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Maria Francisca Baía Bastos da Rocha Maia

Evolução temporal da sépsis de início tardio e da meningite em recém-nascidos de muito baixo peso entre 2000 e 2013: Resultados de uma unidade de cuidados intensivos neonatais de nível terciário em Portugal

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Dedicatória

À minha irmã, Margarida, pela paciência que teve em ler e reler a minha tese.

À minha mãe por me ajudar a racionalizar nos momentos de maior stress.

Aos meus avós maternos por acompanharem de perto o meu percurso académico.

À minha restante família e aos meus amigos por fazerem parte da minha vida.

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

Abstract

Objective: To assess the evolution of the prevalence of late onset sepsis and meningitis and its predictors in a Portuguese tertiary level Neonatal Intensive Care Unit (NICU) during the participation in the Vermont Oxford Network (VON) between 2000 and 2013.
Methods: Descriptive retrospective study of all Very Low Birth Weight infants admitted to 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 late onset sepsis were compared.
Results: The prevalence of late onset sepsis 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 late onset sepsis (LOS) (65.6%) than neonates with 32-36 weeks (20.9%). Similarly, smaller infants (weighing ≤ 1000g) had more LOS (59.4%) than babies with a weight > 1000g (33.3%). Late onset sepsis was significantly associated with a gestational age between 22 and 27 weeks, mechanical ventilation, nasal CPAP, necrotizing enterocolitis and the use of steroids for bronchopulmonary dysplasia.
Conclusions: Preterm infants require many invasive devices to ensure their survival, namely mechanical ventilation, which greatly increases their infection risk. To minimize this risk, it is crucial to guarantee that better practices of asepsis are followed, being necessary to carry out regular audits. It is really important to know the data about late onset sepsis of 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

Introduction

During the last years, there was a significant decrease in childhood mortality worldwide. However, the decrease in neonatal mortality occurred at much lower rates, considering that in 1990, 37.4% of under-5 deaths were due to neonatal mortality and in 2013, that percentage was 41.6% [1].

The third leading cause of neonatal mortality happens to be neonatal sepsis, only behind preterm birth complications and intrapartum-related complications. Of all deaths in children under the age of 5 registered in 2010, 64.0% were attributable to infectious causes and 40.3% occurred in neonates [2].

Although there were advances in neonatal care which 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, those who weigh less than 1500g) infants in Neonatal Intensive Care Units (NICU) [3,4].

Apart from the mortality caused by neonatal sepsis, late onset sepsis significantly influences late neurodevelopment at the corrected age of 2 years old in premature infants with VLBW, being the gram-positive bacteria associated with a motor deficit. At a follow-up for up to 24 months of corrected age, among VLBW preterm infants with late onset sepsis, 6.1% of neonates had severe neurodevelopmental impairment and 3.2% of infants had cerebral palsy [5,6].

All around the world, there are neonates who are affected by sepsis, which happens more frequently with premature and low birth weight (LBW) infants [7–9].

Infants in NICUs all around the world (6.3 in 1000 admissions), mainly preterm and LBW neonates, are affected by sepsis. A study found a LOS cumulative incidence of 6.3 episodes per 1000 NICU admissions [7]. The incidence of LOS considerably varies from centre to centre, ranging from 10.6% to 31.7% [8].

Fungal sepsis is less common than bacterial sepsis (incidence between 0.3% to 6.7%), however, it results in great mortality and morbidity [9]. Benjamin et al. found that 73% of extremely low birth weight (ELBW) infants who developed candidiasis ended up dead or having some neurodevelopment impairment [10].

In a study performed in this NICU, they found 549 (13.9%) patients with clinical or confirmed sepsis between 2003 and 2012. Fifteen of which (2.7%) had confirmed fungal sepsis on blood cultures and all of them had low birth weight (LBW), 13 (86.7%) had VLBW and 9 (60%) had extremely low birth weight (ELBW) [9].

From all live births, VLBW neonates take up a percentage of 1.5% of live births. Nonetheless, they account for more than 50% of infant deaths in the United States [11].

The association between birth weight and mortality is among the strongest in epidemiology. A mortality of at least 100-fold higher than those with an optimal weight (the weight associated with the lowest mortality) is found in neonates weighing less than 1500 g [12].

Over the last four decades, it was possible to observe an improvement on neonatal survival, particularly in the developed countries which have witnessed an increasing survival of extremely low birth weight infants during this period [13].

Nevertheless, and contributing to their special vulnerability to nosocomial infections, preterm and VLBW infants are particularly immature regarding their immune system [14].

Preterm birth was found to be the major risk factor for neonatal sepsis, given that the risk of infection among premature neonates is 11 times greater than among full term infants. Premature neonates' skin and mucous barriers are immature, and they possess underdeveloped defence mechanisms against infection. The risk of developing neonatal sepsis is inversely proportional to birth weight and gestational age [5].

Appropriately, preterm newborns with late onset sepsis (LOS) had lower birth weight and gestational age, worse perinatal conditions and higher severity scores on the first day of life. Within hospitalization, they had higher morbidity and invasive devices were used more frequently when compared with infants without infection [15].

