Late Onset Sepsis in Very Low Birth Weight Infants in the South American NEOCOSUR Network

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Background: The main aim is to determine the incidence and associated factors of late onset sepsis (LOS) in very low birth weight infants (500–1500 g), from the NEOCOSUR Network during years 2001–2013. Secondary objectives are to describe the microbiology of the first and second episode of LOS and to study the association between catheter dwell time and LOS.
Methods: Demographic information and outcome data are prospectively and routinely collected across the network using predefined diagnostic criteria and online data entry. LOS was confirmed by isolation of the organism in blood or through cerebrospinal fluid in cultures. The participating countries were Argentina, Brazil, Chile, Paraguay, Peru and Uruguay.
Results: Overall incidence was 22.2% (3066/13,821). Infants who developed LOS were smaller by weight and gestational age; also, they feature less prenatal care and prenatal steroids, and longer hospital stays. A greater number of infants in the LOS group had 1 minute Apgar Scores ≤3. Multivariate logistic regression analysis showed a positive association between LOS and necrotizing enterocolitis, mechanical ventilation requirements, patent ductus arteriosus, oxygen dependency at 36 weeks and death. The majority of first LOS episode was caused by coagulase-negative staphylococci (44.3%). An increased risk of LOS was observed in relation to catheter dwell time (6% per day of stay of central lines).
Conclusions: The incidence of LOS was associated with mechanical ventilation, patent ductus arteriosus, necrotizing enterocolitis and death. LOS was an important cause of morbidity and mortality in very low birth weight infants in our network, and coagulase-negative staphylococci was the most frequent causative microorganism.

Key Words: very low birth weight, late-onset sepsis, preterm infants, neonatal network, central lines

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Late onset sepsis (LOS) is a common complication of very low birth weight (VLBW; birth weight ≤1500 g) infants admitted to neonatal intensive care units (NICUs) and is an important cause of morbidity and mortality. The risk of LOS increases with decreasing birth weight and gestational age. Besides immaturity, other risk factors for LOS include the long-term use of invasive interventions, such as mechanical ventilation and intravascular catheterization, the delay of enteral human milk feeding, a prolonged duration of parenteral nutrition, the duration of hospital stay, surgery and underlying respiratory and cardiovascular diseases.[1] Extremely low birth weight (birth weight ≤1000 g) infants who developed sepsis are more likely to have neurodevelopmental impairment[2] and some studies point out that sepsis is one of the major risk factors for developmental delay and cerebral palsy.[3] Association of LOS with unfavorable neurodevelopmental outcomes may be explained as a result of a systemic inflammatory response and increasing comorbidities.[4]

LOS increases medical costs, and each center has a role in the incidence of LOS in neonatal networks, given the great center variability.[5] Evidence-based intervention strategies have been designed to reduce the high rate of hospital-acquired infections.[6] All efforts are targeted to minimize the risk to patients in an attempt to reduce both morbidity and mortality.

Regarding NICU, central line–associated bloodstream infection is the most common health care–associated infection and is a significant cause of morbidity and mortality in high-risk neonates.[7] Most reported LOS episodes are caused by Gram-positive organisms, such as coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*.[8,9] Although less common, Gram-negative bacillary infections have a higher mortality rate.[10]

NEOCOSUR is a voluntary nonprofit association of NICUs with 26 participating centers from 6 South American countries that represent both public and private institutions whose primary mission is the improvement of neonatal care and outcome in this region. This study was undertaken to determine the incidence, associated factors and microbiology of LOS in a large South American population of VLBW from the NEOCOSUR network; also to establish the risk of LOS in relation to catheter dwell time and identify a threshold beyond which time the daily risk of LOS increases.

PATIENTS AND METHODS

Demographic information and outcome data are prospectively and routinely collected across the NEOCOSUR Neonatal Network using predefined diagnostic criteria by consensus and online data entry. This database was the source of information for the present study.

This study included VLBW infants (500–1500 g), admitted to NEOCOSUR network centers from years 2001–2013. Outborn newborns were excluded. LOS was defined by the isolation of a microorganism in blood or cerebrospinal fluid in cultures obtained at more than 72 hours after birth. Only one blood culture was considered for the diagnosis of sepsis, including CoNS.

Prenatal care was defined in the database of the NEOCOSUR network as at least 1 prenatal visit to an obstetrician. Though this is an arbitrary definition, it stablishes minimum care and we

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are convinced that this is meaningful in our region, when compared with mothers with absolutely no prenatal visits.

