www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2020;9(1):e090120
doi: 10.7363/090120
Received: 2019 Apr 07; revised: 2019 Jun 16; accepted: 2019 Jul 03; published online: 2020 Mar 04

Original article

Time trends in late-onset sepsis and meningitis in very low birth weight infants from 2000 to 2013: results from a Portuguese tertiary level Neonatal Intensive Care Unit

Maria Francisca Maia[1], Joselina Barbosa[1], Sandra Costa[1,2], Susana Pissarra[1,2], Hercília Guimarães[1,2,3]

[1]Faculty of Medicine, University of Porto, Porto, Portugal

[2]Neonatal Intensive Care Unit, Centro Hospitalar Universitário de São João, Porto, Portugal

[3]Cardiovascular R&D Unit, Faculty of Medicine, University of Porto, Porto, Portugal

Abstract

Objective: To assess the evolution of the prevalence of late-onset sepsis (LOS) and meningitis and its predictors in a Portuguese tertiary level Neonatal Intensive Care Unit (NICU) during its participation in the Vermont Oxford Network (VON) between 2000 and 2013.

Methods: Descriptive retrospective study of all very low birth weight infants admitted to a level-III NICU between 2000 and 2013. Outborn infants, infants who died in the delivery room and neonates who died during the first 12 hours in NICU were excluded. Patients' demographic characteristics and clinical data were collected. Data from neonates with and without LOS were compared.

Results: The prevalence of LOS significantly decreased from 56.3% between 2000 and 2004 to 26.5% between 2010 and 2013. Infants with a gestational age of 22-27 weeks had more LOS (65.6%) than neonates with 32-36 weeks (20.9%). Similarly, smaller infants (weighing ≤ 1,000 g) had more LOS (59.4%) than babies with a weight > 1,000 g (33.3%). LOS was significantly associated with a gestational age between 22 and 27 weeks, mechanical ventilation (MV), nasal CPAP, necrotizing enterocolitis and the use of steroids for bronchopulmonary dysplasia.

Conclusions: Preterm infants require many invasive devices to ensure their survival, such as MV, which greatly increases their infection risk. To minimize this risk, it is crucial to guarantee that better practices are followed,

necessitating the use of regular audits. It is really important to know the data about LOS from our NICU, which allows sharing and comparison with peers in order to improve nosocomial infection prevention and control practices.

Keywords

Late-onset sepsis, VLBW infants, Neonatal Intensive Care Unit, nosocomial infection, preterm infants, VON database.

Corresponding author

Maria Francisca Maia, Faculty of Medicine, Porto University, Porto, Portugal; address: Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal; phone: +351 919 082 220; e-mail: franciscabbmaia@gmail.com.

How to cite

Maia MF, Barbosa J, Costa S, Pissarra S, Guimarães H. Time trends in late onset sepsis and meningitis in very low birth weight infants from 2000 to 2013: results from a Portuguese tertiary level Neonatal Intensive Care Unit. J Pediatr Neonat Individual Med. 2020;9(1):e090120. doi: 10.7363/090120.

Introduction

Although there have been advances in neonatal care that have improved survival and reduced complications in preterm infants, sepsis continues to be a major cause of mortality and morbidity among very low birth weight (VLBW) infants in Neonatal Intensive Care Units (NICUs) [1, 2].

The incidence of late-onset sepsis (LOS) considerably varies from centre to centre, ranging from 10.6% to 31.7% [3].

In a study performed at our NICU, 549 (13.9%) of all admitted patients presented with clinical or confirmed sepsis between 2003 and 2012. Of these, 15 (2.7%) had confirmed fungal sepsis on blood cultures and all of them were low birth weight (LBW), 13 (86.7%) were VLBW and 9 (60%) were extremely low birth weight (ELBW) [4].

It is important to implement measures to prevent nosocomial infections, since they decrease the incidence density of nosocomial sepsis, as we concluded from a study in our NICU which showed that the incidence density of nosocomial sepsis decreased significantly from 8.6 to 4.8 per 1,000 days (44%) after a new preventive bundle implementation [5].

Freitas et al. showed that newborns who developed LOS were more exposed to invasive procedures, including the use of mechanical ventilation (MV) and peripherally inserted central catheters (PICC). They found that there was an association between the use of MV for 10 or more days and LOS in 80.8% of cases, while PICCs left in place for 11 days or longer were associated with LOS in 76.2% of cases [6].

As one of the largest neonatal databases, the Vermont Oxford Network (VON) has collected and maintained data about VLBW infants and neonates who fulfil other eligibility requirements from many parts of the world since 1989 [7].

In Portugal, there is a National Registration of Very Low Birth Weight Newborns, which was founded in 1994, and allows us to benchmark our practices. In this registration, between 1994 and 1996, sepsis was one of the most frequent pathologies (34%) and with a higher incidence when compared with VON (26%) [8].

