendency. Major congenital anomaly was defined as any alteration of normal anatomic structure, which was present at birth and severe enough to reduce the normal life expectancy or compromise its normal function, e.g., neural tube defect, cleft lip, congenital hydrocephalus, gastroschisis, omphalocele, etc.[20]

Sepsis definition based on laboratory test: positive blood culture result, leukopenia (total leukocyte count <5,000/μL), leukocytosis (total leukocyte count > 30,000/μL), thrombocytopenia (platelet count <150,000/uL), increase of immature to total neutrophil ratio (I/T ratio) >0,2, or increased serum CRP ≥ 6 mg/L.[18,21] Early onset sepsis was defined as the development of neonatal sepsis within the first 3 days (72 hours) of life.[18] Late onset sepsis was defined as the development of neonatal sepsis after the first 3 days (72 hours) of life.[18]

Statistical analysis

We compared the performance of septic markers to the result of blood culture as a gold standard. We calculated the sensitivity, specificity, positive predictive value

(PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR), and accuracy for each septic marker or in combination were calculated. Receiver operating characteristic (ROC) curve analysis was performed using computerized program. All values were supplied with their 95% convidence intervals where applicable.

Results

There were 190 neonates who eligible for the study during September 2005 until March 2006, admitted to Neonatal Unit Sanglah Hospital. After evaluation of clinical manifestation and septic markers, there were 130 newborn infants diagnosed with suspected sepsis. Four infants were excluded because of major congenital anomalies (one with congenital hydrocephalus, one with gastroschizis, and two with omphalocele), leaving 126 babies for analysis.

Clinical characteristics

The mean age for illness onset was 2.14 days, and 51.6% of the subjects were boys. We identified that 56 (44.4%) blood cultures were positive, from the total of 126 neonates with suspected sepsis. The majority of sepsis occurred in low birth weight (60.7%). Whereas, the incidences of sepsis in early onset group and late onset group were 60.8% and 39.2%, respectively. The most common pathogen found on this study was *Coagulase-positive Staphylococci* (50%) (data not shown).

Septic markers

All septic markers had sensitivity of more than 80%. The I/T ratio had the highest sensitivity (96.4%). CRP had the lowest sensitivity and moderate positive likelihood ratio (80.4%). Immature to total neutrophil and combination of thrombocyte count and I/T ratio had the highest likelihood ratios [LR positive was 33.8 (95% CI 8.6;132.4), 60.0 (95% CI 8.6; 42.3), respectively]. Combination among leukocyte count, thrombocyte count, and I/T ratio had the highest sensitivity (85.7%). Using a cut off ≥ 2, the score had a high sensitivity of 85.7% and specificity of 97.1% with 92.1% of accuracy. **Table 1 and 2** show admissions of septic markers values for all study subjects.

By using ROC curve, the cut off points for total leukocyte count, I/T ratio, and thrombocyte count (which had the best sensitivity and specificity) were 4,350 or 35,500, 0.25 and, 100,000, respectively. Area under the ROC curve was 0.89 (95% CI 0.89; 0.99) for CRP, 0.85 (95% CI 0.75; 0.96) for total leukocyte count, 0.93 (95% CI 0.83; 0.97) for thrombocyte count, and 0.89 (95% CI 0.86; 0.99) for I/T ratio (**Data not shown**).

Discussion

Abrupt clinical deterioration of sepsis is a major cause of morbidity and mortality in neonates. In practice, clinical signs and laboratory data have not been perceived as having the adequate sensitivity or specificity for early stages of sepsis. The absence of abnormal laboratory tests however does not exclude infection.[14,17] In order to define better need of antibiotic therapy, there are several tests recommended to diagnose neonatal sepsis.[15,22]

