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ANALYSIS OF THE INDICATION OF ANTIBIOTIC THERAPY IN LOW BIRTH WEIGHT PRETERM INFANTS WITH PRESUMED EARLY-ONSET SEPSIS

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ABSTRACT

Background: Early-onset sepsis (EOS) is a syndrome with high morbidity and mortality, being a significant component of this rate, both due to the difficult clinical and laboratory diagnosis, as well as the urgency of intensive care and antibiotic therapy. The objective of this study was to analyze the criteria used for the empirical treatment of presumed EOS in a public maternity hospital in the state of Pará, Brazil. **Methods:** A nonrandomized case-control study conducted by collecting data from 483 records of low birth weight preterm infants admitted in intensive care unit at a referral hospital in the Amazon region in 2017 and using antibiotic therapy in the first forty-eight hours of life. To analyze the diagnostic criteria of EOS, 152 newborns were divided into two groups with the presence of criteria (case group) and 331 without criteria (control group). **Results:** It was observed that birth weight, gestational age, first minute Apgar score, need of orotracheal intubation resuscitation, hypothermia, cyanosis and bradycardia were the most related neonatal factors to the diagnosis of EOS, associated with the presence of urinary tract infection and leukorrhea during pregnancy. **Conclusion:** Most of the factors related to EOS found in this study are potentially preventable by quality prenatal and perinatal cares, being extremely important for reducing the mortality associated with this cause.

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INTRODUCTION

Neonatal infection is a global public health problem and one of the Millennium Development Goals (MDGs) was to reduce to below 15.7 deaths per 1,000 live births in 2015 (United Nations, 2015). However, the diagnosis of neonatal sepsis is difficult due to the variety and lack of specificity of signs and symptoms (Licona *et al*., 2017; Sweeney *et al*., 2018). Early-onset sepsis (EOS) in the newborn occurs within the first 48 hours and is related to maternal transmission, to contaminated amniotic fluid and the rise of vaginal tract bacteria during the peripartum and intrapartum periods. Whereas, late-onset sepsis is attributed to hospital or community microorganisms from the third day of life (Licona *et al*., 2017; Sweeney *et al*., 2018; Shane, 2017).

On the absence of clinical symptoms, the decision to initiate antibiotics is based on maternal and/or perinatal risk factors and/or laboratory investigations (Sweeney *et al*., 2018; Van Herk *et al*., 2016), such as Rodwell's hematological score (Rodwell, 1988) and serial C-reactive protein (CRP) collection (Licona, 2017; Shabuj, 2017). However, the gold standard diagnosis is the positive blood culture, which results after 48 to 72 hours after collection and can often be false negative because of insufficient blood analysed (Sweeney *et al*., 2018; Van Herk, 2018; Shabuj, 2017). Such diagnostic difficulty, associated with unfavorable outcomes in late-treated septic neonates, leads to intensive care unit (ICU) admissions and initiation of empirical antibiotic therapy in many uninfected infants, increasing hospitalization time and the risk of contamination by microorganisms resistant (Sweeney, 2018;

Gkentzi, 2019). Therefore, it is essential to analyze the used criteria to initiate antibiotic therapy in neonates with presumed EOS, identifying the main neonatal and maternal risk factors for infection in northern Brazil, in view of the scarcity of data regarding the topic in the region and the high morbidity and mortality perinatal.

MATERIALS AND METHODS

Nonrandomized retrospective case-control observational study through the collection of medical records of preterm infants (born less than 37 weeks gestational age) with low birth weight (less than or equal to 2,500 grams) admitted to the ICU of Santa Casa de Misericórdia do Pará Hospital with presumptive EOS and those taking antibiotic therapy in the first 48 hours of life. The regional ethical committee approved the study. The study population was of 856 neonates admitted to the hospital's ICU from January 1th, 2017, through December 31, 2017. Were included 483 preterm infants, low birth weight with presumed EOS and antibiotic therapy within the first 48 hours of life and excluded those with chromosomal malformations, congenital infections and genetic syndromes, composing the studied sample. The infants admitted to the ICU were under continuous monitoring, using a pulse oximeter to record oxygen saturation and heart rate. Two comparison groups were defined according to the presence or absence of pre-established criteria for EOS and initiation of antibiotic therapy: neonates who fill at least one of the analysed criteria composed the case group (clinical, laboratory or microbiological), totaling 152 infants. The control group consisted of 331 neonates who did not meet any of the analyzed criteria.

