Risk Factors for Healthcare Associated Sepsis in Very Low Birth Weight Infants

Fatores de Risco para Sépsis Associada aos Cuidados de Saúde em Recém-nascidos de Muito Baixo Peso

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Healthcare associated infections in very low birth weight infants are associated with significant morbidity and mortality and are also a cause of increased length of stay and hospital costs. The objective of this study was to evaluate the rate of healthcare-associated sepsis and associated risk factors in very low birth weight infants.

Material and Methods: Retrospective observational study including very low birth weight infants hospitalized in a Neonatal Intensive Care Unit during ten years (2005-2014). We evaluated the association between several risk factors and healthcare-associated sepsis.

Results: 461 very low birth weight infants were admitted. There were 110 episodes of HS in 104 very low birth weight infants and 53 episodes of sepsis associated with central vascular catheter. The density of the sepsis was 7.5/1 000 days of hospitalization and the density of central vascular catheter - associated sepsis was 22.6/1 000 days of use. The infants with HS had lower average birth weight and gestational age (959 ± 228 g *vs* 1191 ± 249 g and 27.6 ± 2 *vs* 29.8 ± 2.2 weeks), p < 0.001. After adjusting for birth weight and gestational age we verified an association between healthcare-associated sepsis and antibiotic therapy in D1, the duration of parenteral nutrition and central vascular catheter. After logistic regression only the gestational age and duration of parenteral nutrition remained as independent significant risk factors for healthcare-associated sepsis.

Discussion: The independent factors for healthcare-associated sepsis are gestational age and duration of parenteral nutrition.

Conclusion: For each extra week on gestational age the risk declined in 20% and for each day of NP the risk increased 22%.

Keywords: Cross Infection; Infant, Low Birth Weight; Risk Factors; Sepsis.

RESUMO

Introdução: As infeções associadas aos cuidados de saúde constituem uma importante causa de morbi-mortalidade neonatal, levando a um aumento do tempo de internamento e consequentemente dos seus custos. O objetivo deste estudo foi avaliar a taxa de incidência de infeções associadas aos cuidados de saúde e os seus principais fatores de risco em recém-nascidos de muito baixo peso.

Material e Métodos: Estudo retrospetivo dos recém-nascidos de muito baixo peso internados numa maternidade com apoio perinatal diferenciado, durante um período de 10 anos (2005-2014). Foi analisada a existência de associação entre vários fatores de risco e a ocorrência de infeções associadas aos cuidados de saúde.

Resultados: Foram internados 461 recém-nascidos de muito baixo peso. Houve 110 episódios de infeções associadas aos cuidados de saúde em 104 recém-nascidos e 53 episódios de sépsis associada a cateterismo venoso central. A densidade de sépsis foi 7,5/1 000 dias de internamento e a densidade de sépsis associada ao cateterismo venoso central 22,6/1 000 dias de utilização. Os recém-nascidos com infeções associadas aos cuidados de saúde apresentaram uma média de peso ao nascimento e idade gestacional inferior (959 ± 228 g *vs* 1191 ± 249 g) e (27,6 ± 2 *vs* 29,8 ± 2,2 semanas), *p* < 0,001. Após ajuste à idade gestacional e peso ao nascimento verificámos associação entre infeções associadas aos cuidados de saúde e antibioterapia em D1, duração de cateterismo venoso central e da nutrição parentérica. Após regressão logística, mantiveram-se como fatores de risco independentes com significância estatística, a idade gestacional e a duração da nutrição parentérica.

Discussão: Os fatores de risco independentes para infeções associadas aos cuidados de saúde foram a idade gestacional e a duração da nutrição parentérica.

Conclusão: Por cada semana a mais na idade gestacional o risco de infeções associadas aos cuidados de saúde diminuiu em 20% e por cada dia de nutrição parentérica o risco aumentou em 22%.

Palavras-chave: Factores de Risco;Infecção Hospitalar; Recém-Nascido de Muito Baixo Peso; Sépsis.

