

# Calculator and Prediction Score for Early-onset Neonatal Sepsis in Asymptomatic Term Infant: A Determinant Model

Toto Wisnu Hendarto (✉ [twisnuh@gmail.com](mailto:twisnuh@gmail.com))

Harapan Kita Maternal and Child Hospital Jakarta

**Sri Rezeki Hadinegoro**

Faculty of Medicine, Universitas Indonesia

**Anis Karuniawati**

Faculty of Medicine, Universitas Indonesia

**Abdurachman Sukadi**

Faculty of Medicine, Padjajaran University

**Alison Kesson**

Children Hospital at Westmead and Discipline of Child and Adolescent Health and Marie Bashir Institute, University of Sydney, New South Wales, Australia

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## Research article

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# Abstract

Background Risk estimation of early-onset neonatal sepsis (EONS) in asymptomatic term infants is sometimes considered less often among clinician. The cumulative case number is large and we aimed to develop a calculator and scoring system as a determinant model of early onset neonatal sepsis (EONS) in asymptomatic term infants with premature rupture of the membranes (PROM) by combining maternal factors and umbilical cord blood examination to guide more targeted antimicrobial therapy. Method This is a cross-sectional study involving infants born to mothers with premature rupture of the membranes for > 12 hours who are term and asymptomatic. We investigated the maternal clinical status, maternal blood and urine examination and infant cord blood examination. Independent predictors were identified by using bivariate and multivariable analysis, then developed into a calculator and scoring system with ideal and optimal cut-off. Result A total of 334 infants with PROM were involved in this study with 62 diagnosed with EONS. The overall incidence in all term births of culture-proven EONS was 4.6 per 1,000 live births. Independent predictors were vaginal birth (OR 2.39; 95%CI 1.19, 4.80), foul-smelling amniotic fluid (OR 1.93; 95%CI 1.01 -3.70), maternal blood WBC > 15,000/mm<sup>3</sup> (OR 2.01; 95%CI 1.09-3.73), cord blood WBC > 15,000/mm<sup>3</sup> (OR 1.84; 95%CI 1.01-3.39), cord blood C-reactive protein (CRP) > 0.15 mg/L (OR 1.16; 95%CI 1.01-1.33), and cord blood interleukin-6 (IL-6) > 10 ng/L (OR 5.38; 95%CI 2.88-10.04). We developed two models: IndEONS 1 (with IL-6) and IndEONS 2 (without IL-6), both in the form of a calculator and scoring system. All models have good performance with consistent validity. The result was infant stratification into low, medium, or high EONS risk each with a corresponding management recommendation. Only high risk infants should get empirical antibiotics. Conclusion A new calculator and scoring system are a useful tool to quantify EONS risk among asymptomatic term infants.

## Background

Early-onset neonatal sepsis (EONS) is defined as neonatal sepsis occurring in the first 72 hours of life. EONS contributed to 11.5 – 49.9% of all neonatal mortality.<sup>1</sup> Most of the EONS cases are acquired vertically through maternal-fetal transmission so that intra-amniotic infection is the main risk factor.<sup>2</sup> The most common etiology in the USA is Group B Streptococcus (GBS, *Streptococcus agalactiae*), but recent trends show an increasing isolation of non-GBS pathogen, such as *Klebsiella* sp. and *E. coli*, especially in developing countries.<sup>3</sup>

Rapid diagnosis is the biggest challenge as no parameter is 100% sensitive and 100% specific for prediction of EONS, even a blood culture.<sup>3</sup> Infant blood inflammatory markers have low sensitivity in the first hours of life, while a delay in initiating treatment could be fatal. Therefore, many clinicians tend to start empiric antibiotics without strong evidence of EONS. This practice is found in 30-100% of cases<sup>4</sup> and is against the principles of antibiotic stewardship and could lead to the development of antibiotic resistance in the future.

In 2011, Escobar et al established a neonatal sepsis calculator (Kaiser calculator) a breakthrough in the field of neonatology<sup>5</sup> with good results.<sup>6,7</sup> However, new problems emerged as many countries do not

have the exact EONS incidence number nor maternal GBS screening programs, which are criteria in the Kaiser calculator. Therefore, the ability of the Kaiser calculator to predict EONS (and support optimal patient care and antibiotic stewardship) could be potentially underestimated or overestimated.

