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Clinical and laboratorial parameters related to the diagnosis of late onset neonatal sepsis laboratory-confirmed associated with central venous catheter in newborns in a reference neonatal unit.

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Abstract

Background and Objectives: To evaluate clinical and laboratorial variables associated with diagnosis of laboratory-confirmed sepsis associated with central venous catheter (CVC) in newborns.

Methods: Prospective cohort study carried out in a reference neonatal unit from 2015 to 2017. Newborns using CVC were included and information were obtained from medical records. The outcome was considered an episode of laboratory-confirmed sepsis associated with CVC for evaluation of clinical and laboratorial variables. The SPSS version 20.0 program was utilized for statistical analysis. The study was approved by the ethics committee of institution.

Results: A total of 191 newborns with CVC were identified, which 92 have had 95 episodes of suspected sepsis. Only 33 of them were considered laboratory-confirmed episodes of sepsis by the National Health Surveillance Agency of Brazil criteria, and 20 were considered laboratory-confirmed episodes of sepsis by the Centers for Disease Control and Prevention criteria. The immature/total segmented ratio (I/T ratio) was statistically significant in univariate and multivariate model as an independent variable associated with laboratory-confirmed sepsis associated with CVC ($p=0.009$). In cases confirmed by international criteria, hypothermia and hyperthermia remained as clinically significant changes in laboratory-confirmed CVC-associated sepsis in multivariate analysis.

Conclusion: Higher immature/total neutrophils ratio, increased C-reactive protein and thermal instability are parameters that help in defining CVC-associated sepsis and may contribute to the decision on rational use of antimicrobials, considering the low sensitivity of blood cultures and isolation of skin contaminants in a single sample.

Keywords: Central Venous Catheter; Catheter-Related Infections; Newborn; Sepsis Diagnosis; Neonatal Intensive Care Unit.

Parâmetros clínicos e laboratoriais associados ao diagnóstico de sepse neonatal tardia laboratorialmente confirmada associada ao cateter venoso central em recém-nascidos em unidade neonatal de referência.

Resumo

Justificativa e Objetivos - Avaliar variáveis clínicas e laboratoriais associadas ao diagnóstico de sepse laboratorialmente confirmada associada a cateter venoso central (CVC) em recém-nascidos.

Método - Estudo de coorte prospectivo realizado em unidade neonatal de referência, de 2015 a 2017. Foram incluídos recém-nascidos em uso de cateter venoso central e as informações foram obtidas de prontuários. O desfecho foi considerado episódio de sepse laboratoriamente confirmada associada a CVC para comparação de variáveis clínicas e laboratoriais. Utilizou-se o programa SPSS versão 20.0 para análise estatística. O estudo foi aprovado pelo Comitê de Ética institucional.

Resultados - Foram identificados 191 recém-nascidos com CVC; 92 deles apresentaram 95 episódios suspeitos de sepse. Entretanto, apenas 33 deles foram episódios de sepse laboratorialmente confirmada pelo critério ANVISA e 20 deles episódios de sepse laboratorialmente confirmada pelo critério do *Centers for Disease Control and Prevention*. Para casos confirmados pelos critérios nacionais, a relação neutrófilos imaturos pelo total de segmentados apresentou significância estatística em análise univariada e permaneceu em modelo multivariado como variável independente associada a sepse laboratorialmente confirmada associada a CVC (p=0,009). Para casos confirmados pelos critérios internacionais, hipotermia e hipertermia permaneceram como alterações clínicas significativas de sepse laboratorialmente confirmada associada ao CVC em análise multivariada.

Conclusão – Maior relação neutrófilos Imaturos/Totais, aumento de Proteína C-reativa e instabilidade térmica são parâmetros que auxiliam na definição de sepse associada a CVC e podem contribuir na decisão do uso racional de antimicrobianos, considerando a baixa sensibilidade de hemocultura e isolamento de contaminantes de pele em amostra única.

Palavras-chave: Cateter venoso central; Infecções associadas a cateter; Recém-nascido; Diagnóstico de sepse; Unidades de terapia intensiva neonatal.

