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Original Article

# Clinical Risk Factors for Early-Onset Sepsis in Neonates: An International Delphi Study

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## Abstract

**Background:** Despite growing evidence, there is still uncertainty about potentially modifiable risk factors for neonatal early-onset sepsis (EOS). This study aimed to identify potential clinical risk factors for EOS based on a literature review and expert opinions.

**Methods:** A literature search was conducted in PubMed (MEDLINE), Cochrane, Embase, and Scopus databases. Articles in English, published up to May 2021, on clinical risk factors for neonatal EOS were included. Initially, a questionnaire on risk factors for EOS was developed and validated. The fuzzy Delphi method (FDM) was used to formulate the final version of the questionnaire. The validity of the risk factors was assessed using the Chi square test. $P<0.05$ was considered statistically significant.

**Results:** In the review phase, 30 risk factors were approved by two neonatologists and included in the FDM phase. In total, 25 risk factors met the consensus criteria and entered the validation phase. During the observational study, 114 neonates (31 with and 83 without EOS) were evaluated for two months. The results of the Chi square test showed that cesarean section was not a significant risk factor for EOS ($P=0.862$). The need for mechanical ventilation and feed intolerance was observed in about 70% of neonates with EOS, and therefore considered significant risk factors for EOS ($P<0.001$). Finally, 26 potential clinical risk factors were determined.

**Conclusion:** Neonatal-related risk factors for EOS were birth weight, one-min Apgar score, and prematurity. Maternal-related risk factors were gestational age and urinary tract infection. Delivery-related risk factors were premature rupture of membranes, chorioamnionitis, and intrapartum fever.

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**Keywords** ● Neonatal sepsis ● Risk factors ● Infections ● Infant ● Newborn

## What's Known

- Understanding clinical risk factors for early-onset sepsis (EOS) is important to devise effective strategies for neonates at high risk of sepsis.
- Despite growing evidence, there is still uncertainty about potentially modifiable risk factors common to neonatal EOS.

## What's New

- A set of clinical risk factors is developed for the diagnosis of EOS within the first few hours after birth.
- Neonatal-related risk factors were birth weight, one-min Apgar score, and prematurity. Maternal-related risk factors were gestational age and urinary tract infection. Delivery-related risk factors were premature rupture of membranes, chorioamnionitis, and intrapartum fever.

## Introduction

Neonatal sepsis is a major global health concern and the main cause of morbidity and mortality in newborns. Annually, 2,000 neonates die in the United States due to sepsis during the first month of life, most of which occur within the first week.[1] However, even those that survive may develop life-threatening complications. Sepsis within the first three days (72 h) after birth is defined as early-onset sepsis (EOS), which is difficult to diagnose early.[2, 3] Antimicrobial therapy and supportive care are the only effective treatments for

sepsis. The reproducibility and positive predictive value of diagnostic tests are not optimal, resulting in a low clinical suspicion index and increased empiric antimicrobial treatment. Although clinical suspicion is important to diagnose sepsis, some studies reported that only about 9% of blood cultures are positive for pathogenic bacteria.[1, 3] Another study reported this percentage at 30%-40%.[4] Understanding the risk factors for neonates at high risk of sepsis is essential to devise effective strategies for early-stage diagnosis. Despite growing evidence, there is still uncertainty about potentially modifiable risk factors common in neonatal EOS. A guideline for the management of neonates with EOS risk factors was published in August 2012, and updated in April 2021, by the National Institute for Health and Clinical Excellence (NICE).[2] NICE introduced a strategy for early diagnosis of neonatal sepsis based on 26 risk factors and clinical indicators. In addition, in 2010, the Centers for Disease Control and Prevention (CDC) published a guideline concerning the prevention of perinatal group B streptococcal disease.[5] The CDC guideline defined 11 risk factors for neonatal sepsis.

Among the methods used to collect and distill expert opinions, the Delphi method is regarded as the best approach, since it allows participating experts to reach a consensus on important features of issues under investigation. It is an iterative process based on data collection and analysis techniques. It includes two or more rounds of questionnaires and is interspersed with a feedback mechanism.[6] However, the traditional Delphi method has certain shortcomings, e.g., vagueness, ambiguity, and uncertainty in the decision-making dataset. These limitations lead to low convergence in retrieving results and a potential loss of important information. To overcome these, the traditional Delphi method is combined with the fuzzy set theory,[7] called the fuzzy Delphi method (FDM).[6]

Unlike a recent study that reviewed risk factors for both EOS and late-onset sepsis,[8] despite their different etiologies, we focused on neonatal EOS risk factors based on published literature and expert opinions. The risk factors were identified through a review of various databases, and the FDM was used to determine common risk factors for neonatal EOS. The validity of risk factors was assessed through a prospective observational evaluation of neonates, representative of the target population.

## Materials and Methods

This study was conducted in 2020 in three phases, namely literature review, obtaining expert opinions using the FDM, and external validation. The study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (code: IR.TBZMED.REC.1399.031).

### *Literature Review*

The clinical risk factors for EOS were collected through a literature search in PubMed (MEDLINE), Cochrane, Embase, and Scopus databases. All articles in English, published up to May 2021, were included. Keywords used to search for relevant articles in each database are described below.

*PubMed/Medline*: ((newborn [mesh] OR newborn [Title/Abstract] OR Infant [Title/Abstract] OR Neonatal [Title/Abstract] OR neonate*[Title/Abstract]) AND (sepsis [mesh] OR sepsis [Title/Abstract] OR Infection* [mesh] OR “blood infection”[Title/Abstract] OR “blood infections” [Title/Abstract]) AND (“early onset” [Title/Abstract] OR “early-onset” [Title/Abstract]) AND (risk factor[mesh] OR “risk factors” [Title/Abstract]))

*Cochrane*: (newborn OR infant OR neonatal OR neonate*) AND (sepsis OR infection* OR “blood infection” OR “blood infections”) AND (“early onset” OR “early-onset”) AND (“risk factor” OR “risk factors”)

*Embase*: (newborn: ti,ab,kw OR infant: ti,ab,kw OR neonatal: ti,ab,kw OR neonate*:ti,ab,kw) AND (sepsis: ti,ab,kw OR infection*:ti,ab,kw OR ‘blood infection’: ti,ab,kw OR ‘blood infections’: ti,ab,kw) AND (‘early onset’: ti,ab,kw OR ‘early-onset’: ti,ab,kw) AND (‘risk factor’: ti,ab,kw OR ‘risk factors’: ti,ab,kw)

*Scopus*: (newborn OR infant OR neonatal OR neonate) AND (sepsis OR infection* OR (blood infection) OR (blood infections)) AND (early onset) AND (risk factor)

The references of retrieved articles were reviewed for possible additional information. Articles whose full text was not accessible through the central library of Tabriz University of Medical Sciences, were excluded from the study. Two neonatologists evaluated the extracted risk factors and classified them into three categories, namely maternal, delivery, and neonatal.