There is also a protocol for epidemiological surveillance of nosocomial infections in NICUs in Portugal, whose objectives are to establish the impact of infection in those NICUs, to find the use of invasive devices in function of the total days of hospital stay, to determine infection rates and their distribution per site, to compare the performance between NICUs in terms of the parameters described before, to benchmark national data and to continually improve practices according to the obtained results [9].

A more complete picture of the epidemiology of neonatal infections is provided by multicentre studies, which show greater scope for the development of successful interventions [10].

Rates of LOS and hospital-acquired bloodstream infections (HABSIs) provide vital information regarding the success of hospital guidelines concerning infection control procedures, such as hand hygiene, cot separation and central line care [10].

Neonatal infection surveillance networks serve several purposes, such as knowing about LOS incidence and its variability, comparing results with those of other networks and proposing public health policies to improve neonatal care quality and safety [11, 12].

This study aims to assess the evolution of the prevalence of LOS and meningitis and its predictors in the NICU of Centro Hospitalar Universitário de São João during the participation in the VON between 2000 and 2013.

Methods

The data of the NICU of Centro Hospitalar Universitário de São João were collected from the VON files, between 2000 and 2013, the period of our participation in the network. The inclusion criteria were: any inborn infant with a birth weight between 401 and 1,500 g or a gestational age between 22 weeks and 0 days and 29 weeks and 6 days. Outborn infants were also included if transferred from another institution to our hospital within 28 days from birth, without having been discharged home first, and whose birth weight was between 401 and 1,500 g or whose gestational age was between 22 weeks 0 days and 29 weeks 6 days.

We collected and analysed LOS and meningitis items from the VON database between 2000 and 2013.

Definitions for demographic and clinical data were provided in the "*Manual of Operations*" of VON [13].

The Ethics Committee of Centro Hospitalar Universitário de São João approved this study.

Study sample definition

At the beginning of the study, 607 babies were identified. Ninety-five outborn infants were excluded. Six infants died in the delivery room. Eighteen infants died during the first 12 hours in NICU. Finally, 55 infants had missing information on the outcome. The final sample for the study was 433 infants (**Fig. 1**).

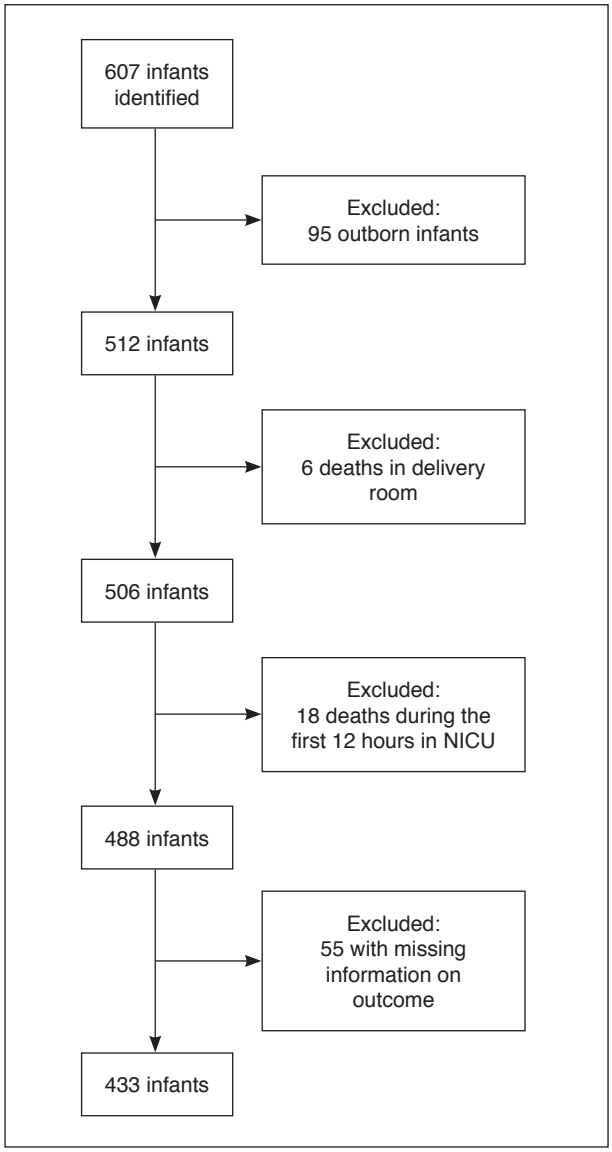

Figure 1. Flowchart for the study sample definition.

Statistical analysis

The statistical analysis was performed using SPSS® for Windows®, version 25. Categorical variables were characterized by absolute and relative frequencies. Chi-Square or Fisher's exact test was used to compare categorical variables with Bonferroni's correction on pairwise comparisons.

A multivariate analysis by logistic regression was performed to evaluate predictive factors for LOS. The strength of the association was measured by Odds Ratio (OR) and 95% confidence intervals (95% CI). Only variables that presented significance up to 0.05 and those clinically relevant in the univariate analysis were included in the model. A p-value of less than 0.05 was considered statistically significant. To create the most parsimonious model, variables that did not reach a significance level of p-value < 0.05 in the multivariable model were backward eliminated one by one.