Introduction

Neonatal sepsis is a serious infection and it is known as one of the main causes of morbidity and mortality in neonatal intensive care units (NICU), resulting in prolonged hospital stays and increased costs in caring for hospitalized newborns.[1-3] There are many risk factors that contribute to its occurrence, and the use of invasive devices, such as the central venous catheter (CVC), is considered one of the most important. [4-7]

Early diagnosis of neonatal sepsis remains a challenge for the care team due to nonspecific signs.[8,9] The definitive diagnosis is defined with the isolation of the pathogen in blood culture. However, the sensitivity of this test is low and the result, with antibiogram, may only be available after 24 to 48 hours. Without the isolation of microorganisms, there is no accurate diagnostic model with high prediction for its confirmation or exclusion, although several studies have tried to define clinical and laboratory markers and predictors that could help in the diagnosis.[9-11]

Bloodstream infection criteria of the Centers for Disease Control and Prevention/National Healthcare Safety Network – EUA (CDC/NHSN) and the National Health Surveillance Agency (ANVISA - Brazil) aim to establish definitions for reporting healthcare-associated infections (HAI).[2,12] These criteria differ in terms of clinical manifestations, inclusion of laboratory alterations in the newborn, or isolation of contaminating agents in blood cultures when laboratory-confirmed sepsis associated with CVC is considered.

It should be noted that the difficulty in obtaining the diagnosis may result in the excessive use of antibiotics, which can contribute to the development of bacterial resistance, delay in adequate treatment and increase in mortality rates and other frequent complications in the NICU.[13] Given this situation, clinical and laboratorial assessment information could potentially contribute to the identification of patients most likely to have CVC-associated late-onset neonatal sepsis and assist in treatment decisions.

This study aimed to evaluate clinical and laboratorial parameters associated with the occurrence of laboratory-confirmed late onset neonatal sepsis associated with CVC based on ANVISA and CDC/NHSN criteria.

Methods

Study design and participants

This prospective cohort study was conducted at the Neonatal Unit of the Hospital das Clínicas of Universidade Federal de Minas Gerais from December 2015 to May 2017.

Inclusion and exclusion criteria

Were included all neonates up to 28 days of age admitted to the Neonatal Unit undergoing central venous catheterization in the neonatal unit (Percutaneous Inserts Central Catheter — PICC or catheter inserted with surgical technique — puncture or dissection) identified in the records of CVC-insertion checklist forms, performed routinely by professionals in the unit.

Exclusion criteria include newborns who had a CVC inserted outside the Neonatal Unit or who did not obtain the consent form from their legal guardians.

Data collection

Data collection was performed by consulting the medical records of the neonates included. Clinical and laboratorial criteria considered in the suspicion of late neonatal sepsis associated with CVC were evaluated. Clinical data and laboratorial tests were considered on the day of blood collection in case of sepsis suspicion, in addition to blood culture, concomitant with the use of the CVC or up to two days after its withdrawal according to CDC and ANVISA definitions.[2,12]

Definitions

Late-onset neonatal sepsis was defined as bloodstream infections without another associated focus that occurred after 48 h of life for both criteria. The terms bloodstream infection and sepsis were used synonymously.

According to ANVISA criteria, the presence of Primary Laboratory Bloodstream Infection was defined when: a) there were one or more positive blood cultures by microorganisms non-skin contaminating and the microorganism was not related to infection at another site; b) there were the presence of one or more clinical signs without other recognized non-infectious cause and relation to infection at another defined site (thermal instability, bradycardia, apnea, food intolerance, worsening of respiratory distress, glucose intolerance, hemodynamic instability, hypo-activity/lethargy), with isolation of a skin-contaminating microorganism cultured in at least one blood culture of peripheral blood in a patient with CVC.[12]

According to the CDC/NHSN criteria, the presence of sepsis was considered only when there was isolation of an associated microorganism and was defined when: a) isolation of a recognized pathogen identified from one or more blood cultures and not related to an infection in another site; or isolated skin-contaminating microorganism, such as coagulase-negative staphylococci (CoNS), identified from two or more blood cultures collected on separate occasions (on the same day or on consecutive days); b) neonate presenting at least one of the clinical signs: fever (> 38.0 ºC), hypothermia (< 36 ºC), apnea or bradycardia; and the pathogenic microorganism identified from the blood unrelated to an infection elsewhere.[2]

The target population included all neonates using CVC and the outcome was considered to be laboratory-confirmed sepsis associated with CVC. Thus, two groups were considered for comparative analysis:

- Case group: neonates with laboratory-confirmed sepsis and presence of CVC.
- Control group: neonates without suspected sepsis or only diagnosed with clinical sepsis without laboratory confirmation.