### *Delphi Method*

The Delphi method traditionally begins with open-ended questions to collect specific information in the field of expertise of the Delphi participants. However, in the first round, certain modifications (based on a comprehensive literature review) are permitted to develop a structured questionnaire.[7]

*Development of the Initial Questionnaire:* Clinical risk factors of EOS reported in at least two articles were used to formulate a structured questionnaire. The initial questionnaire consisted of three sections in which each risk factor was rated based on a five-point scale ranging from very unimportant to very important. In addition, a blank space was reserved for the experts to give additional recommendations and feedback on each risk factor. To assess the content validity ratio (CVR), the questionnaire was emailed to 10 neonatologists with at least 15 years of experience in the neonatal intensive care unit (NICU). Their responses were received within a week. The content validity index (CVI) was separately assessed by the experts based on three criteria, namely simplicity, appropriateness, and certainty. One week after receiving their responses, another email was sent to the experts requesting their feedback, based on which the test-retest reliability of the questionnaire was determined (Spearman correlation coefficient: 79%).

*Participants*: The purposive sampling method was used to identify internationally recognized neonatal experts. Potential participants were identified from publications on neonatal sepsis in Medline, CINAHL, and Scopus databases. The inclusion criteria were a minimum of two publications on neonatal sepsis during the previous 10 years and primary activity in the field of neonatology and pediatric infectious diseases. A total of 57 experts with an h-index of 3 to 57 in Scopus were identified. According to the Expertscape website (www.expertscape.com), 13 experts were ranked among the top 100 neonatologists with expertise in neonatal sepsis. All 57 experts were contacted by email to gauge their willingness to participate. Introductory information on the aim of the study, the questionnaire, and a timetable was attached. Based on the first round of FDM, the participants were requested to rank the 30 identified risk factors. Risk factors approved by more than 15% of the participants were added to the questionnaire for the second round of FDM. The updated questionnaire was emailed to the participants, requesting their response within a maximum of 21 days.

*Fuzzification*: Triangular fuzzy number (TFN)[6] was used to convert the response from the experts. The five-point scale was then represented as very important (0.7, 0.9, 0.9), important (0.5, 0.7, 0.9), moderate (0.3, 0.5, 0.7), unimportant (0.1, 0.3, 0.5), very unimportant (0.1, 0.1, 0.3). Three values, namely minimum value ($n_1$), most sensible value ($n_2$), and maximum value ($n_3$) were considered for each response in the fuzzification step, i.e., the score given by the participants was the three values of $n_1$, $n_2$, and $n_3$. The mean of each fuzzy score for each risk factor was calculated as $m_1$, $m_2$, and $m_3$.

*Defuzzification*: All risk factors were ranked in terms of importance to decide on their inclusion or rejection. The selection of risk factors based on importance was performed using the below formula.[6]

$$A_{max} = {}^{1}/_{3}\,(m_1 + m_2 + m_3)$$

The prerequisites for risk factor acceptance were threshold value (d), the consensus of participants ≥75%, and fuzzy score value $A_{max}$≥0.5. The threshold value indicates the consensus of participants for each risk factor. Based on the below formula, only a risk factor with d≤0.2 was accepted.[6]

$$d(\tilde{m}, \tilde{n}) = \sqrt{{}^{1}/_{3}\,[(m_1 - n_1)^2 + (m_2 - n_2)^2 + (m_3 - n_3)^2]}$$

$$Threshold\ Value = \frac{\sum Average\ Threshold\ Value, (d) for\ each\ risk factor}{Total\ participants \times Total\ risk\ factors\ in\ each\ categori}$$

Risk factors with a consensus of less than 75% were included in the second round of FDM. This process was repeated until full consensus was achieved for all risk factors or the results stabilized in consecutive rounds. Between the rounds, the results of the previous round were presented to the participants to evaluate their responses against that of their peers. Participants were asked to revise or qualify their responses after considering group opinions. To achieve a high response rate, two reminder emails were sent to the participants. Microsoft Excel 2016 (Microsoft, Redmond, Washington, USA) was used to manage the data.

*Prospective Evaluation and External Validation*: External validation was performed by conducting a two-month prospective observational study at the NICU of two tertiary hospitals in Iran. EOS risk factors were assessed in neonates admitted to the NICU within the first hours after birth and followed up until final diagnosis by the physician. Neonates born to mothers with some types of immunological deficiency and newborns with major congenital malformations were excluded from the study. Finally, the Chi square test (significant level P≤0.05) was used to determine group differences in terms of risk factors. All data were analyzed using SPSS software, version 23.0 (IBM Corp, Armonk, NY, USA).

## Results

The flow diagram illustrating the search strategy and selection process of articles on clinical risk factors for sepsis is shown in figure 1.

In total, 35 articles were included in the review study (table 1). Out of the 41 risk factors extracted from the articles, 30 were approved by the two neonatologists and were included in the FDM phase. These risk factors were in the categories of neonatal (n=11), maternal (n=11), and delivery (n=8) (table 2). The CVR values for all items in the questionnaire ranged from 0.7 to 1. The CVI values for all items varied between 0.8 and 1. The calculated reliability of the questionnaire, using Cronbach's alpha coefficient, was 0.924.

Out of the 57 selected experts, 24 agreed to participate in the study (42% response rate). The number of participants in the second round of FDM was 23 (95% response rate); one participant withdrew without notice. In the first round of FDM, the participants suggested rephrasing one item from "X is a risk factor for neonatal EOS" to "neonatal EOS is more common in neonates with X". In the second round of FDM, the results of the first round together with an updated version of the questionnaire containing reformulated items and additional risk factors were emailed to the participants. Eventually, the participants reached a consensus about the items, and the questionnaire was approved (table 3). The threshold value was higher than 0.2 for all three categories. Out of a total of 34 risk factors, 25 met the consensus criteria. In the first round, all participants agreed on the EOS risk factors included in the neonatal categories (very low birth weight [VLBW], one-min Apgar <7, and prematurity). In addition, the maternal category (gestational age <37 weeks) and delivery category (premature rupture of membranes [PROM] >18, chorioamnionitis, and intrapartum fever >38 °C) were confirmed as EOS risk factors by all participants. During the first round of FDM, four additional risk factors were proposed by at least 15% of the participants, namely apnea, seizure, newborn temperature, and intrauterine growth restriction (IUGR). These were discussed in the second round of FDM, of which apnea, seizure, and neonate temperature met the consensus criteria. However, IUGR did not meet the criteria and was omitted.

During the observational study, 136 neonates were admitted to the NICU, out of which three neonates died within the first 72 h, five were transferred, and 14 were excluded, since they did not meet the inclusion criteria. Finally, 114 neonates (31 with and 83 without EOS) were included in the study. Among the neonates with EOS, 9.67%, 16.12%, and 74.19% had at least 1, 2, or ≥3 risk factors per category, respectively. In addition to the identified risk factors, the need for mechanical ventilation and feed intolerance were also observed in about 70% of neonates with EOS. However, these were not identified in the previous phases of the study. The risk factors related to EOS are presented in table 4.