Results

*Demographic characteristics of the study population (**Tab. 1**)*

Our population was composed of 221 female infants (51.0%) and 212 male newborns (49.0%). Most of the infants were born between 28 and 31 weeks of gestation (230, 53.1%). Furthermore, 93 newborns were born between 22 and 27 weeks of gestation (21.5%) and 110 between 32 and 36 weeks (25.4%). In our sample, 114 infants (26.3%) were small for gestational age.

At birth, 160 neonates weighed 1,000 g or less (37.0%); in relation to pregnancies, 287 (66.3%)

Table 1. Infants' demographic characteristics.

Characteristic		No. (%) of infants (n = 433)
Sex of the infant	Female	221 (51.0%)
	Male	212 (49.0%)
Gestational age (weeks)	22-27	93 (21.5%)
	28-31	230 (53.1%)
	32-36	110 (25.4%)
Small for gestational age	Yes	114 (26.3%)
	No	319 (73.7%)
Birth weight (grams)	≤ 1,000	160 (37.0%)
	> 1,000	273 (63.0%)
Multiple gestation	No	287 (66.3%)
	Yes	146 (33.7%)
Mode of delivery	C-section	314 (72.5%)
	Vaginal	119 (27.5%)
Apgar score at 5 minutes	< 7	58 (13.4%)
	≥ 7	375 (86.6%)

were gestations with only one foetus and two or more foetuses were documented during 146 (33.7%) pregnancies; 314 neonates were born by C-section (72.5%) and 119 babies were born by vaginal delivery (27.5%).

Finally, an Apgar score at 5 minutes of less than 7 was registered in 58 newborns (13.4%), whereas 375 infants had an Apgar score at 5 minutes equal to or higher than 7 (86.6%).

*Late-onset sepsis according to the year of birth (**Tab. 2**)*

Between 2000 and 2013, 43% of the infants had at least one episode of LOS. The most frequent aetiology was a coagulase-negative staphylococcal infection, since 34.2% of all infants had an infection caused by this microorganism. A total of 16.4% of infants had other bacterial pathogens identified as the cause of LOS and only 3.2% had a fungal infection.

From 2000 to 2004, 94 (56.3%) out of 167 infants had LOS. The most frequent aetiology of LOS between these years was coagulase-negative *Staphylococcus* (78 infants, corresponding to 46.7% of the total 167 newborns). Only 7 infants (4.2%) had LOS caused by fungi.

Between 2005 and 2009, 61 out of 149 (40.9%) infants developed LOS. Once again, most of the infected neonates had a coagulase-negative staphylococcal infection (33.6%, 50/149). During the last years of this study (2010-2013), 31 out of 117 infants had LOS (26.5%). Among infected newborns, 20 had coagulase-negative staphylococcal LOS (17.1%), 14 developed LOS provoked by other bacteria (12.0%) and 1 child had a fungal infection (0.9%).

More than one agent was identified in some patients.

*Late-onset sepsis according to gestational age (**Tab. 3**)*

In the group of infants born between 22 and 27 weeks of gestation, 65.6% had LOS (61/93). Among infants with this range of gestational ages, 43 out of 93 (46.2%) had LOS caused by coagulase-negative *Staphylococcus*, 27 developed LOS from other bacteria (29.0%) and 8 had a fungal infection (8.6%).

For infants born between 28 and 31 weeks of gestation, 102 out of 230 had LOS (44.3%). The most frequent aetiology was coagulase-negative *Staphylococcus* infection, with a prevalence of 37.8% (87/230). Infections caused by other bacterial pathogens registered a prevalence of 16.5% (38/230) and by fungal organisms showed a prevalence of 1.7% (4/230).

Finally, newborns with a gestational age between 32 and 36 weeks registered a prevalence of LOS of 20.9% (23/110). 18 out of 110 neonates had a coagulase-negative staphylococcal infection, whose prevalence was 16.4%. Other bacterial infections showed a prevalence of 5.5%, since 6 out of 110 had infections caused by other bacteria apart from coagulase-negative *Staphylococci*. Fungal infections exhibited a prevalence of 1.8% (2/110).

*Late-onset sepsis according to birth weight (**Tab. 4**)*

The group of infants born with a weight equal to or less than 1,000 g presented a prevalence of LOS of 59.4% (95/160). In this group, 70 out of 160 had a coagulase-negative staphylococcal infection (43.8%), 26.9% had LOS caused by other bacteria (43/160) and 10 developed a fungal infection (6.2%).

Differently, neonates whose birth weight was greater than 1,000 g had a prevalence of LOS of 33.3% (91/273). Among these children, 78 had a coagulase-negative staphylococcal infection (28.6%), 28 developed LOS provoked by other bacterial microorganisms (10.3%) and 4 had a fungal infection (1.5%).

Table 2. Late-onset sepsis (LOS) and meningitis according to year of birth.