According to the routine of the microbiology laboratory of the service, the microorganism was isolated in blood culture and analyzed by an automated method and the antibiotic susceptibility test was performed using the agar diffusion disk (Kirby Bauer®).

Sample calculation

For sample size calculations, a test power of 80% was considered to identify an effect of the predictor variable of late-onset neonatal sepsis with a proportion of cases equal to 0.30 or an odds ratio (OR) of 1.9, according to a previous local study.[14]

Statistical analysis

Quantitative data were described using the arithmetic average, standard deviation and median; demographic variables were given by absolute frequencies and percentages. The

logistic regression model was used to study the association between independent variables and the presence of laboratory-confirmed late-onset neonatal sepsis associated with CVC defined by the CDC/NHSN and ANVISA criteria.[2,12]

Univariate analysis of predictor variables for the outcome CVC-associated late onset neonatal sepsis was performed, including clinical variables (thermal instability, respiratory effort, apnea, bradycardia, glucose intolerance, hemodynamic instability, food intolerance) and laboratory variables (C-reactive protein - CRP, platelet count, global leukocyte count, neutrophil count, I/T ratio). Variables with $p \leq 0.20$ entered a multivariate model. In multivariate analysis, significant variables in the final model were considered with $p \leq 0.05$. The estimated association measure was the OR and its respective 95% confidence interval (CI).

The fit of both models was evaluated using the Hosmer & Lemeshow test. SPSS software version 20.0 was used in this analysis.

Patients were admitted to the study after they agreed and signed the Free and Informed Consent Form by their legal guardians. This study was approved by the Ethics and Research Committee on Human Beings of Federal University of Minas Gerais – COEP/ UFMG.

Results

A total of 191 newborns with CVC in the period evaluated were included in the study, 70 of whom did not have blood cultures collected, therefore, they did not present late-onset neonatal sepsis that was laboratory-confirmed (Figure 1).

Fifty-two newborns had an episode of late-onset neonatal sepsis associated with CVC according to the ANVISA criteria, 47 of them had only one episode and three newborns had two episodes, resulting in 53 (55.8%) episodes, with 33 episodes of laboratory-confirmed sepsis associated with CVC (62.3%) and another 20 (37.7%) episodes of sepsis clinically excluded from the outcome of laboratory-confirmed sepsis.[12]

According to CDC/NHSN criteria, 20 (21%) episodes were classified as laboratory-confirmed late neonatal sepsis associated with CVC. All these episodes were also classified as late-onset neonatal sepsis by the ANVISA criteria associated with CVC.[2]

Table 1 presents the univariate logistic model of clinical data and laboratory tests evaluated for the diagnosis of late-onset neonatal sepsis according to ANVISA criteria. The variables with $p \leq 0.20$, which entered the multivariate model, were thermal instability and food intolerance. For laboratory variables, alterations in CRP, leukocyte count and I/T ratio were identified.