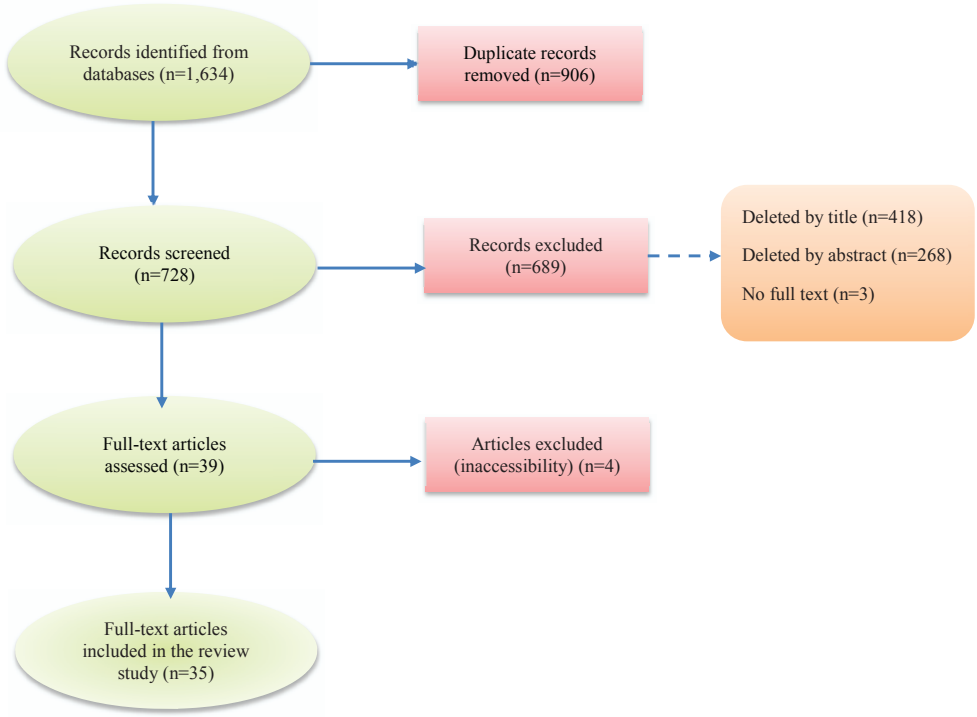


**Figure 1:** Flow diagram illustrates the search strategy and selection process of articles.

**Table 1:** Summary of the included articles

| Author | Year | Study type | Country | Sample size | Method |
|---|---|---|---|---|---|
| Adatara et al.[1] | 2019 | Retrospective case-control | Ghana | 900 neonates (103 cases, 797 controls) | Binary and multivariate logistic regression |
| Yismaw et al.[4] | 2019 | Cross-sectional | Ethiopia | 423 neonates | Bivariate and multivariable logistic regression |
| Adatara et al.[9] | 2018 | Retrospective case-control | Ghana | 383 Neonates (67 cases, 316 controls) | Univariate and multivariate logistic regression |
| Hayun et al.[10] | 2015 | Retrospective cohort | Indonesia | 221 neonates (62 cases, 159 controls) | Multivariate analysis and logistic regression |
| Polcwiartek et al.[11] | 2021 | Cohort | USA | 1,197 neonates | Multivariable logistic regression |
| Akalu et al.[12] | 2020 | Case-control | Ethiopia | 231 neonates (77 cases, 155 controls) | Binary and multivariate logistic regression |
| Salem et al.[13] | 2006 | Prospective observational | Bosnia and Herzegovina | 200 neonates | Multivariable analysis |
| Gebremedhin et al.[14] | 2016 | Case-control | Ethiopia | 234 neonates (78 cases, 156 controls) | Binary logistic regression |
| Siakwa et al.[15] | 2014 | Prospective case-control | Ghana | 196 neonates (96 cases, 100 controls) | Logistic regression |
| Klinger et al.[16] | 2009 | Population-based observational study | Israel | 383 neonates | Multivariable analysis |
| Giannoni et al.[17] | 2018 | Prospective population-based cohort | Switzerland | 429 neonates | Multinomial logistic regression |
| Cizmeci et al.[18] | 2015 | Case-control | Turkey | 83 neonates (40 cases, 43 controls) | Logistic regression |
| Leal et al.[19] | 2012 | Prospective cohort study | Mexico | 11,790 neonates | Logistic regression |
| Utomo et al.[20] | 2010 | Case-control | Indonesia | 97 neonates (31 cases, 66 controls) | Logistic regression |
| Schrag et al.[21] | 2012 | Cohort | South Africa | 8,129 neonates | Multinomial logistic regression |
| Schuchat et al.[22] | 2000 | Case-control | USA | 101 neonates (41 cases, 61 controls) | Logistic regression |
| Gómez et al.[23] | 2018 | Case control | Colombia | 549 neonates (183 cases, 366 controls) | Logistic regression |
| Kabwe et al.[24] | 2016 | Cross-sectional observational | Zambia | 313 neonates | Multivariate analysis |
| Verstraete et al.[25] | 2015 | Prospective cohort | Belgium | 5,134 neonates | Univariate and logistic regression |
| Boia et al.[26] | 2010 | Retrospective cohort | Romania | 34 neonates | - |
| Babazono et al.[27] | 2008 | Retrospective cohort | Japan | 871 neonates | Multiple logistic regression |
| Dutta et al.[28] | 2010 | Prospective cohort | India | 601 neonates | Multivariable logistic regression |
| Palatnik et al.[29] | 2019 | Case-control | USA | 779 neonates (73 cases, 706 controls) | Bivariate and multivariable logistic regression |
| Simarmata et al.[30] | 2016 | Observational and prospective basis | Indonesia | 100 neonates | - |
| Mugalu et al.[31] | 2006 | Prospective cohort | Uganda | 293 neonates | Logistic regression |
| Ogunlesi et al.[32] | 2011 | Retrospective (2006-2007), Prospective (2008) | Nigeria | 1,050 neonates | Descriptive and inferential statistics |
| Jiang et al.[33] | 2013 | Case-control | China | 735 neonates (147 cases, 588 controls) | Univariate and multivariate logistic regression |
| Kawagoe et al.[34] | 2001 | Prospective cohort | Brazil | 1,544 neonates | Univariate and multivariate |
| Puopolo et al.[35] | 2011 | Case-control | USA | 1,413 Neonates (350 cases, 1,063 controls) | Multivariate analysis and split validation |
| Woldu et al.[36] | 2017 | Prospective cross-sectional | Ethiopia | 306 neonates | Binary logistic regressions |
| Masanja et al.[37] | 2019 | Case-control | Tanzania | 322 neonates (105 cases, 217 controls) | Bivariate and multiple logistic regression |
| Jabiri et al.[38] | 2016 | Cross-sectional | Tanzania | 220 neonates | Logistic regression |
| Bayih et al.[39] | 2021 | Case-control | Ethiopia | 246 neonates (82 cases, 164 controls) | Multivariable logistic regression |
| Agnche et al.[40] | 2020 | Cross-sectional | Ethiopia | 352 neonates | Multivariable logistic regression |
| López et al.[41] | 2019 | Case control | Colombia | 555 neonates (186 cases, 368 controls) | Bivariate and logistic regression |