Aetiology	Year of birth				p-value
	2000-2004 (n = 167)	2005-2009 (n = 149)	2010-2013 (n = 117)	Total (n = 433)	
LOS from all causes, n (%)	94 (56.3%) [a]	61 (40.9%) [b]	31 (26.5%) [c]	186 (43.0%)	< 0.001 [d]
Coagulase-negative staphylococcal infection, n (%)	78 (46.7%) [a]	50 (33.6%) [a]	20 (17.1%) [b]	148 (34.2%)	< 0.001 [d]
Other bacterial pathogens, n (%)	46 (27.5%) [a]	11 (7.4%) [b]	14 (12.0%) [b]	71 (16.4%)	< 0.001 [d]
Fungal infection, n (%)	7 (4.2%)	6 (4.0%)	1 (0.9%)	14 (3.2%)	0.229 [e]

LOS: late-onset sepsis.
[a, b, c] are different letters that indicate significant differences between years' groups based on pairwise comparison. For example, if one group has a superscript [a] and another has a superscript [b], this means that the differences between these two groups are statistically significant.
[d] Chi-square test; [e] Fisher's exact test.

Table 3. Late-onset sepsis (LOS) and meningitis according to gestational age.

Aetiology	Gestational age				p-value
	22-27 weeks (n = 93)	28-31 weeks (n = 230)	32-36 weeks (n = 110)	Total (n = 433)	
LOS from all causes, n (%)	61 (65.6%) [a]	102 (44.3%) [b]	23 (20.9%) [c]	186 (43.0%)	< 0.001 [d]
Coagulase-negative staphylococcal infection, n (%)	43 (46.2%) [a]	87 (37.8%) [a]	18 (16.4%) [b]	148 (34.2%)	< 0.001 [d]
Other bacterial pathogens, n (%)	27 (29.0%) [a]	38 (16.5%) [b]	6 (5.5%) [c]	71 (16.4%)	< 0.001 [d]
Fungal infection, n (%)	8 (8.6%) [a]	4 (1.7%) [b]	2 (1.8%) [a, b]	14 (3.2%)	0.010 [e]

LOS: late-onset sepsis.
[a, b, c] are different letters that indicate significant differences between gestational age groups based on pairwise comparison. For example, if one group has a superscript [a] and another has a superscript [b], this means that the differences between these two groups are statistically significant.
[d] Chi-square test; [e] Fisher's exact test.

Table 4. Late-onset sepsis (LOS) and meningitis according to birth weight.

Aetiology	Birth weight			p-value
	≤ 1,000 g (n = 160)	> 1,000 g (n = 273)	Total (n = 433)	
LOS from all causes, n (%)	95 (59.4%)[a]	91 (33.3%)[b]	186 (43.0%)	< 0.001 [d]
Coagulase-negative staphylococcal infection, n (%)	70 (43.8%)[a]	78 (28.6%)[b]	148 (34.2%)	0.001 [d]
Other bacterial pathogens, n (%)	43 (26.9%)[a]	28 (10.3%)[b]	71 (16.4%)	< 0.001 [d]
Fungal infection, n (%)	10 (6.2%)[a]	4 (1.5%)[b]	14 (3.2%)	0.007 [d]

LOS: late-onset sepsis.
[a, b, c] are different letters that indicate significant differences between birth weight groups based on pairwise comparison. For example, if one group has a superscript [a] and another has a superscript [b], this means that the differences between these two groups are statistically significant.
[d] Chi-square test.

Univariate/comparative analysis of infants with and without late-onset sepsis

There was no statistically significant difference in the prevalence of LOS between female and male infants (p-value = 0.990), neither between different types of delivery – C-section versus vaginal delivery (p-value = 0.087) – or between neonates with Apgar score < 7 and ≥ 7 (p-value = 0.757).

Among the ventilated neonates, 54.1% developed LOS, whereas only 25.1% of infants who did not require conventional ventilation had LOS (p-value < 0.001).

Among infants who had respiratory distress syndrome (RDS), 50.2% had LOS, when compared with 34.7% of those who did not have RDS (p-value = 0.001).

In the group of patients with necrotizing enterocolitis (NEC), 76.5% developed LOS, while only 41.6% of the infants without NEC had LOS (p-value = 0.004).

In the case of children with patent ductus arteriosus (PDA), 61.1% of them had LOS,

compared with 36.9% of those who did not have PDA (p-value < 0.001).

There was no statistically significant difference in the prevalence of LOS between individuals with neurologic morbidity or those without it, given there was no statistically significant difference between infants with cystic periventricular leukomalacia (cPVL) and those without cPVL (p-value = 0.112) neither between neonates with intraventricular haemorrhage (IVH) ≥ III and those without IVH ≥ III (p-value = 0.478).

The administration of steroids for broncho-pulmonary dysplasia (BPD) showed a statistically significant impact on the prevalence of LOS (82.6% of the infants that took steroids for BPD had LOS versus 40.7% of the newborns that did not take steroids for BPD) (p-value < 0.001).