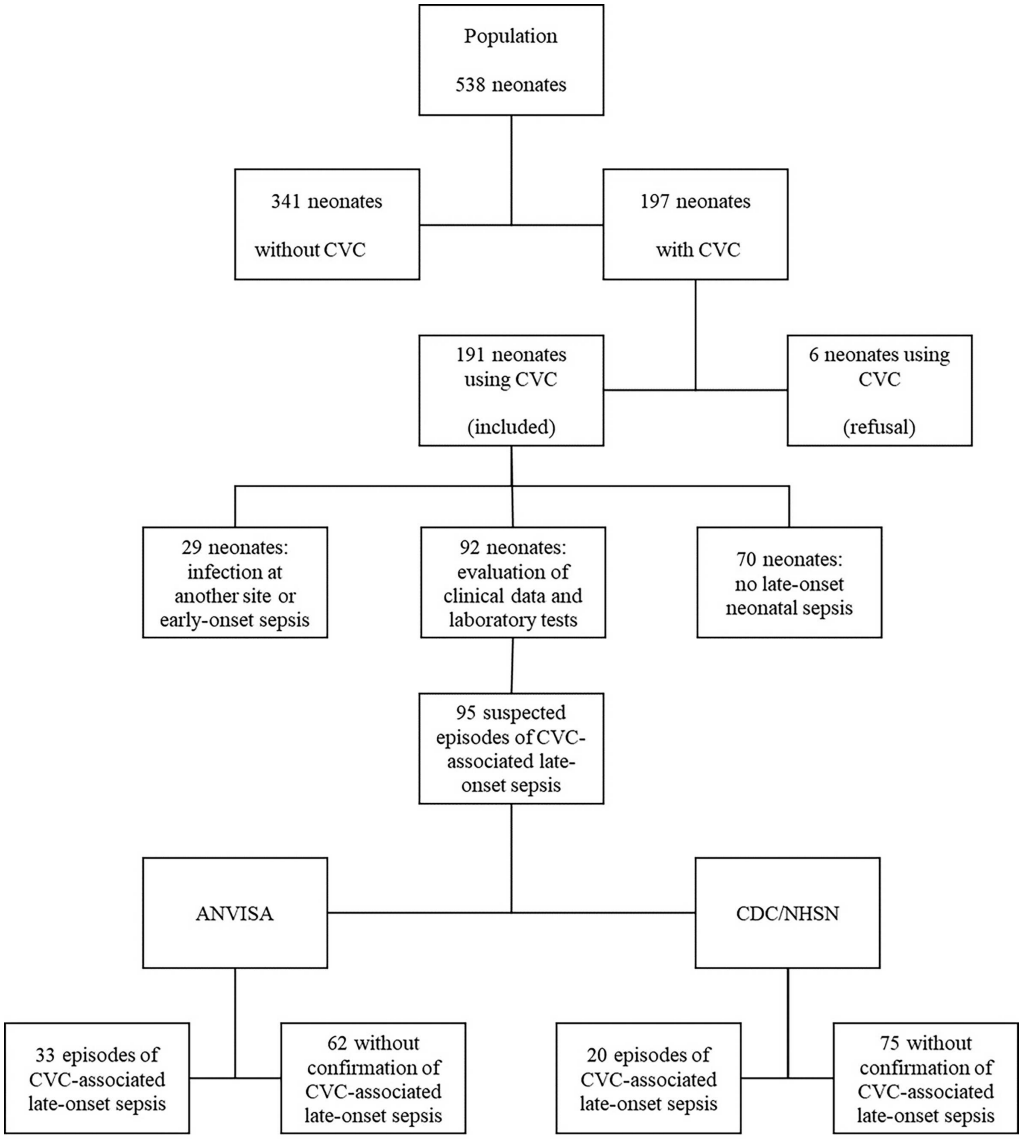

Figure 1. Flowchart with classification of newborns with suspected late-onset neonatal sepsis associated with central venous catheter, according to ANVISA and CDC/NHSN, admitted to the Neonatal Unit, Hospital das Clínicas - UFMG, from 2015 to 2017.
CVC: C*entral Venous Catheter*; ANVISA: *National Health Surveillance Agency*; CDC/NHSN: *Disease Control and Prevention/National Healthcare Safety Network – EUA*

Table 1 — Clinical and laboratorial variables of laboratory-confirmed late onset neonatal sepsis associated with Central Venous Catheter according to ANVISA criteria, newborns admitted to the Neonatal Unit, Hospital das Clínicas – UFMG, from 2015 to 2017.