INTRODUCTION

Healthcare-associated infections (HAI) are a serious problem in neonatal intensive care units (NICUs), associated to increased morbidity and mortality, length of stay and related costs.[1,2]

Rates of HAI in neonatal care, with severe associated conditions such as sepsis, described in international studies, have varied between 0.1% in full-term and 21-30% in very low birth weight (VLBW) infants and inversely proportional to birth weight.[1,3]

Technical improvements and improved healthcare in NICUs have led to an increased survival in extreme preterm babies as well as in extremely low birth weight infants over the last few years. This is mostly due to the increased use of invasive procedures (central venous catheter [CVC], parenteral nutrition [PN], invasive mechanical ventilation [IMV]) as well as broad-spectrum antibiotics, associated to longer length of stay and multiple carers. These factors are associated to immaturity of the immune and digestive

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system, as well as to immaturity of epidermal barrier and promoting colonization and invasion by potentially pathogenic microorganisms, leading to HAI - one of the most frequent complications in NICUs.[4-6]

Different risk factors for sepsis,[7-9] including for CVC-related bloodstream infection (CRBSI)[10,11] and risk factors for some types of microorganisms have been described in literature.[12-15] CRBSI are mostly caused by coagulase negative staphylococci (CoNS) or other colonizing microorganisms of the skin surrounding catheter entry site or catheter connections.

Prospective monitoring of sepsis incidence rates is considered as a crucial tool in quality control.[16]

Epidemiological monitoring in NICUs was included into the National Infection Control Program *Programa Nacional de Controlo da Infeção (PNCI)* from 2001, allowing for a better knowledge of the Portuguese reality.

Monitoring of individual risk factors in NICUs is crucial to more efficient and better targeted infection control measures.

Our study aims the assessment of the incidence rate of HAI, namely the incidence of sepsis, CRBSI, ventilator-associated pneumonia (VAP) and the identification of risk factors for HAI in VLBW infants.

MATERIAL AND METHODS

This was a retrospective, observational, longitudinal and analytical study of VLBW infants attending NICU at a maternity hospital with perinatal care capability, over a ten-year period (1st Jan 2005 to 31 Dec 2014).

Infection criteria defined by the PNCI were used in this study.[17]

Whenever clinical signs and symptoms occurred more than 72 hours upon admission to hospital, the presence of HAI was considered.

Clinical sepsis is defined by the presence of two of the following clinical signs and symptoms of systemic infection: fever (axillary temperature > 38ºC), thermal instability, hypothermia (axillary temperature < 36.5ºC), episodes of apnoea (> 20 seconds), episodes of bradycardia (HR < 80/min), tachycardia (> 200/min), capillary refilling time > two seconds, metabolic acidosis (base excess - BE ≤ 12 mEq/l) with no other reason, unexplained hyperglycaemia (> 140 mg/dL), increased oxygen demand, deterioration of ventilation parameters, need for re-intubation, hypotonia, hyporeactivity, food intolerance and at least one of the following: positive C-reactive protein (> 2 mg/dL), leukocytosis/leukopenia (> 30,000/mm^3 / < 5,000/mm^3), immature-to-total-neutrophil ratio > 0.2.

Septicaemia is defined as clinical sepsis with positive blood culture (aseptic blood sampling by venipuncture).

Whenever peripheral blood and catheter cultures in a patient with a CVC or having had a CVC up to 48 hours before sign and symptom onset were both positive for the same microorganism, with the same antibiogram, CRBSI was considered.

CVC utilization ratio was defined as the total number of central line days per total number of patient-days x 100.

ETT (endotracheal tube) utilization ratio was defined as the total number of ETT days per total number of patient-days x 100.

Incidence rates of device-related infections (CVC, ETT) associated to risk exposure were obtained.

Device-related infections were considered whenever any invasive device was used up to 48 hours before onset of signs and symptoms of infection. One day of device utilization was considered whenever the patient used the device for at least 12 hours.

VAP rate was defined as the number of VAP episodes in ventilated patients per 1,000 ventilator days.

Descriptive analysis of cumulative incidence of sepsis (number of patients with sepsis per 100 at-risk neonate patients), incidence density rate for sepsis (number of patients with sepsis per 1,000 patient-days), frequency and percentage of microorganisms identified and global mortality (number of deaths in studied neonate patients) was carried out.

HAI-NNP group included neonate patients presenting with HAI and NHAI-NNP group included the remaining patients. Univariate analysis of the presence of sepsis and the different variables was carried out: maternal age, antenatal corticosteroid therapy, gestational age (GA), birth weight (BW), gender, delivery type (caesarean section or vaginal delivery), small for gestational age (SGA) – neonate infants whose weight falls below the 10th percentile on the Fenton Growth Chart,[18] initial neonatal risk assessed by the Clinical Risk Index for Babies (CRIB) score,[19] place of birth ('inborn' babies when having born at the maternity hospital where the study took place and 'outborn' when born elsewhere), required neonate resuscitation in delivery room, antibiotic therapy from Day 1, timing of onset of enteral nutrition, length of stay and mortality. The presence and duration of any risk factor or use of invasive procedure, namely conventional mechanical ventilation (CMV), non-invasive ventilation (NIV), CVC and parenteral nutrition (PN). Ventilation and parenteral nutrition in HAI-NNP were considered as risk factors only when these were being used at diagnosis and patients in need for these procedures within the course of the sepsis were excluded from the study.