Central line-associated bloodstream infections (CLASBI) are caused by indwelling intravascular central-lines (IICL) in 1-20% of hospitalized newborns, which represents an important and

preventable cause of nosocomial sepsis. Beside IICL, there are other risk factors for nosocomial infections that increase the burden of late onset sepsis. These risk factors include long-term use of other invasive interventions, such as mechanical ventilation and parenteral nutrition, skin sores, prolonged hospitalization stay, surgeries and underlying respiratory and cardiovascular diseases. Consequently, preventive strategies should be adopted in NICU to reduce colonization [5,14,16]. Since the central lines are one of the leading causes of nosocomial infections, a study was performed in this NICU and Soares et al. showed that infectious complications occurred in 20% patients (CLASBI rate of 12.4/1000 catheter days). Of the 51 (12.8%) CLASBI episodes, a positive blood culture was obtained in 35 (68.6% of infected central lines). As expected, preterm birth was a risk factor for indwelling complication [17].

It is important to implement some measures to prevent nosocomial infections, since they decrease the incidence density of nosocomial sepsis, as we concluded with a study in this NICU that showed that the incidence density of nosocomial sepsis decreased significantly from 8.6 to 4.8 per 1000 days (44%) after a new preventive bundle implementation [14].

Freitas et al. showed that newborns who developed late onset sepsis 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 mechanical ventilation for 10 or more days and late onset sepsis in 80.8% of cases, while PICCs left in place for 11 days or longer were associated with LOS in 76.2% of cases [18].

The technique and scientific evolution of Neonatology during the years allowed the reduction of the viability threshold and a bigger survival with less morbidity [19].

In fact, as the incidence of LOS increased, the survival of premature infants consequently followed, especially in VLBW neonates. This indicates the role of hospitalization, invasive procedures and life-sustaining medical devices in the pathogenesis of neonatal LOS [4,20]. Therefore, the advance in neonatal intensive care medicine is a double-edged sword, in one hand causing improved survival of neonates, and in the other increased rate of LOS [16].

Coagulase-negative *Staphylococcus* represents the commonest microorganism that provokes LOS in developed countries, since it is responsible for 39-54% of episodes [21]. Gram-negative pathogens accounted for 18% of first episodes of LOS, being *Escherichia coli*, *Klebsiella* sp, *Pseudomonas aeruginosa*, *Enterobacter* sp and *Serratia* sp the most frequent Gram-negative bacteria. Finally, fungal microorganisms caused 12% of all first episode infections, with *Candida albicans* being the third most common isolated microorganism (6%) [8]. Comparatively, late onset pathogens tend to be more resistant to monotherapy antibiotic regimens than early onset ones [21,22].

Meningitis remains a frequent presentation of late onset group B streptococcal (GBS) disease and despite reduced mortality, it continues to entail a significant morbidity among GBS survivors, who present serious neurologic sequelae and permanent impairment [3,23]. It is more common in the first month of life than in any other age group. Its nonspecific clinical presentation, indistinguishable from that caused by sepsis, especially late onset sepsis, makes it difficult but imperative to identify [24]. In developing countries, neonatal meningitis is present in 0.8-6.1 per 1000 live births [21].

As one of the largest neonatal databases, the Vermont Oxford Network (VON) collects and maintains data about VLBW infants and neonates who fulfil other eligibility requirements from many parts of the world since 1989 [25].

Newborns are eligible for the VLBW database if they are born with a weight between 401 and 1500g, or with a gestational age between 22 and 29 weeks, and if they are born at the member hospital or are transferred to it within 28 days of birth. Neonates born at a participating hospital whose deaths happened in the delivery room or before NICU admission are included [26].

Currently, VON includes more than 1200 centres around the world that voluntarily submit data about the care and outcomes of high risk newborns. The VON databases have the primary goal of assisting member hospitals in understanding their performance for purposes of quality improvement [26,27].

VON serves as a neutral, independent party in analysing data for their member centres and facilitating voluntary benchmarking activities [28].

VON has sponsored many quality improvement collaboratives that have improved both treatment practice and outcomes [29].
Besides VON, there is a National Registration of Very Low Birth Weight Newborns in Portugal, which was founded in 1994 and was composed by 13 NICUs. The data from this little sample allows us to identify the main problems of these Portuguese infants and to assess how each unit works. From 1996, the registration was extended to a new NICU and to 18 special care units [30]. In this registration, between 1994 and 1996, they found sepsis as one of the most frequent pathologies (34%) and with an incidence significantly higher when compared with VON (26%). Regardless of the cause of death, sepsis was one of the most frequent diseases found in dead VLBW infants (38%) [30].
The collection of the prospective data on infections episodes from NICUs by these neonatal infection surveillance programmes has the aim of monitoring the changes in the epidemiology of pathogens and their antibiotic resistance over time. This information is important to benchmark clinical practice, inform policy and improve quality of care [31,32].
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 [31].
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 [31].
To improve our understanding of the epidemiology and create quality improvement programmes, neonatal infection surveillance programmes represent a valuable tool. Their aim is to reduce infection rates and effectively prevent the development of resistance [31].
Neonatal infection surveillance networks serve several purposes, like 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 [15,33].
This study aims to assess the evolution of the prevalence of late onset sepsis and meningitis and its predictors in the NICU of Centro Hospitalar Universitário de São João during the participation in the Vermont Oxford Network (VON) between 2000 and 2013.

