



## Factors associated with late-onset sepsis in neonates admitted to Neonatal Intensive Care Unit in southern Brazil

*Fatores associados a sepse tardia em neonatos assistidos em uma Unidade de Terapia Intensiva Neonatal no sul do Brasil*  
*Factores asociados a sepsis de inicio tardío en neonatos ingresados en la Unidad de Cuidados Intensivos Neonatales en el sur de Brasil*

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### ABSTRACT

**Background and Objectives:** Late-onset neonatal sepsis is one of the main healthcare-associated infections affecting newborns admitted to neonatal intensive care units, with high incidence rates and a significant impact on neonatal morbidity and mortality. The objective of the study was to analyze factors associated with the development of late-onset sepsis in newborns admitted to neonatal intensive care units (NICUs). **Methods:** Retrospective documentary cohort study. Data were collected from the medical records and discharge summaries of neonates admitted to the NICU from January 2016 to December 2020 at a philanthropic general hospital in the northwestern region of the state of Rio Grande do Sul, Brazil. The data were analyzed using descriptive, analytical, and inferential statistics. **Results:** Late-onset sepsis occurred in 34% of the 494 newborns included in the study. The mean age at diagnosis of late-onset sepsis was 10 days; 52.9% of blood cultures were positive. Late-onset sepsis was associated with a lower number of prenatal appointments ( $p = 0.003$ ), gestational age and prematurity ( $p = 0.001$ ), complications during pregnancy ( $p = 0.001$ ), blood transfusion ( $p < 0.001$ ), corticosteroid use ( $p = 0.02$ ), resuscitation at birth ( $p = 0.01$ ), and very low birth weight ( $p = 0.001$ ). **Conclusion:** The incidence of late-onset sepsis in the NICU was high compared with rates reported in the literature. Developing strategies to reduce these rates is necessary, focusing on the quality of care and prevention measures while considering the different risk factors present during the hospitalization and hospital stay of newborns.

**Keywords:** *Newborn. Neonatal sepsis. Neonatal Intensive Care Units. Preterm Birth.*

### RESUMO

**Justificativa e Objetivos:** A sepse neonatal tardia é uma das principais infecções associadas à assistência à saúde que afetam recém-nascidos internados em unidades de terapia intensiva neonatal, com altas taxas de incidência e impacto significativo na morbidade e mortalidade neonatal. O objetivo deste estudo foi analisar os fatores associados ao desenvolvimento de sepse neonatal tardia em recém-nascidos internados em unidades de terapia intensiva neonatal (UTIN). **Métodos:** estudo de coorte, documental e retrospectivo. A coleta das variáveis de interesse foi realizada por meio de prontuários e resumos de alta de neonatos internados em UTIN, no período de janeiro de 2016 a dezembro de 2020, em um hospital geral filantrópico da região noroeste do estado do Rio Grande do Sul, Brasil. Os dados foram analisados por meio de estatística descritiva, analítica e inferencial. **Resultados:** 34% dos 494 recém-nascidos incluídos apresentaram sepse tardia. A média de idade em que os recém-nascidos foram diagnosticados com sepse tardia foi de 10 dias; 52,9% das hemoculturas foram positivas. A sepse tardia mostrou-se associada a: menor número de consultas de pré-natal ( $p = 0,003$ ); idade gestacional; prematuridade ( $p = 0,001$ ); complicações na gestação ( $p = 0,001$ ); transfusão sanguínea ( $p < 0,001$ ); uso de corticoides ( $p = 0,02$ ), reanimação ao nascimento ( $p = 0,01$ ) e muito baixo peso ao nascer ( $p = 0,001$ ). **Conclusão:** as taxas de sepse tardia encontradas em UTIN são elevadas quando comparadas à literatura. É necessário o desenvolvimento de ações para a redução desses índices, as quais devem ser pautadas na qualidade da assistência e em estratégias de prevenção, considerando os diferentes momentos de risco durante a admissão e permanência hospitalar dos recém-nascidos.