SPSS version 20 software was used in statistical analysis. Bivariate analysis used Mann-Whitney's test for quantitative variables and chi-square/Fisher's test/linear trend chi-square (based upon Cochran rules) were used for categorical variables. Odds-ratio (OR) and 95% confidence intervals were obtained. The effect of risk factors was adjusted for GA and BW (ORa) and a logistic regression analysis was carried out for all variables; statistically significant differences were considered for a likelihood ratio <0.1. Only GA was introduced into the model, due to collinearity between GA and BW. Statistical significance was considered for $p < 0.05$.

ROC (receiver operating characteristic)-curve was used for the definition of the best cut-off points of PN and CVC

timing for the presence of HAI.

RESULTS

In total, 461 neonate infants with birth weight <1,500 g were admitted to the NICU during the study period (2005-2014), corresponding to 17.3% (461/2,655) of total admissions to the NICU.

Average GA was 29.3 weeks (sd ± 2.4) and average BW was 1,139 g (sd ± 263 g – minimum 440 g and maximum 1,490 g); male: female ratio was 1.25:1.

From total VLBW infants, 127 (27.5%) SGA, 64 (13.9%) outborn and 317 (68.7%) caesarean section births were found.

Average CRIB score was 2.48 (sd ± 2.89).

From total VLBW infants, 104 (22.5%) presented with HAI (HAI-NNP = 104), corresponding to 110 episodes of sepsis (one patient presented with three episodes of sepsis and four patients presented with two episodes). All patients having presented with more than one HAI episode were ELBW (extremely low birth weight), ventilated, under PN and CVC.

Median (10th and 90th percentile) diagnosis-timing was 9.1 days (5.3 – 25.8 days).

In total, 461 neonate infant patients stayed in hospital for 14,572 days, with an average length of 31.6 ± 25.7 days. Total number of CVC days was 2,345.

In total, 20 patients (4.3%) died over the study period.

Clinical and demographic characteristics of our group of patients are shown in Table 1.

A 7.5 per 1,000 patient-days (110/14,572) incidence density rate for sepsis in VLBW infants was found and 22.6 episodes per 1,000 days of CVC use (53/2,345) was the incidence density rate found for CRBSI.

Incidence of sepsis, incidence density rate for HABSI and incidence density rate for CRBSI in our group of patients (VLBW and ELBW [<1,000 g]) are shown in Table 2. When compared to VLBW, ELBW patients showed higher rate and higher incidence rate for sepsis. Positive blood cultures were obtained within 73 episodes of sepsis (66.4%), corresponding to the isolation of 79 microorganism species.

CoNS (47/73), followed by *Staphylococcus aureus* (12/73 – 4 positive blood cultures for MRSA - methicillin-resistant S. *aureus*), *Escherichia coli* (7/73) and *Candida spp* (6/73) were the most frequently isolated microorganisms. No extended-spectrum beta-lactamase (ESBL)-producing Gram negative bacteria were identified. Data regarding isolated microorganisms are shown in Table 3.

Univariate analysis of risk factors for the presence of HAI is shown in Table 4**.** Average age when enteral nutrition was started was 3.0 ± 1.2 days in HAI-NNP and 2.1 ± 1.2 days in NHAI-NNP.

Statistically significant risk factors for HAI, upon adjustment for GA and BW included antibiotic therapy from Day 1 (ORa = 1.828, 95% CI = 1.049 – 3.185; $p = 0.033$), number of PN days (ORa = 1.226, 95% CI = 1.139 – 1.320. $p < 0.001$), delayed enteral feeding onset (ORa = 1.285, 95% CI = 1.061 – 1.551; $p = 0.01$) and total number of CVC