Of neonates who required nasal CPAP, 48.5% developed LOS versus 24.2% who did not use nasal CPAP (p-value < 0.001).

There was no statistically significant difference between newborns who needed high-frequency ventilation (HFV) and those who did not require HFV (p-value = 0.069).

Among children who had retinopathy of prematurity (ROP) ≥ stage 2, 71.4% developed LOS compared with those without ROP ≥ stage 2, whose prevalence of LOS was 52.7% (p-value = 0.037).

Finally, there was no statistically significant difference in LOS between infants with and without major birth defects (p-value = 0.416).

*Predictor factors for late-onset sepsis (**Tab. 5**)*

When the gestational age was analysed, we found an OR of 3.348 for the group with gestational age between 22 and 27 weeks (95% CI, 1.544-7.263, p-value = 0.002) and an OR of 1.533 for the group of infants born with a gestational age between 28 and 31 weeks (95% CI, 0.830-2.834, p-value = 0.172).

We found that neonates with conventional ventilation were 1.912 times more likely to have LOS compared with others who did not require ventilation (95% CI, 1.138-3.210, p-value = 0.014). Newborns who used nasal CPAP were 3.385 times more likely to have LOS versus the ones who did not have to use nasal CPAP (95% CI, 1.849-6.197, p-value < 0.001) and newborns with NEC were 5.103 times more likely to develop LOS than those without NEC (95% CI, 1.534-16.970, p-value = 0.008).

Infants who took steroids for BPD were 4.145 times more likely to have LOS than those that did not take steroids for BPD (95% CI, 1.282-13.398, p-value = 0.018).

Discussion

This study allowed us to draw conclusions about the evolution of the prevalence of LOS and meningitis during the years of participation (from 2000 to 2013) of Centro Hospitalar Universitário de São João in the VON. In addition, this study made it possible for us to conclude which variables are the predictors of LOS.

As expected, since it was verified in other studies, the prevalence of LOS significantly decreased (56.3% vs. 26.5%, p-value < 0.001) between 2000-2004 and 2010-2013. Effectively, Bizzarro et al. reported that rates of LOS showed a significant decrease from 2004 to 2013 [14].

Table 5. Predictor factors for late-onset sepsis (LOS).

Predictors			OR	95% CI	p-value
Gestational age	22-27 weeks		3.348	[1.544; 7.263]	0.002
	28-31 weeks		1.533	[0.830; 2.834]	0.172
	32-36 weeks	Ref			
Conventional ventilation	Without	Ref			
	With		1.912	[1.138; 3.210]	0.014
Nasal CPAP	Without	Ref			
	With		3.385	[1.849; 6.197]	< 0.001
NEC	Without	Ref			
	With		5.103	[1.534; 16.970]	0.008
Steroids for BPD	Without	Ref			
	With		4.145	[1.282; 13.398]	0.018

NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia.

We verified that coagulase-negative *Staphylococcus* was the most frequent pathogen found as a causative agent of LOS in our NICU. In fact, coagulase-negative *Staphylococci* have emerged as the predominant pathogens of LOS, accounting for 53.2%-77.9% of LOS in industrialised countries and 35.5%-47.4% in some developing regions [15].

The decline in the prevalence of coagulase-negative staphylococcal (46.7% vs. 17.1%) and other bacterial infections (27.5% vs. 12.0%) during the years of this study was statistically significant too (p-value < 0.001). Bizzarro and colleagues found that the prevalence of LOS rates attributed to coagulase-negative *Staphylococcus* decreased too [14].

In contrast, the prevalence of fungal infections did not suffer a statistically significant decrease (4.2% vs. 0.9%, p-value = 0.229), probably because the incidence of fungal infections in this NICU is relatively low. Similarly, in a German study, only 4.3% of LOS episodes were caused by *Candida spp.* Gram-positive bacteria were documented in 77.4% of the cases, coagulase-negative *Staphylococci* being the most predominant pathogens (48.5%). 18.3% of episodes were caused by Gram-negative bacilli [16].

These results make sense in the light of constantly improving infection prevention initiatives developed over the years. Indeed, we can infer that the improvement in outcomes relative to LOS was due to the improvement of practices and from what we have learned in comparison with the experience of other neonatal centres.

Besides VON, there is a National Registration of Very Low Birth Weight Newborns in Portugal that collects data about neonatal infection, and it has also contributed to the decrease of nosocomial infection registered over the years.

As mentioned before, the lower the gestational age, the higher the prevalence of LOS. Therefore, the incidence of LOS was higher in newborns with 22-27 weeks (65.6%) compared to the group of infants that were born with 28-31 weeks (44.3%) and the group of infants with 32-36 weeks (20.9%) (p-value < 0.001). These results are in agreement with other studies that reported higher incidence of LOS in neonates with less than 28 weeks (36.3% versus 29.6% among infants with a gestational age of 29-32 weeks versus 17.5% in infants born with 33-36 weeks) [15]. In fact, a North American study showed similar tendencies between infants with different gestational ages. They reported an incidence of LOS of 20% in newborns with 28 weeks compared with 58% among newborns with a gestational age of 22 weeks [17].