**Descritores:** *Recém-nascido. Sepse neonatal. Unidades de Terapia Intensiva Neonatal. Nascimento Prematuro.*

### RESUMEN

**Justificación y Objetivos:** La sepsis neonatal de aparición tardía es una de las principales infecciones asociadas a la atención sanitaria que afectan a los recién nacidos ingresados en unidades de cuidados intensivos neonatales, con altas tasas de incidencia y un impacto significativo en la morbilidad y mortalidad neonatal. El objetivo del estudio fue analizar los factores asociados al desarrollo de sepsis de aparición tardía en recién nacidos ingresados en unidades de cuidados intensivos neonatales (UCIN). **Métodos:** Estudio de cohorte, documental y retrospectivo. La recopilación de variables de interés se realizó a través de historias clínicas y resúmenes de alta de neonatos ingresados en la UCIN entre enero de 2016 y diciembre de 2020, en un hospital general filantrópico de la región noroeste del estado de Rio Grande do Sul, Brasil. Los datos se analizaron mediante estadística descriptiva, analítica e inferencial. **Resultados:** El 34% de los 494 recién nacidos incluidos presentaron sepsis de inicio tardío. La edad media de diagnóstico de sepsis de inicio tardío fue de 10 días; el 52,9% de los hemocultivos fueron positivos. La sepsis de inicio tardío se asoció con: menor número de citas prenatales ( $p = 0,003$ ); edad gestacional, prematuridad ( $p = 0,001$ ); complicaciones durante el embarazo ( $p = 0,001$ ); transfusión sanguínea ( $p < 0,001$ ); uso de corticosteroides ( $p = 0,02$ ), reanimación al nacer ( $p = 0,01$ ) y muy bajo peso al nacer ( $p = 0,001$ ). **Conclusión:** Las tasas de sepsis tardía en la UCIN son altas en comparación con la literatura. Es necesario desarrollar acciones para disminuir estos índices, las cuales deben basarse en la calidad de la atención y las estrategias de prevención, considerando los diferentes factores de riesgo durante el ingreso y la estancia hospitalaria de los recién nacidos.

**Palabras Clave:** *Recién nacido. Sepsis neonatal. Unidades de Cuidado Intensivo Neonatal. Nacimiento Prematuro.*

## INTRODUCTION

Bacterial sepsis is an important cause of morbidity and mortality in newborns and may lead to severe neurological sequelae, hypoxemia secondary to septic shock, persistent pulmonary hypertension, and severe parenchymal lung disease.<sup>1</sup> Despite advances in neonatal intensive care and improvements in neonatal survival, healthcare-associated infections (HAIs) remain highly prevalent and may represent one of the main factors limiting neonatal survival.<sup>2</sup> In this context, neonatal intensive care units (NICUs) are specialized environments intended for the admission and care of high-risk neonates, providing adequate physical infrastructure, equipment, materials, and a multidisciplinary team trained to deliver specialized care.<sup>3</sup>

In Brazil, sepsis accounts for approximately 30.2% of intensive care unit (ICU) bed occupancy, with mortality rates reaching 52–59%.<sup>4</sup> Neonatal sepsis, defined as sepsis occurring within the first 28 days of life, is a global health problem associated with high mortality and unfavorable long-term outcomes, especially in low-resource settings. Estimates indicate that late-onset sepsis occurs in 3 to 6 cases per 1,000 live births, whereas early-onset sepsis ranges from 0.9 to 3.5 cases per 1,000 live births. However, early recognition and diagnosis remain challenging. The low positive predictive value and limited reproducibility of currently available diagnostic tests contribute to low clinical suspicion and high rates of empirical antimicrobial therapy.<sup>5,6</sup>

Neonatal late-onset sepsis (LOS) is defined as sepsis occurring after 72 hours of age. It is more common among newborns who require a prolonged stay in the NICU, particularly those born extremely preterm and those with very low birth weight.<sup>7</sup> Other risk factors include disruption of protective barriers, central catheter use, invasive procedures, and prolonged empirical antibiotic therapy.<sup>2,8</sup>

The incidence of late-onset neonatal sepsis varies according to the region. In Peru, between 2015 and 2019, late-onset neonatal sepsis affected 7.4% of hospitalized neonates, corresponding to 10.04 cases per 1,000 live births.<sup>9</sup> In a Brazilian NICU cohort, the incidence of late-onset neonatal sepsis was approximately 22% among hospitalized neonates, with an incidence density of 18.6 cases per 1,000 central venous catheter-days. The incidence was significantly higher among very low birth weight neonates (34%). In addition, the literature highlights numerous studies focusing on low birth weight or preterm neonates. For example, a study conducted at a hospital in Bahia evaluating preterm newborns found that approximately 20% developed late-onset sepsis.<sup>10</sup> Among very low

birth weight neonates, studies conducted in Brazil have reported incidence rates ranging from 9% to 29%.<sup>11,12</sup>

Despite the high incidence and clinical relevance of late-onset neonatal sepsis, important knowledge gaps remain regarding its local epidemiology and specific clinical and obstetric risk factors. Although data on neonatal sepsis have been reported in other regions and countries, regional variations in healthcare infrastructure, clinical protocols, and population profiles can significantly alter the risk dynamics. Evidence focused on the southern region of Brazil remains scarce.<sup>13–16</sup> Therefore, local epidemiological investigations are essential not only to address this gap in the literature, but also to provide robust data that can support tailored prevention strategies, optimize clinical decision-making, and ultimately improve outcomes in neonatal intensive care units. In this context, the objective of this study was to analyze factors associated with the development of LOS in newborns admitted to a NICU.