Bronchopulmonary dysplasia (BPD) was defined as oxygen dependency at 36 weeks postmenstrual age.[11] Patent ductus arteriosus (PDA) was diagnosed clinically and whenever available confirmed by echocardiography. Necrotizing enterocolitis (NEC) was confirmed by radiologic (pneumatosis and/or perforation) or surgical findings, and only confirmed cases of NEC were included for analysis (Bell's stages IIA or more). Periventricular leukomalacia was diagnosed by the presence of intraparenchymatous necrotic lesion in the white matter by ultrasound cerebral.[12] The intraventricular hemorrhage was diagnosed by ultrasound cerebral and was classified according to the criteria of Papile et al.[13] Retinopathy of prematurity was diagnosed by an examination by an ophthalmologist as of 28 days after birth and was classified in grades 1–5 according to the International Classification.[14]

Other analyzed data included the age at first episode of LOS, number of subsequent episodes, microbial isolates for the first and subsequent episodes, catheter dwell time and mortality. All kinds of central line catheters were included, without distinguishing its type.

Statistical Analysis

The χ^2 test was used to compare categorical variables and the *t* test to compare continuous variables. Logistic regression was used to calculate risk factors. A step-wise procedure was used to select those factors that independently contribute to explain the outcome. The effect of each factor was expressed as odds ratio and 95% confidence intervals. *P* values <0.05 were considered significant. Statistical analyses were conducted using SPSS version 17.0 (IBM, Armonk, NY). The data were not adjusted per each center.

RESULTS

A total of 14,780 VLBW infants were registered in the NEOCOSUR network database from years 2001–2013. A total of 8.9% died during the first 72 hours, with variability between centers of 2.2% and 18.4%.

This population belongs to public and private hospitals and has different socioeconomic and educational levels. The average gestational age at birth was 28.8 weeks, with a birth weight of 1085 g. The average maternal age was 27.9 years old, with 70% cesarean deliveries. The incidences of severe intraventricular hemorrhage and NEC were 10% and 10.8%, respectively. The percentages of use of prenatal corticosteroids and prenatal antibiotics were 76.4% and 34.6%, respectively. The mortality in the delivery room was 4.7%, and the mortality postadmission was 21.1%. The overall mortality was 25.8%.

The following results are based on 13,821 neonates who survived at least 3 days from 2001 to 2013 in NEOCOSUR network (26 centers included).

The incidence of LOS was 22.2% (3066/13,821) with a variation from 6.7% to 36.5% among the different centers ($P < 0.05$). Its occurrence was 23.9% during the initial 4-year period (2001–2005), 21.2% during 2006–2008 and 21.5% during 2009–2013, with a significative decrease across the time ($P < 0.05$).

Infants who developed LOS were significantly smaller by weight and gestational age; they had less prenatal care, less use of prenatal steroids and more use of perinatal antibiotics. The clinical variables premature rupture of membranes, PDA, NEC, retinopathy of prematurity and periventricular leukomalacia were more frequent in infants with LOS. LOS was also associated with greater mechanical ventilation requirements and length of hospital stay. Also, the babies with LOS had a higher mortality after 3 days than babies without LOS, with statistically significant differences ($P < 0.001$) and increased use of oxygen at 36 weeks. There were more infants in the LOS group with Apgar Scores ≤3 at the first minute. Finally, maternal hypertension and cesarean section (CS) were less frequent in infants with LOS (Table 1).

After adjustment by multivariate logistic regression, LOS was associated with an increased risk of PDA, NEC, mechanical ventilation requirements, lower birth weight, oxygen dependency at 36 weeks and death. Prenatal steroids, CS and higher birth weight were associated with decreased risk of LOS (Fig. 1). Most of the first episodes of LOS (58.7%) were caused by Gram-positive pathogens. CoNS were the most frequent late onset pathogens (44.3% of all infections). It should be noted that Candida sp. was present in 7% of LOS episodes (Fig. 2A). The most frequent pathogen in the second episode of LOS was also CoNS (37.5%), followed by Serratia sp. (15.0%) and Group B Streptococcus (GBS) (10.3%), while 6.4% of cases of the second episode of LOS were explained by the pathogen *Stenotrophomona maltophila* (Fig. 2B).

The median time of diagnosis of LOS was 14 days. The average age for the first episode of late-onset sepsis was 22 ± 0.5 days. The diagnosis of LOS was carried out between 3 and 150 days of life.

An increased risk of LOS was observed in relation to catheter dwell time. The risk of LOS increased 6% per each day duration of central lines (95% confidence interval: 5.6%–6.4%; Table 2).

Finally, there is a marked decrease in the incidence of LOS as the birth weight ranges increase (Fig. 3).

