

RISK FACTORS FOR NEONATAL SEPSIS IN NEONATAL INTENSIVE CARE UNIT: EVIDENCE STUDY

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ABSTRACT: Integrative literature review aimed to present the main evidence of risk factors for neonatal sepsis in newborns admitted to a Neonatal Intensive Care Unit. The search was performed between the months of July and August 2015, in the databases Scientific Electronic Library Online, SciVerse Scopus and PubMed, using the following descriptors: risk factors, neonatal intensive care unit, newborn and the following keywords: neonatal sepsis and prematurity. The search included 31 publications whose outcomes showed that the predictive factors for neonatal sepsis are associated to gestational age, premature rupture of amniotic membranes and maternal infection. Birth conditions, low weight and prematurity are strong evidence of sepsis. The factors related to the environment of the neonatal intensive care unit are potential contributing factors associated to late-onset sepsis. **DESCRIPTORS:** Neonatal nursing; Risk factors; Sepsis; Neonatal Intensive Care Units.

FATORES DE RISCO PARA SEPSE NEONATAL EM UNIDADE DE TERAPIA: ESTUDO DE EVIDÊNCIA

RESUMO: Revisão integrativa da literatura com o objetivo de apresentar as principais evidências de fatores de risco para sepse neonatal em recém-nascidos internados em Unidade de Terapia Neonatal. A busca foi realizada entre os meses de julho e agosto de 2015, nas bases de dados *Scientific Eletronic Library Online*, *SciVerse Scopus* e *PubMed*, utilizando como descritores: fatores de risco, unidade de terapia intensiva neonatal, recém-nascido e as seguintes palavras-chaves: sepse neonatal e prematuridade. A busca totalizou 31 publicações cujos resultados mostraram que os fatores preditivos para a sepse neonatal estão associados à idade gestacional, ruptura prematura das membranas amnióticas e infecção materna. Condições de nascimento, baixo peso e prematuridade são fortes evidências para sepse. Os fatores relacionados ao ambiente da unidade de terapia intensiva neonatal contribuem fortemente para a sepse tardia.

DESCRIÇÕES: Enfermagem neonatal; Fatores de risco; Sepse; Unidades de Terapia Intensiva Neonatal.

FACTORES DE RIESGO PARA SEPSIS NEONATAL EN UNIDAD DE TERAPIA: ESTUDIO DE EVIDENCIA

RESUMEN: Revisión integrativa de literatura cuya finalidad fue presentar las principales evidencias de factores de riesgo para sepsis neonatal en recién nacidos internados en Unidad de Terapia Neonatal. La búsqueda fue hecha entre los meses de julio y agosto de 2015, en las bases de datos *Scientific Eletronic Library Online*, *SciVerse Scopus* y *PubMed*, utilizándose los descriptores: factores de riesgo, unidad de terapia intensiva neonatal, recién nacido; y las siguientes palabras claves: sepsis neonatal y prematuridad. La búsqueda totalizó 31 publicaciones cuyos resultados mostraron que los factores predictivos para sepsis neonatal están asociados a edad gestacional, ruptura prematura de las membranas amnióticas e infección materna. Condiciones de nacimiento, bajo peso y prematuridad son fuertes evidencias para sepsis. Los factores referentes al ambiente de la unidad de terapia intensiva neonatal contribuyen mucho para la sepsis tardía.

DESCRIPTORES: Enfermería neonatal; Factores de riesgo; Sepsis; Unidades de Terapia Intensiva Neonatal.

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● INTRODUCTION

Neonatal sepsis is a major cause of newborn deaths worldwide and one of the main factors that contribute to high neonatal mortality rates.

Neonatal sepsis accounts for five million newborn deaths, and is mostly diagnosed in underdeveloped countries or in developing countries, like Brazil. The most affected subjects are low-birth weight infants subjected to invasive procedures during their hospitalization in the Neonatal Intensive Care Unit (NICU) ⁽¹⁾.

Infection may occur at an early stage, during the first 48 hours of life, and after this period it is characterized as a late onset, usually caused by contact with pathogens acquired after birth ⁽²⁾.

The signs and symptoms are nonspecific, may be unapparent for some time and mistaken for conditions typical of this period of life, such as respiratory disorders caused by prematurity. Also, for every septic newborn, there are many infants with presumed suspected clinical sepsis⁽¹⁾.