Methods

The data were collected from the VON in which Neonatal Intensive Care Unit (NICU) of Centro Hospitalar Universitário de São João participated from 2000 to 2013 with the registration of all inborn and outborn VLBW infants (any infant who is born alive at our hospital and whose birth weight is between 401 and 1500 grams or whose gestational age is between 22 weeks 0 days and 29 weeks 6 days and any outborn infant who is admitted to our hospital within 28 days of birth, without first having gone home, and whose birth weight is between 401 and 1500 grams or whose gestational age is between 22 weeks 0 days and 29 weeks 6 days).
We collected data about infants who had late onset sepsis and meningitis from the files we registered on VON during these 13 years. Demographic and clinical data of VLBW infants who had late onset sepsis and meningitis admitted to our NICU in that period were analysed.
Definitions for demographic and clinical data were provided in the "Manual of Operations: Part 2" by the VON.

Demographic data

We registered the gender (female or male), the gestational age in weeks and days and birth weight in grams, location of birth – inborn, if the infant was delivered at our centre and outborn if the infant was delivered outside our centre.
Multiple gestation, if two or more live foetuses were documented at any time during the pregnancy, which resulted in the birth of the infant and mode of delivery (C-section or vaginal delivery) were registered.

Clinical data

Clinical data collected in delivery room were Apgar score and neonatal resuscitation, including nasal CPAP (Continuous Positive Airway Pressure). In NICU, we registered data of conventional ventilation and oxygen therapy.
It was reported that newborns received steroids for chronic lung disease (CLD) if systemic corticosteroids were used after birth to treat or prevent bronchopulmonary dysplasia or chronic lung disease.
For the diagnosis of Patent Ductus Arteriosus (PDA), at least one of the following findings needs to be present: left to right or bidirectional ductal shunt on Doppler echo, systolic or continuous murmur and at least two of the following findings are present: hyperdynamic precordium, bounding pulses, wide pulse pressure, pulmonary vascular congestion, cardiomegaly or both.
Indomethacin was administered after birth for treatment of PDA and Ibuprofen for the prevention or treatment of PDA.
The neonates with severe retinopathy of prematurity (ROP) were identified. Severe ROP is defined by: stage 2- presence of intraretinal ridge; stage 3- presence of a ridge with extraretinal fibrovascular proliferation; stage 4- partial retinal detachment; stage 5- total retinal detachment.
If infants had necrotizing enterocolitis (NEC), diagnosed prior to initial disposition, and/or following readmission after initial transfer without being discharged home, they were referred as NEC carriers. The following clinical and radiographical criteria were used: at least one of the following clinical signs must be present – bilious gastric aspirate or emesis, abdominal distension, occult or gross blood in stool (no fissure) and at least one of the following radiographic findings must be present – pneumatosis intestinalis, hepatobiliary gas, pneumoperitoneum.
According to the development of sepsis on or before day 3, children were categorized as having early onset sepsis if a bacterial pathogen**,** coagulase-negative staphylococcal or fungal was recovered from a blood and/or cerebrospinal fluid culture obtained on day 1, 2 or 3 of life.
On the other hand, individuals were classified as having late onset sepsis and/or meningitis, if a bacterial pathogen, coagulase-negative staphylococcal or fungal was recovered from a blood and/or cerebral spinal fluid culture obtained after day 3 of life at our hospital prior to initial disposition.
Respiratory distress syndrome (RDS) is defined as $PaO_2 < 50$ mmHg in room air, central cyanosis in room air, a requirement for supplemental oxygen to maintain $PaO_2 > 50$ mmHg, or a requirement for supplemental oxygen to maintain a pulse oximeter saturation over 85% within the first 24 hours of life and a chest radiograph consistent with RDS (reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) within the first 24 hours of life.
Children were marked as having severe Periventricular-Intraventricular Haemorrhage (PIH) when they had PIH grade 3 (intraventricular blood, ventricular dilation) or PIH grade 4 (intraparenchymal haemorrhage) at our hospital prior to initial disposition or following readmission after initial transfer without being discharged home.
Likewise, infants with Cystic Periventricular Leukomalacia (CPVL) were referred like that when they had evidence of cystic periventricular leukomalacia on a cranial ultrasound, computed tomography, or magnetic resonance imaging scan obtained at any time.
The major birth defects found in this sample include tracheoesophageal fistula, oesophageal atresia, obstructive uropathy with congenital hydronephrosis, pulmonary atresia with ventricular septal defect, interrupted aortic arch, double outlet right ventricle, duodenal atresia, omphalocele, pulmonary stenosis, trisomy 21, tetralogy of Fallot with or without pulmonary atresia, trisomy 13, cleft palate, gastroschisis, congenital hydrocephalus, Prader Willi (SALSA MLPA Kit P245- A2), pulmonary atresia with intact ventricular septum and complete atrioventricular canal.