Asymptomatic term infants are a segment of the population of newborns which should also be considered, especially because EONS may be missed after hospital discharge. Although, in a study from the United States, the incidence is less than 1 per 1,000 live births, the cumulative case number is large often with long-term neurological sequelae in approximately 50%.<sup>8</sup> Recent studies support the use of umbilical cord blood inflammatory markers and cord blood culture as promising diagnostic tools for detection of EONS,<sup>9</sup> but no studies have developed a predictive scoring system. Therefore, we aimed to develop a calculator and scoring system as a determinant model by combining maternal factors and umbilical cord blood examination in order to guide clinicians to accurately diagnose and manage EONS in asymptomatic term infants.

## Methods

We conducted an observational cross-sectional study of term infants born to mothers with premature rupture of membrane (PROM) >12 hours who were asymptomatic. We choose PROM >12 hours as a risk factors for chorioamnionitis since previous studies reported no significant difference in EONS compared with PROM of >18 hours.<sup>2,5</sup> Exclusion criteria were infants with congenital abnormalities, including congenital heart disease and those who were unable to be followed for 72 hours of life. Sampling was begun in February 2013 until May 2014 in three hospitals in Jakarta, Indonesia with level III and IV neonatal care (Harapan Kita Women and Children Hospital, Budi Kemuliaan Maternity and Children Hospital, and Tarakan General Hospital).

We grouped predictors of EONS into clinical and laboratory determinants. Clinical determinants were mode of delivery, infant gender and clinical sign of intra-amniotic infection (maternal fever > 37.8°C, uterine tenderness, maternal tachycardia, fetal tachycardia and foul-smelling amniotic fluid). For laboratory determinants, we investigated a urinary tract infection marker, maternal urine white blood cells (WBC) and an intra-amniotic infection marker (maternal blood WBC, cord blood WBC, cord blood neutrophil count, cord blood high-sensitivity C-reactive protein (hs-CRP), cord blood neutrophil immature-to-total (I:T) ratio, and cord blood interleukin-6 (IL-6). All patients had a 5 mL volume of umbilical cord blood drawn immediately after delivery. The cord blood culture was performed using the BacTec culture system. Cut-off values of each laboratory determinant were based on previous studies<sup>10,11</sup>, except for cord blood leukocyte, neutrophil, I:T ratio, hs-CRP and IL-6. We used the highest sensitivity and specificity according to area under the curve (AUC) of a receiver operator characteristic (ROC) curve from our study for those variables. Diagnosis of EONS was made based on clinical examination and positive cord blood culture result.

### *Laboratory testing*

Blood cultures were collected into BacTec blood culture bottles and incubated at 37°C for up to 6 days. Positive blood cultures were Gram stained and sub-cultured onto blood agar and MacConkey agar. The agar plates were incubated at 37°C with MacConkey plates in air and blood agar in 5% CO<sub>2</sub>. Individual colonies were then identified and antibiotic sensitivities performed.

### *Data analysis*

Subject characteristics were presented as number and percentage for categorical data and median and range (5<sup>th</sup> to 95<sup>th</sup> percentile) for numerical data. Bivariate analysis using Chi-square for categorical data or t-test for numerical data were done between each determinant and EONS diagnosis as the dependent outcome. Variables with p-value < 0.25 were defined as a significant predictor and thus included in a multivariable analysis. We used a logistic regression model to find independent determinants of EONS.

Finally, a scoring system was developed by converting each variable's coefficient result from backward stepwise multiple logistic regression analysis into an integer. The decision whether to include or exclude a variable in the regression analysis was based on clinical and statistical judgment. The final score was categorized into three main categories based on the ideal (best sensitivity-specificity) and optimal (highest specificity) cut off point. Sepsis probability was formulated as  $p = 1 / \{1 + \exp(-y)\}$ .

