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ARTIGO ORIGINAL

Nosocomial infections in a Brazilian neonatal intensive care unit: a 3-year cohort study

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RESUMO

Resumo: O avanço na tecnologia de cuidados médicos tem contribuído para uma maior sobrevida e hospitalização mais prolongada de recém-nascidos com imunidade reduzida e que são expostos a procedimentos invasivos frequentes. Os objetivos deste estudo foram determinar a incidência, as infecções mais freqüentes e os fatores de risco para as infecções hospitalares em uma unidade de terapia intensiva neonatal no sul do Brasil. Foi realizado um estudo de coorte com 503 recém-nascidos internados por mais de 24 horas, de fevereiro de 2004 a outubro de 2007, identificando aqueles que desenvolveram infecção. Os resultados foram submetidos ao teste do χ^2 e à análise multivariada.

A taxa de infecção foi de 55,9% e a densidade de incidência de 64,7 infecções por 1.000 pacientes-dia. Os sítios de infecção, em ordem de frequência, foram: pneumonia (43,8%), infecção primária da corrente sanguínea (31,6%), meningite (11,0%), infecção de pele (6,8%) e enterocolite necrosante (6,4%). A análise multivariada identificou 4 fatores de risco independentes: ventilação mecânica, nutrição parenteral total, cateter central de inserção periférica e peso de nascimento. Os agentes isolados mais comuns foram *Staphylococcus* coagulase-negativos (45,4%), *Candida* spp (25,8%) e bacilos Gram-negativos (20,6%).

As infecções mais frequentes foram semelhantes às relatadas na literatura, porém a incidência foi mais elevada. A identificação dos fatores de risco, embora já descritos por outros autores, foi inédita no setor e útil para a conscientização de toda a equipe profissional.

Palavras-chave: *infecção hospitalar; recém-nascido; fatores de risco; incidência; neonatologia.*

ABSTRACT

Abstract: Advances in medical care technology have contributed to longer survival and prolonged hospitalization of immunologically compromised neonates that are exposed to frequent invasive procedures. The objectives of this study were to determine the incidence, the most common infections and the risk factors for nosocomial infections (Nis) in a neonatal intensive care unit (NICU) in the south of Brazil.

A cohort study was conducted with 503 neonates, from February 2004 to October 2007, identifying those with NIs. All neonates were followed-up and the exposure to risk factors was assessed. The results were submitted to χ^2 test and to multivariate analysis.

The infection rate and the incidence density were 55.9% and 64.7 infections per 1000 patient-days, respectively. The sites of infection, in order of frequency were: pneumonia, primary bloodstream infection, meningitis, skin infection and necrotizing enterocolitis. The multivariate analysis identified 4 independent risk factors for nosocomial infection: mechanical ventilation, total parenteral nutrition (TPN), peripherally inserted central catheter (PICC) and birth weight. The most prominent isolated pathogens were coagulase-negative *Staphylococcus* (45.4%), *Candida* spp (25.8%) and Gram-negative rods (20.6%).

The most common infections were consistent with the literature; however, the incidence was much higher than in other studies. Although the risk factors have already been reported by many authors, they had not been identified in our unit before and, therefore, they were valuable in raising the awareness of our health care professionals.

Keywords: nosocomial infection; neonate; risk factors; incidence; neonatology.

INTRODUCTION

The improved survival of very low birth weight (VLBW) neonates has created a unique population at high risk for nosocomial infections (NIs). The advance in medical care technology has contributed to prolonged hospitalization of patients with impaired defense mechanisms that are exposed to invasive monitoring and supportive care.[1,2-5]

The high cost of hospitalization has resulted in studies all over the world with widely varying incidence rates of NIs. However, there are significant differences in methodology and definitions for NIs, with no pattern to allow a satisfactory comparison.[6,7] In Brazil, there are few systematic studies in neonatal intensive care units (NICUs), making it difficult to establish an epidemiologic profile of NIs in our developing country.[8-11]

The aims of this study were to determine the incidence rate and the most common NIs in a NICU in the South of Brazil, and to identify the risk factors associated with the development of NIs.