Study sample definition

At the beginning of the study, 607 babies were identified, from which 95 outborn infants were excluded. Then, 6 infants died in the delivery room, so, at that point, there were 506 infants. 18 of these infants died during the first 12 hours in NICU. Finally, 55 infants had missing information on outcome. The final sample for the study was 433 infants (Figure 1).

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 were 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 late onset sepsis. 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 less than 0.05 was considered statistically significant. To create the most parsimonious model, variables that did not reach significance level of p-value < 0.05 in the multivariable model were backward eliminated one by one.
The Ethics Committee of Centro Hospitalar Universitário de São João approved this study.

Results

Demographic characteristics of study population (Table 1)

Our population was composed by 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%).
At birth, 160 neonates weighed 1000 grams or less (37.0%) and there were 273 babies whose weight was greater than 1000g (63.0%).
In relation to the number of foetuses found in pregnancies, 287 (66.3%) were gestations with only one foetus and were documented two or more foetuses during 146 (33.7%) pregnancies.
Regarding the type of delivery, 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 or higher than 7 (86.6%).

Late onset sepsis outcomes according to year of birth (Table 2)

Between 2000 and 2013, 43% of the infants had at least one episode of late onset sepsis. The most frequent aetiology was coagulase-negative staphylococcal infection, since 34.2% of all infants had an infection caused by this microorganism. A total of 16.4% infants had other bacterial pathogen 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 late onset sepsis. The most frequent aetiology of late onset sepsis between these years was coagulase-negative *Staphylococcus* (78 infants, corresponding to 46.7% of the total 167 newborns), followed by other bacterial pathogens' infections whose prevalence was 27.5% (46/167). Only 7 infants (4.2%) had late onset sepsis caused by fungi.
Between 2005 and 2009, 61 out of 149 (40.9%) infants developed late onset sepsis. Once again, most of the infected children had coagulase-negative staphylococcal infection (33.6%, 50/149). On the other hand, 11 neonates had LOS caused by other bacteria (7.4%) and 6 babies had fungal infection (4.0%).

During the last years of this study (2010-2013), 31 out of 117 infants had late onset sepsis (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%).

Late onset sepsis outcomes according to gestational age (Table 3)

In the group of infants born between 22 and 27 weeks of gestation, 65.6% had late onset sepsis (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 late onset sepsis (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).
At last, 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 outcomes according to birth weight (Table 4)

The group of infants born with a weight equal to or less than 1000g presented a prevalence of late onset sepsis of 59.4% (95/160). In this group, 70 out of 160 had coagulase-negative staphylococcal infection (43.8%), 28.9% had LOS caused by other bacteria (43/160) and 10 developed a fungal infection (6.2%).
Differently, neonates whose birth weight was greater than 1000g had a prevalence of LOS of 33.3% (91/273). Among these children, 78 had coagulase-negative staphylococcal infection (28.6%), 28 developed LOS provoked by other bacterial microorganisms (10.3%) and 4 had a fungal infection (1.5%).

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

Relatively to the gender of the infants, there was no statistically significant difference in the prevalence of LOS between female and male infants (p-value = 0.990).
There was no statistically significant difference in the prevalence of LOS in terms of type of delivery – C-section versus vaginal delivery (p-value = 0.087). Similarly, there was no statistically significant difference in LOS between neonates with Apgar score < 7 and ≥ 7 (p-value = 0.757).
The majority of newborns who did not require mechanical ventilation did not develop LOS (74.9%), whereas neonates that needed ventilation had a prevalence of LOS of 54.1% (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 without it, given there was no statistically significant difference between infants with cystic periventricular leukomalacia (CPVL) and without CPVL (p-value = 0.112) neither between neonates with intraventricular haemorrhage (IVH) $\geq$ III and without IVH $\geq$ III (p-value = 0.478).
The administration of steroids for bronchopulmonary dysplasia showed a statistically significant difference on the prevalence of LOS (82.6% of the infants that took steroids for

bronchopulmonary dysplasia (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 (Table 5)

When the gestational age was analysed, we found an Odds Ratio (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).
Regarding the use of mechanical ventilation, we found that neonates with conventional ventilation were 1.912 more likely to have LOS compared with others who did not require ventilation (95% CI, 1.138 – 3.210, *p*-value = 0.014).
On the other hand, newborns who used nasal CPAP were 3.385 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).
In terms of necrotizing enterocolitis, 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).
In this study, we found that infants who took steroids for bronchopulmonary dysplasia were 4.145 times more likely to have LOS that 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 late onset sepsis 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 possible to conclude which variables are the predictors of late onset sepsis.
As expected, since it was verified in other studies, the prevalence of LOS from all causes 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 late onset sepsis subsequently showed a significant decrease from 2004 to 2013 [34].
We verified that coagulase-negative *Staphylococcus* was the most frequent pathogen found as a causative 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 [16].
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 significative too (*p*-value < 0.001). Bizzarro and colleagues found that the prevalence of late onset sepsis rates attributed to coagulase-negative *Staphylococcus* decreased too [34].
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 late onset sepsis episodes were caused by *Candida spp.* Gram-positive bacteria were documented in 77.4% of the cases, being coagulase-negative staphylococci the most predominant pathogens (48.5%). 18.3% episodes were caused by gram-negative bacilli [35].