**Table 2:** Results of the literature review on the risk factors associated with early-onset sepsis

| Category | Risk factor | Reference number |
|---|---|---|
| Neonatal | One-min Apgar <7 | 1, 4, 9, 10, 12, 19, 33, 41 |
| | Five-min Apgar <7 | 1, 9, 11, 14, 33 |
| | Five-min Apgar <3 | 13 |
| | Resuscitation at birth | 12, 15, 16, 38-40 |
| | Prematurity <37 weeks | 18-21, 24, 29, 33, 35, 41 |
| | VLBW <1500 g | 9, 10, 16, 17, 21, 25-30, 33, 41 |
| | LBW <2500 g | 19, 20, 41 |
| | Not crying | 14, 15, 39 |
| | Male sex | 15, 27, 28, 30, 31, 40 |
| | Jaundice | 13, 33 |
| | Asphyxia (ph<7, BE<-16 mmol/L) | 19, 40 |
| | Respiratory distress | 19, 41 |
| | Congenital anomaly | 4 |
| Maternal | Parity | 1, 15 |
| | GBS | 11, 17, 22, 24, 34, 35 |
| | UTI | 12, 14, 15, 34, 36, 40 |
| | Gestational age <32 weeks | 26, 29, 30, 32 |
| | Gestational age <34 weeks | 17, 41 |
| | Gestational age <30 weeks | 28 |
| | Gestational age <37 weeks | 10, 15, 19, 39 |
| | Age 31-40 years | 15, 30, 38, 40 |
| | Onset of sexual activity | 41 |
| | Bleeding disorder | 40 |
| | Gestational age 37-42 weeks | 40 |
| | Gestational age >42 weeks | 40 |
| | Gestational age <28 weeks | 13 |
| | Foul-smelling vaginal discharge | 4, 15 |
| | Multiple digital vaginal examinations>3 | 37, 40, 41 |
| | Level of education | 23, 41 |
| | Origin | 23, 41 |
| | Lower levels of cord-blood 25(OH)D | 18 |
| Delivery | Cesarean section | 1, 9, 11, 20, 33, 36, 41 |
| | PROM >18 hours | 12, 14, 22, 23, 32-35, 37, 39, 41 |
| | PROM >24 hours | 16, 19 |
| | PROM >12 hours | 4 |
| | Chorioamnionitis | 16, 28, 37, 41 |
| | Intrapartum fever >38 °C | 4, 12, 14, 15, 22, 23, 29, 35, 41 |
| | Abnormal amniotic liquid | 19, 33 |
| | Abnormal placenta | 33 |
| | No intrapartum antibiotic prophylaxis | 22, 28, 35 |
| | MSAF | 9, 12, 15, 20, 21, 29 |

VLBW: Very low birth weight; LBW: Low birth weight; GBS: Group B Streptococcus; UTI: Urinary tract infection; PROM: Premature rupture of membranes; MSAF: Meconium-stained amniotic fluid

## Discussion

Of the 26 risk factors identified in this study, 14 were included in the NICE guideline, namely nine neonatal-related risk factors (prematurity, respiratory distress, apnea, fever, seizures, resuscitation at birth, jaundice, feed intolerance, and need for mechanical ventilation), one maternal-related risk factor (Guillain-Barré syndrome [GBS]), and four delivery-related risk factors (PROM >18, chorioamnionitis, intrapartum fever >38 °C, and PROM >24). Risk factors included in the CDC guideline were prematurity, GBS, gestational age <34, PROM >18, chorioamnionitis, intrapartum fever >38 °C, and no intrapartum antibiotic prophylaxis. The other risk factors identified in our study were not included in the NICE and CDC guidelines.

Among the neonatal risk factors, consensus on VLBW was reached in the first round of FDM. It had the highest level of evidence as a risk factor in 13 (37.14%) articles. However, it was not viewed as a potential EOS risk factor in the NICE guideline. A review study reported a 10-fold increase in the incidence rate of EOS in infants with VLBW compared to those with normal birth weight.[42]

**Table 3:** The results of the fuzzy Delphi method

| Risk factor | | First round FDM | | | Second round FDM | | | Rank |
|---|---|---|---|---|---|---|---|---|
| | | Consensus (%) | Average fuzzy number | Result | Consensus (%) | Average fuzzy number | Result | |
| Neonatal | VLBW | 100 | 0.884 | Accepted | 100 | 0.884 | Accepted | 1 |
| | One-min Apgar <7 | 100 | 0.884 | Accepted | 100 | 0.884 | Accepted | 1 |
| | Prematurity <37 weeks | 100 | 0.884 | Accepted | 100 | 0.884 | Accepted | 1 |
| | Five-min Apgar <7 weeks | 85 | 0.773 | Accepted | 98 | 0.772 | Accepted | 2 |
| | Respiratory distress | 79 | 0.768 | Accepted | 98 | 0.772 | Accepted | 2 |
| | Apnea#-hypopnea index | 53 | 0.756 | - | 98 | 0.763 | Accepted | 3 |
| | Neonatal temperature# | 34 | 0.728 | - | 91 | 0.758 | Accepted | 4 |
| | Seizures# | 46 | 0.746 | - | 90 | 0.752 | Accepted | 5 |
| | Asphyxia (ph<7, BE<-16 mmol/L) | 76 | 0.628 | Accepted | 87 | 0.72 | Accepted | 6 |
| | LBW | 79 | 0.653 | Accepted | 85 | 0.68 | Accepted | 7 |
| | Resuscitation at birth | 79 | 0.634 | Accepted | 90 | 0.68 | Accepted | 7 |
| | Jaundice | 76 | 0.502 | Accepted | 87 | 0.534 | Accepted | 8 |
| | Not crying | 76 | 0.401 | Rejected | 89 | 0.399 | Rejected | 0 |
| | Male sex | 56 | 0.399 | Rejected | 86 | 0.284 | Rejected | 0 |
| Maternal | Gestational age <32 weeks | 100 | 0.884 | Accepted | 100 | 0.884 | Accepted | 1 |
| | UTI | 78 | 0.752 | Accepted | 100 | 0.884 | Accepted | 1 |
| | GBS | 75 | 0.742 | Accepted | 95 | 0.768 | Accepted | 2 |
| | Multiple digital vaginal examinations>3 | 75 | 0.501 | Accepted | 89 | 0.555 | Accepted | 3 |
| | Gestational age <34 weeks | 73 | 0.545 | Rejected | 98 | 0.548 | Accepted | 4 |
| | Parity | 75 | 0.543 | Accepted | 85 | 0.413 | Rejected | 0 |
| | Age (31-40) (Year) | 65 | 0.532 | Rejected | 98 | 0.434 | Rejected | 0 |
| | Gestational age <37 weeks | 73 | 0.44 | Rejected | 95 | 0.433 | Rejected | 0 |
| | Level of education | 54 | 0.419 | Rejected | 91 | 0.398 | Rejected | 0 |
| | Origin | 41 | 0.41 | Rejected | 88 | 0.418 | Rejected | 0 |
| | Foul-smelling Vaginal discharge | 69 | 0.301 | Rejected | 86 | 0.3 | Rejected | 0 |
| Delivery | PROM >18 hours | 100 | 0.884 | Accepted | 100 | 0.884 | Accepted | 1 |
| | Chorioamnionitis | 100 | 0.884 | Accepted | 100 | 0.884 | Accepted | 1 |
| | Intrapartum fever >38 °C | 100 | 0.802 | Accepted | 100 | 0.884 | Accepted | 1 |
| | No intrapartum antibiotic prophylaxis | 75 | 0.732 | Accepted | 88 | 0.793 | Accepted | 2 |
| | Abnormal amniotic liquid | 78 | 0.752 | Accepted | 98 | 0.753 | Accepted | 3 |
| | MSAF[6] | 75 | 0.698 | Accepted | 97 | 0.753 | Accepted | 3 |
| | PROM >24 hours | 75 | 0.461 | Rejected | 86 | 0.545 | Accepted | 4 |
| | Cesarean section | 75 | 0.432 | Rejected | 76 | 0.534 | Accepted | 5 |
| | IUGR# | 38 | 0.546 | - | 79 | 0.428 | Rejected | 0 |