Clinical variables and laboratory tests	**Laboratory-confirmed late onset neonatal sepsis associated with CVC**		**Univariate Analysis**		
	YES n (%)	**NO n (%)**	**OR**	**CI 95%**	**p**
CLINICAL VARIABLES					

Thermal instability					
Yes	23 (41.8)	32 (58.2)	2.16	0.88–5.27	**0.092**
No	10 (25.0)	30 (75.0)	1.00		
Apnea					
Yes	12 (44.4)	15 (55.6)	1.79	0.72–4.48	0.213
No	21 (30.9)	47 (69.1)	1.00		
Bradycardia					
Yes	16 (41.0)	23 (59.0)	1.60	0.68–3.75	0.284
No	17 (30.4)	39 (69.6)	1.00		
Worsening respiratory distress					
Yes	24 (36.9)	41 (63.1)	1.37	0.54–3.46	0.511
No	9 (30.0)	21 (70.0)	1.00		
Glucose intolerance					
Yes	4 (50.0)	4 (50.0)	2.10	0.48–9.21	0.327
No	21 (32.3)	44 (67.7)	1.00		
Hemodynamic instability					
Yes	9 (34.6)	17 (65.4)	1.00	0.39–2.60	0.988
No	24 (34.8)	45 (65.2)	1.01		
Food intolerance					
Yes	23 (40.4)	34 (59.6)	1.89	0.77–4.64	**0.162**
No	10 (26.3)	28 (73.7)	1.00		
LABORATORY VARIABLES					
CRP					
Changed	30 (39.5)	46 (60.5)	3.59	0.74–17.3	**0.112**
Normal	2 (15.4)	11 (84.6)	1.00		
Platelet count					
Changed	13 (39.4)	20 (60.6)	1.37	0.56–3.32	0.488
Normal	19 (32.2)	40 (67.8)	1.00		
Leukocyte count					
Changed	5 (20.8)	19 (79.2)	1.00	0.83–7.51	**0.102**

Normal	27 (39.7)	41 (60.3)	2.50		
I/T ratio					
Changed	9 (69.2)	4 (30.8)	5.48	1.53–19.58	**0.009**
Normal	23 (29.1)	56 (70.9)	1.00		
Neutropenia					
Present	4 (30.8)	9 (69.2)	1.00	0.35–4.38	0.743
Absent	28 (35.4)	51 (64.6)	1.24		

ANVISA: *National Health Surveillance Agency*; CVC: *central venous catheter;* CRP: *C-reactive protein;* OR: *Odds ratio;* CI: Confidence Interval.

Table 2 presents the multivariate model, in which the I/T ratio remained an independent laboratory variable associated with laboratory-confirmed sepsis associated with CVC (p=0.017) and the Hosmer & Lemeshow test showed an adequate fit of the model (p=0.842).
In the evaluation of clinical variables related to the diagnostic criteria of late neonatal sepsis laboratory confirmed associated with CVC by the CDC/NHSN, the variables that entered the multivariate model were hypothermia and hyperthermia, and both remained significant. The result of the Hosmer & Lemeshow test showed adequate model adjustment for the analysis (p = 0.558).

Table 2 – Evaluation of clinical variables for laboratory-confirmed late onset neonatal sepsis associated with Central Venous Catheter by the CDC/NHSN criteria, newborns admitted to the Neonatal Unit, Hospital das Clínicas – UFMG, from 2015 to 2017.

	Laboratory-confirmed late onset neonatal sepsis associated with CVC		**Univariate Analysis**			**Multivariate Analysis**		
	YES n (%)	**NO n (%)**	**OR**	**CI 95%**	**p**	**OR**	**CI 95%**	**P**
Hypothermia								
Yes	9 (39.1)	14 (60.9)	3.57	1.24 - 10.24	**0.018**	4.83	1.50 - 15.52	**0.008**
No	11 (15.3)	61 (84.7)	1.00			1.00		
Hyperthermia								
Yes	9 (40.9)	13 (59.1)	3.9	1.35 - 11.32	**0.012**	5.24	1.62 - 16.92	**0.006**
No	11 (15.1)	62 (84.9)	1.00			1.00		
Bradycardia								
Yes	9 (23.1)	30 (66.9)	1.23	0.45 - 3.32	0.687			
No	11 (19.6)	45 (80.4)	1.00					
Apnea								

Yes	7 (25.9)	20 (74.1)	1.48	0.52 - 4.24	0.464
No	13(19.1)	55 (80.9)	1.00		

CDC/NHSN: *Disease Control and Prevention/National Healthcare Safety Network – EUA*; OR: *Odds ratio;* CI: Confidence Interval.