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 asepsis 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 late onset sepsis. 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% with a gestational age of 29-32 weeks versus 17.5% in infants born with 33-36 weeks) [16]. 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 [3].
Stoll et al. registered that, among infants who survived more than 3 days, 32% were diagnosed with late onset sepsis, with the percentage increasing with decreasing gestational age (28 weeks: 20%, 22 weeks: 61%) [36].
As previously stated, VLBW infants are especially susceptible to nosocomial infections. Regarding birth weight, the group of infants with ≤ 1000g had more LOS (59.4%) than the neonates that were born with > 1000 g (33.3%) (*p*-value < 0.001). These results match with those of others that conclude that the incidence of LOS is especially high in preterm newborns, with a birth weight of less than 1500 grams [24]. In fact, low birth weight is the single most important variable in the predisposition for sepsis. The high incidence of sepsis in very low birth weight was confirmed in a study performed in our NICU, which found 28% of confirmed sepsis and 15% of probable sepsis [37].
Given that there are studies that reported that respiratory distress syndrome is a determinant factor for poor clinical outcome in neonatal sepsis [38], we analysed whether individuals with respiratory distress syndrome had more LOS than those without RDS and we found that the prevalence of LOS was statistically significantly higher in neonates with RDS (71.4% vs 52.7%, *p*-value = 0.001). Similarly, Tewabe and colleagues found that newborns with a history of respiratory distress syndrome were 74.2% more likely to develop poor neonatal outcome [38].
Fehlmanna et al. reported that RDS was associated with an increased risk in the incidence of late onset sepsis. They found that, in neonates with less than 1500 g, RDS was associated independently and significantly with an increased risk of LOS [39].
Although it was not statistically significant in the multivariable model, in the univariate analysis, we found that children with Patent Ductus Arteriosus (PDA) had more LOS than neonates without PDA (61.1% vs 36.9%, *p*-value <0.001). This finding met 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) [40].
As we expected based on other studies, a higher percentage of individuals with retinopathy of prematurity (ROP) ≥ stage 2 developed sepsis in relation 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 [41].
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% [42]. 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 infection rate 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 rate than neonates that were born with 32-36 weeks.
Neonates that required mechanical ventilation 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 mechanical ventilation. The use of mechanical ventilation (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) [43].
On the other hand, newborns who used nasal CPAP showed a 3.385 (95% CI, 1.849 – 6.197, *p*-value <0.001) higher prevalence 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 mechanical ventilation to less invasive assisted ventilation, such as nasal CPAP, is important to reduce the incidence of LOS in extremely preterm babies [44]. Another study conducted in Turkey demonstrated that the duration of mechanical ventilation was significantly long, and the duration of CPAP was not significant in the patients who died because of sepsis [45].
Since intestinal microbial overgrowth contributes to the development of necrotizing enterocolitis, it can be said that necrotizing enterocolitis is also an infection like LOS. Taking this issue into account, it was expected that 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) [44].
It is important to emphasize that the data collected in the VON database concerned individuals who took steroids for bronchopulmonary dysplasia, which may underestimate the prevalence of BPD in this population because steroids are only given in severe cases of BPD.
We found that infants who took steroids for bronchopulmonary dysplasia had a 4.145 (95% CI, 1.282 – 13.398, *p*-value = 0.018) higher infection rate than newborns that did not take steroids for BPD.
In fact, considering that prolonged invasive mechanical ventilation increases the risk of bronchopulmonary dysplasia, neonates with BPD required mechanical ventilation for a longer period, which raises the risk of developing nosocomial infections. In addition, newborns with respiratory pathology are more likely to require intravenous support, a critical way of pathogen entry into the bloodstream [46].
Underlying secondary pulmonary hypertension (due to severe BPD) was significantly associated with higher risk of sepsis attributable mortality and BPD predisposed neonates to higher rates of ventilator associated pneumonia [47]. Moreover, late onset sepsis was found to be a risk factor for bronchopulmonary dysplasia [48].

Limitations of the study

This study has the disadvantages inherent to a retrospective study.
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 mechanical ventilation, which had missing values in most individuals.