#New risk factor suggested by <15% of the participants. VLBW: Very low birth weight; LBW: Low birth weight; GBS: Group B Streptococcus; UTI: Urinary tract infection; PROM: Premature rupture of membranes; MSAF: Meconium-stained amniotic fluid; IUGR: Intrauterine growth restriction; The threshold value (d) of risk factors associated with neonatal, maternal, and delivery categories in the first and second rounds of the fuzzy Delphi model (FDM) was 0.00, 0.01, and 0.02, respectively.

**Table 4:** Risk factors related to early-onset sepsis

| Final risk factor | | Case (N=31) | Control (N=83) | Chi square | P value |
|---|---|---|---|---|---|
| | | N (%) | N (%) | | |
| Neonatal | Birth weight <1,500 g | 14 (45.1) | 5 (6) | 24.891 | <0.001 |
| | One-min Apgar <7 | 10 (32.2) | 12 (14.4) | 4.592 | 0.032 |
| | Prematurity <37 weeks | 17 (54.8) | 4 (4.8) | 37.577 | <0.001 |
| | Five-min Apgar <7 | 16 (51.6) | 10 (12) | 20.068 | <0.001 |
| | Respiratory distress | 18 (58) | 12 (14.4) | 22.134 | <0.001 |
| | Apnea-hypopnea index | 17 (54.8) | 10 (12) | 22.864 | <0.001 |
| | Fever | 22 (70.9) | 13 (15.6) | 32.447 | <0.001 |
| | Seizures | 12 (38.7) | 9 (10.8) | 11.663 | 0.001 |
| | Asphyxia (ph<7, BE<-16 mmol/L) | 20 (64.5) | 13 (15.6) | 26.190 | <0.001 |
| | Birth weight <2,500 g | 13 (41.9) | 16 (19.2) | 6.109 | 0.013 |
| | Resuscitation at birth | 13 (41.9) | 6 (7.2) | 19.575 | <0.001 |
| | Jaundice | 11 (35.4) | 15 (6) | 3.887 | 0.049 |
| | Feed intolerance | 22 (70.9) | 12 (14.4) | 34.437 | <0.001 |
| | Need for mechanical ventilation | 21 (87.7) | 6 (7.2) | 45.726 | <0.001 |
| Maternal | Gestational age <32 weeks | 12 (38.7) | 1 (1.2) | 31.424 | <0.001 |
| | UTI | 18 (58) | 12 (14.4) | 22.134 | <0.001 |
| | GBS | 13 (41.9) | 9 (10.8) | 14.010 | <0.001 |
| | Multiple digital vaginal examinations>3 | 27 (87) | 34 (40.9) | 19.309 | <0.001 |
| | Gestational age <34 weeks | 11 (35.4) | 10 (12) | 8.249 | 0.04 |
| Delivery | PROM >18 hours | 18 (58) | 10 (12) | 25.794 | <0.001 |
| | Chorioamnionitis | 19 (61.2) | 5 (6) | 41.477 | <0.001 |
| | Intrapartum fever >38 °C | 15 (48.3) | 11 (13.2) | 15.825 | <0.001 |
| | No Intrapartum antibiotic prophylaxis | 8 (25.8) | 7 (8.4) | 5.961 | 0.026 |
| | Abnormal amniotic liquid | 18 (58) | 30 (36.1) | 4.449 | 0.03 |
| | MSAF | 9 (29) | 3 (3.6) | 15.482 | <0.001 |
| | PROM >24 hours | 7 (22.5) | 2 (2.4) | 12.629 | 0.001 |
| | Cesarean section | 17 (54.8) | 44 (53) | 0.030 | 0.862* |

*Not a significant risk factor. UTI: Urinary tract infection; GBS: Group B Streptococcus; PROM: Premature rupture of membranes; MSAF: Meconium-stained amniotic fluid

Moreover, low birth weight (LBW) was considered a risk factor and ranked seventh in the FDM study. A meta-analysis of six cross-sectional and two cohort studies investigated the association between birth weight and EOS in 9,032 live births. A significant relationship between sepsis and LBW with an odds ratio (OR) of 1.42 (95% CI: 1.07-1.88) was reported, i.e., the OR of LBW for EOS is 1.42 times higher than the newborns with normal weight.[43]

In our review, we found that eight studies reported a low one-min Apgar score as a risk factor for EOS (ranked first in the FDM). In addition, five other studies considered five-min Apgar as a risk factor for EOS (ranked second in the FDM). Whereas, this parameter is not directly considered a risk factor in the NICE guideline. During the second round of FDM, a participant commented: *"The evidence shows that one-min Apgar score depends on the cord blood hydrogen potential (pH) and intrapartum depression, whereas five-min Apgar score indicates a change in the condition of neonates upon resuscitation. Therefore, it is necessary to consider both Apgar scores in assessing the risk of EOS."* Various studies showed that infants with low Apgar scores have a 2.7-fold higher risk of EOS compared to other newborns.[33, 41]

Apnea was indicated as a risk factor by 53% of the experts during the first round of FDM. A participant commented: "*Several studies demonstrated that immaturity of the respiratory center in the brain is the most common cause of apnea, and it may occur on days 2-7 after birth. However, apnea immediately after birth is indicative of another complication and could be a potential risk factor for EOS.*"

Fever and seizure were other risk factors identified by the experts. We noted that 48% of the experts categorized a body temperature >38 °C as fever. However, based on the NICE guideline, 32% of the experts considered newborn body temperature of <36 °C and >38 °C as abnormal.