Discussion

A higher number of episodes of late-onset neonatal sepsis defined by the ANVISA compared to episodes of sepsis defined by the CDC/NHSN criteria were observed due to the difference in criteria, considering the isolation of CoNS in blood culture. There is a requirement of two or more blood cultures within a maximum interval of two consecutive days by the CDC/NHSN, which was confirmed in 20 neonates; there is a requirement of only one blood culture in the presence of CVC by the ANVISA criteria (n=33).[2,12]

The results of this study showed that hyperthermia and hypothermia were variables significantly associated with the diagnosis of late-onset neonatal sepsis associated with CVC, which are signs presented by the CDC/NHSN criteria.[2] Regarding the diagnosis, according to the ANVISA diagnostic criteria, both signs are included in the definition of thermal instability and this variable was not significant for the sepsis criterion in the multivariate analysis.[12] Regarding the increase in temperature, the results corroborate a prospective cross-sectional study carried out in a neonatal unit in Tanzania with 300 neonates, which showed a significant association with the isolation of microorganisms in late onset sepsis (p=0.008), but there was no significance for early neonatal sepsis (p=0.214).[12] It is noteworthy that in the present study only late onset neonatal sepsis was evaluated. Bekhof et al performed a prospective cohort study in a level III NICU in the Netherlands, where 142 neonates with clinically or laboratory confirmed sepsis were investigated and nonsignificant association was found for thermal instability (p=0.40), hyperthermia (p=0.49) or hypothermia (p=0.99) for the outcome of laboratory-confirmed sepsis.[8] In addition, the cited studies did not define inclusion only of newborns with CVC. On the other hand, in the study by Griffin et al, in NICU at the University of Virginia with 337 newborns, found that thermal instability was twice as likely to be present after the diagnosis of clinical or laboratory sepsis.[16] Retrospective cohort study by Healy et al evaluated 95 episodes of CoNS sepsis, did not find an association with the confirmation of the diagnosis (p=0.269), although there was an association of the presence of CVC with probable diagnosis (p<0.001) or confirmed and confirmed diagnosis (p<0.001).[17] In this sense, the present study evaluated neonates with CVC, as it is a device propitious to the formation of biofilm and sepsis, especially in preterm infants.

Although food intolerance is one of the clinical signs considered by the ANVISA, there was no association with the diagnosis of laboratory-confirmed sepsis associated with CVC in a multivariate model, as demonstrated in the study by Bekhof et al, in which diet intolerance was not significant (p=0.40 and p=0.63 for laboratory-confirmed sepsis or clinical sepsis associated with laboratory-confirmed sepsis) even in univariate analysis.[8,12] The study by Kayange et al included early and late neonatal sepsis and identified dietary intolerance as a factor associated with the isolation of microorganisms in blood cultures.[15] The study by Healy et al demonstrated an association of gastric residues with a confirmed or probable diagnosis of neonatal sepsis with isolation of CoNS.[17] The study by Giffin et al showed an association of food intolerance seven times

greater after the diagnosis of clinical or laboratory neonatal sepsis.[16] Similar to the present study, Ohlin et al evaluated predictive clinical signs for laboratory-confirmed neonatal sepsis including diet intolerance and found significance (p=0.03; OR 1.91 CI 95% 1.06–3.41), but only when the analysis was not adjusted for multivariate (p= 0.054; OR 2.0 CI 95% 0.99–4.07).[18] Although other clinical signs considered by the CDC and ANVISA criteria have not been shown to be associated with CVC-associated laboratory-confirmed late onset neonatal sepsis, the differential diagnosis of other conditions inherent to the neonate such as respiratory and metabolic disorders and the primary thermal instability should be investigated to adequate management, because the clinical signs of the neonate are nonspecific.[2,12] In a prospective study carried out in Sweden with 401 newborns suspected sepsis, hypotension or skin pallor (p=0.005; OR 2.45 CI 95% 1.31–4.59), in addition to apnea (p=0.001; OR 4.19 CI 95% 1.82–9.64) and tachypnea (p=0.044; OR 2.00 CI 95% 1.02–3.92), which showed a significant association with laboratory confirmation of the sepsis episode, adjusted for sex, gestational age and other signs.[18] In the Bekof et al cohort, skin pallor/cyanosis and decreased capillary perfusion were associated with clinically or laboratory confirmed late onset neonatal sepsis, but only decreased capillary perfusion remained predictive when considering only episodes of laboratory confirmed late neonatal sepsis. In a multivariate analysis, capillary perfusion > 2 seconds proved to be significant, with a chance twice as high in patients with sepsis (p=0.029; OR 2.20 CI 95% 1.09–4.48). The authors also evaluated tachypnea, dyspnea and increased need for ventilatory support and oxygen. The increase in ventilatory support was predictive for laboratory-confirmed or clinical sepsis (p<0.001; OR 4.25 CI 95% 2.30–7.87) and for laboratory-confirmed sepsis (p=0.004; OR 2.74 CI 95% 1.37–5.47), but the increase in oxygen remained significant only for laboratory-confirmed or clinical sepsis (p=0.001; OR 3.725 CI 95% 1.64–6.41).[8]

