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Original Article

# Diagnostic accuracy of the 2004 Indonesian Pediatric Society medical standard of care for neonatal sepsis

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## Abstract

***Background*** Neonatal sepsis is a leading cause of neonatal morbidity and mortality. There are no pathognomonic signs or symptoms to diagnose neonatal sepsis. Blood culture is the standard tool for sepsis diagnosis, but it is not available in most district hospitals. In 2004, the Indonesian Pediatric Society (IPS) developed a medical standard of care to diagnose neonatal sepsis, but its accuracy has not been adequately verified.

***Objective*** To evaluate the diagnostic accuracy of the IPS medical standard of care 2004 to diagnose neonatal sepsis.

***Methods*** We conducted diagnostic testing at the Perinatal Ward, Dr. Sardjito Hospital, Yogyakarta, from June to November 2010. Inclusion criteria were neonates with signs and symptoms of infection. We excluded neonates with congenital anomalies, blood disorders, or whose mothers received peripartum antibiotic treatment. All neonates were assessed by the 2004 IPS medical standard of care for neonatal sepsis and by blood culture examinations.

***Results*** A total of 193 neonates with signs and symptoms of infection were evaluated. The IPS medical standard had a sensitivity of 88% (95% CI 81 to 94), specificity of 17% (95% CI 2 to 25), positive predictive value of 53% (95% CI 45 to 60), negative predictive value of 57% (95% CI 39 to 75), positive likelihood ratio of 1.06 (95% CI 0.94 to 1.19), and negative likelihood ratio of 0.71 (95% CI 0.36 to 1.42).

***Conclusion*** The 2004 IPS medical standard of care showed adequate sensitivity for diagnosing neonatal sepsis, but its low specificity limits its use as a diagnostic tool. **[Paediatr Indones. 2012;52:86-90]**.

***Keywords****: diagnostic test, 2004 IPS medical standard of care, neonatal sepsis*

The prevalence of neonatal sepsis cases admitted to neonatal wards is high. In developing countries, sepsis is the most common cause of morbidity and mortality in the neonatal period.[1] The prevalence of neonatal sepsis in some referral hospitals has ranged from 8.8% to 30.3%, with mortality of 11.5% to 49.9%. Early diagnosis of neonatal sepsis is important especially since its prognosis is determined by prompt identification and treatment.[2] There is no pathognomonic sign or symptom for neonatal sepsis, thus making clinical diagnosis of neonatal septicemia difficult.[1,3]

The standard of neonatal sepsis diagnosis is blood culture. However, blood culture takes time, is costly, and is not always available in some health facilities.[3] In 2004, the IPS proposed a medical standard of care to diagnose neonatal sepsis. However, its level of accuracy has not been adequately tested.

The aim of this study was to evaluate the accuracy of clinical diagnosis of neonatal sepsis using the 2004 IPS medical standard of care.

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## Methods

We conducted this study to determine the accuracy of clinical diagnosis for neonatal sepsis using the 2004 IPS medical standard of care. Subjects were neonates admitted to the Perinatal Ward of Dr. Sardjito Hospital, Yogyakarta, Indonesia, from June to November 2010. Inclusion criteria were (1) neonates with signs and symptoms of infection, such as "not doing well", poor feeding, weak sucking, lethargy, hyper- or hypothermia, shortness of breath, vomiting, or diarrhea, (2) had no previous antibiotic treatment, and (3) had a parent/guardian consent to participate in the study. We excluded neonates with (1) congenital anomaly, (2) surgical problems, or (3) maternal peripartum antibiotic treatment.

The 2004 IPS medical standard of care for neonatal sepsis consisted of two categories, A and B. Great suspicion for neonatal sepsis was based on ≥ 2 positive findings in category A: difficulty breathing, shortness of breath, seizure, lack of conciousness, temperature instability, delivery process that is not sterile, and deteriorating condition. Likewise, ≥ 3 positive findings in category B indicated neonatal sepsis: lethargy, reduced activity, irritability, vomiting, bloating, signs appearing after the 4th day of life, meconium-stained amniotic fluid, and poor feeding.

Data was collected on the baseline characteristics of subjects, including sex, age, gestational age, birth weight, maternal illness during pregnancy, presence of peripartum fever, and color of amniotic fluid. Age was defined as days between birth and the date of septic appearance. Gestational age was defined as completed weeks between the first day of the mother's last menstrual period and the delivery time. Birth weights were categorized as extremely low birth weight (less than 1000g), very low birth weight (1000g to 1499g), low birth weight (1500g to 2499g), normal birth weight (2500g to 3999g), and high birth weight (more than 4000g).