In reference to pre-established criteria, the clinical criterion of EOS was defined as the association of at least two clinical signs of the infant added to at least one maternal risk factor11. The clinical signs analyzed were observed at the first evaluation of the newborn, such as hypothermia (skin temperature <36ºC), apnea (respiratory pause lasting more than 20 seconds), tachypnea (> 60 breaths per minute), bradycardia (<100 beats per minute) and/or central cyanosis. Besides maternal risk factors were urinary tract infection, leukorrhea, rupture of membranes time greater than or equal to 18 hours and chorioamnionitis. Chorioamnionitis was considered as a maternal temperature > 38°C in the absence of another infectious outbreak, and two or more of the following parameters: maternal tachycardia (> 100 beats per minute); fetal tachycardia (> 160 beats per minute); persistent uterine pain or discomfort; fetid amniotic fluid; leukocytosis (> 15.000). For the laboratory criterion, Rodwell's hematological score(6) was used in infants whose score was greater than or equal to three in the first blood count. By the following parameters: leukocytosis (≥ 30.000) or leukopenia (≤ 5.000); neutrophilia (> 12.000) or neutropenia (<7.000); increase of immature neutrophils (> 1.280); increased neutrophil index (> 0.16); ratio of immature to segmented neutrophils ≥ 0.3; degenerative alterations in neutrophils with vacuolization and toxic granulation; thrombocytopenia (<150.000).

The first positive blood culture collected up to the first 48 hours of life was the microbiological criterion (Agência Nacional de Vigilância Sanitária, 2017). The data collected was organized into a database using Microsoft Office Excel spreadsheets. For the analysis of the neonatal and maternal factors determinants to the case and control groups, Chi-square and G-tests were used in the Bioestat 5.3 program. For the present research, the significance index adopted was 95% with p value <0.05.

RESULTS

The sample of 483 preterm infants was composed mainly of no twin (82.8%), with weight between 1,499 and 1,000 grams in 38.1% (184), born at 31 to 34 weeks and 6 days of gestational age (42.4%), small for gestational age (64.6%) and Apgar greater than seven at fifth minute in 89.2% (431) of the records. Major of the infants (83.6%) infants required neonatal resuscitation skills, with positive pressure ventilation (PPV) associated with endotracheal intubation (ETI) as the most frequent (72.3%). The main signs of respiratory discomfort were tachypnea (72.7 %) and central cyanosis (21.9%). The most frequent maternal age group was 21 to 34 years old (58.4%), with a little emphasis on multiparous women (52%). The principal complications during pregnancy were urinary tract infection (41%), leukorrhea (39.6%) and hypertensive disease of pregnancy (20.5%). Caesarean section and rupture of membranes at delivery occurred in more than half of the parturients of the study, 54% and 60.2% respectively. Majority of infants (69.4%) were discharged from the neonatal ICU to other intermediate care units at hospital. Almost one-third (30.6%) died in the ICU and 56.1% of these deaths occurred early (early neonatal death less than seven days of life), about half of them caused by septic shock (41, 2%). The case group consisted of 152 (31.5%) preterm infants low birth weight and the remaining 331 (68.5%) made up the control group. Among the newborns of the case group, 57 (37.5%) presented only clinical criteria and almost half (42.8%) only laboratory criteria. The first blood culture was positive in just 11 infants (7.2%) (Table 1).

Table 1. Distribution of criteria for early-onset sepsis in the case group. Belém- Pará, Brazil. 2017. (N = 152)

	N	%
Clinical	57	37.5
Laboratory	65	42.8
Bloodculture	11	7.2
Laboratory + Clinical	11	7.2
Bloodculture + Clinical	2	1.3
Bloodculture + Laboratory	5	3.3
Bloodculture + Clinical + Laboratory	1	0.7
Total	152	100

N- Absolute frequency of cases Source: Medical Record Search

Gram positive were the main microorganisms found in the blood cultures: *Staphylococcus haemolyticus* (21.1%), *Staphylococcus aureus* (15.8%) and *Streptococcus epidermidis* (15.8%). From the analysis of neonatal risk factors for sepsis, was observed that birth weight and Apgar score less than seven at the first minute were significantly related to the sepsis criteria group (Table 2). The preterm infants in the case group had more clinical signs of respiratory distress at birth, requiring positive pressure ventilation with endotracheal intubation when compared to the group without clinical criteria for EOS and initiation of antibiotic therapy. The presence of hypothermia, cyanosis or bradycardia was significant for the diagnosis of sepsis. However, apnea or tachypnea did not show statistical significance (Table 3). Between maternal risk factors, only urinary tract infection and leukorrhea were significant to neonatal sepsis, when comparing the research groups (Table 4).