Moreover, consolidated data on the incidence of infections in neonatal units, including sepsis, is not yet available in Brazil. Only data from regional studies is available, which can vary greatly depending on the institution. According to national studies published, these infections are related to birth weight, use of central venous catheter (CVC) and time of mechanical ventilation ⁽²⁾.

Therefore, the investigation of risk factors for neonatal sepsis is important for the implementation of measures aimed to improve the care delivered to neonates, and particularly the prevention of risks associated to exposure to pathogens that cause sepsis⁽³⁾.

The present study is justified by the need for clarification on risk factors for neonatal sepsis, in order to establish the appropriate care to premature newborns, reducing mortality rates at this age range.

The objective of the present study consists in seeking the main evidence available in the literature regarding risk factors for neonatal sepsis in infants hospitalized in Neonatal Intensive Care Units.

● METHOD

This is a traditional integrative literature review: identification of the theme and formulation of the guiding question, search in the literature and selection of studies based on identified criteria, critical assessment of the studies, interpretation of the outcomes and comparisons with other studies, and report of the review and results synthesis.

The guiding question proposed for this review was "What are the main risk factors for sepsis in newborns admitted to a NICU?".

The subsequent step was a bibliographic survey of scientific articles published and indexed in the following electronic databases: Scientific Electronic Library Online (SciELO), SciVerse Scopus (Scopus) and PubMed, using the descriptors risk factors, neonatal intensive care unit, newborn and the following keywords: neonatal sepsis and prematurity. These descriptors and keywords were selected because of the focus on publications related to characteristics of the study object.

The following inclusion criteria were used: studies on risk factor for neonatal sepsis; full original articles indexed in the databases selected for the study published in Portuguese, English or Spanish and that included the abovementioned descriptors or keywords, from 2005 to 2015. The exclusion criteria were editorials, letters to the editor, expert opinions and those unrelated to the object of the study.

The following cross-searches were made to meet the objective of the study: Risk factors (AND) Neonatal sepsis, Risk factors (OR) Neonatal sepsis, Risk factors (AND) Neonatal Intensive Care Unit, Risk factors (OR) Neonatal Intensive Care Unit, Neonatal sepsis (AND) Neonatal Intensive Care Unit, Neonatal sepsis (OR) Neonatal Intensive Care Unit, Neonatal sepsis (AND) Newborn, Neonatal sepsis (OR) Newborn, Neonatal sepsis (AND) Prematurity, Neonatal sepsis (OR) Prematurity.

Because of the different aspects involved in the access to each database, the strategies used to find the articles were adapted to each database. The strategies were based on the guiding question and the previously established inclusion criteria to ensure consistency and prevent possible biases.

The search was performed by online access to the relevant articles in the months of July and August 2015. The tool used was adapted for the search and included the following indicators: identification of the original article, methodological characteristics of the study, assessment of methodological quality, interventions measured and results obtained.

For analysis of the articles selected and presentation of the outcomes, a chart containing the title of the article, author, study design and main results was developed.

● RESULTS

The initial search generated 2,597 articles. After applying the inclusion and exclusion criteria, 107 potentially relevant publications were identified, which were carefully read for refining. After analysis, 27 relevant articles were selected and 80 were excluded for not meeting the inclusion criteria. Duplicate references were removed for articles referenced in more than one database.

Most publications were found in international journals and concerned studies in neonatal intensive care units aimed to investigate the predictive factors for the outcome early or late neonatal sepsis.

Regarding the design of the assessed studies, the sample included: seven cross-sectional descriptive studies (22.6%), five case-control studies (16.1%), five longitudinal observational studies (16.1%), four retrospective quantitative analyzes (12.9%), four integrative reviews (12.9%), three cohort studies (9.7%), two narrative reviews (6.5%) and one systematic review and meta-analysis (3.2%). The following charts (1-4) expose the characteristics of the analyzed studies.

