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ORIGINAL ARTICLE

Risk factors for nosocomial infection in a level III Neonatal Intensive Care Unit

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Abstract

Introduction: *Nosocomial infections are a major and a frequent problem in neonatal intensive care units and increase morbidity, mortality, and costs. The objective of this study was to identify the risk factors associated with nosocomial infections in a neonatal intensive care unit.* **Methods:** *Nested case control study. Records from patients were registered: gestational age, sex, birth weight, central venous catheter and other devices, congenital malformations, surgeries, mechanical ventilation, steroid use, H2 blockers, length of stay in neonatal intensive care unit, type of infection, and etiological agent.* **Results:** *We studied 188 cases with nosocomial infections and 192 controls without nosocomial infections. The most frequent infection was sepsis (34.8%) and coagulase negative Staphylococcus was the principal etiological agent (37.2%). The risk factors associated with nosocomial infection were central venous catheter (OR: 7.3; 95% CI: 2.3-22.8), duration of neonatal intensive care unit stay > 14 days (OR: 3.4; 95% CI: 1.7-6.7), H2 blockers (OR: 2.3; 95% CI: 1.2-4.2), number of surgeries ≥ 2 (OR: 3; 95% CI: 1.1-7.9) and mechanical ventilation > 7 days (OR: 2.1; 95% CI: 1.1-4.2).* **Conclusions:** *Some risk factors associated to nosocomial infections in this study are similar to those found previously, with the exception of the number of surgeries that was not reported in previous studies.* (Gac Med Mex. 2015;151:660-8)

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Background

Nosocomial infection (NI) is that systemic or localized condition observed during hospitalization, resulting from an adverse reaction to an infectious agent or its toxins, with no evidence that the infection was present or at incubation period at the moment of admission. The time period between admission and infection onset is from 48 to 72 h in most cases and up to 5 days of stay in fungal infections, according to the invasive procedures or intravascular therapy undergone by the patients. On the other hand, surgical infections can appear 30 days after discharge or even one year later in the case of implantations[1-4].

NIs are serious and common complications in neonatal intensive care units (NICUs), which look after seriously ill patients, with long hospital stays and that frequently undergo invasive procedures. NIs are associated with increased morbidity and mortality, material and human costs and hospital length of stay.

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NI incidence reported in the literature ranges from 6.2 to 33%, and incidence density from 4.8 to 22 cases for each 1,000 hospitalization days[1-5]. In Mexico, an incidence ranging from 4 to 15.4 per 1,000 live births and from 8.8 to 41.1 for each 100 discharges has been reported[6-8]. In the NICU of a Social Security hospital in Mexico City, an incidence rate of NI of 25.6 cases is reported per 1,000 patient-days[9].

The most common neonatal NIs are central venous catheter (CVC)-associated sepsis and bacteremia, followed by pneumonia[2-4,8-13]. Neonatal infection bacterial etiology changes at different units and different moments. Currently, most frequently reported neonatal NI-causative microorganisms are gram-positive, with coagulase-negative *Staphylococcus* and *Staphylococcus aureus* standing out, followed by gram-negative microorganisms, such as *Klebsiella pneumoniae* and *Escherichia coli.* Fungal etiology is less common[1,3,8,11-16].

Neonates are particularly susceptible to become infected as a result of interaction of several risk factors. A range of NI-associated risk factors in NICUs has been described in the literature, such as the use of CVC[6,10,17-20], prolonged time of CVC permanence[21-24], birth weight[15,19,22,23,25], mechanical ventilation (MV)[6,17,23,25-27], parenteral nutrition[15,17,18,22,25,26], gestational age, use of antibiotics and congenital malformations[17], exposure to postnatal corticosteroids[28], congenital heart disease[18], chest tubes[18,20], respiratory distress syndrome[23], patent ductus arteriosus[23], intraventricular hemorrhage[23], metabolic acidosis[23], necrotizing enterocolitis[24], vesical catheter[20], male gender[19], postnatal exposure to the combination of steroids and H_2 blockers[29], use of orogastric feeding tube[29], general and highly complex surgery[29], and prolonged hospital stay[20].