Stoll et al. registered that, among infants who survived more than 3 days, 32% were diagnosed with LOS, with the percentage increasing with decreasing gestational age (28 weeks: 20%, 22 weeks: 61%) [18].

As previously stated, VLBW infants are especially susceptible to nosocomial infections. In our NICU, the group of infants with ≤ 1,000 g had more LOS (59.4%) than the neonates that were born with > 1,000 g (33.3%) (p-value < 0.001). These results match with those of others that concluded that the incidence of LOS is especially high in preterm newborns, with a birth weight of less than 1,500 g [19]. In fact, LBW is the single most important variable in the predisposition for sepsis. The high incidence of sepsis in VLBW was confirmed in a study performed in our NICU, which found 28% of confirmed sepsis and 15% of probable sepsis [20].

Individuals with RDS had more LOS than those without RDS and we found that the prevalence of LOS was statistically significantly higher in neonates with RDS (50.2% vs. 34.7%, p-value = 0.001). Similarly, Tewabe and colleagues found that newborns with a history of RDS were 74.2% more likely to develop poor neonatal outcome [21].

Fehlmann et al. reported that RDS was associated with an increased risk in the incidence of LOS. They found that, in neonates with less than 1,500 g, RDS was associated independently and significantly with an increased risk of LOS [22].

Although it was not statistically significant in the multivariable model, in the univariate analysis, we found that children with PDA had more LOS than neonates without PDA (61.1% vs. 36.9%, p-value < 0.001). This finding is in accordance with the conclusions of another study conducted in Taiwan, in which they found that neonates with PDA had a relatively higher rate of recurrent sepsis than those without PDA (25.3% vs. 15.2%, p-value = 0.079) [23].

As we expected based on other studies, a higher percentage of individuals with ROP ≥ stage 2 developed sepsis compared to those without ROP ≥ stage 2 (71.4% vs. 52.7%, p-value = 0.037). For example, Leviton et al. found that some of the disorders that occur preferentially in the extremely low gestational age neonates tend to occur together more commonly than expected if they

were independent, which was most evident for severe NEC and LOS. Both occurred more often than expected in infants who had severe BPD and severe ROP [24].

A Portuguese study found that infants with a gestational age of less than 28 weeks had an OR of 5.4 (95% IC, 3.1-9.4, p-value < 0.001) for infections associated with health care. They also concluded that for each additional week in gestational age the risk of infection associated with health care decreased by 20% [25]. When the gestational age was analysed, we found that infants with a gestational age between 22 and 27 weeks had a 3.348 (95% CI, 1.544-7.263, p-value = 0.002) higher risk of developing infection than neonates that were born with 32-36 weeks and infants born with a gestational age between 28 and 31 weeks had a 1.533 (95% CI, 0.830-2.834, p-value = 0.172) higher infection risk than neonates that were born with 32-36 weeks.

Neonates that required MV were 1.912 (95% CI, 1.138-3.210, p-value = 0.014) more likely to have LOS compared with the ones who did not require MV. The use of MV was already recognized as a risk factor for LOS in other studies. One of those reported that in the LOS group, MV was used in 79.5% of the infants vs. 34.3% in the non-LOS group (p-value < 0.001) [26].

On the other hand, newborns who used nasal CPAP showed a 3.385 (95% CI, 1.849-6.197, p-value < 0.001) higher risk of LOS compared with the infants who did not have to use nasal CPAP. However, a study conducted in South Korea suggested that aggressive early weaning from more invasive intubation and MV to less invasive assisted ventilation, such as nasal CPAP, is important to reduce the incidence of LOS in extremely preterm babies [27]. Another study conducted in Turkey demonstrated that the duration of MV was significantly long, and the duration of CPAP was not significant in the patients dying due to sepsis [28].

As expected, newborns with NEC were 5.103 (95% CI, 1.534-16.970, p-value = 0.008) times more likely to develop LOS than those without NEC. Similarly, Kim et al. reported that neonates with NEC were 3.628 times more likely to have sepsis than those without NEC, especially in infants born with 23-24 weeks of gestation (95% CI, 1.332-9.883, p-value = 0.012) [27].

We found that infants receiving steroids for BPD had a 4.145 (95% CI, 1.282-13.398, p-value = 0.018) higher infection risk.

Newborns with respiratory pathology are more likely to require intravenous support, a critical way of pathogen entry into the bloodstream [29].

Underlying secondary pulmonary hypertension (due to severe BPD) has been significantly associated with a higher risk of sepsis attributable mortality and BPD predisposed neonates to higher rates of ventilator-associated pneumonia [30]. Moreover, LOS was found to be a risk factor for BPD [31].

Limitations of the study

This study has the disadvantages inherent in a retrospective study.