Table 1 - Clinical and demographic characteristics

Maternal age (years), mean/sd	30.2 ± 5.7
Antenatal corticosteroid therapy; n (%)	344 (90%)
GA (weeks), mean/sd	29.3 ± 2.4
BW (g), mean/sd	1,139 ± 263
Male gender; n (%)	260 (56%)
CRIB score, mean/sd	2.48 ± 2.89
SGA; n (%)	127 (27.5%)
Outborn; n (%)	64 (13.9%)
Caesarean section; n (%)	317 (68.7%)
Length of stay, mean/sd Total patient-days, days	31.6 ± 25.7 14,572
Number of patients with CVC (%) Total CVC days	254 (55%) 2,345
CVC utilization ratio	22.6
CMV duration, mean/sd	11.9 ± 19
Number of patients with ETT (%) Total ETT days	237 (51%) 2,252
ETT utilization ratio	2.8
Mean PN duration, mean/sd	5.0 ± 4.6
Mortality; n (%)	20 (4.3%)

GA: gestational age; BW: birth weight; CRIB: Clinical Risk Index for Babies score; SGA: small for gestational age; sd: standard deviation; CVC: central vascular catheter; CMV: conventional mechanical ventilation; PN: parenteral nutrition; ETT: endotracheal tube.

Table 2 - Incidence rate and incidence density rate for HABSI

	VLBW	ELBW
Sepsis rate	23%	44%
Rate of sepsis with positive blood culture	16%	33%
Incidence density rate for sepsis	7.5	11.2
Incidence density rate for sepsis with positive blood culture	5.8	7.4
Incidence density rate for CRSBI	22.6	23.7
Incidence density rate for CRSBI with positive blood culture	15.6	19.1

CVC: central venous catheter; VLBW: very low birth weight infant; ELBW: extremely low birth weight infant.

days (ORa = 1.047, 95% CI = 1.002-1.094; $p = 0.042$).

Gestational age (OR = 0.80; 95% CI = 0.681 – 0.938; $p = 0.006$) and PN duration (OR = 1.22; 95% CI = 1.122 – 1.332. $p < 0.0001$) were identified as independent risk factors for HAI upon logistic regression.

Cut-off point (Youden index) from which patients show statistically significant risk for HAI was obtained. This was established with PN or CVC duration of 6.5 days or above (AUC = 0.82 and AUC = 0.73 respectively, $p < 0.0001$) (Fig. 1 and 2).

DISCUSSION

Incidence rate of healthcare-associated bloodstream infections (HABSI) found in our study was below what has been described in literature as well as in HAI registry within the PNCI for NICUs – 7.5/1,000 *vs.* 9/1,000.[17] Even though similar average BW and GA lower incidence rates tended to be found.

HAI-NNP showed lower BW and GA when compared to NHAI-NNP. Due to the fact that these were statistically different groups, all risk factors were adjusted for GA and BW. In our study and in line with other unicentric and multicentric studies, lower BW and GA are associated to higher risk for HAI.[7,20-28] Risk for HAI is reduced in 20% per each additional week of gestational age. A 5.4 OR (95% CI = 3.1-9.4, p <0.001) was found in infants with less than 28 weeks' GA and 5.2 OR (95% CI: 3.1 – 8.8, $p < 0.001$) in infants less than 1,000 g birth weight.

Table 3 - Microorganisms isolated from blood cultures and associated mortality

Microorganisms	n	Mortality (n = 20)
Gram +	63	4 (20%)
CoNS	47	2
Staphylococcus aureus	12	1
Enterococcus spp	4	1
Gram -	10	4 (20%)
Escherichia coli	7	3
Klebsiella spp	1	0
Pseudomonas spp	1	0
Enterobacter spp	1	1
Candida spp	6	2 (10%)
TOTAL	79	10 (50%)

CoNS: *Coagulase* negative *staphylococci*

Some studies have suggested male gender as a risk factor,[28] in line with what was found in our study, although with no statistical significance.

Infants with higher CRIB score (CRIB ≥ 5) were associated to higher rate of inpatient HAI, in line with other studies.[26]

PN has been described as one of the major risk factors for HAI,[7,10,22,25,26] in line with what was found in our study. A 22% risk for HAI was found per each additional PN day. This was found in our group of patients and reinforces the important role of optimizing clinical good practice and hygiene measures regarding preparation, handling and administration of therapy.

Early onset enteral feeding is a protective measure against HAI, associated to accelerated bowel maturation, reducing intestinal permeability and therefore reducing bacterial translocation, apart from reducing PN duration.[5,21,22,29,30] In our study, HAI-NNP had later enteral feeding when compared to NHAI-NNP. A 28.5% increase in the risk for HAI per each additional day of enteral feeding was found.