In a meta-analysis published by Verstraete et al, with 1,295 episodes of suspected sepsis and 434 laboratory-confirmed sepsis, nine articles were evaluated with 12 prediction models.[3] In addition to hyperthermia and diet intolerance, variables that indicate hemodynamic instability such as hypotension, tachycardia, respiratory failure, bradycardia, skin pallor, and peripheral capillary perfusion > 2 seconds were included in predictive scores with clinical signs predictive of laboratory-confirmed late onset neonatal sepsis.[3] Several studies also demonstrate, by monitoring vital signs and predictive models, that changes in heart rate and breathing pattern occur approximately 24 to 72 minutes before other clinical manifestations and confirmation of the episode.[16,19-22]

Regarding laboratory tests as predictors, CRP, leukocyte count and I/T ratio were included in the multivariate analysis, but only the I/T ratio was statistically significant in univariate and multivariate analysis.

CRP has been presented in several studies as a marker of neonatal sepsis, although with variation in sensitivity, its increase in 48 hours is considered to be associated with several perinatal factors and recommended for monitoring the response to antimicrobial therapy according to guidelines.[23-26] In the study by Ohlin et al, CRP change > 10mg/dl was predictive of laboratory-confirmed neonatal sepsis in multivariate analysis with clinical signs (p<0,0001; OR 5,59 CI 95% 2,13–14,7).[18] Yang et al in a retrospective study with 120 neonates, showed that CRP > 8 mg/dl was associated with laboratory confirmed sepsis (p=0.001), with a chance of 40.3 (CI 95% 2.92–555.53).[27] In the prospective study by Dimitriou et al, which evaluated predictors for persistent CoNS bacteremia in neonates, CRP was not significantly at the beginning of diagnosis (8.9; 0.5-26.9 mg/dl), but it was higher when compared to cases without persistent bacteremia.[28] On the other hand, Furuichi et al evaluated 76 episodes of CVC-related neonatal sepsis caused by

CoNS and CRP positivity had a significant difference in the persistence of bacteremia.[29] Ponnusamy et al evaluated the removal of 189 CVCs, with 47 (25%) of the cases with episodes of CVC-associated infection in neonates, and of these, 80% had CRP >10 mg/dl.[30] In the present study, CRP positivity was not associated with CVC-associated late onset neonatal sepsis, as in the study by Ozdemir et al, who studied a group of 127 neonates in which 40% had proven sepsis, observed that CRP levels did not differ between both groups (p=0.23), but identified an accuracy of 78% (CI 95% 0.74–0.82) for a higher neutrophil/lymphocyte ratio (average 3.69±3) for newborns with confirmed sepsis.[31] As CRP is an acute phase protein associated with inflammation, several factors may be associated with the variability of results, including the timing of gathering and the use of antimicrobials.