We did a calibration by using the Hosmer-Lemeshow goodness-of-fit test and discrimination using c-statistics ROC curve analysis to assess the scoring system performance. A two-sided p-value below 0.05 was considered significant. Internal validation was done by comparing both calibration and discrimination test result to 50% of randomly chosen data from the original data set. External validity was assessed using this final scoring system for 24 infants after the end of this study period. All tests were done in SPSS 14 for Windows.

## **Results**

From 410 asymptomatic term infants with PROM > 12 hours born during the study period, 334 infant met the criteria for inclusion in this study (81.5%). 63.8% of infants were born via vaginal delivery, 54.8% were male, and 55.4% had a history of fetal tachycardia. The summary of the subject's characteristics is shown in Table 1. Positive culture results were found in 62 out of 334 infants supporting the diagnosis of EONS and giving an incidence of 185 per 1,000 live term births with PROM compared with a diagnosed EONS incidence of 4.7 per 1000 of all live births (with and without PROM) during the study period. This demonstrates that PROM is a significant risk factor for EONS. The most common etiology were *Escherichia coli* (22%) and *Staphylococcus aureus* (9%).

The bivariate analysis among clinical and laboratory determinants are present in Table 2. We found eight variables that have significant p-values and/or odds ratio (OR). Although statistically not significant, intrapartum fever and maternal tachycardia were included in the multivariable analysis due to their clinical importance according to the CDC 2002 guidelines on neonatal sepsis management.<sup>12</sup>

Multivariable analysis, using multiple logistic regression, was performed to assess the independence of each variable to EONS. We found vaginal birth, foul-smelling amniotic fluid, maternal blood WBC  $\geq 15.000/\text{mm}^3$ , cord blood WBC  $\geq 15.000/\text{mm}^3$ , cord blood CRP (both the numerical value and  $\geq 0.15$  mg/L), and cord blood IL-6 (both the numerical value and  $\geq 10$  ng/L) as independent predictors of EONS in asymptomatic term infant, shown in Table 3.

### *Model development and performance analysis*

We developed a calculator for categorical-numerical data output and a scoring system for categorical data output. The final products are IndEONS (*Indonesia determinant for early-onset neonatal sepsis*) calculator and score. Both have two sub-models: IndEONS 1 calculator/score (complete version) and IndEONS 2 calculator/score (alternative version, excluding IL-6 from the regression) (Table 4). The IndEONS 2 model is suitable for clinicians working in neonatal care with limited resources. The score was calculated by dividing the coefficient/standard error (B/SE) ratio of each variable to the smallest B/SE ratio and rounded to the nearest integer. The model development is presented in Table 5. The regression equation is shown in Appendix 1. The final calculator was made using Microsoft Access and will soon be accessible on the internet. The final scoring system is presented in Table 5.

Cut-off values of this prediction score were based on optimal and ideal cut-offs. The probabilities of EONS for each score in both models are also shown in Table 6. This predictive performance is consistent during internal validation with Hosmer-Lemeshow  $p = 0.836, 0.443, 0.488, 0.827$  and c-statistics AUC =  $0.754$  (95% CI  $0.664 - 0.844$ ),  $0.752$  (95% CI  $0.657 - 0.846$ ),  $0.816$  (95% CI  $0.740 - 0.892$ ) and  $0.743$  (95% CI  $0.656 - 0.831$ ) for IndEONS 1 and 2 calculator and IndEONS 1 and 2 score, respectively. External validity from 24 new cases showed a good result with 95.8% specificity and 100% negative predictive value.

## **Discussion**

This is the first calculator and scoring system to guide early diagnosis of EONS in asymptomatic term infants by using a combination of maternal factors and umbilical cord blood analysis. Besides the being the highest proportion of infants in the clinical settings, the term infant population was chosen in order to avoid the confounding effect of immature adaptive immunity in preterm infants.<sup>13</sup> The incidence of proven EONS in this study was 18.5% of infants born to mother with PROM, while the global EONS incidence is 2.2 – 9.8 per 1,000 live birth.<sup>14</sup>

There have been few studies of EONS in asymptomatic infants born after PROM. According to CDC 2002 guidelines<sup>12</sup>, asymptomatic term infants born after PROM should be observed in the first 48 hours to detect any clinical sign of EONS. The decision to start antibiotics should then be supported by septic screening results.<sup>12</sup> Yet, no consensus was agreed for infants born to mothers with unknown GBS status. In addition, the most common etiology of EONS cases which occur in developing countries are Gram negatives such as *E. coli* or *Klebsiella* sp. rather than GBS which would be evident on both the sub-

cultured blood and MacConkey agar plates.<sup>3, 15</sup> The establishment of this calculator and scoring system would give additional valuable evidence for clinicians to consider when to start antibiotics in well-appearing newborns.