Breastfeeding has been considered beneficial for the reduction of the incidence of HABSI.[5,21,22,30,31] No statistically significant association was found in our study, even with $p = 0.006$, which we found as being related to high breastfeeding use in both groups.

A statistically significant relationship was found between CVC use and HAI, in line with different national and international studies,[14,20,22,25-28] probably related to contamination during insertion, excessive handling, disruption of the closed system for blood draws and medication administration, use of contaminated solutions or contamination of the skin surrounding catheter entry site.[32] Different studies have shown that the risk for sepsis drastically increases beyond 15 CVC days.[30] In our patients, we found that each additional CVC day involved a 4.7% higher risk for HAI and this was statistically significant for 6.5 CVC days and beyond.

The use of broad-spectrum antibiotics in infants has also been described as a risk factor for HAI[33] and may induce changes in patient's flora and/or in environmental flora that may lead to the presence of multi-resistant strains.[32] The use of antibiotics from Day 1 was associated to a higher risk

Table 4 - Risk factors for HAI

	HAI-NNP n = 104	NHAI-NNP n = 357	OR (95% CI)	ORa (95% CI)	*p*
GA (weeks), mean/sd	27.6 ± 2	29.8 ± 2.2			< 0.001
BW (g), mean/sd	959 ± 228	1,191 ± 249 g			< 0.001
Male gender, n (%)	36 (34.6%)	110 (30,8%)			ns
SGA, no. (%)	20 (19.2%)	107 (30%)	0.5 (0.3 - 0.9)	ns	0.031
CRIB score > 4, mean/sd	4.3 ± 3.3	1.9 ± 2,4		ns	< 0.001
Outborn, n (%)	23 (22%)	41 (11.5%)	2.1 (1.2 - 3.8)	ns	0.006
Need for resuscitation, n (%)	73 (70%)	177 (49.7%)	2.3 (1.4 - 3.8)	ns	< 0.001
Antibiotic therapy from Day 1, n (%)	78 (75%)	155 (43.9%)	3.8 (2.3 - 6.2)	1.8 (1.1 - 3.6)	< 0.001
CMV, n (%)	72 (69%)	133 (37%)	3.7 (2.3 - 6.0)	ns	< 0.001
CMV days, mean/sd	11.9 ± 19	2.9 ± 9.7		ns	< 0.001
NIV, n (%)	93 (89.4%)	201 (56%)	6.5 (3.3 - 12.6)	ns	< 0.001
NIV days, mean/sd	19.5 ± 18	5.9 ± 11		ns	< 0.001
CVC > 6 days, n (%)	68 (80%)	128 (43%)	5.3 (2.9 - 9.5)	2.1 (1.1 - 4.1)	< 0.001
CVC days, mean/sd	8.8 ± 6.7	4 ± 5.6		1.1 (1.05 - 1.2)	< 0.001
PN > 6days, n (%)	99 (95%)	218 (61.1%)	12.6 (5 - 31)		< 0.001
PN days, mean/sd	9.1 ± 4.5	3.8 ± 4.1		1.2 (1.1 - 1.3)	< 0.001
Average age at EN onset (days), mean/sd	3.0 ± 1.2	2.1 ± 1.2		1.3 (1.1 - 1.6)	< 0.001
TEN days, mean/sd	10.9	6.1			< 0.001
Breastfeeding, n (%)	91 (88%)	328 (93%)			ns

HAI-NNP: neonate patients with healthcare-associated infection; NHAI-NNP: neonate patients without any HAI; sd: standard deviation; GA: gestational age; BW: birth weight; SGA: small for GA; CRIB: Clinical Risk Index for Babies score; CMV: conventional mechanical ventilation; NIV: non-invasive ventilation; CVC: central venous catheter; PN: parenteral nutrition; EN: enteral nutrition; TEN: total enteral nutrition; OR: odds ratio; ORa: adjusted OR for GA and BW; ns: non-significant.