MATERIAL AND METHODS

From February 2004 to October 2007, all patients born in the NICU of Hospital Universitario de Londrina and stayed more than 24 hours were included in the study and evaluated with respect to the development of NI, death, and transfer to other units. They were followed until 48 hours after discharge from the unit.

Patients with clinical evidence of infection or risk of maternally acquired infections were followed-up as per the standard diagnostic routines of the unit. The classification of NI was made according to definitions from the National Nosocomial Infection Surveillance System, Centers for Disease Control and Prevention, for patients 12 months of age or younger.[12]

Infections that developed earlier than 48 hours after admission were defined as *early onset infections*, and those acquired after this period were recorded as *late onset infections*.

Primary bloodstream infections include both clinical sepsis and laboratory confirmed sepsis. Clinical sepsis was defined as clinical evidence of infection with deterioration in the infant's condition. A blood culture positive for recognized pathogens was not required. Laboratory confirmed bloodstream infections required 2 positive blood cultures for skin contaminant that was not related to infection at another site.[13]

Differences between groups with and without NI were assessed for statistical significance by use of the χ^2 distribution test. The following risk factors were assessed: birth weight, gestational age, mechanical ventilation, nasal continuous positive airways pressure (CPAP), total parenteral nutrition (TPN), umbilical catheter, peripherally inserted central catheter (PICC), prior use of antibiotics, use of chest tube, surgical procedures and intubation in the delivery room. All possible associations with P values < .20 were included in the multivariate logistic regression analysis.

The level of significance adopted was 5% ($P < .05$). The study protocol was reviewed and approved by the State University of Londrina Bioethical Research Committee.

RESULTS

During the study, 512 neonates were admitted and remained at least 24 hours, of which 503 were eligible for inclusion in the cohort, corresponding to 4,360 patient-days. A total of 257 patients developed 281 NIs according to the adopted criteria (incidence rate of 55.9% and incidence density rate of 64.7/1000 patient-days). Of these infections, 17.4% (n = 49) were maternally acquired.

The most common NIs were pneumonia (n = 123), primary bloodstream infections (n = 89), meningitis (n = 31), skin and soft tissue infections (n = 19) and necrotizing enterocolitis (n = 18). In 34.5% (97/281) of all infections, pathogens were isolated in blood cultures (Table 1).

A total of 97 pathogens were isolated from blood cultures from patients with clinical evidence of infection. The most common etiologic agents were coagulase-negative staphylococci (n = 44), *Candida* sp (n = 25), gram-negative rods (n = 20) and *Staphylococcus aureus* (n = 4).

For the statistical analysis of the risk factors we excluded the early onset infections. The following factors showed an association with NI: low birth weight, decreased gestational age, mechanical ventilation, nasal CPAP, TPN, PICC, umbilical catheter, previous use of antibiotics and intubation in the delivery room (Tables 2, 3 and 4).

The multivariate analysis identified 4 independent risk factors for late onset NIs: mechanical, TPN, PICC and birth weight (Table 5).

The device associated infection rates were 62.5 pneumonias per 1000 ventilator-days and 28.5 primary bloodstream infections per 1000 central line-days.

The mortality rate in neonates with NI was 17.5% and the overall mortality was 14.3%.

Table 1 – Distribution of nosocomial infections.