Considering that the data collected by VON do not allow one to distinguish which infants had LOS or meningitis, it was not possible to differentiate which data and predictors influence LOS and meningitis separately.

In addition, it might be interesting to analyse other data such as the presence of catheters, which was not registered in the VON database, or the duration of MV, which had missing values in most individuals.

Other important outcomes, which were not registered in the VON database, such as complications due to sepsis, relapses, delay in development and maturation of organs and tissues, would be relevant to document.

Furthermore, it was not possible to report anything about the use of antibiotics nor the antimicrobial resistance over the time of this study because there were no data about these variables in the VON database.

Study strengths

This study was relevant to show the importance of participating in networks, such as VON, that allows benchmarking among the various neonatal centres in order to improve practices in the prevention and control of neonatal infection.

Conclusion

During the time of the participation of our NICU in the VON database, the prevalence of LOS significantly decreased from 56.3% between 2000 and 2004 to 26.5% between 2010 and 2013.

Gestational age between 22 and 27 weeks, MV, nasal CPAP, NEC and steroids for BPD were found to be statistically significant predictors of LOS.

Sure enough, preterm infants require many invasive devices to ensure their survival, such as MV, which greatly increases their infectious risk. To minimize this risk, it is crucial to guarantee that better practices of asepsis are followed, necessitating the use of regular audits.

In conclusion, this study shows the importance of knowing the data about LOS from our NICU, which allows sharing and comparison with peers in order to improve nosocomial infection prevention and control practices.

Disclaimer

The Vermont Oxford Network had no role in the concept, design, analysis, or formulation of this research report. The discussion and views belong solely to the co-authors and do not represent the opinions of the Vermont Oxford Network.

Declaration of interest

The Authors declare that there is no conflict of interest. No funding was used to carry out the present study.

References

1. Shah BA, Padbury JF. An old problem with new insights. Virulence. 2014;5(1):170-8.
2. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-Five Years of Neonatal Sepsis at Yale: 1928–2003. Pediatrics. 2005;116(3):595-602.
3. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, Lemons JA, Donovan EF, Stark AR, Tyson JE, Oh W, Bauer CR, Korones SB, Shankaran S, Laptook AR, Stevenson DK, Papile LA, Poole WK. Late-Onset Sepsis in Very Low Birth Weight Neonates: The Experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2 Pt 1):285-91.
4. Silva R, Grilo M, Pissarra S, Guimarães H. Fungal sepsis in a Level III Neonatal Intensive Care Unit: a 10-year retrospective analysis. J Pediatr Neonat Individual Med. 2014;3(2):e030212.
5. Almeida CC de, Pissarra da Silva SMS, Flor de Lima Caldas de Oliveira FSD, Guimarães Pereira Areias MHF. Nosocomial sepsis: evaluation of the efficacy of preventive measures in a level-III neonatal intensive care unit. J Matern Fetal Neonatal Med. 2017;30(17): 2036-41.
6. Freitas B, Peloso M, Manella L, Franceschini S, Longo G, Gomes A, Batista R. Late-onset sepsis in preterm children in a neonatal intensive care unit: a three-year analysis. Rev Bras Ter Intensiva. 2012;24(1):79-85.
7. Chee YY, Wong MSC, Wong RMS, Wong KY. Neonatal outcomes of preterm or very-low-birth-weight infants over a decade from queen mary hospital, Hong Kong: Comparison with the Vermont Oxford Network. Hong Kong Med J. 2017;23(4):381-6.
8. Peixoto JJL. Registo Nacional dos Recém-Nascidos de Muito Baixo Peso. Rede de Investigação Neonatal Nacional. Acta Pediátrica Port. 1999;30:485-91.
9. https://www.dgs.pt/programa-nacional-de-controlo-da-infeccao/vigilancia-epidemiologica/infecao/infecoes-nas-uci-recem-nascidos/como-aderir-ao-programa.aspx, last access: March 2019.
10. Cailes B, Vergnano S, Kortsalioudaki C, Heath P, Sharland M. The current and future roles of neonatal infection surveillance programmes in combating antimicrobial resistance. Early Hum Dev. 2015;91(11):613-8.
11. de Souza Rugolo LMS, Bentlin MR, Mussi-Pinhata M, de Almeida MFB, Lopes JM de A, Marba STM, Fiori HH, Procianoy RS, Leone CR; Brazilian Network on Neonatal Research. Late-onset sepsis in very low birth weight infants: A Brazilian neonatal research network study. J Trop Pediatr. 2014;60(6):415-21.
12. Gray JW. Surveillance of infection in neonatal intensive care units. Early Hum Dev. 2007;83(3):157-63.
13. https://vtoxford.zendesk.com/hc/en-us/categories/360000861394-Manuals-and-Forms, last access: March 2019.
14. Bizzarro MJ, Shabanova V, Baltimore RS, Dembry L, Ehrenkranz RA, Gallagher PG. Neonatal Sepsis 2004–2013: The Rise and Fall of Coagulase Negative Staphylococci. J Pediatr. 2016;166(5): 1193-9.
15. Dong Y, Speer CP. Late-onset neonatal sepsis: Recent developments. Arch Dis Child Fetal Neonatal Ed. 2015;100(3):F257-63.
16. Härtel C, Faust K, Avenarius S, Bohnhorst B, Emeis M, Gebauer C, Groneck P, Heitmann F, Hoehn T, Hubert M, Kribs A, Küster H, Laux R, Mögel M, Müller D, Olbertz D, Roll C, Siegel J, Stein A, Vochem M, Weller U, von der Wense A, Wieg C, Wintgens J, Hemmelmann C, Simon A, Herting E, Göpel W; German Neonatal Network (GNN). Epidemic microclusters of blood-culture proven sepsis in very-low-birth weight infants: Experience of the German Neonatal Network. PLoS One. 2012;7(6):e38304
17. Cohen-Wolkowiez M, Moran C, Benjamin DK, Smith PB. Early and Late Onset Sepsis in Late Preterm Infants. Pediatr Infect Dis J. 2009;28(12):1052-6.
18. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039-51.
19. Amorim Melo ERA, de Barros Lima Filho A, Furtado Ferreira AC, de Sousa Carvalho G, da Conceição Brito JJ, da Silva Farias PI, Silva Rego AG, Pinheiro Falcão B. Prevalence of Meningitis in Patients with Late Neonatal Sepsis in a Reference Maternity. Ann Pediatr Child Health. 2018;6(3):1148.
20. Costa A, Guimarães H, Souto A, Martins A, Orey CD, Mateus M, Silva G, Teixeira Santos N. Sépsis no recém-nascido de muito baixo peso. Acta Med Portug. 1996;9(10-12):331-4.