Table 2. Interference of neonatal risk factors in case and control groups. Belém- Pará, Brazil. 2017. (N = 483)

	Group Case n=152	%	GroupControl n=331	%	p-value[a]
BirthWeight (grams)					
< 2.500	41	27.0	109	32.9	0.0058*
< 1.500	49	32.2	135	40.8	
< 1.000	62	40.8	87	26.3	
Gestational Age					
35 – 36 w[b] 6 dc	24	15.8	63	19.0	0.0923
31 – 34 w 6 d	57	37.5	148	44.7	
≤ 30 w 6 d	71	46.7	120	36.3	
Size					
AGA[d]	48	31.6	122	36.9	0.2945
SGA[e]	104	68.4	208	62.8	
Sex					
Feminine	67	44.1	157	47.4	0.5565
Male	85	55.9	174	52.6	
Apgar 1st minute < 7					
Yes	113	74.3	162	48.9	<0.0001*
No	39	25.7	169	51.1	
Apgar 5th minute < 7					
Yes	23	15.1	29	8.8	0.0524
No	129	84.9	302	29.0	
Twins					
Yes	21	13.8	62	18.7	0.2302
No	131	86.2	269	81.3	

[a]Chi-square test. *Significant p-value. [b] Weeks. [c] Days. [d] Appropriate for gestational age. [e] Small for Gestational Age. Source: Medical Record Search

Table 3. Influence of clinical signs and neonatal resuscitation skills on case and control groups. Belém- Pará, Brazil. 2017. (N = 483)

	Group Case n=152	%	Group Control n=331	%	p-value
Hypothermia					
Yes	37	24.3	23	6.9	< 0.0001[a*]
No	115	75.7	308	93.1	
Apnea					
Yes	6	3.9	3	0.9	0.0650[b]
No	146	96.1	328	99.1	
Tachypnea					
Yes	114	75.0	237	71.6	0.5038[a]
No	38	25.0	94	28.4	
Cyanosis					
Yes	62	40.8	44	13.3	< 0.0001[a*]
No	90	59.2	287	86.7	
Bradycardia					
Yes	17	11.2	10	3.0	0.0001[a*]
No	135	88.8	321	97.0	
PPV[c] in Ambient Air					
Yes	6	3.9	22	6.6	0.3324[a]
No	146	96.1	309	93.4	
PPV[c]withOxygen					
Yes	5	3.3	13	3.9	0.9321[a]
No	147	96.7	318	96.1	
PPV[c] + ETI[d]					
Yes	123	80.9	226	68.3	0.0056[a]
No	29	19.1	105	31.7	
PPV[c] + ETI[d] + CM[e]					
Yes	1	0.7	2	0.6	0.5574[b]
No	151	99.3	329	99.4	
PPV[c]+ETI[d] +CM[e] + D[f]					
Yes	1	0.7	5	1.5	0.7259[b]
No	151	99.3	326	98.5	

[a] Chi-square test. [b] G-test. * Significant p-value. [c] Positive Pressure Ventilation. [d] Endootracheal Intubation. [e] Cardiac Massage. [f] Drugs. Source: Medical Record Search

DISCUSSION

In this study, only one third of low birth weight premature infants with presumed EOS admitted to the ICU had clinical, and/or laboratory, and/or microbiological indication for antibiotic therapy, composing the group with criteria for sepsis (case group). The significant neonatal risk clinical signs for sepsis were birth weight, Apgar score less than seven at first minute, hypothermia, cyanosis and bradycardia.

Table 4. Influence of maternal factors on case and control groups. Belém- Pará, Brazil. 2017 (N = 483)

	Group Case n=152	%	Group Control n=331	%	p-value [a]
Maternal Age (years)					
≤ 20	32	21.1	73	22.1	0.5328
21-34	97	63.8	220	66.5	
≥ 35	23	15.1	38	11.5	
Urinary TractInfection					
Yes	76	50.0	122	36.9	0.0086*
No	76	50.0	209	63.1	
Leukorrhea					
Yes	68	44.7	110	33.2	0.0197*
No	84	55.3	221	66.8	
Chorioamnionitis					
Yes	7	4.6	5	1.5	0.0864
No	145	95.4	326	98.5	
ROM[b] ≥ 18 hours					
Yes	40	26.3	62	18.7	0.0756
No	112	73.7	269	81.3	

[a] Chi-square test. * Significant p-value. [b] Rupture of Membranes. Source: Medical Record Search