Chart 1 – Studies relating neonatal sepsis to maternal risk factors. Natal, RN, Brazil, 2015 (continues)

Author	Object of the study	Method	Outcome/Risk factor
Berardi A, Cattelani C, Creti R, Berner R, Pietrangioliillo Z, Immaculada M, et al. 2015 ⁽¹⁾	Determine whether maternal antimicrobial prophylaxis for group B streptococcus, up to four hours before delivery, increases the rates of diagnosis of clinical neonatal sepsis.	Retrospective quantitative analysis	Antibiotic maternal prophylaxis up to four hours before delivery reduces the risk for neonatal sepsis
Pinheiro RS, Ferreira LCL, Brum IR, Guilherme JP, Monte RL, 2007 ⁽⁴⁾	Identify the maternal risk factors involved in early-onset neonatal sepsis	Prospective longitudinal cohort study	Lack of prenatal care follow-up, prolonged rupture of fetal membranes and bacterial infection
Goulart AP, Valle CF, Dal-Pizzol F, Cancelier ACL, 2006 ⁽⁵⁾	Identify the risk factors associated to early-onset neonatal sepsis	Case-control study	Maternal infection, previous child with neonatal sepsis and prolonged rupture of fetal membranes
Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, et al. 2011 ⁽⁶⁾	Estimate early-onset sepsis according to intra-uterine risk factors	Case-control study	Increase intrauterine temperature
Alam MM, Saleem AF, Shaikh AS, Munir O, Qadir M, 2014 ⁽⁸⁾	Report the incidence of risk factors for neonatal sepsis	Quantitative descriptive analysis	Maternal infection and prolonged rupture of fetal membranes

Chart 1 – Studies relating neonatal sepsis to maternal risk factors. Natal, RN, Brazil, 2015 (continuation)

Mukhopadhyay S, Puopolo KM, 2012 ⁽⁹⁾	Assess clinical signs and risk factors for neonatal sepsis	Integrative review	Gestational age >37 weeks, premature rupture of fetal membranes and low birth weight are risk factors for neonatal sepsis
Chan GJ, Lee ACC, Baqui AH, Tan J, Black RE, 2013 ⁽¹²⁾	Identify vertical transmission of neonatal sepsis	Systematic review with meta-analysis	Maternal colonization and premature rupture of fetal membranes
Jiang Z, Ye Y, 2013 ⁽²⁴⁾	Investigate the main risk factors for early-onset sepsis and establish prevention measures	Case-control study	Amniotic fluid and prolonged rupture of fetal membranes

Chart 2 – Studies relating neonatal sepsis to neonatal risk factors. Natal, RN, Brazil, 2015

Author	Object of the study	Method	Outcome/Risk factors
Yilmaz NO, Agus N, Helvacı M, Kose S, Ozer E, Sahbudak Z, 2010 ⁽¹¹⁾	Associate risk factors with mortality by neonatal sepsis	Quantitative observational study	Birth weight and infection by <i>Klebsiella</i> are associated to mortality by neonatal sepsis
Carvalho JK, Moore DB, Luz RA, Xavier-Elsas PP, Gaspar-Elsas MIC, 2013 ⁽¹³⁾	Use of genotyping to identify the risk for sepsis	Narrative review	No positive association was found between specific polymorphisms and increased risk for sepsis
Karambin M, Zarkesh M, 2010 ⁽¹⁴⁾	Determine the prevalence of infectious agents associated with neonatal sepsis	Prospective study	Prematurity and low birth weight are associated to neonatal sepsis
Seale AC, Mwaniki M, Newton CR, Berkley JA, 2009 ⁽¹⁵⁾	Identify the etiology, incidence and risk factors for neonatal and maternal sepsis in Africa.	Narrative review	Prematurity and low birth weight are risk factors for sepsis
Gessner BD, Castrodale L, Soriano-Gabarro M, 2005 ⁽¹⁶⁾	Identify the etiology of neonatal sepsis in Alaska	Integrative review	Premature infants with pneumonia and low birth weight are susceptible to infection
Madan JC, Salari RC, Saxena D, Davidson L, O'Toole GA, Moore JH, et al. 2011 ⁽²⁶⁾	Understand microbial colonization of premature infants.	Prospective longitudinal study	Meconium aspiration by low birth weight neonates increases the risk for neonatal sepsis.