Sites of infection	Early-onset		Late-onset		Total	
	n	%	n	%	n	%
Pneumonia	*31*	*25.2*	*92*	*74.8*	*123*	*43.8*
*Confirmed PBSI**	*2*	*4.3*	*45*	*95.7*	*47*	*16.7*
Clinical sepsis	*12*	*28.6*	*30*	*71.4*	*42*	*14.9*
Meningitis	*2*	*6.5*	*29*	*93.5*	*31*	*11*
Skin infection	*1*	*5.3*	*18*	*94.7*	*19*	*6.8*
NEC¶	*1*	*5.6*	*17*	*94.4*	*18*	*6.4*
Urinary tract infection	*0*	*0*	*1*	*100*	*1*	*0.4*
Total	*49*	*17.4*	*232*	*82.6*	*281*	*100*

**Primary bloodstream infection; ¶Necrotizing enterocolitis*

Table 2 – Comparison of birth weight categories and NI.

Birth weight	N. of patients	Length of stay		N. of NI	Incidence Rate	Incidence Density*	Mortality
		With NI	Without NI				
<1000g	122	37.6±23.3	10.7±13.7	100	89.3	28.7	40.2%
1001 to 1500g	143	24.3±15.6	11.4±6.9	88	61.5	32.8	10.5%
1501 to 2500g	160	14.9±14.5	5.1±4.3	59	36.9	43.3	6.9%
>2500g	88	10.6±6.3	5.6±4.3	34	38.6	51.4	1.1%

χ^2 = 51.85, P < .0001, for difference in groups with and without infection with respect to birth weight; *per 1000 patient-days.

Table 3 – Comparison of gestational age categories and NI.

Gestational age	N. of patients	Length of stay		N. of NI	Incidence Rate	Incidence Density*	Mortality
		With NI	Without NI				
<28 weeks	128	36.6±22.2	10.3±11.4	114	89.1	29.3	37.5%
29 - 32 weeks	158	22.2±16.1	9.7±8.1	85	53.8	33.5	7.0%
33 - 36 weeks	164	14.0±13.7	5.2±4.2	56	34.1	42.4	6.1%
>36 weeks	53	10.8±6.1	6.3±5.2	26	49.1	57.9	5.7%

χ^2 = 56.47, P < .0001, for difference in groups with and without infection with respect to gestational age; *per 1000 patient-days.

Table 4 – Neonates with and without infection and exposure do risk factors.

Risk Factors	With infection (n=215)		Without infection (n=288)		Total (n=503)		p value*
	n	%	n	%	n	%	%
Mechanical Ventilation	145	67.4	95	33.0	240	47.7	<.0001
Nasal CPAP	71	33.0	66	22.9	137	27.2	.0118
TPN	163	75.8	106	36.8	269	53.5	<.0001
PICC	80	37.2	31	10.8	111	22.1	<.0001
Umbilical catheter	168	78.1	135	46.9	303	60.2	<.0001
Use of antibiotics	142	66.0	130	45.1	272	54.1	.0001
Chest tube	5	2.4	9	3.1	14	2.8	.5897
Intubation (birth)	109	50.7	79	27.4	188	37.4	<.0001
Surgical Procedures	8	3.7	7	2.4	15	3.0	.3999

*χ^2 Distribution

Table 5 – Logistic regression.

Risk Factors	Odds Ratio	C.I. 95%	p
Mechanical Ventilation	2.37	1.36-4.13	.0023
Nasal CPAP	1.09	0.66-1.80	.7382
TPN	1.81	1.06-3.09	.0307
PICC	2.17	1.22-3.88	.0086
Umbilical catheter	1.40	0.83-2.37	.2091
Use of antibiotics	1.46	0.86-2.47	.1569
Intubation at birth	0.88	0.53-1.46	.6218
Birth weight <1000g	8.58	2.52-29.19	.0006
Birth weight 1000-1500g	5.99	2.01-17.82	.0013
Birth weight 1501-2500g	3.06	1.20-7.82	.0194
Gestational age <28 weeks	0.44	0.12-1.61	.2165
Gestational age 29-32 weeks	0.33	0.11-0.99	.0481
Gestational age 33-36 weeks	0.23	0.09-0.61	.0033