The maternal risk factors were urinary tract infection and leukorrhea. About 54% of the case group obtained at least three points in Rodwell's hematological score to define laboratory criteria and 12.5% of infants with sepsis presented isolated microorganism in blood culture collected in the first 48 hours of life. There is no consensus in the literature of the diagnostic criteria for neonatal sepsis and vary substantially. Some studies use maternal risk factors, newborn's clinical symptoms and laboratory findings (Licona *et al*., 2017) and others organize a diagnostic tripod based on maternal and/or fetal risk factors, clinical evolution with recognition of signs suggestive of infection and serial laboratory tests (Stocker, 2017). Furthermore, another define as sepsis without positive culture the presence of at least two signs, such as temperature instability, irritability or lethargy, capillary filling time greater than two seconds, apnea, tachypnea (Duvoisin, 2014). Like these authors, this research used the association of some neonatal and maternal clinical data, laboratory and blood cultures to differentiate the group with the criteria established for EOS (case group) from the group with just presumptive sepsis (control group). However, low positivity at first blood culture was observed in case group of EOS. In accordance with studies at United Kingdom (Blackburn, 2012), where approximately 50% of all blood cultures are collected on day of birth and only 0.8% of them are positive. In Switzerland, it is estimated that 1 in 700 live births developed culture-proven neonatal sepsis (Giannoni, 2018). In Norway, only 5.9% of the sample had positive blood culture confirming EOS (Fjalstad *et al*., 2016).

According to a recent literature review (Klingenberg, 2018), most infants who evolved with clinical signs or risk factors for early sepsis had a negative blood culture. This may be justified by several factors, such as the need to collect the appropriate volume of one milliliter of blood in two samples, to perform concurrent aerobic and anaerobic culture and to collect the samples after the start of antibiotic therapy, possibly masking the result (Puopolo, 2017; Palatnik *et al*., 2019). In this context, such difficulties can also be used to justify the low frequency (3.9%) of positive first blood culture in the sample of this study. The most frequently isolated microorganism in blood cultures was *Staphylococcus haemolyticus* (21.1%) followed by *Staphylococcus aureus*, which is in contrast to the most

frequent agents found in the literature. In a research at United States (Bizzarro *et al*., 2015), the most frequently isolated organism was *Escherichia coli* (45%) and *Staphylococcus aureus* occupied the fourth position. In Norway (2016), *Streptococcus agalactiae* (GBS) was found in most, besides *coagulase negative Staphylococcus* prevailed in Mexico (Anaya-Prado, 2017). Therefore, these authors reinforce that each unit has its own microbial profile, as we found in this study. When comparing the groups, it was verified that early prematurity and very low birth weight are determinant variables to sepsis. Other studies also agreed and emphasized that premature and low birth weight newborns have an incidence of early sepsis three to ten times higher those at term and those with adequate birth weight (Cetinkaya *et al*., 2015). Furthermore, have observed rates of early sepsis per 1000 live births ten times higher in extremely low birth weight and very low birth weight infants compared to heavier babies, as well as in extreme premature infants and early preterm infants (Bizzarro *et al*., 2015). Factors such as longer length of stay at ICU and the need of invasive procedures may be related to this high rate of EOS in infants with extremely low birth weight and gestational age. This is a possible explanation to neonatal resuscitation with an endotracheal intubation be associated with the case group in this research (Puopolo, 2017; Murthy, 2019; Puopolo, 2018). Urinary tract infection was the main maternal risk factor for EOS found in the study. In comparison, a study at Santa Catarina city reported 37% of the newborns with sepsis were children of pregnant women with this complication (Puopolo, 2018). Chorioamnionitis and rupture of membranes time greater than or equal to eighteen hours were not significant in this study. This is comparable with some authors that didn't use these parameters as isolated indicators of EOS (Puopolo *et al*., 2017; Cuna, 2014; Kiser, 2014).

Conclusion

More than half of the low birth weight preterm infants admitted to the ICU of the reference public maternity hospital in Pará did not fill in the criteria for EOS, but received antimicrobial therapy due to the diagnosis of presumed sepsis. Among infants with criteria for initiation of antibiotic therapy, factors related to weight, clinical signs and the need for endotracheal intubation constitute the main risks to the development of sepsis in the first days of life. The retrospective nature of the study and the lack of detailed medical records represented the major limitations of this research. Although, it was possible to demonstrate a significant percentage of non-septic infants in antibiotic therapy.

Therefore, future prospective researches may will evaluate the indiscriminate use of antibiotics and their harm in this neonatal population.

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