DISCUSSION

This is a retrospective analysis of prospectively collected data from clinical records of a network of South American NICUs. Although VLBW infants represent about 1% of all live births in the region, they heavily impact on mortality rates.

Results from this cohort of inborn neonates showed that 22.2% of VLBW infants included in the database, that survived 72 hours, suffered at least 1 episode of LOS, with a wide variation among centers (6.7%–36.5%). It is important to take in account that

TABLE 1. Perinatal and Clinical Variables in VLBW Infants With Sepsis and Without Sepsis

Variables	No Sepsis (n = 10,755)	Sepsis (n = 3066)	*P* Value
Birth weight (g) (X ± SD)	1158 ± 252	994 ± 252	<0.001
Gestational age (wk) (X ± SD)	29 ± 2	28 ± 2	<0.001
Male gender (%)	49.7	53.0	<0.001
Multiple pregnancies (%)	20.0	17.8	0.008
Prenatal control (%)	89.9	86.4	<0.001
Prenatal steroids (%)	81.0	75.8	<0.001
Perinatal antibiotics (%)	34.2	38.0	<0.001
PROM (%)	25.9	27.8	0.030
Apgar score ≤3 at 1 min (%)	14.7	22.8	<0.001
Cesarean (%)	75.2	68.3	<0.001
Maternal hypertension (%)	31.3	26.2	<0.001
Mechanical ventilation (%)	55.8	84.6	<0.001
PDA (%)	35.0	55.5	<0.001
NEC (%)	9.1	23.6	<0.001
PVL (%)	5.3	9.0	<0.001
O_2 36 wk (%)	15.3	34.1	<0.001
ROP (%)	19.7	43.1	<0.001
Length of stay (d)	52.2 + 39	72.8 ± 49	<0.001
Death after 3 d	11.0	22.9	<0.001

O_2 36 weeks indicates oxygen at 36 wk; PROM, premature rupture of membranes; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SD indicates standard deviation.

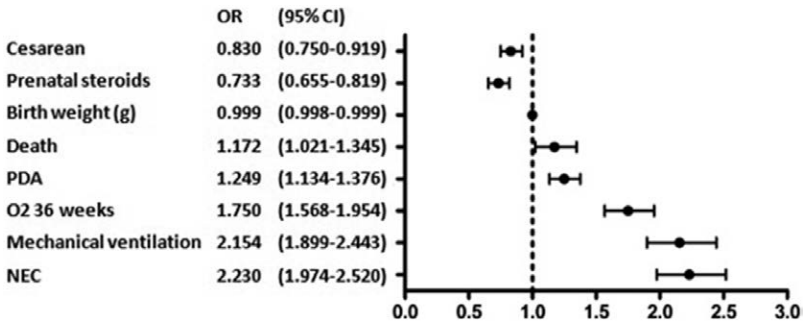

FIGURE 1. Variables associated with LOS by multivariate logistic regression. CI indicates confidence interval; O_2 36 weeks, oxygen at 36 weeks; OR, odds ratio.