A high sensitivity and high specificity diagnostic marker is desirable in severe disease such as neonatal sepsis. All septic markers in our study showed sensitivity more than 80%, I/T ratio had the highest sensitivity 96.4% and CRP had the lowest sensitivity 80.4%. CRP is synthesized within six to eight hours of exposure to an infective process or tissue damage.[23] The degree of CRP response or rise in serum may be dependent on the amount of tissue damage. CRP levels in healthy full-term and preterm infants may range from 2 to 5 mg/L during the first few days of life. During the neonatal period, an established upper normal CRP level of 10 mg/L has been identified in many studies but other research teams have used upper normal reference levels ranging from 6 to 20 mg/L as cut off levels that indicate the presence of sepsis.[23] As the concentration of CRP increase rather slowly in the initial phase, the sensitivity at the time of sepsis evaluation is 60%. Serial estimation at 24 and 48 hours after onset of illness considerably improves the sensitivity 82% and 84%. The specificity and PPV of CRP ranges from 93% to 100%, thus CRP can be considered specific. The sensitivity, specificity, and positive predictive value of CRP in this study were 80.4%, 88.6%, and 84.9% respectively, with 84.9% accuracy. Our findings confirm the results of

Table 1. Test characteristics for selected septic markers

Septic markers	Sen (%)	Spe (%)	LR (+)	LR (-)	PPV (%)	NPV (%)	Accuracy (%)
WBC	89.3 (79.0 to 95.5)	97.1 (90.9 to 99.5)	31.3 (7.9 to 122.9)	0.11 (0.05 to 0.24)	96.2	91.9	93.7
CRP	80.4 (68.4 to 89.2)	88.6 (79.5 to 94.6)	7.0 (3.6 to13.7)	0.22 (0.13 to 0.38)	84.9	84.9	84.9
I/T ratio	96.4 (88.7 to 99.4)	97.1 (90.9 to 99.5)	33.8 (8.6 to 132.4)	0.04 (0.01 to 0.14)	96.4	97.2	96.8
Platelet count	87.5 (76.8 to 94.4)	92.9 (84.9 to 97.3)	12.3 (5.2 to 28.7)	0.13 (0.07 to 0.27)	90.7	90.3	90.5

Sen indicates sensitivity, Spe = Specificity, LR (+)= Positive likelihood ratio, LR (-)= Negative likelihood ratio, PPV = Positive predictive value, NPV = Negative predictive value

Table 2. Test characteristics for combination of septic markers

Septic markers	Sen (%)	Spe (%)	LR (+)	LR (-)	PPV (%)	NPV (%)	Accuracy (%)
CRP + WBC	78.6 (66.4 to 87.8)	98.6 (93.2 to 99.9)	55.0 (7.8 to 386.9)	0.22 (0.13 to 0.36)	97.8	85.2	89.7
CRP + platelet count	78.6 (66.4 to 87.8)	98.6 (93.2 to 99.9)	55.0 (7.8 to 386.9)	0.22 (0.13 to 0.36)	97.8	85.2	89.7
CRP + I/T ratio	78.6 (66.4 to 87.8)	98.6 (93.2 to 99.9)	55.0 (7.8 to 386.9)	0.22 (0.13 to 0.36)	97.8	85.2	89.7
WBC + platelet count	85.7 (74.7 to 93.1)	97.1 (90.9 to 99.5)	30.0 (7.6 to 118.1)	0.15 (0.08 to 0.28)	95.9	89.5	92.1
WBC + I/T ratio	85.7 (74.7 to 93.1)	97.1 (90.9 to 99.5)	30.0 (7.6 to 118.1)	0.15 (0.08 to 0.28)	95.9	89.5	92.1
WBC + I/T ratio	85.7 (74.7 to 93.1)	98.6 (93.2 to 99.9)	60.0 (8.6 to 42.3)	0.14 (0.08 to 0.28)	97.9	89.6	92.9
CRP + WBC + platelet count	76.8 (64.4 to 86.4)	97.1 (90.9 to 99.5)	26.9 (6.8 to 106.1)	0.24 (0.15 to 0.39)	95.6	83.9	88.1
WBC + platelet count + I/T ratio	85.7 (74.7 to 93.1)	98.6 (93.2 to 99.9)	60.0 (8.6 to 42.3)	0.14 (0.08 to 0.28)	97.9	89.6	92.9
CRP + WBC + I/T ratio	76.8 (64.4 to 86.4)	97.1 (90.9 to 99.5)	26.9 (6.8 to 106.1)	0.24 (0.15 to 0.39)	95.6	83.9	88.1
CRP + WBC + Platelet count + I/T ratio	76.8 (64.4 to 86.4)	97.1 (90.9 to 99.5)	26.9 (6.8 to 106.1)	0.24 (0.15 to 0.39)	95.6	83.9	88.1