The literature tries to define leukocyte count values and reference intervals in newborns, with evaluation of values and predictive score for neonatal sepsis. Manroe et al evaluated neutrophil counts by peripheral blood count of neonates with and without sepsis and neutropenia associated with respiratory distress, in the first 72 hours, presented an 84% probability of bacterial neonatal sepsis.[32] Rodwell et al proposed a hematological score system (HSS) with a score of 1 point for each of the seven blood count parameters, with six associated with the leucogram: abnormal total leukocyte count, abnormal total neutrophil count, elevated immature neutrophil count, elevated proportion of immature neutrophils to the total number of these cells (I/T), proportion of immature neutrophils to the number of mature neutrophils equal to or greater at 0.3, degenerative polymorphonuclear changes, in addition to a platelet count less than or equal to 150,000 /mm^3. In 298 evaluations, it was observed that 26 of the 27 (96%) neonates with sepsis and all 23 neonates with probable infection had a score > 3. On the other hand, with a score < 2, the probability of absence of sepsis was 99%.[11]

Although the white blood cells (WBC) count was not significant in the multivariate analysis in the present study, neutropenia is the WBC change with the highest association with neonatal sepsis.[10,33–34]

In the study conducted by Berger et al, with 33 cases of confirmed neonatal sepsis in the first three days since birth, leukopenia, neutropenia and I/T ratio had sensitivity and specificity of 67% and 90%; 78% and 80%; 78% and 73%, respectively, and were considered parameters with greater diagnostic accuracy for early neonatal sepsis. In the same study, the authors also evaluated CRP elevation, which proved to be the most accurate parameter and a negative predictive value (NPV) of 99% in sepsis after the third day of life.[35]

Manucha et al, in a cohort study with 150 neonates up to three days of age with clinical suspicion of infection and 21 (14%) of them with sepsis confirmed by isolation of microorganisms in blood culture, also evaluated hematological parameters. The hematological parameters with a significant difference between groups were: total leukocytes, neutrophil and platelet counts (with the lowest value in laboratory-confirmed sepsis) and immature/total neutrophil ratio (with the highest value in laboratory-confirmed sepsis). The composite analysis of hematological parameters showed that the presence of three of them reached a specificity of 81% and with five of them it was observed 98%. On the other hand, sensitivity and NPV were 100% when only one change was observed. The combination of CRP and the hematological scoring system did not present any advantage when associated with hematological parameters. Although the authors exclusively evaluated early sepsis, the I/T ratio was significantly higher in infected patients, as was observed in the present study, which evaluated only laboratory-confirmed late onset neonatal sepsis associated with CVC.[36]

The predictor variable for neonatal sepsis associated with CVC in the varied analysis in the present study was the I/T ratio, which considered values above 0.30, according to the scores proposed by Rodwell et al, but there are studies carried out that consider values > 0.20.[11,15,34,37] Debroy et al evaluated hematological parameters of 40 episodes of late neonatal sepsis, the I/T ratio showed positive predictive value (PPV) and NPV of 100 and 96.6%, in addition to LR+ 22.5 e LR- 0.1 for the criterion of laboratory confirmed sepsis.[38]

Can et al in a prospective observational study investigated the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in 78 full-term newborns diagnosed with early onset sepsis (EOS) and with 44 healthy controls. Although no difference was observed in the immature/total segmented ratio, the EOS group had higher neutrophil counts and lower lymphocyte counts, higher neutrophils/lymphocytes ratio and platelets/lymphocytes ratio, in addition to significantly higher CRP and pro-calcitonin in the case group compared with the control group.[39]

Other authors have also evaluated the neutrophil/lymphocyte ratio, although they have not evaluated the I/T ratio. Sumitro et al, in a cross-sectional study involving neonates admitted to a NICU with clinical manifestations of early and late onset neonatal sepsis. The neutrophil/lymphocyte ratio showed the highest sensitivity (80.8%). The neutrophil/lymphocyte ratio >2.2 presented an accuracy of 63% and the authors also evaluated a CRP > 2.7 mg/dl presented an accuracy of 69%. The association of the two variables reached an accuracy of 72%.[40]

The limitation of this study may be considered by the small number of episodes of neonatal sepsis. The prospective data collection and the use of national and international diagnostic criteria subsidize parameters for comparing inter-institutional data.

The number of episodes of late-onset neonatal sepsis associated with CVC was higher when using the national diagnostic criteria (ANVISA) when compared to the diagnostic criteria of the CDC/NHSN, due to the use of clinical criteria, parameters associated with laboratory tests and the evaluation of only one blood culture positive for skin contaminating microorganisms in the presence of CVC.[2,12]

In daily practice, clinical information should be combined with laboratory information in the diagnosis of late-onset neonatal sepsis associated with CVC to favor a rational and timely diagnosis and treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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