Chart 3 – Studies relating neonatal sepsis to external factors. Natal, RN, Brazil, 2015

Author	Object of the study	Method	Outcome/Risk factors
Verstraete EH, De Coen K, Vogelaers D, Blot S, 2015 ⁽³⁾	Describe the risk factors for bloodstream infection	Cohort study	Weight, parenteral nutrition and mechanical ventilation are risk factors
Romanelli RMC, Anchieta LM, Carvalho EAA, Glória e Silva LF, Nunes RVP, Mourão PH, et al. 2014 ⁽¹⁸⁾	Identify the risk factors for sepsis after surgery	Case-control study	Mechanical ventilation, premature infants who underwent surgery and duration of parenteral nutrition
Li Z, Xiao Z, Li Z, Zhong Q, Zhang Y, Xu F, 2013 ⁽²²⁾	Explore risk factors, antibiotics for neonatal sepsis	Retrospective quantitative analysis	Peripherally inserted central catheter (PICC) was the main risk factor for neonatal sepsis
Marchant EA, Boyce GK, Sadarangani M, Lavoie PM, 2013 ⁽¹⁹⁾	Review the epidemiology of immunological risk factors for neonatal sepsis.	Integrative review	Invasive procedures in NICUs are the main risk factors for neonatal sepsis
Turrentine MA, Greisinger AJ, Brown KS, Wehmanen OA, Mouzoon ME, 2013 ⁽¹⁰⁾	Identify the association of empirical antibiotic treatment with late-onset sepsis	Cohort study	Intrapartum antibiotics treatment is related to worsening of symptoms
Lin CB, Hornik CP, Clark R, Cotten CM, Benjamin Jr DK, Cohen-Wolkowicz M, et al, 2012 ⁽²³⁾	Assess the association between positive blood culture and late-onset neonatal sepsis	Retrospective quantitative analysis	This study found no association between positive blood culture and late onset of sepsis
Leal YA, Álvarez-Nemegyei J, Velázquez JR, Rosado-Quiab U, Diego-Rodríguez N, Paz-Baeza E, et al, 2012 ⁽⁷⁾	Identify the risk factors for neonatal sepsis prognosis	Quantitative descriptive analysis	Respiratory complications, need for assisted ventilation and surgical procedure are risk factors for neonatal sepsis
Hsieh E, Smith PB, Jacqz-Aigrain A, Kaguelidou F, Cohen-Wolkowicz M, Manzoni P, et al. 2012 ⁽²¹⁾	Identify the risk factors for neonatal sepsis related to <i>Candida</i> and report its treatment	Quantitative descriptive analysis	<i>Candida</i> , prior exposure to cephalosporins and presence of central venous catheters are risk factors for sepsis.

Chart 4 – Studies relating neonatal sepsis to external factors. Natal, RN, Brazil,

Author	Object of the study	Method	Outcome/Risk factor
Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, et al. 2011 ⁽⁶⁾	Estimate early onset sepsis according to intrauterine risk factors	Case-control study	Correlation with neonatal sepsis: increased intrauterine temperature and length of exposure to premature rupture of membranes.
Goulart AP, Valle CF, Dal-Pizzol F, Cancelier ACL, 2006 ⁽⁵⁾	Investigate the risk factors associated to neonatal septicemia	Quantitative descriptive analysis	Enteral nutrition is a risk factor for sepsis
Meireles LA, Vieira AA, Costa CR, 2010 ⁽¹⁷⁾	Describe the clinical characteristics of neonates with proven and unproven late onset sepsis	Quantitative descriptive analysis	Length of hospital stay and presence of neutrophils are risk factors for neonatal sepsis.
Borges RM, Soares LR, de Brito CS, Brito DVD, Abdallah VOS, Gontijo Filho PP, 2009 ⁽²⁵⁾	Investigate <i>Candida albicans</i> as colonization and sepsis agent and the risk factors for neonatal sepsis	Quantitative observational study with secondary data	Previous antibiotic treatment and use of umbilical venous catheter are risk factors for neonatal sepsis
Tragante CR, Ceccon MEJR, Falcão MC, Seiti M, Sakita N, Vieira RA, 2008 ⁽²⁰⁾	Determine the prevalence and mortality of neonatal sepsis by Gram-negative bacteria	Retrospective and descriptive study	Mortality related to sepsis was higher in nosocomial infection by Gram-negative bacteria.

● DISCUSSION

The outcomes described in these publications showed that the risk factors for the development of neonatal sepsis are related to three conditions: gestational and maternal factors; birth conditions and prematurity, and factors related to NICU environment.

Gestational and Maternal Factors

The relationship between the presence of maternal risk factors and the possibility of infection in infants is evident in several studies of this review, with emphasis to infection during the gestational period and premature rupture of the membranes.