Study strengths

This study was relevant to show the importance of participating in networks, such as VON, that allow 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 VON database, the prevalence of late onset sepsis significantly decreased from 56.3% between 2000 and 2004 to 26.5% between 2010 and 2013.
A gestational age between 22 and 27 weeks, mechanical ventilation, nasal CPAP, necrotizing enterocolitis and steroids for bronchopulmonary dysplasia were found to be statistically significant predictors of late onset sepsis.
Sure enough, preterm infants require many invasive devices to ensure their survival, namely mechanical ventilation, which greatly increases their infectious risk. To minimize this risk, it is crucial to guarantee that better practices of asepsis are followed, being necessary to carry out regular audits.
In conclusion, this study shows the importance of knowing the data about late onset sepsis of our NICU, which allows sharing and comparison with peers in order to improve nosocomial infection prevention and control practices.

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Declaration of interest

The authors declare no conflict of interest.

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Figures and tables

Figure 1. Flowchart for study sample definition

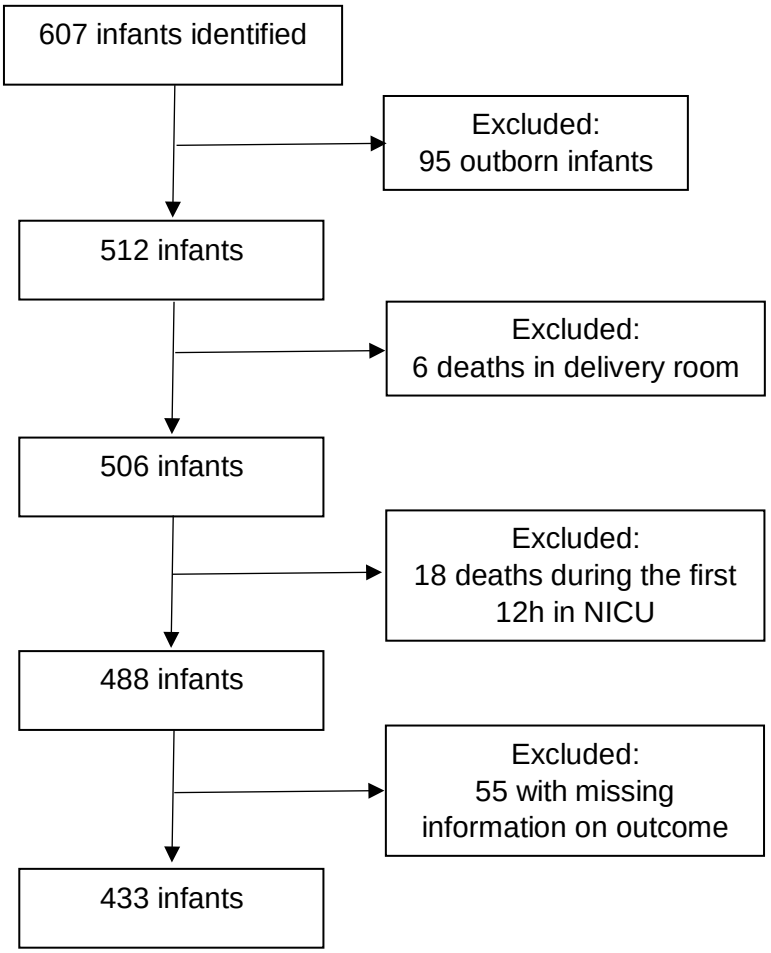

Table 1. Infants' demographic characteristics

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%)
Birth weight (grams)	
≤ 1000	160 (37.0%)
> 1000	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%)

Table 2. Infants who had at least one episode of 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 (%)					
Yes	94 (56.3%)[a]	61 (40.9%)[b]	31 (26.5%)[c]	186 (43.0%)	<0.001*
No	73 (43.7%)[a]	88 (59.1%)[b]	86 (73.5%)[c]	247 (57.0%)	
Coagulase-negative staphylococcal infection, n (%)					
Yes	78 (46.7%)[a]	50 (33.6%)[a]	20 (17.1%)[b]	148 (34.2%)	<0.001*
No	89 (53.3%)[a]	99 (66.4%)[a]	97 (82.9%)[b]	285 (65.8%)	
Other bacterial pathogens, n (%)					
Yes	46 (27.5%)[a]	11 (7.4%)[b]	14 (12.0%)[b]	71 (16.4%)	<0.001*
No	121 (72.5%)[a]	138 (92.6%)[b]	103 (88.0%)[b]	362 (83.6%)	
Fungal infection, n (%)					
Yes	7 (4.2%)	6 (4.0%)	1 (0.9%)	14 (3.2%)	0.229†
No	160 (95.8%)	143 (96.0%)	116 (99.1%)	419 (96.8%)	

Note that different superscript letters indicate significant differences between years' groups.