## METHODS

### Study design

This was a retrospective analytical cohort study based on a review of medical records.

### Setting

The study was conducted in the Neonatal Intensive Care Unit (NICU) of a philanthropic macroregional hospital located in northwestern Rio Grande do Sul, southern Brazil. The NICU has eight beds, with a mean monthly occupancy rate of 87.5%.<sup>17</sup> The study included admissions occurring between January 1, 2016, and December 31, 2020. Data were collected between February and June 2021.

### Participants

The established inclusion criteria were being a newborn up to 28 days of age and having been admitted to the NICU for a minimum of five days between January 1, 2016, and December 31, 2020. The exclusion criterion was admission to the NICU at more than 28 days of age. Initially, a population of 498 neonates was screened. Four neonates admitted after 28 days of life were excluded, representing 0.8% of the total population, resulting in a final sample of 494 participants.

### Data sources and measurements

Data were extracted from electronic medical records and neonatal discharge summaries using a standardized data collection instrument developed by the research team.

## Variables

The obstetric variables collected were number of prenatal appointments, maternal disease or infection during pregnancy, premature rupture of membranes, complications, use of antibiotics during pregnancy, antenatal corticosteroid therapy, type of delivery, and place of birth. The neonatal variables were gestational age at birth, sex, birth weight, Apgar score, need for resuscitation at birth, diagnosis of neonatal sepsis, LOS starting day, blood culture results obtained based on clinical symptoms, use of mechanical ventilation, use of parenteral nutrition, and use of inotropes or antibiotics. Laboratory variables included C-reactive protein (CRP) levels and leukopenia on the complete blood count, as well as clinical outcome (discharge or death).

The definition of sepsis used in this study was a life-threatening organ dysfunction caused by a dysregulated host response to infection, based on clinical and laboratory criteria, neonatal LOS is considered when the clinical status starts after 72 hours of age, definition accepted worldwide, and defined by the hospital's own protocol.<sup>6,18,19</sup> The hospital protocol defined late-onset neonatal sepsis as the presence of signs and symptoms suggestive of sepsis in patients older than 72 hours of life, associated with one or more of the following laboratory findings: an immature-to-total neutrophil ratio  $\geq 0.2$ ; leukopenia ( $<5,000/\text{mm}^3$ ) associated with neutropenia ( $<1,000/\text{mm}^3$ ) or leukocytosis ( $>25,000/\text{mm}^3$ ); C-reactive protein (CRP)  $>10 \text{ mg/L}$ ; or a platelet count  $<50,000/\text{mm}^3$ . A confirmatory positive blood culture was not required for diagnosis.

The main clinical signs of neonatal infection included the following: Thermal instability: hypothermia (axillary temperature  $<36.5^\circ\text{C}$ ) or hyperthermia (axillary temperature  $>37.5^\circ\text{C}$ ); Apnea, bradycardia, tachypnea, grunting, respiratory distress, nasal flaring, or cyanosis; Hypotonia or seizures; Irritability (high-pitched crying), lethargy, or hypertonia; Abdominal distension, vomiting, gastric residuals, or feeding intolerance; Idiopathic jaundice; Skin pallor, cold and clammy skin, hypotension, or capillary refill time  $\geq 3$  seconds; Signs of bleeding, with clinical manifestations suggestive of disseminated intravascular coagulation; and Subjective assessment that the newborn "did not appear well." The analysis of LOS was carried out considering the data from the day of identification and its evolution in the discharge summary.

Neonates born alive before 37 completed weeks of gestation were considered preterm. Preterm birth was categorized according to gestational age at birth as follows: extremely preterm,  $<28$  weeks; very preterm, 28 to  $<32$  weeks; and moderate-to-late preterm, 32 to 36 weeks and 6 days.<sup>20</sup>

## Study size

The study sample consisted of all eligible neonates admitted during the study period; therefore, no sample size calculation was performed.

## Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22.0, and R software (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at  $p < 0.05$ . The normality of quantitative variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Categorical variables were described using absolute and relative frequencies, whereas continuous variables were expressed using measures of central tendency and dispersion. Associations between categorical variables were assessed using the chi-square test. Relative risks (RR) and respective 95% confidence intervals (CIs) were estimated.

Variables that showed statistical significance were included in the multivariate statistical model. The matrix was then subjected to eigenvalue and eigenvector estimation for the patients and measured variables. A Principal Component Analysis Biplot was then applied, which decreased the variability in the representative dimensions of variation.

## Ethical aspects

The study was conducted in accordance with the ethical standards established by Resolution no. 466/2012 of the Brazilian National Health Council and approved by the Institutional Research Ethics Committee (CAAE no. 42342521.1.0000.5350; approval no. 4.601.870, March 19, 2021).