Sexual dimorphism affects the human immune response. Women are less susceptible to infection than men due to more intense cellular and humoral immune responses to infection.[44] Six studies reported that boys are more likely to develop EOS than girls. However, this notion was ruled out by our experts.

In the maternal category, gestational age <32

weeks had the highest level of evidence as a risk factor and consensus on this topic was reached in the first round of FDM. However, CDC and NICE guidelines included a gestational age of <34 weeks and <37 weeks as a risk factor for sepsis[5] and EOS,[2] respectively. A meta-analysis on the association between gestational age and EOS reported that neonates with gestational age <32 weeks were 3.36 times more likely to develop sepsis than other neonates.[45]

Urinary tract infection (UTI) was also reported as a potential risk factor for EOS in six studies. Consensus on this risk factor was reached by the experts in the first round of FDM. However, NICE and CDC guidelines did not include UTI as a risk factor. A systematic review and meta-analysis of 27 studies assessing the effect of UTI and intrapartum fever on the risk of EOS reported that neonates born to mothers with UTI had a 3.55-fold higher risk of EOS (95% CI: 2.04, 5.06) than other infants.[11] A participant stated: *"UTI is an important risk factor for EOS, especially if not treated in the third trimester of pregnancy. Evidence indicates that EOS may be developed by infectious agents colonizing the birth canal."*

In our review, vaginal examination ranked fourth among all EOS risk factors. The cervical canal is prone to infection due to vaginal organisms, even in sterile conditions. A vaginal examination can increase the risk of vaginal infection. However, some studies reported no significant relationship between vaginal examination and EOS.[14] Such conflicting results could be attributed to different study settings and the difference in the quality of obstetrics and neonatal health care services between primary and referral hospitals.

All participants agreed that PROM, chorioamnionitis, and intrapartum fever are potential risk factors for EOS. Several studies indicated that PROM is a common and significant cause of preterm labor.[12, 17] In line with NICE and CDC guidelines, in our review, 11 studies reported that PROM>18 h is a risk factor for EOS.[2, 5] Since the birth canal is colonized with aerobic and anaerobic pathogens, it might cause ascending amniotic fluid and, as a result, infect the neonates at birth. These bacterial agents might transmit from mother to fetus in the uterus during labor and delivery, leading to EOS.[12] Chorioamnionitis was reported in four of the reviewed articles. A meta-analysis of 107 studies reported a positive correlation between chorioamnionitis and EOS (OR: 4.29, 95% CI: 3.63-5.06).[3] Another meta-analysis of 55 studies also reported a relationship between chorioamnionitis and EOS (OR: 4.42, 95% CI: 2.68-7.29).[46] These results were supported by NICE and CDC guidelines, indicating chorioamnionitis as a risk factor for EOS.[2, 5] Intrapartum fever was reported in nine studies, and our experts were in full agreement on this. The results of a meta-analysis showed that intrapartum fever increased the risk of EOS by a factor of 3.36 (95% CI: 1.64-5.62).[39] During the first round of FDM, two participants stated: *"Evidence from studies indicate that fever is a clear sign of an infection, which can be transmitted to infants and cause EOS."*

Some experts believed that EOS mainly develops as a result of vertical transmission and, consequently, a cesarean section cannot be a risk factor for EOS. The results of our Chi square test also showed that cesarean section was not a significant risk factor for EOS (P=0.862). Nonetheless, 76% of the experts considered cesarean section as a risk factor, since the normal flora in neonates could be affected by this procedure. Infants born by cesarian delivery have a lower amount of bifidobacteria, and the incidence of Bacteroides spp. is also lower.[29] Neonates with normal flora have a stronger immune system. A change in normal flora will lead to an increased risk of EOS. The latter was confirmed by the CDC guideline.

The main strength of our study is a comprehensive literature review of risk factors associated with neonatal EOS in terms of maternal, delivery, and neonatal categories. Another strength is related to the way FDM was conducted. The participants were selected based on strict requirements, namely knowledge and active engagement with the research topic, willingness to participate, readiness to dedicate time and effort to group sessions, and effective communication between the research team and experts. But above all, the selection of participating specialists was based entirely on their expertise. Each study round lasted 21 days and regular communication between the parties involved was ensured. We sought the opinion of leading experts from around the world, which in turn gave us confidence that we have identified the main risk factors for neonatal EOS. Last but not least, we took full advantage of FDM by effectively clarifying any ambiguities in the opinion of the experts, saving time by using a shortened questionnaire, and reducing costs compared to other methods (e.g., focus group discussion).

As the main limitation of the study, despite our effort to conduct FDM as fully as possible, some participants did not fully respond to the questionnaire and overlooked certain questions. In addition, we only considered risk factors related to the first few hours after birth and did

not include the risks associated with the quality of care and length of stay at the NICU. It is recommended to address these topics in future studies.

## Conclusion

Neonatal-related risk factors for EOS were birth weight <1,500 g, one-min Apgar <7, and prematurity. Maternal-related risk factors were gestational age <32 weeks and UTI. In addition, delivery-related risk factors were PROM >18, chorioamnionitis, and intrapartum fever >38 °C. Our findings will facilitate accurate diagnosis of early-onset sepsis, prevent unnecessary use of antibiotics, and can be used to develop guidelines for the diagnosis and treatment of neonatal EOS.

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## Authors' Contribution

N.M: Study concept and design, statistical analysis, and drafting; T.S.S: Statistical analysis, interpretation of data, and drafting; K.M: Study concept and design, and critical revision; A.E: Analysis and interpretation of data, and drafting; M.S.T: Analysis and interpretation of data, and critical revision; P.R.H: Study concept and design, and drafting; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of Interest:** None declared.

## References

1 Adatara P, Afaya A, Salia SM, Afaya RA, Konlan KD, Agyabeng-Fandoh E, et al. Risk Factors Associated with Neonatal Sepsis: A Case Study at a Specialist Hospital in Ghana. ScientificWorldJournal. 2019;2019:9369051. doi: 10.1155/2019/9369051. PubMed PMID: 30692878; PubMed Central PMCID: PMCPMC6332869.

2 Caffrey Osvald E, Prentice P. NICE clinical guideline: antibiotics for the prevention and treatment of early-onset neonatal infection. Arch Dis Child Educ Pract Ed. 2014;99:98-100. doi: 10.1136/archdischild-2013-304629. PubMed PMID: 24334339.

3 Villamor-Martinez E, Lubach GA, Rahim OM, Degraeuwe P, Zimmermann LJ, Kramer BW, et al. Association of Histological and Clinical Chorioamnionitis With Neonatal Sepsis Among Preterm Infants: A Systematic Review, Meta-Analysis, and Meta-Regression. Front Immunol. 2020;11:972. doi: 10.3389/fimmu.2020.00972. PubMed PMID: 32582153; PubMed Central PMCID: PMCPMC7289970.