NI-associated risk factors in the NICU change in time and place and for this reason it is important to assess each unit where newborns (NB) are cared for; therefore, the purpose of this study was to identify NI-associated risk factors in NB admitted in a tertiary level Intensive Care Unit where patients with both medical and medical-surgical resolution conditions are treated.

Material and methods

The study was conducted at the NICU of the Pediatrics Hospital of the Centro Médico Nacional Siglo XXI of the Instituto Mexicano del Seguro Social in Mexico City, which is a tertiary care reference hospital where patients with conditions requiring medical or medical-surgical treatment are received.

Design

Nested case control study.

Study groups

Patients who developed some type of NI during their stay in the NICU were considered as cases. The controls were those patients who were admitted at the NICU during the same period as the cases and did not develop NIs during their hospitalization in the NICU. Patients who at admission had any infection, confirmed or suspected, acquired in the referring hospital, were excluded. Subjects without the complete data required by the study were censored.

The criteria of the Centers for Disease Control (CDC)[30] and the international pediatric sepsis consensus[31] were used to diagnose each NI.

Methodology

For identification of patients who entered in the study, two of the investigators made daily follow-up of the patients who were admitted in the NICU until their discharge due to improvement, transfer to another hospital or death. The investigators examined the patient and the laboratory and/or imaging tests to corroborate if the criteria for the diagnosis of NI were met. Additional data were retrieved from the clinical record.

Once the complete data were obtained, they were entered in an electronic database for analysis. The statistical program SPSS, version 17 (Chicago IL, USA), was used to create the database and for statistical analysis.

Variables

Dependent variable: NI. Independent variables: CVC, CVC duration, fasting, parenteral nutrition, parenteral nutrition duration, postnatal steroid (intravenous dexamethasone), gastric acid inhibitors (ranitidine and omeprazole), nasogastric feeding tube, vesical catheter, chest tube, MV, MV duration, patent ductus arteriosus, congenital malformations, intraventricular hemorrhage, surgery, type of surgery, number of surgeries, NICU stay and use of antibiotics prior to admission, in addition to demographic variables such as gestational age, birth weight, sex and age at NICU admission.

Sample size

For the sample size calculation, a formula for the design of case-control studies was used, with the following

Table 1. Demographic characteristics of the 380 NBs

	Cases (n = 188)		Controls (n = 192)		Sig.
	Median	Interval	Median	Interval	p
Gestational age (weeks)	35	25-42	34	26-41	0.66
Birth weight (g)	2,007	540-4,650	1,725	425-5,000	0.42
1-minute Apgar	7	2-9	7	1-9	0.16
5-minute Apgar	8	3-10	8	4-9	0.13
Sex					0.48
Male	100*	53.2%	109*	56.8%	
Female	88*	46.8%	83*	43.2%	
Age at admission (days)	9	1-122	12	1-169	0.005
Hospital stay (days)	27	2-117	7	1-47	0.0001
CVC	184*	97.9%	126*	65.6%	0.0001
CVC duration (days)	10	1-49	7	1-13	0.0001
Fasting	182*	96.8%	155	80.7%	0.0001

*Frequency
p: Mann-Whitney U-test or Mantel-Haenszel chi-square test.

parameters: 95% confidence interval; 80% power; patient exposition of 33.3%; odds ratio (OR): 2; case-control 1:1 ratio; and a minimum sample size of 372 (186 cases and 186 controls) was obtained.

Statistical analysis

Descriptive statistics with frequencies and percentages calculation was used for qualitative variables, and for quantitative variables, the mean and the interval were calculated as central tendency measures because the population distribution did not appear to be normal. For group comparison, the Mann-Whitney U-test was used for quantitative variables and Mantel-Hanzel chi-square test was used for qualitative variables.

The OR and its 95% confidence interval (CI) were calculated as an association measure. Variables with a p-value ≤ 0.05 underwent a non-conditioned logistic regression analysis for independent risk factors identification.

Ethical aspects

The protocol was approved by the Local Committee on Research and Ethics of the Pediatrics Hospital with the registry number R-2010-3603-44.

Results

A total of 380 NBs were included, out of which 188 formed the group of cases (with NI) and 192 the control group (without NI).

Table 1 shows the patient demographics: the male gender is observed to predominate in both groups; median birth weight in the cases was 2,007 g, whereas in controls it was 1,725 g; and median gestational age for the cases was 25 weeks, while in the controls it was 34 weeks.