*Chi-square test

† Fisher's exact test

Table 3. Late onset sepsis 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 (%)					
Yes	61 (65.6%)[a]	102 (44.3%)[b]	23 (20.9%)[c]	186 (43.0%)	<0.001*
No	32 (34.4%)[a]	128 (55.7%)[b]	87 (79.1%)[c]	247 (57.0%)	
Coagulase-negative staphylococcal infection, n (%)					
Yes	43 (46.2%)[a]	87 (37.8%)[a]	18 (16.4%)[b]	148 (34.2%)	<0.001*
No	50 (53.8%)[a]	143 (62.2%)[a]	92 (83.6%)[b]	285 (65.8%)	
Other bacterial pathogens, n (%)					
Yes	27 (29,0%)[a]	38 (16.5%)[b]	6 (5.5%)[c]	71 (16.4%)	<0.001*
No	66 (71.0%)[a]	192 (83.5%)[b]	104 (94.5%)[c]	362 (83.6%)	
Fungal infection, n (%)					
Yes	8 (8.6%)[a]	4 (1.7%)[b]	2 (1.8%)[a, b]	14 (3.2%)	0.010†
No	85 (91.4%)[a]	226 (98.3%)[b]	108 (98.2%)[a,b]	419 (96.8%)	

Note that different superscript letters indicate significant differences between gestational age groups based on pairwise comparisons.

*Chi-square test

† Fisher's exact test

Table 4. Late onset sepsis and meningitis according to birth weight

Aetiology	Birth weight			*p-value*
LOS from all causes, n (%)	≤1000 g (n=160)	>1000 g (n=273)	Total (n=433)	
Yes	95 (59.4%)[a]	91 (33.3%)[b]	186 (43.0%)	<0.001*
No	65 (40.6%)[a]	182 (66.7%)[b]	247 (57.0%)	
Coagulase-negative staphylococcal infection, n (%)				
Yes	70 (43.8%)[a]	78 (28.6%)[b]	148 (34.2%)	0.001*
No	90 (56.2%)[a]	195 (71.4%)[b]	285 (65.8%)	
Other bacterial pathogens, n (%)				
Yes	43 (26.9%)[a]	28 (10.3%)[b]	71 (16.4%)	<0.001*
No	117 (73.1%)[a]	245 (89.7%)[b]	362 (83.6%)	
Fungal infection, n (%)				
Yes	10 (6.2%)[a]	4 (1.5%)[b]	14 (3.2%)	0.007*
No	150 (93.8%)[a]	269 (98.5%)[b]	419 (96.8%)	

Note that different superscript letters indicate significant differences between birth weight groups based on pairwise comparisons.

*Chi-square test

† Fisher's exact test

Table 5. Predictor factors for late onset sepsis

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
Necrotizing Enterocolitis			
Without	Ref		
With	5.103	[1.534; 16.970]	0.008
Steroids for Bronchopulmonary Dysplasia			
Without	Ref		
With	4.145	[1.282; 13.398]	0.018

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ANEXOS

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Videos, audios and 3D illustrations must be **original**.

References

Please list the references **in order of citation** in the text, in **square brackets**.

For each entry, please clearly indicate the following data: names of **all the authors**, title of the article/book, publication year. Moreover, for journal articles, indicate the abbreviated journal title, volume, issue, first and last page of the article; for websites, indicate the last access; for books, indicate the book publisher and its head office. If you want to quote a chapter within a book, please add information on the chapter (title and authors). Examples:

- **article (see and follow Pub Med citations)**: Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005;365(9466):1231-8.
- **book**: Cowan CP, Cowan PA. When partners become parents: the big life change for couples. New York: Basic Books, 1992.
- **chapter within a book**: Eyben E. Fathers and sons. In: Rawson B (Ed.). Marriage, divorce and children in ancient Rome. Oxford: Clarendon Press, 1991.
- **website**: http://guidance.nice.org.uk/CG54, last access: April 2012.

Author Listing

For each author, please list the following items: name, surname, institutional affiliations.

To facilitate the publisher's communication with authors, please list also the e-mail addresses.

Further requirements

Please indicate a conflict of interest statement and a funding acknowledgement statement.

In case of human experimentation, please indicate which ethical standards were followed and write an informed consent statement.

In experiments on animals, please indicate an animal rights statement.

Copyright agreement

Please note that before the article final publication the corresponding author will have to send a signed copyright agreement, where he/she agree to transfer the copyright to the journal's publisher. The copyright agreement can be read here.

Unidade de Investigação

Tomei conhecimento. Nada a opor.

29 de Janeiro de 2019

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

DIRECÇÃO CLÍNICA

Aprovado. Ao CA. 1 02 2019

(Prof.ª Doutora Ana Azevedo)

n.º 22 / 19

SÃO JOÃO

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração do Centro Hospitalar de São João

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 05 FEV 2019

Presidente do Conselho de Administração

(Dr. António Oliveira e Silva)

Diretor Clínico | Enfermeira Diretora | Vogal Executivo | Vogal Executivo

(Prof. Dr. José Artur Paiva) | (Enf.ª Filomena Cardoso) | (Dr. Luís Porto Gomes) | (Dr. Renato Matos)

Nome do Investigador Principal:

Maria Francisca Baía Bastos da Rocha Maia

Título da Investigação:

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

Pretendendo realizar no(s) Serviço(s) de:

Neonatologia

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos. *O Investigador/Promotor*

Porto, 6 *de* Dezembro *de* 2018. Mª Francisca Maia

assinatura

Centro Hospitalar São João
Centro de Epidemiologia Hospitalar
21/1/2019

CES-IM005-0

Comissão de Ética

Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Parecer

Título do Projecto: 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

Nome da Investigadora Principal: Maria Francisca Baía Bastos da Rocha Maia, aluna do Mestrado Integrado em Medicina da FMUP

Onde decorre o Estudo: Serviço de Neonatologia. Dispõe de autorização da Prof.ª Doutora Hercília Guimarães, que também é a orientadora.