Maternal illness during pregnancy was defined as gestational diabetes mellitus if there had been any degree of blood glucose intolerance with onset or first recognition during pregnancy. Hypertension was defined as diastolic blood pressure of 90 mmHg or more, while preeclampsia was defined as new hypertension and significant proteinuria at or after 20 weeks of pregnancy, that was confirmed with resolution following delivery. Eclampsia was considered to be new onset grand mal seizure and/or unexplained coma during pregnancy or the postpartum period in a mother with preeclampsia. Peripartum fever was defined as maternal fever > 38°C during labor. Amniotic fluid color was confirmed from history-taking as to whether it was clear, yellowish, turbid, and/or green or brown.

This study involved two pediatric residents conducting tests in 25 neonates to assess the interobserver agreement of sepsis based on the 2004 IPS medical standard of care. A Kappa test result was 0.75 (P=0.02, Fisher's exact test).[4,5]

**Table 1**. Baseline characteristics of subjects

| Characteristics | |
|---|---|
| Sex, n (%) | |
| Male | 124 (64.2) |
| Female | 69 (35.8) |
| Gestational age, n (%) | |
| <37 weeks | 79 (40.9) |
| 37-42 weeks | 113 (58.5) |
| >42 weeks | 1 (0.5) |
| Median Apgar score | |
| 1 minutes | 6 |
| 5 minutes | 8 |
| Birth weight, n (%) | |
| <1000 grams | 5 (2.6) |
| 1000-1499 grams | 27 (14.0) |
| 1500-2499 grams | 65 (33.7) |
| 2500-3999 grams | 93 (48.2) |
| >4000 grams | 3 (1.6) |
| Maternal illness during pregnancy, n (%) | |
| No illness | 154 (79.8) |
| Gestational diabetes mellitus | 2 (1.0) |
| Hypertension | 5 (2.6) |
| Preeclampsia/eclampsia | 20 (10.4) |
| Other | 12 (6.2) |
| Rupture of the membrane before labor, n (%) | |
| <18 hours | 179 (92.7) |
| ≥18 hours | 14 (7.3) |
| Peripartum fever, n (%) | |
| Yes | 1 (0.5) |
| No | 192 (99.5) |
| Color of the amniotic fluid, n (%) | |
| Clear | 164 (85.0) |
| Turbid | 29 (15.0) |
| Type of delivery, n (%) | |
| Spontaneous | 115 (59.6) |
| Vacuum extraction | 9 (4.7) |
| Breech presentation | 1 (0.5) |
| Cesarean section | 68 (35.2) |
| Condition at discharge, n (%) | |
| Eligible for discharge | 160 (82.9) |
| Died | 28 (14.5) |
| Discharged against medical advice | 5 (2.6) |

Sample size was estimated using formula based on the average prevalence of neonatal sepsis in Dr. Sardjito Hospital (14%), with $\alpha=0.05$ and $d=0.15$. The estimated minimum sample size required was 192.

Blood cultures of all neonates included in the study were examined by the BacT/Alert® microbial detecting system. Data was analyzed for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio ($LR^+$), and negative likelihood ratio ($LR^-$) using *CATmaker* for Windows from Centre for Evidence Based Medicine, University of Oxford.

## Results

The characteristics of 193 neonates included in this study are shown in **Table 1**. Blood cultures were positive in 99 subjects (51.3%).

**Table 2.** Sepsis diagnosis based on 2004 IPS medical standard of care measured against blood culture results

| Diagnosis of IPS medical standard of care 2004 | Blood culture | |
|---|---|---|
| | Positive | Negative |
| Sepsis (+), n | 87 | 78 |
| Sepsis (-), n | 12 | 16 |
| Total | 99 | 94 |

**Table 3.** Accuracy of clinical diagnosis for neonatal sepsis

| | Value | 95% CI |
|---|---|---|
| Sensitivity, % | 88 | 81 to 94 |
| Specificity, % | 17 | 9 to 25 |
| Positive predictive value, % | 53 | 45 to 60 |
| Negative predictive value, % | 57 | 39 to 75 |
| Positive likelihood ratio | 1.06 | 0.94 to 1.19 |
| Negative likelihood ratio | 0.71 | 0.36 to 1.42 |

Common clinical manifestations observed were hypo- or hyperthermia (87.0%), reduced activity (70.5%), vomiting (68.4%), deteriorating condition (45.1%), ill-looking appearance (41.5%), dyspnea (31.1%), poor feeding (28.5%), and lethargy (24.9%).