Vaginal birth and foul-smelling amniotic fluid are well known independent risk factors for EONS.<sup>15</sup> Consistent with previous studies, elevated maternal and cord blood WBC is also an accurate laboratory parameter of EONS in this study.<sup>16</sup> However, in contradiction, our study found that cord neutrophil count was not a predictor of EONS. This may be because the neutrophil count can fall significantly in severe sepsis so it is hard to interpret and therefore has low diagnostic prediction.<sup>17</sup> We do not consider the history of intrapartum antibiotic administration as a protective factor since it is done routinely in less than 25% of low and middle income countries as there is no GBS screening performed.<sup>18</sup>

Recent studies showed that the use of umbilical cord blood examination is a promising diagnostic tools in EONS diagnosis. Cord blood culture has comparable organism detection to peripheral venous blood culture.<sup>19</sup> The sensitivity of cord blood culture is 80-100% and specificity is 91-94%, while the positive and negative predictive value are 33-72% and 94-100%, respectively.<sup>19, 20</sup> It is less invasive and painful, easier to perform, and a larger volume of blood is available compared with peripheral blood cultures. A good technique will reduce the risk of contamination.<sup>21</sup>

We found that umbilical cord blood infection markers played an important role in predicting EONS. The median of hs-CRP in this study was lower than previous studies.<sup>22</sup> but still is a significant predictor as it accurately reflects an inflammatory process in the placenta.<sup>23</sup> This study also investigated IL-6 as a specific independent cytokine that arises in the early choriovasculitis and funisitis stages of chorioamnionitis. We found that IL-6 was a strong predictor of EONS which is consistent with the result of a previous systematic review.<sup>24</sup> It identified 12 out of the 31 patients in the IndEONS 1 model. Since measuring IL-6 requires an advanced laboratory we excluded IL-6 in our second model (IndEONS 2) so that clinicians in resource limited neonatal care settings could still use this scoring system, albeit the simplified one.

We provide two models for clinicians with different resource settings. Both models have good discrimination and calibration performance and have been validated internally and externally. In advanced neonatal care, IndEONS 1 is a good prediction tools to estimate the possibility of EONS in asymptomatic term infants with PROM. This would optimize the role of umbilical cord blood examination, mainly hs-CRP and IL-6, in clinical practice. Umbilical cord blood examination has now become a routine practice in developing countries. IndEONS 2 score, with a quite similar performance, is provided to help clinicians in resource limited settings. With two cut-off values, we expect no potentially fatal cases would be missed. The performance between calculator and scoring system is comparable. While the IndEONS score is practically easier to use, the IndEONS calculator provides more precision.

Strict criteria were made in our model in order to enforce antibiotic stewardship. The first cut-off (optimal cut-off), with the highest diagnostic performance based on AUC, would only exclude samples with the

lowest possibility of predicting EONS. Infants with this criteria could immediately be discharged from the newborn nursery to have rooming-in with their mothers. On the other hand, a second cut-off (ideal cut-off), would include those infants most likely to have EONS to receive antibiotics and have rigorous vital sign monitoring. These tight criteria are not expected to overestimate a diagnosis of EONS which has then been proven in internal and external validity analysis.

The utilization of these scoring systems among infants born without prior cord blood collection is the main limitation. Another possible limitation is the routine practice of cord blood examination. Physicians should be encouraged to routinely do this examination since it has proven to be a more reliable predictor of EONS than peripheral venous blood examination.