Objectivos do Estudo:

Este trabalho de investigação, de índole retrospectiva, tem como principal objectivo avaliar a evolução da prevalência do início tardio da sepsis e da meningite e RNMBPN na UCIN durante a participação da Unidade no Vermont Oxford Network entre 2000 e 2013

Estudo realizado no âmbito do Mestrado Integrado em Medicina da FMUP, sob orientação da Prof.ª Doutora Hercília Guimarães.

Benefício/risco: Não aplicável

Confidencialidade dos dados: Os dados serão recolhidos sem a identificação dos participantes.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável

***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: Março de 2019

Conclusão: Proponho um parecer favorável à realização deste projecto de investigação.

Porto, 18 janeiro de 2019

O Relator da CE

Prof Doutor Filipe Almeida

SÃO JOÃO

U.PORTO FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Questionário para submissão de Investigação

Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto,

Pretendendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.

IDENTIFICAÇÃO DO ESTUDO

Título da investigação: 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 (NICU)

Nome do investigador: Maria Francisca Baía Bastos da Rocha Maia

Endereço eletrónico: franciscabbmaia@gmail.com **Contacto telefónico:** 919082220

Caracterização da investigação:

☒ Estudo retrospetivo ☐ Estudo observacional ☐ Estudo prospetivo

☐ Inquérito ☐ Outro. Qual? _____

Tipo de investigação:

☐ Com intervenção ☒ Sem intervenção

Formação do investigador em boas práticas clínicas (GCP): ☐ Sim ☒ Não

Promotor *(se aplicável)*: _____

Nome do orientador de dissertação/tese *(se aplicável)*: Dra. Hercília Guimarães

Endereço eletrónico: herciliaguimaraes@gmail.com

Local/locais onde se realiza a investigação: Serviço de Neonatologia do Centro Hospitalar São João

Data prevista para início: 02 / 01 / 2019 Data prevista para o término: 04 / 03 / 2019

PROTOCOLO DO ESTUDO

Síntese dos objetivos:

This study aims to assess the evolution on prevalence of late onset sepsis and meningitis in this NICU during the participation in the Vermont Oxford Network (VON) between 2000 and 2013.

Fundamentação ética (ganhos em conhecimento/inovação; ponderação benefícios/riscos):

This study is important to benchmark the practice of this NICU.

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?
Data were collected without the identification of the patients.

O investigador necessita ter acesso a dados do processo clínico? ☐ Sim ☒ Não

Está previsto o registo de imagem ou som dos participantes? ☐ Sim ☒ Não

Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☒ Não

CONSENTIMENTO

O estudo implica recrutamento de:

Doentes: ☐ Sim ☒ Não Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☐ Sim ☒ Não

Outras pessoas sem capacidade do exercício de autonomia: ☐ Sim ☒ Não

A investigação prevê a obtenção de Consentimento Informado: ☐ Sim ☒ Não

Se não, referir qual o fundamento para a isenção:
We analyse data from an official database.

Existe informação escrita aos participantes: ☐ Sim ☒ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

☐ Investigador ☐ Promotor ☐ Ambos ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:
None.

Riscos/incómodos previsíveis:
None.

São dadas contrapartidas aos participantes:

- *pela participação* ☐ Sim ☐ Não ☒ Não aplicável
- *pelas deslocações* ☐ Sim ☐ Não ☒ Não aplicável
- *pelas faltas ao emprego* ☐ Sim ☐ Não ☒ Não aplicável
- *por outras perdas e danos* ☐ Sim ☐ Não ☒ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

☐ Investigador ☐ Promotor ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

Existe protocolo financeiro? ☐ Sim ☒ Não

LISTA DE DOCUMENTOS ANEXOS

- [x] Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João *(se aplicável)*
- [ ] Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto *(se aplicável)*
- [x] Protocolo do estudo
- [x] Declaração do Diretor de Serviço onde decorre o estudo
  (sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- [ ] Profissional de ligação
- [x] Informação dos orientadores
- [ ] Informação ao participante
- [ ] Modelo de consentimento
- [ ] Instrumentos a utilizar *(inquéritos, questionários,escalas, p.ex.)*: _____
- [x] Curriculum Vitae abreviado *(máx. 3 páginas)*
- [ ] Protocolo financeiro
- [ ] Outros:

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, 6 de Dezembro de 2018

Nome legível: Maria Francisca Baia Bouça da Rocha Maia Mª Francisca Maia
assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/ FMUP Emitido na reunião plenária da CE de 18 / 01 / 19

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.