## RESULTS

The total number of newborns included in the study was 494, of whom 168 (34%) developed late-onset sepsis (LOS), corresponding to an incidence of 34 cases per 100 neonates. Among preterm neonates, the incidence was 40 cases per 100 newborns, whereas among term neonates the incidence was 21 cases per 100 newborns. The mean age at LOS diagnosis was 10 days (standard deviation: 6.1 days), ranging from 4 to 32 days of life. Positive blood cultures were identified in 52.9% of the cases.

Obstetric and neonatal factors associated with the occurrence of LOS were also evaluated. No statistically significant associations were observed between LOS occurrence and sex or type of delivery. Regarding prenatal care, neonates whose mothers attended fewer than six prenatal consultations had a higher probability of developing LOS ( $p = 0.003$ ). Preterm neonates presented a significantly higher frequency of LOS (39.7%) compared with term neonates (21.3%). In

addition, a higher proportion of LOS (38.8%) was observed among newborns whose mothers experienced

complications during pregnancy (Table 1).

**Table 1.** Obstetric and neonatal characteristics associated with the occurrence of late-onset sepsis in neonates admitted to a neonatal intensive care unit. Ijuí, Brazil, 2016-2020.

| Characterization                        | Categories                    | LOS       |           |            | Relative risk<br>(IC = 95%) | p-value |
|-----------------------------------------|-------------------------------|-----------|-----------|------------|-----------------------------|---------|
|                                         |                               | Yes (%)   | No (%)    | Total (%)  |                             |         |
| Sex                                     | Feminine                      | 73(36.5)  | 127(63.5) | 200(40.6)  | 1.198<br>(0.821-1.748)      | 0.350   |
|                                         | Masculine                     | 95(32.4)  | 198(67.6) | 293(59.4)  |                             |         |
| Type of delivery                        | Vaginal                       | 43(35.2)  | 79(64.8)  | 122(24.7)  | 1.071<br>(0.679-1.646)      | 0.750   |
|                                         | Cesarian                      | 125(33.7) | 246(66.3) | 371(75.3)  |                             |         |
| Prenatal appointments                   | < 6 appointments              | 65(43.6)  | 84(56.4)  | 149(30.2)  | 1.811<br>(1.217-2.695)      | 0.003*  |
|                                         | ≥ 6 appointments              | 103(29.9) | 241(70.1) | 344(69.8)  |                             |         |
| Place of birth                          | In the institution            | 132(36.1) | 234(63.9) | 366(74.2)  | 1.426<br>(0.917 - 2.216)    | 0.110   |
|                                         | Other institution             | 36(28.3)  | 91(71.7)  | 127(25.8)  |                             |         |
| Gestational age                         | Preterm                       | 136(39.7) | 207(60.3) | 343(69.6)  | 2.423<br>(1.550-3.786)      | 0.001*  |
|                                         | Term                          | 32(21.3)  | 118(78.7) | 150(30.4)  |                             |         |
| Complications during pregnancy          | Not                           | 24(19.7)  | 98(80.3)  | 122(24.7)  | 0.386<br>(0.236-0.632)      | 0.001*  |
|                                         | Yes                           | 144(38.8) | 227(61.2) | 371(75.3)  |                             |         |
| Premature rupture of membranes          | Yes                           | 24(30.8)  | 54(69.2)  | 78(15.8)   | 0.836<br>(0.496-1.409)      | 0.500   |
|                                         | Not                           | 144(34.7) | 271(65.3) | 415(84.2)  |                             |         |
| Use of corticosteroids during pregnancy | Yes                           | 77(40.5)  | 113(59.5) | 190(38.5)  | 1.587<br>(1.086-2.321)      | 0.020*  |
|                                         | Not                           | 91(30.0)  | 212(70.0) | 303(61.5)  |                             |         |
| Use of antibiotics during pregnancy     | Yes                           | 49(37.1)  | 83(62.9)  | 132(26.8)  | 1.201<br>(0.792-1.819)      | 0.390   |
|                                         | Not                           | 119(33.0) | 242(67.0) | 361(73.2)  |                             |         |
| Blood transfusion                       | Yes                           | 128(65.6) | 67(34.4)  | 195(39.6)  | 12.322<br>(7.894-19.234)    | <0.001* |
|                                         | Not                           | 40(13.4)  | 258(86.6) | 298(60.4)  |                             |         |
| Apgar at 5 minutes                      | < 7                           | 12(35.3)  | 22(64.7)  | 34(6.9)    | 1.059<br>(0.511-2.197)      | 0.870   |
|                                         | ≥ 7                           | 155(34.0) | 301(66.0) | 456(93.1)  |                             |         |
| Resuscitation at birth                  | Not                           | 102(30.4) | 234(69.6) | 336 (68.2) | 0.601<br>(0.406-0.890)      | 0.010*  |
|                                         | Yes                           | 66(42.0)  | 91(58.0)  | 157(31.8)  |                             |         |
| Birth weight                            | Adequate (≥2,500 g)           | 46(23.2)  | 152(76.8) | 198(40.2)  | -                           | 0.001*  |
|                                         | Low weight (1,000 to 2,500 g) | 98(36.4)  | 171(63.6) | 269 (54.6) |                             |         |
|                                         | Very low weight (<1,000 g)    | 24(92.3)  | 2(7.7)    | 26(5.3)    |                             |         |

Abbreviation: \*Statistically significant by the chi square test ( $p < 0.05$ ). LOS (late-onset sepsis).