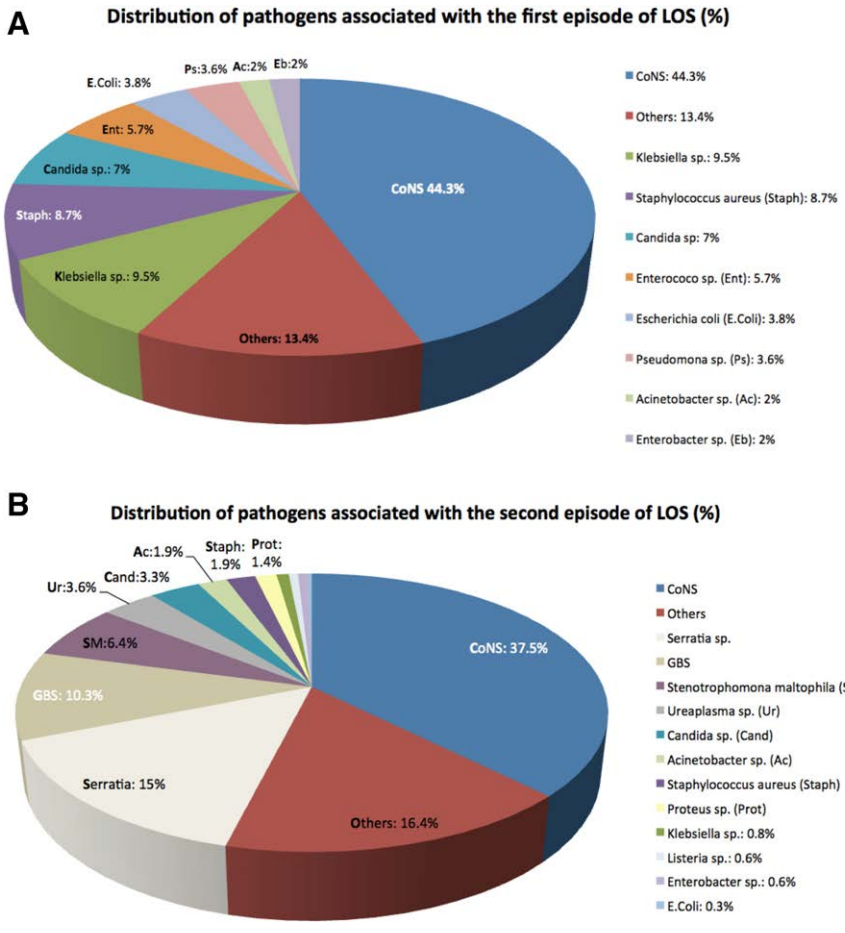

FIGURE 2. Distribution of pathogens associated with the first episode (3.066 cases included) and second episode of LOS (212 cases included). full color online

TABLE 2. Catheter Dwell Time and Risk of LOS

Catheter Dwell Time (d)	OR (95% CI)
≥7	2.7 (2.42–3.02)
≥10	3.1 (2.82–3.42)
≥15	4.1 (3.80–4.53)

CI indicates confidence interval; OR, odds ratio.

these data represent only inborn infants and may not be comparable with other population series that include outborn patients.

Different networks have reported significant variability in the incidence of LOS in VLBW infants. Our incidence is similar to the one indicated by the NICHD Neonatal Research Network (21%)[4] and the EuroNeoNet network (22.6%).[15]

On the other hand, our incidence is lower than results reported by other networks, such as Israel Neonatal Network (30%)[6] and the Brazilian Neonatal Research Network (27.5%),[16] and higher than results reported by The Australian and New Zealand Neonatal Network (12%)[17] and the Canadian Neonatal Network (19.6%).[18] It is important to mention that the Australian and New Zealand Neonatal Network defines LOS with a positive culture after 48 hours of life,[16] in contrast with our definition, which is the most commonly used, after 72 hours of life.

Multivariate logistic regression analysis showed a strong positive association between LOS and NEC, BPD, PDA, mechanical ventilation and death; prenatal steroids and cesarean delivery

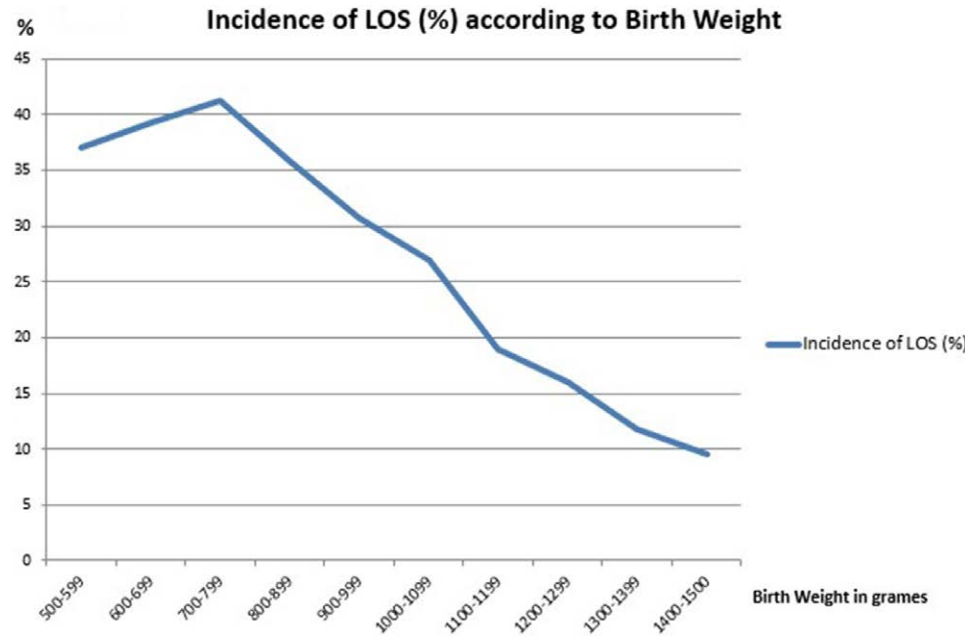

FIGURE 3. Incidence of LOS according to birth weight.
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were associated with a decreased risk of LOS. Several studies have found an increased risk for LOS in VLBW infants who required prolonged periods of mechanical ventilation.[5,19] The mechanisms by which infection leads to BPD may involve an inflammatory process, which results in damage to lung tissue. Infection also increases ductal dilatory prostaglandins and therefore the risk of PDA which increases pulmonary blood flow and interstitial edema.[20,21] The role of infection in the pathogenesis of NEC is well recognized.[22]

One possible explanation for the protective effect of prenatal steroids in this study is that it decreases the incidence and severity of respiratory distress syndrome (RDS) and the need for invasive mechanical ventilation as reported by our network, among others.[23] Along with invasiveness, more interventions and therapies are applied, and recurrent episodes of sepsis are more likely to occur.