4 Yismaw AE, Abebil TY, Biweta MA, Araya BM. Proportion of neonatal sepsis and determinant factors among neonates admitted in University of Gondar comprehensive specialized hospital neonatal Intensive care unit Northwest Ethiopia 2017. BMC Res Notes. 2019;12:542. doi: 10.1186/s13104-019-4587-3. PubMed PMID: 31455414; PubMed Central PMCID: PMCPMC6712769.

5 Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases NCfI, Respiratory Diseases CfDC, Prevention. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59:1-36. PubMed PMID: 21088663.

6 Khan MJ, Kumam P, Liu P, Kumam W, Ashraf S. A novel approach to generalized intuitionistic fuzzy soft sets and its application in decision support system. Mathematics. 2019;7:742. doi: 10.1016/j.ins.2012.09.010.

7 McPherson S, Reese C, Wendler MC. Methodology Update: Delphi Studies. Nurs Res. 2018;67:404-10. doi: 10.1097/NNR.0000000000000297. PubMed PMID: 30052591.

8 Araújo BC, Guimarães H. Risk factors for neonatal sepsis: an overview. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM). 2020;9:e090206.

9 Adatara P, Afaya A, Salia SM, Afaya RA, Kuug AK, Agbinku E, et al. Risk Factors for Neonatal Sepsis: A Retrospective Case-Control Study among Neonates Who Were Delivered by Caesarean Section at the Trauma and Specialist Hospital, Winneba, Ghana. Biomed Res Int. 2018;2018:6153501. doi: 10.1155/2018/6153501. PubMed PMID: 30662911; PubMed Central PMCID: PMCPMC6313993.

10 Hayun M, Alasiry E, Daud D, Febriani DB, Madjid D. The risk factors of early onset neonatal sepsis. American Journal of clinical and experimental medicine. 2015;3:78-82. doi:

10.11648/j.ajcem.20150303.11.
11 Polcwiartek LB, Smith PB, Benjamin DK, Zimmerman K, Love A, Tiu L, et al. Early-onset sepsis in term infants admitted to neonatal intensive care units (2011-2016). J Perinatol. 2021;41:157-63. doi: 10.1038/s41372-020-00860-3. PubMed PMID: 33070153; PubMed Central PMCID: PMCPMC7568457.
12 Akalu TY, Gebremichael B, Desta KW, Aynalem YA, Shiferaw WS, Alamneh YM. Predictors of neonatal sepsis in public referral hospitals, Northwest Ethiopia: A case control study. PLoS One. 2020;15:e0234472. doi: 10.1371/journal.pone.0234472. PubMed PMID: 32579580; PubMed Central PMCID: PMCPMC7314009.
13 Salem SY, Sheiner E, Zmora E, Vardi H, Shoham-Vardi I, Mazor M. Risk factors for early neonatal sepsis. Arch Gynecol Obstet. 2006;274:198-202. doi: 10.1007/s00404-006-0135-1. PubMed PMID: 16491366.
14 Gebremedhin D, Berhe H, Gebrekirstos K. Risk Factors for Neonatal Sepsis in Public Hospitals of Mekelle City, North Ethiopia, 2015: Unmatched Case Control Study. PLoS One. 2016;11:e0154798. doi: 10.1371/journal.pone.0154798. PubMed PMID: 27163290; PubMed Central PMCID: PMCPMC4862626.
15 Siakwa M, Kpikpitse D, Mupepi SC, Semuatu M. Neonatal sepsis in rural Ghana: A case control study of risk factors in a birth cohort. International Journal of Research. 2014;4:2307-83.
16 Klinger G, Levy I, Sirota L, Boyko V, Reichman B, Lerner-Geva L, et al. Epidemiology and risk factors for early onset sepsis among very-low-birthweight infants. Am J Obstet Gynecol. 2009;201:38 e1-6. doi: 10.1016/j.ajog.2009.03.006. PubMed PMID: 19380122.
17 Giannoni E, Agyeman PKA, Stocker M, Posfay-Barbe KM, Heininger U, Spycher BD, et al. Neonatal Sepsis of Early Onset, and Hospital-Acquired and Community-Acquired Late Onset: A Prospective Population-Based Cohort Study. J Pediatr. 2018;201:106-14. doi: 10.1016/j.jpeds.2018.05.048. PubMed PMID: 30054165.
18 Cizmeci MN, Kanburoglu MK, Akelma AZ, Ayyildiz A, Kutukoglu I, Malli DD, et al. Cord-blood 25-hydroxyvitamin D levels and risk of early-onset neonatal sepsis: a case-control study from a tertiary care center in Turkey. Eur J Pediatr. 2015;174:809-15. doi: 10.1007/s00431-014-2469-1. PubMed PMID: 25504199.
19 Leal YA, Alvarez-Nemegyei J, Velazquez JR, Rosado-Quiab U, Diego-Rodriguez N, Paz-Baeza E, et al. Risk factors and prognosis for neonatal sepsis in southeastern Mexico: analysis of a four-year historic cohort follow-up. BMC Pregnancy Childbirth. 2012;12:48. doi: 10.1186/1471-2393-12-48. PubMed PMID: 22691696; PubMed Central PMCID: PMCPMC3437209.
20 Utomo MT. Risk factors of neonatal sepsis: a preliminary study in Dr. Soetomo hospital. Indonesian journal of tropical and infectious disease. 2010;1:23-6. doi: 10.20473/ijtid.v1i1.3718.
21 Schrag SJ, Cutland CL, Zell ER, Kuwanda L, Buchmann EJ, Velaphi SC, et al. Risk factors for neonatal sepsis and perinatal death among infants enrolled in the prevention of perinatal sepsis trial, Soweto, South Africa. Pediatr Infect Dis J. 2012;31:821-6. doi: 10.1097/INF.0b013e31825c4b5a. PubMed PMID: 22565291.
22 Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera 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. doi: 10.1542/peds.105.1.21. PubMed PMID: 10617699.
23 Gómez JL, González SC, Baldiris RM, Díaz-Pérez A, Perez I. Prognostic factors of early neonatal sepsis in the city of Cartagena Colombia. Global Journal of Health Science. 2018;10:1-30. doi: 10.5539/gjhs.v10n12p30.
24 Kabwe M, Tembo J, Chilukutu L, Chilufya M, Ngulube F, Lukwesa C, et al. Etiology, Antibiotic Resistance and Risk Factors for Neonatal Sepsis in a Large Referral Center in Zambia. Pediatr Infect Dis J. 2016;35:e191-8. doi: 10.1097/INF.0000000000001154. PubMed PMID: 27031259.
25 Verstraete EH, De Coen K, Vogelaers D, Blot S. Risk Factors for Health Care-Associated Sepsis in Critically Ill Neonates Stratified by Birth Weight. Pediatr Infect Dis J. 2015;34:1180-6. doi: 10.1097/INF.0000000000000851. PubMed PMID: 26244835.
26 Boia M, Ilie C, Ioanăş L, Manea A, Iacob D, Cioboata D. Neonatal Septicemia–Retrospective Study on Premature Newborn. Revista Societății Române De Chirurgie Pediatrică. 2010;8:27.
27 Babazono A, Kitajima H, Nishimaki S, Nakamura T, Shiga S, Hayakawa M, et al. Risk factors for nosocomial infection in the neonatal intensive care unit by the Japanese Nosocomial Infection Surveillance (JANIS). Acta Med Okayama. 2008;62:261-8. doi:

10.18926/AMO/30938. PubMed PMID: 18766209.
28 Dutta S, Reddy R, Sheikh S, Kalra J, Ray P, Narang A. Intrapartum antibiotics and risk factors for early onset sepsis. Arch Dis Child Fetal Neonatal Ed. 2010;95:F99-103. doi: 10.1136/adc.2009.163220. PubMed PMID: 19996327.
29 Palatnik A, Liu LY, Lee A, Yee LM. Predictors of early-onset neonatal sepsis or death among newborns born at <32 weeks of gestation. J Perinatol. 2019;39:949-55. doi: 10.1038/s41372-019-0395-9. PubMed PMID: 31089257.
30 Simarmata YBC, Harahap U, Djipta G. Identification of risk factors caused neonatal sepsis of prem ature neonatus in adam malik general hospital center. Birth. 2016;5:25.
31 Mugalu J, Nakakeeto MK, Kiguli S, Kaddu-Mulindwa DH. Aetiology, risk factors and immediate outcome of bacteriologically confirmed neonatal septicaemia in Mulago hospital, Uganda. Afr Health Sci. 2006;6:120-6. doi: 10.5555/afhs.2006.6.2.120. PubMed PMID: 16916305; PubMed Central PMCID: PMCPMC1831983.
32 Ogunlesi TA, Ogunfowora OB, Osinupebi O, Olanrewaju DM. Changing trends in newborn sepsis in Sagamu, Nigeria: bacterial aetiology, risk factors and antibiotic susceptibility. J Paediatr Child Health. 2011;47:5-11. doi: 10.1111/j.1440-1754.2010.01882.x. PubMed PMID: 20973858.
33 Jiang Z, Ye GY. 1:4 matched case-control study on influential factor of early onset neonatal sepsis. Eur Rev Med Pharmacol Sci. 2013;17:2460-6. PubMed PMID: 24089224.
34 Kawagoe JY, Segre CA, Pereira CR, Cardoso MF, Silva CV, Fukushima JT. Risk factors for nosocomial infections in critically ill newborns: a 5-year prospective cohort study. Am J Infect Control. 2001;29:109-14. doi: 10.1067/mic.2001.114162. PubMed PMID: 11287879.
35 Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, et al. Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. Pediatrics. 2011;128:e1155-63. doi: 10.1542/peds.2010-3464. PubMed PMID: 22025590; PubMed Central PMCID: PMCPMC3208962.
36 Woldu MA, Guta M, Lenjisa J, Tegegne G, Tesafye G, Dinsa H. Assessment of the incidence of neonatal sepsis, its risk factors, antimicrobial use and clinical outcomes in Bishoftu General Hospital, Neonatal Intensive Care Unit, Debrezeit-Ethiopia Pediat Therapeut. Int J Contemp Pediatr. 2014;4:2161. doi: 10.5455/2349-3291.ijcp20141102.
37 Masanja PP, Kibusi SM, Mkhoi ML. Predictors of Early Onset Neonatal Sepsis among Neonates in Dodoma, Tanzania: A Case Control Study. J Trop Pediatr. 2020;66:257-66. doi: 10.1093/tropej/fmz062. PubMed PMID: 31539064.
38 Jabiri A, Wella HL, Semiono A, Saria A, Protas J. Prevalence and factors associated with neonatal sepsis among neonates in Temeke and Mwananyamala Hospitals in Dar es Salaam, Tanzania. Tanzania Journal of Health Research. 2016;18. doi: 10.4314/thrb.v18i4.4.
39 Bayih WA, Ayalew MY, Chanie ES, Abate BB, Alemayehu SA, Belay DM, et al. The burden of neonatal sepsis and its association with antenatal urinary tract infection and intra-partum fever among admitted neonates in Ethiopia: A systematic review and meta-analysis. Heliyon. 2021;7:e06121. doi: 10.1016/j.heliyon.2021.e06121. PubMed PMID: 33644445; PubMed Central PMCID: PMCPMC7887389.
40 Agnche Z, Yenus Yeshita H, Abdela Gonete K. Neonatal Sepsis and Its Associated Factors Among Neonates Admitted to Neonatal Intensive Care Units in Primary Hospitals in Central Gondar Zone, Northwest Ethiopia, 2019. Infect Drug Resist. 2020;13:3957-67. doi: 10.2147/IDR.S276678. PubMed PMID: 33177846; PubMed Central PMCID: PMCPMC7650015.
41 López-Martínez F, Núñez-Valdez ER, Gomez JL, García-Díaz V. A neural network approach to predict early neonatal sepsis. Computers & Electrical Engineering. 2019;76:379-88. doi: 10.1016/j.compeleceng.2019.04.015.
42 Cortese F, Scicchitano P, Gesualdo M, Filaninno A, De Giorgi E, Schettini F, et al. Early and Late Infections in Newborns: Where Do We Stand? A Review. Pediatr Neonatol. 2016;57:265-73. doi: 10.1016/j.pedneo.2015.09.007. PubMed PMID: 26750406.
43 Belachew A, Tewabe T. Neonatal sepsis and its association with birth weight and gestational age among admitted neonates in Ethiopia: systematic review and meta-analysis. BMC Pediatr. 2020;20:55. doi: 10.1186/s12887-020-1949-x. PubMed PMID: 32020850; PubMed Central PMCID: PMCPMC7001294.
44 Ornoy A, Ergaz Z. Parvovirus B19 infection during pregnancy and risks to the fetus. Birth Defects Res. 2017;109:311-23. doi: 10.1002/bdra.23588. PubMed PMID: 28398685.
45 Murthy S, Godinho MA, Guddattu V, Lewis

LES, Nair NS. Risk factors of neonatal sepsis in India: A systematic review and meta-analysis. PLoS One. 2019;14:e0215683. doi: 10.1371/journal.pone.0215683. PubMed PMID: 31022223; PubMed Central PMCID: PMCPMC6483350.

46 Beck C, Gallagher K, Taylor LA, Goldstein JA, Mithal LB, Gernand AD. Chorioamnionitis and Risk for Maternal and Neonatal Sepsis: A Systematic Review and Meta-analysis. Obstet Gynecol. 2021;137:1007-22. doi: 10.1097/AOG.0000000000004377. PubMed PMID: 33957655; PubMed Central PMCID: PMCPMC8905581.