Neonates diagnosed with LOS had higher frequencies of antenatal corticosteroid use, blood transfusion, resuscitation at birth, and very low birth weight. All of these associations were statistically significant. (Table 1).

The evaluation of relative risk showed that neonates whose mothers attended fewer than six prenatal consultations had an 82% higher risk of developing LOS. Preterm birth was associated with a 2.5-fold higher risk of LOS, antenatal corticosteroid use was associated with a 58% higher risk, and blood transfusion was associated with a 12-fold higher risk of developing LOS.

The results regarding care interventions, clinically relevant laboratory tests, and mortality among the 168 neonates who developed LOS are described below. Most neonates (88.7%) had central venous access, and 47.6% had negative blood cultures at the time of sepsis diagnosis. Additionally, 76.2% were receiving total parenteral nutrition, and 64.3% were receiving mechanical ventilation. The diagnostic tests showed that a high percentage of the neonates (56.5%) had C-reactive protein (CRP) <6, which was considered a negative result according to the reference parameters of the health service under study. Leukopenia was observed in 22.6% of the neonates. The percentage of patients with LOS who died was 3.6% (Figure 1).

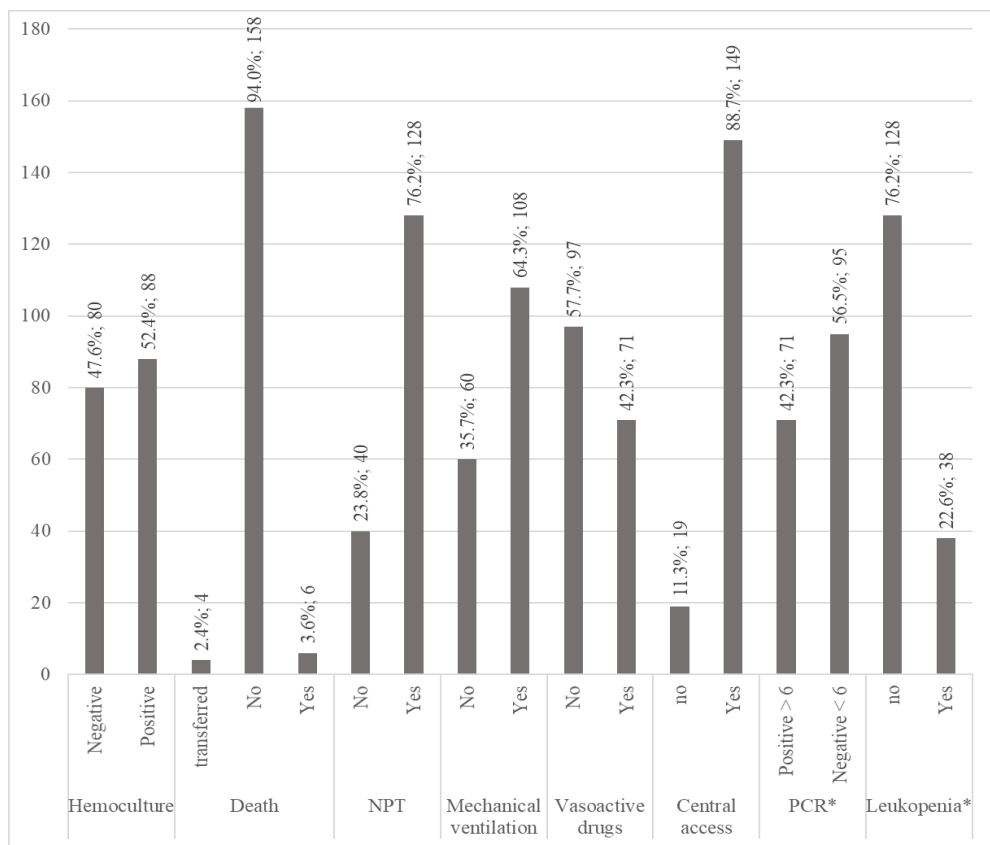


**Figure 1.** Diagnosis and clinical procedures among neonates admitted to a neonatal intensive care unit according to the occurrence of late-onset sepsis. Ijuí, Brazil, 2016-2020.  
 Abbreviations: TPN = total parenteral nutrition; CRP = C-reactive protein. \* Not informed.