In contrast to our findings, CS was associated with an increased risk of LOS in the Israeli network and their explanation was that CS rates are higher in pregnancies associated with a variety of obstetric complications, which may influence the infants' subsequent outcome. In agreement with our results, a report from the Canadian Network from 2005 encountered a decreased risk of LOS after a CS in a VLBW infant's population.[24] We do not have an explanation for these nonconsistent results.

In the present study, the length of hospital stay was longer for septic infants. Other published data have found an increase in the length of stay in VLBW with LOS.[21,23] Though cost analysis was not included as part of our study, undoubtedly prolongation of hospital course is responsible for increased costs for NICUs in the region.[25]

When considering the proportion of Gram-negative microorganisms, NEOCOSUR is halfway between the Israeli Network[6] and the NICHD Neonatal Research Network.[5] Gram-positive organisms were the most commonly isolated pathogens. Gram-negative bacillary and Candida infections have become another principal cause of neonatal sepsis, similar to that reported in other studies.[26] However, in the second episode, the microbiologic profile changed with the presence of new aggressive bacteria like *Serratia* sp., *S. maltophila* and *Acinetobacter baumanii*. One possible explanation for this finding could be the early use of broad spectrum antibiotics at the NICUs.

The median time of diagnoses of LOS was 14 days, similar to previously reported.[7] Infants with prolonged duration of central catheters increase the risk of LOS for each day with central catheters. The stronger association is with catheter dwell time longer than 15 days. These data suggest that efforts to initiate enteral feedings as early as possible, to minimize the use of central venous catheters, and to reduce the number of catheter days may help to decrease the risk of LOS. Though the first few days may set the stage, most infants in the cohort developed infections closer to the end of the second week of life. Similar results were found by the Australian Study Group[27] though in their case only CoNS sepsis was analyzed. However, since many septic episodes were because of CoNS, probably other chronic treatment-related interventions (such as TPN with lipids), frequently associated with LOS staphylococcus infections were important.[27,28]

Finally, nosocomial infections are a good indicator of the quality of care. These are the first baseline data on LOS comprising a large cohort of infants in a multicultural, varied environment, in the South of Latin America. As such, they are both valuable and necessary for the development of local guidelines. Improvement in the diagnosis of sepsis, as well as in the handling of tiny infants, is needed for improvements in care. This improvement is a necessary step toward an increase in survival in the VLBW infants born in the South American region. The large variability in the incidence of LOS among centers suggests that there is an opportunity for better performance.

One of the limitations of this study is the fact that this is a retrospective analysis of those data that were collected over an extended period (13 years), during which changes in clinical practices might have taken place. Some of these might have been changes in antibiotic treatment schemes and different resources available within that period, as well as central line bundles. These factors could have contributed to the observed decrease in the incidence of LOS over time in the NEOCOSUR Network. On the other hand, there is no uniformity among centers in protocols neither for the use of antibiotics or postnatal steroids (that may increase risk of LOS) nor for strategies to prevent LOS. The type of milk used in the study was not registered (breast milk, donated milk or formula), and human milk has been associated to a decreased risk of LOS. Another limitation may be the stringent criteria for case definition (1 blood culture) that probably underestimated the true LOS infection rate. On the other hand, CoNS sepsis may be overestimated

because of the fact that contamination rather than sepsis with this microorganism's is hard to distinguish.

The strengths of this study are that it includes a large sample size and population diversity from several South American NICUs, with prospectively collected and predefined information. We hope these results reinforce the importance of adopting strategies to reduce this serious complication that is associated with increased mortality and severe morbidity that all together contribute to a worse long-term outcome in surviving VLBW infants.

CONCLUSIONS

The incidence of LOS was 22.2% in VLVW infants through a 13-year period, and it was associated with many factors, namely, mechanical ventilation, PDA, NEC, BPD and death. CoNS remains the principal cause of LOS, both for the first and second episodes. An increased risk of LOS was observed in relation to catheter dwell time. LOS continues being an important cause of morbidity and mortality in VLBW preterm infants.

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APPENDIX

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