**Table 2** shows clinical neonatal sepsis cases compared to blood culture results. **Table 3** shows the diagnostic test of the IPS medical standard of care based on blood culture results. The types of bacteria identified on positive cultures are shown in **Table 4**. Sepsis caused by coagulase-negative staphylococci and *Klebsiella pneumoniae* contributed to more than 50% of the positive cultures.

## Discussion

Upon analysis of the 2004 IPS medical standard of care compared to blood culture for diagnosing neonatal sepsis, we found a sensitivity of 88% (95% CI 81 to 94). This sensitivity is quite adequate for the screening of neonatal sepsis, since only 12% will be false negatives. High sensitivity for an acute and serious illness is of value to start immediate treatment before it is too late, such as in cases of neonatal sepsis.[6-9]

However, we found the specificity of the IPS medical standard of care to be as low as 17%. Low specificity may lead to identifying many false positives, so that a substantial proportion of non-septic neonates would be diagnosed as septic and receive unnecessary antibiotics.[7-10]

When applied to the normogram curve of *Bayes' theorem* using the prevalence (pretest probability, 51%) and likelihood ratio (1.06) in our study, we calculated

**Table 4.** Bacterial species found in blood cultures

| Bacteria | Early onset sepsis (Age<72 h), n | Late onset sepsis (Age ≥ 72 h), n | Total, n (%) |
|---|---|---|---|
| Coagulase-negative staphylococci (CONS) | 18 | 16 | 34 (31.2) |
| Klebsiella pneumoniae | 14 | 9 | 23 (21.1) |
| Pseudomonas aeruginosa | 14 | 5 | 19 (17.4) |
| Klebsiella oxytoca | 8 | 5 | 13 (11.9) |
| Streptococcus fecalis | 4 | 2 | 6 (5.5) |
| Escherichia coli | 2 | 1 | 3 (2.8) |
| Acinetobacter calcoacea | 1 | 2 | 3 (2.8) |
| Enterobacter aerogenes | 2 | 1 | 3 (2.8) |
| Serratia marcescens | - | 1 | 1(0.9) |
| Staphylococcus aureus | - | 1 | 1 (0.9) |
| Klebsiella sp | 2 | 1 | 3 (2.8) |

a posttest probability of 52%. Given that the increase in the post-test probability was deemed too low to be clinically significant, further tests are needed.[11-13]

Since treatment for neonatal sepsis, i.e. antibiotics, has little chance of causing serious harm to neonates as opposed to missing cases of neonatal sepsis which might be fatal, clinicians would rather take the chance of overtreatment. The low specificity of the 2004 IPS medical standard of care for neonatal sepsis observed in this study necessitates the addition of further tests to exclude infection. Simple laboratory tests have been reported to be of clinical importance in the decision of whether it is safe to withhold or discontinue antibiotic therapy, such as total WBC <5000/$\mu$L (specificity 91%, NPV 91%), platelet count <150.000/ $\mu$L (specificity 82-99%, NPV 93%), IT ratio (ratio of immature forms over total neutrophil count) > 0.2 (specificity 50-78%, NPV 99-100%), and WBC vacuolization or toxic granulation (specificity 90-93%, NPV 96-98%).[14]

We found 51.3% of our subjects had positive cultures. Two Indonesian studies in two hospitals reported that positive blood cultures were observed in 58.5% of cultures in Cipto Mangunkusumo Hospital and in 83.3% of cultures in Soetomo Hospital. Other hospitals observed various levels of positivity, ranging from 30-74%.[1-3,15-17]

Bacterial species found in our subjects were mostly gram-negative microorganisms (62.5%), affecting both early and late onset of sepsis. These findings were similar to that of other observations.[18-20]

Factors that might cause a negative culture result in the presence of sepsis include peripartum maternal antibiotic therapy, previous antibiotic treatment of the neonate, organisms requiring a specific methods to isolate (e.g. anaerobes), and sampling errors, i.e., small sample volumes (less than 0.5 ml), inappropriate site drawings and/or methods of blood sampling.[3,20]

The 2004 IPS medical standard of care showed high sensitivity in our study. This protocol is expected to be a reference for early clinical diagnosis of neonatal sepsis, since it is economical and can be done by a good history-taking and physical examination, especially in areas with limited resources. It was hoped that it will improve the prognosis of neonatal sepsis cases. However, without addition of further investigations or tests, it has low specificity, and is limited in its use as a diagnostic tool. Protocol revision needs to be done now that it is 7 years following its establishment. Further research involving a larger spectrum of patients, such as patients in district hospitals, with limited laboratory facilities, is needed.

We suggest adding simple laboratory examinations to the criteria of the 2004 IPS medical standard of care to improve its diagnostic accuracy, e.g., total leukocyte count less than 5000/$\mu$L or IT ratio > 0.2.[14]

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