Coagulase-negative staphylococci were the most frequently identified causative agents of LOS, accounting for 70% of cases. Blood cultures were positive in 52.9% of cases; among the positive cultures, 78.6% yielded Gram-positive organisms, predominantly coagulase-negative staphylococci, while 6.7% yielded *Klebsiella pneumoniae* and 7.8% yielded *Acinetobacter* spp. (Figure 2). Regardless of the agent, all patients received adequate treatment.

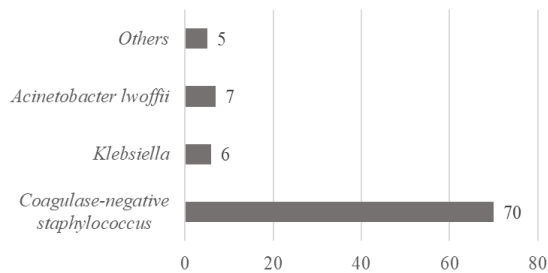


**Figure 2.** Causative agents of late-onset sepsis diagnosed in neonates admitted to a neonatal intensive care unit. Ijuí, Brazil, 2016-2020.

PCA was performed as an exploratory multivariate approach to identify clustering patterns among variables associated with late-onset sepsis. It demonstrated that neonates with late-onset sepsis showed greater clustering of variables related to prematurity and clinical severity, including antenatal corticosteroid exposure, pregnancy complications, blood transfusion, and the need for resuscitation. These findings suggest that late-onset sepsis is associated with a profile of greater neonatal vulnerability and intensive clinical support.

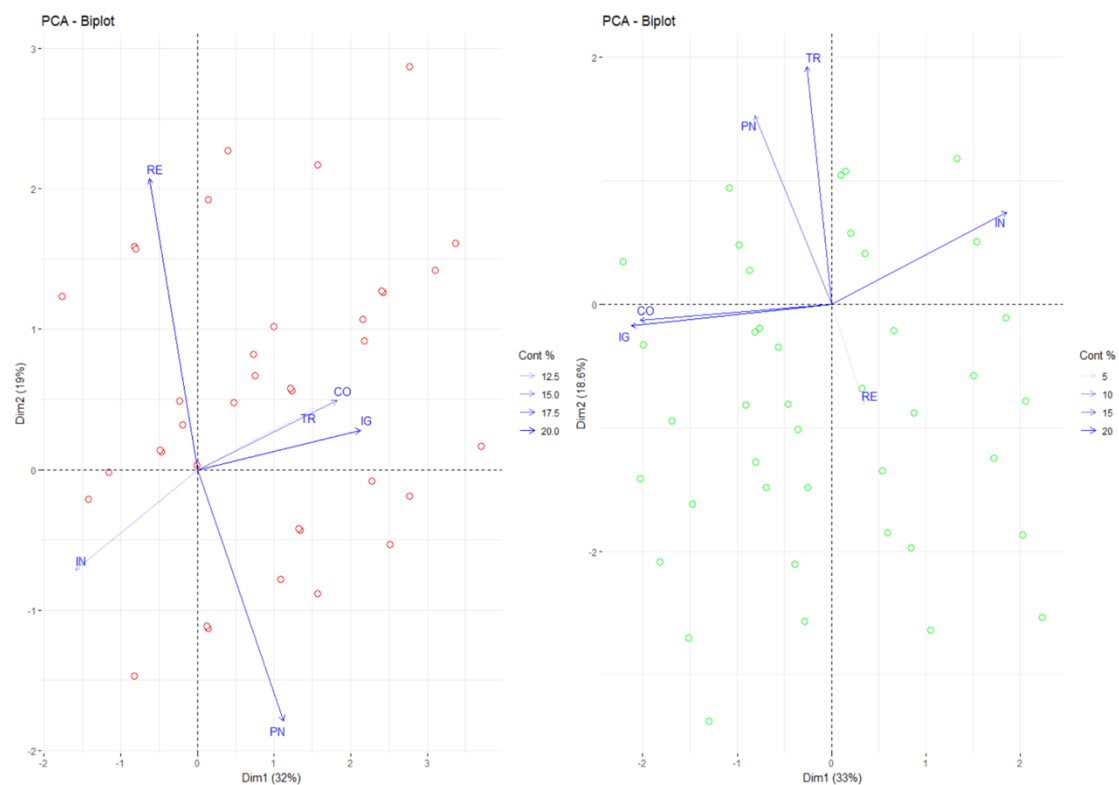


**Figure 3.** Principal Component Analysis (PCA)-Biplot illustrating the multidimensional relationship among clinical variables in neonates with and without late-onset sepsis. Patients with (left) and without (right) late-onset sepsis. Ijuí, Brazil, 2016-2020. Abbreviations: PN = prenatal; COM = complications; COR = corticosteroids; RE = resuscitation; BT = blood transfusion; GE = gestational age.