We recommend the IndEONS calculator as it would present the probability of EONS and risk stratification after the physician had input all the data. Meanwhile, physicians could directly interpret the final score if using the IndEONS score. We recommend that low risk infants should have essential newborn care and rooming-in with the mother so that they do not experience a delay of early breastfeeding. Medium risk infants should have close observation in a neonatal nursery without antibiotic administration, but we suggest a blood culture. Antibiotics could be started if any clinical deterioration occurs or if the blood culture becomes positive. High risk infants should have immediate empirical antibiotic administration. We recommend a complete septic workup before antibiotic administration and rigorous monitoring of vital signs. Transfer to a higher care and consultation with a neonatologist should also be considered. We suggest another research group conduct a prospective multicenter study in order to test and external validity of our models. A comparison study to CDC guidelines or the Kaiser calculator should also be done in the future.

## **Conclusion**

A calculator and scoring system based on maternal factors and combination of maternal and umbilical cord blood laboratory examination are useful tools to quantify the risk of EONS among asymptomatic term infants born after PROM. Optimization of umbilical cord blood examination increase the diagnostic performance as its changes reflect the early stages of inflammation in EONS pathogenesis. This system would benefit clinical practice in a neonatal center without knowledge of EONS incidence and no routine GBS screening protocol.

## **Declarations**

### **Ethics approval and consent to participate**

This study has been approved by Ethical Committee Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia (number 620/H2.F1/ETIK/2012). This study follows the Declaration of Helsinki. Written informed consent was obtained from every participant parent.

### **Consent for publication**

Not applicable

### **Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

### **Competing interests**

The authors declare that they have no competing interests

### **Funding**

The authors declare no funding from third parties during this research

### **Authors' contributions**

This study design was mainly proposed by TWH with strong discussion with SRH, A, and AK<sub>1</sub>. TWH collect primary data from patients. TWH analyzed and interpreted the patient data regarding the sepsis status and its determinant factors. TWH, SRH, A, AK<sub>1</sub> and AK<sub>2</sub> interpret data, conduct analysis and develop calculator and scoring system. TWH and AK<sub>2</sub> was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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### **Authors' information (optional)**

TWH is a senior neonatology consultant in Indonesia, currently as head of neonatology working group, Indonesian Pediatric Society. TWH also contribute in making several clinical pathways and guideline in neonatology area in Indonesia.

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## Appendix 1

Sepsis probability =  $1 / \{1 + \exp(-y)\}$

y value for each model:

IndEONS calculator 1:

$y = -3.471 + 0.659 (\text{vaginal birth}^*) + 0.447 (\text{foul-smelling amniotic fluid}^*) + 0.852 (\text{maternal WBC} \geq 15.000/\text{mm}^3)^* + 0.851 (\text{cord blood WBC} \geq 15.000/\text{mm}^3)^* + 0.157 (\text{CRP value in mg/L}^{\uparrow}) + 0.005 (\text{IL-6 value in ng/L}^{\uparrow})$

IndEONS calculator 2:

$y = -2.920 + 0.528 (\text{vaginal birth}^*) + 0.481 (\text{foul-smelling amniotic fluid}^*) + 0.791 (\text{maternal WBC} \geq 15.000/\text{mm}^3)^* + 0.709 (\text{cord blood WBC} \geq 15.000/\text{mm}^3)^* + 0.178 (\text{CRP value in mg/L}^{\uparrow})$

IndEONS score 1:

$y = 3.656 + 0.425 (\text{vaginal birth}^*) + 0.834 (\text{foul-smelling amniotic fluid}^*) + 0.663 (\text{maternal WBC} \geq 15.000/\text{mm}^3)^* + 0.537 (\text{cord blood WBC} \geq 15.000/\text{mm}^3)^* + 0.13 (\text{CRP} \geq 0.15 \text{ mg/L}^*) + 1.601 (\text{IL-6} \geq \text{ng/L}^*)$

IndEONS score 2:

$y = -3.079 + 0.674 (\text{vaginal birth}^*) + 0.594 (\text{foul-smelling amniotic fluid}^*) + 0.772 (\text{maternal WBC} \geq 15.000/\text{mm}^3)^* + 0.591 (\text{cord blood WBC} \geq 15.000/\text{mm}^3)^* + 0.533 (\text{CRP} \geq 0.15 \text{ mg/L}^*)$

Note:

\*if yes = 1, otherwise 0

¶ fill by its continuous data

## Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

## Supplementary Files

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