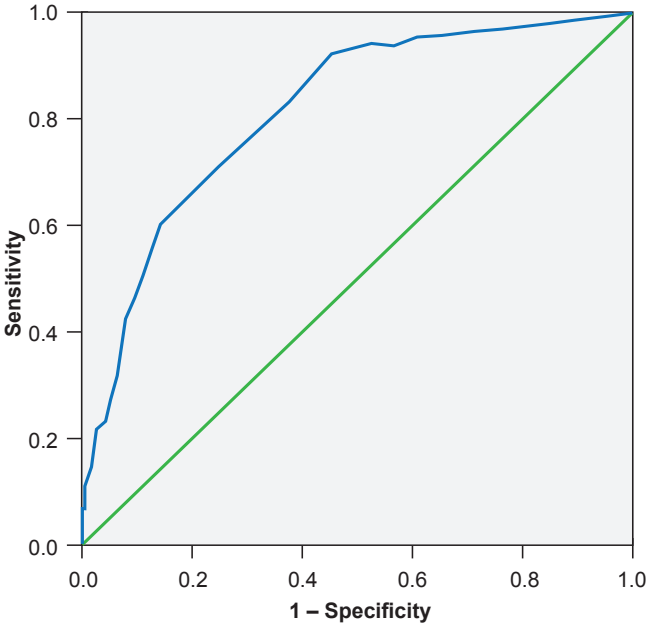

Figure 1 - Youden cut-off point between PN duration and the presence of HABSI: 6.5 days. Discriminatory ability (area-under-the ROC curve; AUC = **0.815**; 95% CI = 0.77 - 0.861).

PN: parenteral nutrition; ROC: receiver operating characteristic; AUC: area under the curve.

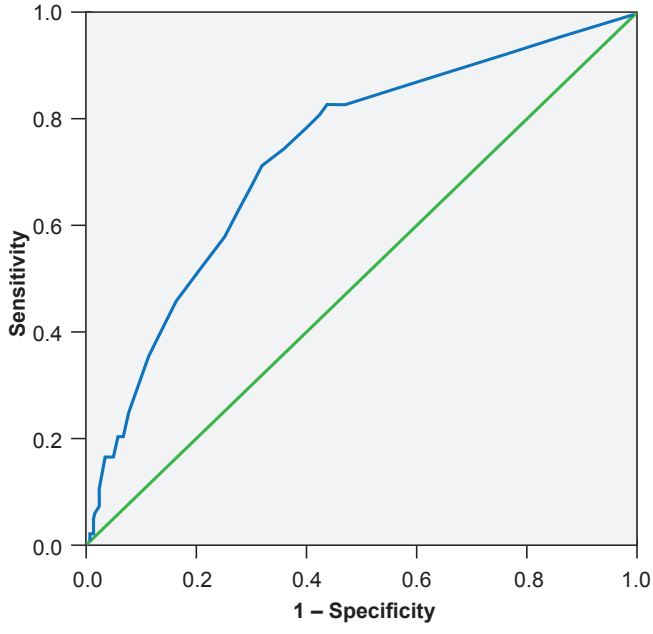

Figure 2 - Youden cut-off point between CVC duration and the presence of HABSI: 6.5 days. Discriminatory ability (area-under-the ROV curve; AUC = **0.734**; 95% CI = 0.679 - 0.788).

CVC: central venous catheter; ROC: receiver operating characteristic; AUC: area under the curve.

for sepsis in our study.

Apart from intrinsic and extrinsic risk factors there are also environmental risk factors that may a have a role in HABSI, namely regarding overcrowded patient wards, the number of healthcare professionals, poor adherence to hand hygiene or to disinfection of insertion site, as well as catheter monitoring and handling, which were not assessed in our study.[33]

HAI prevention is based on strategies aimed to reducing the risk for infection through protecting healthcare professionals from occupational transmission of microorganisms (hand hygiene and careful aseptic CVC insertion and monitoring), careful antibiotic use, breastfeeding promotion and early enteral feeding.[17]

Prevention of preterm birth would be one the most effective strategies, although extremely difficult to be achieved, due to its complexity involving medical, educational and social issues.

Epidemiological surveillance in NICUs is crucial as it allows for improved knowledge regarding specific epidemiological reality and as it may help healthcare professionals for a targeted practice improving neonate clinical safety as well as healthcare quality.

CONCLUSIONS

Incidence density rate for sepsis found in our study was below the national registry.

Statistically significant risk factors for HAI included PN duration and GA. A 20% reduction in the risk for infection was found per each additional week in GA and a 22% increase was found per each additional PN day.

A statistically significant risk for HAI was found for a 6.5-day PN or CVC duration and beyond, upon cut-off point (Youden index) determination.

Good practice improvement in HAI prevention, including careful aseptic techniques, early onset of enteral feeding and minimizing long-term or inadequate use of broad-spectrum antibiotics should be a daily challenge. Continuous training of healthcare professionals, aimed to improving adherence to hygiene measures is a relevant strategy.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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