Likelihood ration test = 159.14, P <.0001

DISCUSSION

There is wide variation in the rate of NIs in NICUs reported in the literature, ranging from 6 to 57.5 infections per 100 patients.[11,14,15]

However, there are significant differences in methodology and adopted criteria by various authors. Some authors report general infection rates, whereas others prefer site specific infection rates. Some studies include only bacterial infections and/or do not include infections developing within 48 hours of birth.[6,16]

The overall incidence rate of infections in this prospective study was 55.9%, much higher than those reported by other authors, but similar to another Brazilian study.[11]

The NI patient-day rate gives some consideration to differences in the length of stay at different institutions. A couple of possible reasons for the high incidence density of 64.7 infections per 1000 patient-days reported in this study may be that all early-onset infections (17.4% of total) as well as those with clinical evidence of infection but no positive blood culture for a recognized pathogen were included. Other factors may include the inadequate design of the NICU and its higher than recommended patient to nurse ratio.[14]

Device utilization rates appear to be markers for the type of NICU and may be indicative of the extent of unit's invasive practices. We found in this study 62.6 pneumonias per 1000 ventilator-days and 28.5 primary bloodstream infections per 1000 central line-days. Our device associated rates were much higher, probably for the same reasons previously mentioned.[17]

We evaluated the relationship of well known risk factors to the incidence of late onset NIs in our NICU.[18] The factors with significant association (P < .20) were included in logistic regression multivariate analysis. Mechanical ventilation, TPN, PICC and birth weight were identified as independent risk factors in our NICU.

Low birth weight has been considered a strong predictor of adverse outcomes, including NIs. A 1.47 times increase in the

risk of NI for every 100 g reduction in birth weight has been reported previously. The risk of NIs is 2.69 times greater in neonates weighing less than 1500 g compared with those weighing 1500 g or more.[15,19] Low birth weight was associated with NI in the bivariate analysis and was statistically significant in the multivariate analysis showing inversely proportional correlation.

In a multicenter study by Couto et al,[11] birth weight did not perform well as a variable for risk stratified CVC related bloodstream infection. In contrast, we classified all laboratory confirmed bloodstream infections, CVC related or not, in to one single group. Laboratory confirmation of catheter related infections in neonates is frequently impossible due to the difficulty in obtaining blood to paired culture from peripheral veins and central lines, and because only a relatively small volume of blood can be drawn.[20] Therefore, many CVC related bloodstream infections are not identified. Multiple site sampling for blood cultures may be more informative, but, for those who work with small premature neonates, may be impractical.

According to the literature, the risk of infection is inversely correlated with gestational age.[5] The immunologic immaturity is more profound the earlier during gestation that the infant is born.[21] Whereas decreased gestational age was found to be a significant risk factor in the bivariate analysis, it was not statistically significant in the multivariate analysis.

It is well known that upper respiratory tract infection rates increase when the number and duration of intubations increases.[22,23] Exposure to any respiratory device increases the risk of infection by 4 to 16 times.[24] Mechanical ventilation is also reported as a risk factor for pneumonias in neonates.[25] In this study, 188 patients (37.4%) were intubated in the delivery room, of which 58.0% developed late-onset NIs. Respiratory devices (mechanical ventilation and nasal CPAP) were used in 377 neonates (74.9%), of which 216 (57.3%) acquired late onset infection. Mechanical ventilation was strongly associated with NI in the multivariate analysis, while intubation in the delivery room and nasal CPAP were not statistically significant variables.

Central venous catheters are used very frequently in NICU patients to provide nutrition and to facilitate administration of fluid, blood products and medications.[26] However, the skin insertion site and the catheter hub are portals of entry for organisms causing catheter related infections.[4] Organisms colonizing the hub can migrate along the external or internal surface of the catheter leading to bacteraemia and sepsis. The latter may also be caused by translocation of intestinal pathogens that subsequently infect the central venous catheter.[27,28] Surgically implanted catheters have stronger association with primary bloodstream infections than umbilical catheters.[29] In this study, there was significant difference among neonates that developed NI with respect to the use of umbilical catheter(s) ($P < .0001$), but it was not an independent risk factor in the multivariate analysis.