Nupponen *et al*[24] and Prayoga[26] whom had reported the sensitivity of CRP were 82% and 79.5%, respectively. Siebert *et al*[26] with the same method but using 10 mg/L for cut off level of CRP concentration had found 63% for sensitivity, 70% for specificity, 13% for positive predictive value, 96% for negative predictive value, and 69% for accuracy. This difference results caused by different cut off level of CRP concentrations. The change in pattern of CRP and normalization of raised concentrations are considered to be useful in monitoring the progress of treatment and for guiding antibiotic treatment.[8,20]

The peripheral total white cell counts is the most frequently used indirect indicator of bacterial infection but are not very helpful in evaluating a baby for suspected sepsis because about one-third of all babies with sepsis have normal leukocyte count and about one-half of those babies evaluated for sepsis who have abnormal leukocyte count are not, in fact, septic.[9] Normal counts range from 9000 to 30,000 cells/μL at the time of birth, and differences in the site of sampling and the activity of the baby can affect this measurement. Neutrophile indices absolute neutrophil count, the absolute band count, and the I/T ratio have proved more useful than total leukocyte counts in the diagnosis of neonatal sepsis.[8] Results of white cell counts varied widely across studies with sensitivity and specificity ranging from 17% to 90% and 31% to 100%.[22] In this study sensitivity of the total leukocyte count was 89.3%, specificity was 97.1%, and accuracy was 93.7%. Philip and Hewitt[27] found sensitivity 93% and specificity 88%. Differences of these result caused by different range of total leukocyte count. Philip AG and Hewitt JR had just used total leukocyte count < 5000 cel/μL and in this study we use < 5000 or > 30,000 cel/μLm for diagnosing neonatal sepsis.

Changes in neutrophil number and appearance are often helpful in the diagnosis of bacterial infections. Increased numbers of immature neutrophils and an elevated immature to total neutrophil ratio are seen in neonates with sepsis. During the first two weeks of life immature to segmented neutrophil ratio greater than 0.2 should be considered abnormal.[12] The immature to total neutrophil ratio of equal to or more than 0.2 has a reported sensitivity 80-90%. The sensitivity of I/T ratio in the present study was 96.4%. Rodwell[28] had been reported the same sensitivity of the I/T ratio (96%) with the same criteria on this study.

Thrombocytopenia is a common finding in septic neonates. About 60% newborns with proven infection become thrombocytopenic with platelet counts of less than 100,000/uL, Incidence of thrombocytopenia on neonatal sepsis become 80% if we use cut off point 150,000/uL. The underlying mechanism is probably a mix of diminished production, increased destruction, and sequestration in enlarge spleen and the major mechanism responsible for thrombocytopenia in neonatal sepsis is accelerated platelet destruction.[8,15] In this study we found 42.9% neonatal sepsis with thrombocytopenia. It is different result from study of Andayani[29] which is found 70% neonatal sepsis with thrombocytopenia in Sanglah Hospital. Low thrombocyte count was often severe and late signs of infection.[22]

Combination two or more of septic markers had the high sensitivity and specificity. In general, the combination of total leukocyte count and an elevated I/T ratio seems to be particularly predictive of neonatal sepsis and tend to have high sensitivity and specificity.[30] In this study, combination between total leukocyte count and an elevated I/T ratio, total leukocyte count and thrombocyte count, I/T ratio and thrombocyte count, total leukocyte count, thrombocyte count, and I/T ratio had 85.7% for sensitivity and 97.1% for specificity. The high specificity of this combination also suggested that only 2.9% only of infants suspected of having an infection were unnecessarily treated with antibiotics. In this study, with prevalence was 44.4% with ≥ 2 abnormal of septic markers, can be helpful as a useful marker for neonatal sepsis.

In summary, we conclude that septic markers as part of the work-up for neonatal sepsis can be helpful as a useful marker for neonatal sepsis.

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Editor's note

Clinicians and researchers worldwide has been struggling to find out the best test or combination of tests for diagnosing neonatal sepsis early and accurately. Many tests have been produced but none gave satisfactory results. This study is controversial since the authors used blood culture as the gold standard, while at the same time they stated that blood culture is not a perfect for gold standard for neonatal sepsis, among others, because blood culture has low sensitivity. Readers are advised to refer this statement when reading the results of this study.