With regard to admission diagnoses, the most common were congenital heart diseases, followed by gastrointestinal tract malformations (Table 2).

In the referring hospital, 55.3% of the patients had received one or more antibiotics; the most widely used were aminoglycosides and beta-lactams.

In 81.3% of all patients there was at least one catheter placed. In 43.2% it was by venodissection, in 17.6% percutaneous on the limbs, in 13.4% by subclavian puncture and in 7.4% it was umbilical. Median duration of CVC in NBs of the cases group was 10 days, and in the controls, 7 days.

60.6% of NBs in the group of cases and 39.4% of those in the control group underwent at least one surgical intervention. The most common were: ductus arteriosus ligation, cardiac surgery and abdominal surgery (Table 3).

Table 2. Main NICU-admission diagnoses

	Cases (n = 188)		Controls (n = 192)		
	n	%	n	%	
Congenital heart disease	39	20.7	35	18.2	0.53
Patent ductus arteriosus	19	10.1	43	22.4	0.001
Gastrointestinal tract malformation*	37	19.7	15	7.8	0.0007
Necrotizing enterocolitis	17	9	9	4.7	0.66
Airway lesion	11	5.9	15	7.8	0.44
Other gastrointestinal tract alterations†	11	5.9	10	5.2	0.78
Other malformations‡	7	3.7	8	4.2	0.82
Respiratory distress syndrome	9	4.8	7	3.6	0.58
Perinatal asphyxia	9	4.8	3	1.6	0.07
Central nervous system alterations§	6	3.2	4	2.1	0.5
Retinopathy of prematurity	–	–	12	6.2	0.0006
Congenital diaphragmatic hernia	5	2.7	3	1.6	0.45
Renal and urinary tract malformation	4	2.1	4	2.1	0.97
Others	14	7.4	24	12.5	0.1

*Esophageal atresia, intestinal atresia, anorectal malformation, bile duct atresia, omphalocele, gastroschisis.
†Gastroesophageal reflux, short bowel syndrome, meconium ileus, meconium plug, Hirschsprung disease, cholestatic syndrome.
‡Pulmonary agenesis, VACTER association, laryngomalacia, ectopia cordis, cystic adenomatoid disease, laryngeal cleft.
§Hydrocephalus, seizures, intraventricular hemorrhage, neural tube defects.

There were 247 NI events. In 73.9% of the patients there was one infection; 21.2% had 2 infections and 4.8% had 3 infections. The frequency and type of NI are shown in table 4, where sepsis is observed to be the most common, followed by venous catheter colonization-associated bacteremia and ventilator-associated pneumonia. NI incidence density was 31.1/1,000 patient-days; CVC colonization-associated bacteremia incidence density was 11.5/1,000 catheter-days and that of ventilator-associated pneumonia was 4.85/1,000 ventilation days.

One-hundred and forty microorganisms were identified in blood cultures; main isolates included coagulase-negative *Staphylococcus* (37.2%), *K. pneumoniae* (17.9%), and *E. coli* (13.5%) (Table 5). Microorganisms isolated in different cultures are shown in table 6.Overall mortality was 23.9% (n = 91/380). In children who developed NI, mortality was 35.1% (n = 66/188); infection-related death was 54.9% (n = 50/91).

The results of the univariate analysis for NI-associated risk factors identification are shown in table 7. Five independent risk factors associated with the development of NI were identified in the logistic regression multivariate analysis (Table 8).

Discussion

NICU-hospitalized NBs have considerable risk for acquiring a NI; they are particularly susceptible due to immaturity of their immune system and to exposure to therapeutic interventions that are associated with infectious complications[4,18,32].

NI incidence density was 31.1/1,000 patient-days, which is within ranges reported in other studies, especially in developing countries, where the highest hospital-acquired infection rates are reported[1,2,5-8,33].