## DISCUSSION

Neonatal sepsis remains a major challenge for healthcare professionals seeking to reduce neonatal morbidity and mortality rates. This concern is reinforced by the findings of the present study, which demonstrated an incidence of 34 cases per 100 neonates in a NICU, being nearly twice as high for preterm neonates when compared to term newborns. Previous studies have reported lower incidence rates, with rates of 7.4% among preterm newborns and 2.4% among term newborns.<sup>9</sup>

An international study showed that late-onset sepsis (LOS) occurred in 25.9% of admissions, with 45.5% of cases confirmed by positive blood cultures.<sup>21</sup> In the present study, the incidence of LOS was 34%, which was higher than the rates reported in other studies. For instance, a cohort study found an overall incidence of sepsis of 11.63 per 1,000 live births, and 56.14 per 1,000 intensive care unit admissions.<sup>22</sup> Similarly, a study conducted in Malaysia reported a lower rate, with LOS diagnosed in 22.6% of cases.<sup>23</sup> Therefore, comparing these findings highlights divergent results regarding LOS incidence. Such differences may be attributed to variations in methodological design, study period, and local healthcare contexts, including access to health services, prenatal monitoring, and neonatal care standards, which may limit direct comparisons between studies.<sup>13-16</sup>

The results of the present study demonstrated an association between LOS and preterm birth, pregnancy complications, fewer than six prenatal consultations, antenatal corticosteroid use, blood transfusion, resuscitation at birth, and low birth weight. Birth weight and gestational age are important risk factors for neonatal LOS, as they are major determinants of prolonged NICU hospitalization. The greater the degree of prematurity and the lower the birth weight, the higher the risk of complications and infections.<sup>9,14,21,23,24</sup> Prematurity is considered a major risk factor for LOS because preterm newborns present reduced production of proinflammatory cytokines, impaired cell-mediated immunity, decreased transplacental transfer of immunoglobulins, and lower serum complement levels.<sup>7</sup> In this context, adequate prenatal care and close monitoring of high-risk pregnancies are essential to prevent preterm birth and consequently reduce the risk of LOS.

Preventable deaths still occur in Brazil and are closely related to the quality of healthcare services, including prenatal, delivery, and neonatal care. Adequate prenatal follow-up, an efficient hospital referral system, and skilled care during childbirth are among the main factors that can contribute to reducing maternal and neonatal mortality rates.<sup>25</sup> In this context, attending fewer than six prenatal consultations may reflect structural and socioeconomic barriers to accessing healthcare services, such as difficulties in scheduling appointments, geographic remoteness, low

socioeconomic or educational level, unintended pregnancy, late detection of pregnancy, or deficits in the organization and coverage of primary healthcare networks. These factors hinder timely maternal monitoring and interventions, thereby contributing to unfavorable neonatal outcomes.<sup>25</sup>

In pregnancies at risk of preterm birth, antenatal corticosteroid therapy is a well-established intervention aimed primarily at accelerating fetal lung maturation and reducing severe neonatal morbidity and mortality.<sup>26,27</sup> Consequently, its administration is inherently concentrated in high-risk gestations associated with extreme or early prematurity, a population that is intrinsically at a greater risk for late-onset sepsis due to immunological immaturity and invasive procedures.<sup>27</sup> Therefore, the association between maternal corticosteroid use and neonatal sepsis observed in this study does not imply a direct causal relationship. Instead, it may reflect a selection bias (indication bias), as corticosteroids are more frequently administered to mothers whose infants face the highest baseline vulnerability to infections.<sup>27,28</sup>

Blood transfusion was associated with a 12-fold higher risk for the occurrence of LOS. However, preterm newborns frequently develop anemia, partly due to blood loss and, in some cases, because of blood samples in volumes larger than necessary. As a result, many of these neonates require at least one red blood cell transfusion.<sup>29</sup> The criteria used to determine the need for blood transfusion were not evaluated in the present study, which represents a limitation. Nevertheless, considering the potential impact of blood transfusions on LOS, the development and implementation of transfusion protocols in healthcare services are important, especially in neonatal care.

The rate found for mortality associated with LOS was 3.6%. However, most studies present higher mortality rates, from 20.59% to 24%, which may be explained by the different designs used by these studies, as these studies considered only blood culture-confirmed cases as late-onset sepsis.<sup>9,22</sup>

Newborns with LOS showed a high frequency of total parenteral nutrition use, whereas lower rates have been reported in the literature (60.16%).<sup>24</sup> Early parenteral nutrition in preterm neonates during the first seven postnatal days has been associated with higher survival rates at hospital discharge; however, these neonates also present increased rates of necrotizing enterocolitis, bronchopulmonary dysplasia, LOS, and need for surgical interventions.<sup>30</sup> Although parenteral nutrition is essential for the survival of many newborns, its administration should follow strict protocols and require careful monitoring and rigorous clinical control.