21. Tewabe T, Mohammed S, Tilahun Y, Melaku B, Fenta M, Dagnaw T, Belachew A, Molla A, Belete H. Clinical outcome and risk factors of neonatal sepsis among neonates in Felege Hiwot referral Hospital, Bahir Dar, Amhara Regional State, North West Ethiopia 2016: a retrospective chart review. BMC Res Notes. 2017;10(1):265.
22. Fehlmann E, Tapia JL, Fernández R, Bancalari A, Fabres J, D'Apremont I, García-Zattera MJ, Grandi C, Ceriani Cernadas JM; Grupo Colaborativo Neocosur. [Impact of respiratory distress syndrome in very low birth weight infants: a multicenter South-American study]. [Article in Spanish]. Arch Argent Pediatr. 2010;108(5):393-400.
23. Chiang P, Hsu J, Tsai M, Lien R. The Impact of Patent Ductus Arteriosus in Neonates with Late Onset Sepsis: A Retrospective Matched-Case Control Study. Pediatr Neonatol. 2012;53(5):309-14.
24. Leviton A, Dammann O, Engelke S, Kuban KCK, Paneth N, Lansing E. The clustering of disorders in infants born before the 28th week of gestation. Acta Paediatr. 2015;99(12):1795-800.
25. Pereira H, Grilo E, Cardoso P, Noronha N, Resende C. [Risk Factors for Healthcare Associated Sepsis in Very Low Birth Weight Infants]. [Article in Portuguese]. Acta Med Port. 2016;29(4):261-7.
26. Stevic M, Simic D, Ristic N, Budic I, Marjanovic V, Jovanovski-Srceva M, Repac N, Rankovic-Janevski M, Tasic G. Evaluation of factors for poor outcome in preterm newborns with posthemorrhagic hydrocephalus associated with late-onset neonatal sepsis. Ther Clin Risk Manag. 2018;14:1965-73.
27. Kim JK, Chang YS, Sung S, Ahn SY, Park WS. Trends in the incidence and associated factors of late-onset sepsis associated with improved survival in extremely preterm infants born at 23-26 weeks' gestation: a retrospective study. BMC Pediatr. 2018;18(1):172.
28. Turhan EE, Gürsoy T, Ovalı F. Factors which affect mortality in neonatal sepsis. Turk Pediatri Ars. 2015;50(3):170-5.
29. Correia C, Rocha G, Flor-de-Lima F, Guimarães H. Respiratory morbidity in late preterm infants. Minerva Pediatr. 2018;70(4): 345-54.
30. Wu IH, Tsai MH, Lai MY, Hsu LF, Chiang MC, Lien R, Fu RH, Huang HR, Chu SM, Hsu JF. Incidence, clinical features, and implications on outcomes of neonatal late-onset sepsis with concurrent infectious focus. BMC Infect Dis. 2017;17(1):465.
31. Tapia JL, Agost D, Alegria A, Standen J, Escobar M, Grandi C, Musante G, Zegarra J, Estay A, Ramírez R; NEOCOSUR Collaborative Group. Bronchopulmonary dysplasia: incidence, risk factors and resource utilization in a population of South American very low birth weight infants. J Pediatr (Rio J). 2006;82(1): 15-20.