A study conducted in the state of Amazonas reported that colonization by group *B Streptococcus* (GBS) in pregnant women increases the risk for neonatal sepsis in premature newborns by 15.2%⁽⁴⁾. Other findings from retrospective studies report association between maternal infection by GBS in the urinary tract (62.1%) with prevalence of neonatal sepsis in 1/1,000 infants born alive admitted to neonatal intensive care unit, and that other infections originated during pregnancy are risk factors for neonatal sepsis⁽⁵⁾.

Corroborating the findings of this investigation, some studies report that the frequency of neonatal sepsis after rupture of the membranes occurred more than 18 hours ago is approximately 72.7%, with increased risk when associated to signs and symptoms of chorioamnionitis⁽⁶⁾. It is estimated that premature rupture of fetal membranes occurs in approximately 20% to 25% of the pregnancies, and is more common in women colonized by GBS⁽⁵⁻⁷⁾. Also, it is a major risk factor for prematurity and early onset sepsis, and a leading cause of neonatal mortality and morbidity worldwide⁽⁷⁻⁸⁾.

Finally, the correlation between empirical management of neonatal sepsis using maternal intrapartum antibiotics when there is have prolonged rupture of fetal membranes and decrease in the incidence of neonatal sepsis should be stressed⁽⁹⁾. Although the risk for neonatal septicemia is reduced by this treatment, it persists in 5 to 8% of the cases. However, the decision of beginning this intrapartum antibiotics prophylaxis should be based on the presence or absence of the referred maternal and neonatal factors^(6,10).

Birth Conditions and Prematurity

Prematurity and low birth weight are major risk factors for neonatal sepsis⁽¹¹⁻¹²⁾. In line with these findings, a study conducted in Brazil identified a higher rate of early onset neonatal sepsis in newborns with gestational age between 29 and 34 weeks and weight ≤ 1000 g. These findings corroborate that prematurity and low birth weight are a significant risk factor for sepsis⁽¹³⁾. Moreover, a study carried out in Asia found association between neonatal sepsis diagnosis and the presence of positive blood culture, low birth weight and prematurity⁽¹⁴⁻¹⁵⁾. Therefore, it can be inferred that prematurity associated to low birth weight is a leading risk factor for the development of sepsis^(12, 16-17).

Other studies reveal increased incidence of this disease among infants born to teenage mothers who gave birth prematurely and who had fewer than six routine antenatal care appointments, which is recommended by the Ministry of Health (six appointments). This may contribute to the non-identification of key factors involved in the referred infectious process⁽⁴⁾.

Factors related to the NICU environment

Late-onset sepsis is related to the stay of newborns in NICU where they are exposed to the use of peripherally inserted central catheter (PICC), mechanical ventilation and parenteral nutrition^(17,18-19). One study with newborns who developed sepsis by *Klebsiella pneumoniae* (ESBL) found that central venous catheter, prolonged parenteral nutrition and broad-spectrum antibiotics were used in the treatment of all the participants. Most required mechanical ventilation and stayed in the NICU for more

than 21 days. These findings indicate that the referred factors contribute to the increase in the risk for infections in NICU, due to exposure to several invasive procedures, often required in the treatment of neonatal infections. These procedures associated to constant manipulation of the neonates and their clinical condition increases the risk of mortality of this population⁽²⁰⁻²¹⁾.

Finally, incubators, intravenous nutrition and the use of PICC were also identified as risk factors for neonatal sepsis, and PICC was considered the most serious risk factor⁽²²⁻²³⁾.

● CONCLUSION

In-depth analysis of the studies allowed identifying the risk factors that interfere in the onset of neonatal sepsis. Prematurity and low birth weight were the most prevalent predictive factor in all the studies. Gestational age, infection of the genitourinary tract and premature rupture of fetal membranes were the main gestational risk factors involved in neonatal sepsis. The factors related to the NICU setting include the average length of hospital stay, use of invasive devices such as PICC catheter, invasive mechanical ventilation and parenteral nutrition, which are aggravated by the immunological immaturity of the newborns.

One limitation of this study is the lack of standardization of the methods of investigation of the factors associated to neonatal sepsis. Thus, the outcomes of these studies may vary according to the characteristics of the population investigated.

Therefore, it is concluded that identification of the risk factors associated to the diagnosis of neonatal sepsis may contribute to interventions and research that helps to reduce neonatal mortality resulting from these risks.

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