PICC lines are increasingly being used to maintain long term vascular access in VLBW neonates due to their safety and ease of insertion. As a result, the use of surgically placed catheters has decreased in most NICUs.[3,30] Most catheter related bloodstream infections in neonates with PICCs are caused by coagulase-negative *staphylococci* (CoNS) and derive from intraluminal contamination.[31] According to Mahieu et al,[20] the incidence of PICC related bloodstream infections was 7.2%, which was consistent with the published figures of 1.3 to 12.9%. In our study, we found an incidence of 17% (19 primary bloodstream infections in 112 neonates with PICC) and 41.8 primary bloodstream infections per 1000 PICC-days. PICC lines cannot be blamed for all of these infections, but we thought it was important to report these rates for further observations. There was an association of PICC lines with infection in the bivariate analysis ($P < .0001$) and they were independent risk factors for NIs in the logistic regression. However, they continue to be widely used in neonates as they do not represent additional risk when compared to other types of venous catheters and minimize venepunctures in patients with prolonged intravenous therapy.[32-34]

Lipid emulsions are used to provide better nutrition and to reduce time required to gain birth. However, they increase the risk of CoNS bacteraemia.[35] TPN, as well as the central lines often placed for its administration, have been reported as strong risk factors for primary bloodstream infections.[4,20,27] The exclusive use of TPN with fasting has become a rare intervention. Enteral feeding has both direct trophic and indirect secondary effects due to the release of intestinal hormones, and thus is initiated as soon as the patient's clinical conditions permit.[36,37] The use of TPN was significant for the development of NI in the bivariate analysis and was a significant risk factor in the logistic regression model.

The use of antibiotics has been shown to promote the development of multi-drug resistant organisms in NICUs.[38-40] Antibiotics are risk factors frequently associated with bloodstream infections in premature neonates.[26] It has been reported that between 11 and 23 uninfected neonates are treated with antibiotics for every one that has a true infection.[41] In this study, there was early use of antibiotics in 54.1% of the patients. This was a significant risk factor in the bivariate analysis, but not in the multivariate analysis.

The most common infections in the cohort were: pneumonias (43.8%), primary bloodstream infections (31.6%), meningitis (11.0%), skin and soft tissues infections (6.8%) and necrotizing enterocolitis (6.4%). Our results are very much in agreement with those reported by other authors.[14,17,25] The diagnosis of pneumonia, the most frequent infection, may be overestimated since it is based on clinical data and radiograph findings.

Although the proportion of positive blood cultures was not high, the frequency of infections caused by CoNS and gram-negative rods is consistent with the literature.[11,42] With respect to a previous study in our NICU, it is of note the emergence of *Candida sp* as the second most common pathogen, with high morbidity and mortality, especially among neonates with birth weight < 1500 g.[43]

New techniques for life support may be implicated in the increased number of new risk factors for NIs. Thus it seems impossible to reduce NI rates as these modalities of treatment are tightly tied to contemporary neonatal care. However, judicious use of antibiotics and available technologic advances in medical therapy should be encouraged in the unit to minimize the risks of NI.

CONCLUSION

Incidence rates of NIs in our NICU were high with the most frequent infections similar to those reported in other studies. Multivariate analysis identified 4 independent risk factors for NI. Although they have already been reported by other authors, it was valuable to evaluate the association of these well known risk factors in a developing country NICU in order to draw the attention of health care professionals to a great cause of morbidity and mortality.

This was a descriptive and observational study; employment of new strategies to decrease infections was not one of our objectives. Further studies using other variables and laboratory techniques may help to develop methods for earlier diagnosis and more effective treatment of neonates, thus creating a safer NICU environment.

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