Complementary laboratory tests, such as complete blood count and C-reactive protein (CRP), generally have higher negative predictive values than positive

predictive values. However, in certain situations, serum CRP levels, when interpreted together with the clinical condition of the newborn, may contribute to guiding appropriate treatment decisions.<sup>7</sup> Although new infection biomarkers have been investigated, CRP remains one of the most widely used markers in many NICUs due to its broad availability, rapid and simple measurement, and favorable cost-effectiveness.<sup>2</sup>

Invasive procedures, such as tracheal intubation, increase the risk of sepsis, particularly when repeated intubation procedures are required. In the present study, most patients required mechanical ventilation, a risk factor that has also been reported in previous studies. Another study reported a lower frequency of mechanical ventilation use (21.9%) than that observed in the present study.<sup>21</sup> However, the clinical conditions that indicated the need for mechanical ventilation were not evaluated, which represents a limitation of this study. In addition, the occurrence of reintubation procedures, which may further increase the risk of LOS, was not assessed.

In the present study, 52.4% of the blood cultures collected during episodes of LOS were positive. Lower positivity rates have been reported in the literature. In Southern Brazil, a cross-sectional study identified LOS in 20.9% of patients, of whom 47.9% had positive blood cultures.<sup>24</sup> Similarly, a study conducted in Malaysia reported positive blood cultures in 22.6% of cases.<sup>23</sup> These findings demonstrate considerable variability in the literature, which may be related to differences in study methodologies and population characteristics. Nevertheless, the high rate of positive blood cultures observed in the present study highlights the relevance and severity of LOS in the evaluated population.

Regarding the pathogens identified, coagulase-negative staphylococci were the predominant bacteria in sepsis cases, accounting for 78.6% of the isolates. Exposure to pathogens may occur through contact between newborns and family members or healthcare professionals, as well as through the use of total parenteral nutrition and contaminated medical equipment.<sup>31</sup> Therefore, as infections are mainly from local sources, the differences in the results of research are explained, since the studies found different pathogens as prevalent in sepsis. However, there are similar results in the literature, with higher frequency of coagulase-negative staphylococci, but with different prevalence: 34.7% and 34.65%.<sup>16,22</sup> In the present work, 7.8% of samples presented *Acinetobacter* spp., contrasting with other studies in the literature which found lower values.<sup>22</sup>

Regarding the limitations of this study, although most births in Brazil occur in hospital settings, the study population was restricted to neonates admitted to the NICU, which may have resulted in the underrepresentation of cases involving death before intensive care admission. In addition, data from

neonates transferred to other hospitals, who may subsequently have developed LOS, may not have been captured. Regarding blood culture collection, if the patient had a central line, samples were collected from both the periphery and the central line; if the patient did not have a central line, only a peripheral sample was collected. Furthermore, information regarding the primary focus of infection associated with bacteremia was unavailable. Although documentary studies are subject to missing information and inconsistencies in records, such limitations were not observed in the present study, since the institution had a previously established protocol for standardized medical record documentation, encompassing all variables analyzed in the study. Despite these limitations, this is the first study to investigate sepsis in NICUs in the northwestern region of the state of Rio Grande do Sul, and few such studies exist in Brazil as a whole, a country marked by diverse healthcare services. Furthermore, understanding the indicators and clinical characteristics of this healthcare service is important for evaluating its effectiveness and supporting the planning of strategies aimed at improving neonatal care. Thus, the findings of the present study provide relevant information for NICUs and may contribute to the prevention of LOS through the identification of associated factors.

The present study analyzed factors associated with the development of LOS and identified a positive association with prematurity and low birth weight, variables that are less likely to be influenced by the place of birth and are already well established in the literature. However, the study also highlights relevant factors that may contribute to the review of maternal and neonatal care protocols, particularly regarding antenatal corticosteroid use, pregnancy complications, and adequacy of prenatal care, as well as neonatal blood transfusion and resuscitation at birth, which were also identified as risk factors for LOS. Therefore, the findings are important because they provide essential information about the specific hospital evaluated and may contribute to the development and implementation of new strategies aimed at preventing LOS.

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**Simone Minuzzi Catto Vaz** contributed to the bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, table preparation, conclusions, review, and statistics. **Karine Raquel Uhdich Kleibert** contributed to project management, bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, conclusions, review, and statistics. **Cibele Thome Da Cruz Rebelato** contributed to the abstract writing, methodology, interpretation of results, conclusions, review, and statistics. **Carmen Cristiane Schultz** contributed to the abstract writing, review, and statistics. **Amanda Emanuela Buzanello** contributed to the abstract writing, review, and statistics. **Christiane de Fátima Colet** contributed to project

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