Different international studies have been conducted to determine NI-associated risk factors; however, these

Table 3. Surgical procedures performed in 226 NBs

Type of surgery	Cases (n = 137)		Controls (n = 89)		Sig.
	n	%	n	%	p
Ductus arteriosus ligation	19	13.9	34	38.3	0.0001
Cardiac surgery*	33	24.1	15	16.9	0.19
Abdominal surgery†	53	38.7	16	17.9	0.0009
Esophageal plasty	8	5.8	4	4.5	0.66
Neurosurgery‡	6	4.3	4	4.5	0.96
Diaphragmatic plasty	5	3.7	3	4.5	0.91
Ophthalmologic surgery§	–	–	6	6.7	0.002
Peritoneal dialysis catheter	5	3.6	–	–	0.06
Urologic surgery¶	3	2.2	1	1.1	0.55
Tracheostomy	2	1.5	1	1.1	0.92
Others**	3	2.2	4	4.5	0.32

*Systemic-to-pulmonary fistula, aortic plasty, pulmonary artery cerclage, total anomalous pulmonary venous connection repair, Jatene procedure, atrioseptostomy.
†Ileostomy, intestinal anastomosis, colostomy, intestinal biopsy, gastrostomy, pancreatectomy, bile duct exploration, hepatectomy, abdominal wall plasty, fundoplication, peritoneal drainage, duodenoplasty.
‡Myelomeningocele repair, ventriculostomy, ventriculoperitoneal shunt.
§Cryotherapy, laser application.
¶Nephrectomy, ureteropyeloplasty with double-J catheter placement.
**Hemolymphangioma resection, arthrotomy with drainage, pulmonary wedge resection, lobectomy, sacrococcygeal teratoma resection, pelvic limb amputation.

Table 4. Type of NI in 188 NICU-admitted NBs

Type of infection	Frequency	%
Sepsis	86	34.8
Venous catheter-associated bacteremia	69	28.0
Ventilator-associated pneumonia	25	10.2
Pneumonia	17	6.9
Surgical site infection	16	6.5
Ependymitis	6	2.4
Tracheitis	6	2.4
Endocarditis	5	2.0
Candidemia	4	1.6
Urinary tract infection	4	1.6
Empyema	3	1.2
Peritonitis	3	1.2
Meningitis	2	0.8
Omphalitis	1	0.4
Total	247	100

Table 5. Microorganisms isolated in blood cultures from 188 NBs with NI

	Frequency	%
Gram-positive	71	50.8
Coagulase-negative *Staphylococcus*	52	37.2
Staphylococcus aureus	18	12.9
Enterococcus faecalis	1	0.7
Gram-negative	67	46.4
Klebsiella pneumoniae	25	17.9
Escherichia coli	19	13.5
Enterobacter	8	5.7
Pseudomonas aeruginosa	4	2.9
Burkholderia cepacia	3	2.2
Klebsiella oxytoca	2	1.4
Acinetobacter baumanii	1	0.7
Serratia liquefaciens	1	0.7
Sphingomonas paucimobilis	1	0.7
Stenotrophomonas maltophilia	1	0.7
Fungi	4	2.8
Candida albicans	2	1.4
Non-albicans candida	2	1.4
Total	140	100

Table 6. Microorganisms isolated in different cultures from NBs with NI

	CVC tip	Bronchial secretion	CSF	Puncture aspiration	PF	Urine	Pleural fluid
Gram-positive	22	5	6	6	0	0	3
Coagulase-negative *Staphylococcus*	16 (44.5)*	4 (14.3)	3 (37.5)				2 (66.6)
Staphylococcus aureus	6 (16.5)	1 (3.6)	3 (37.5)	4 (57.1)			1 (33.3)
Bacillus sp.	–			1 (14.3)			
Enterococcus faecalis	–			1 (14.3)			
Gram-negative	13	25	2	1	4	2	0
Klebsiella pneumoniae	4 (11.1)	8 (28.6)				1 (25)	
Enterobacter	3 (8.3)	2 (7.1)	1 (12.5)	1 (14.3)	2 (33.3)		
Escherichia coli	2 (5.6)	8 (17.8)	1 (12.5)			2 (50)	
Burkholderia cepacia	2 (5.6)						
Acinetobacter baumanii	1 (28						
Pseudomonas aeruginosa	1 (2.8)	6 (21.4)			2 (33.3)		
Serratia marcescens		1 (3.6)					
Fungi	1	1	0	0	2	1	0
Candida albicans	1 (2.8)	1 (3.6)			2 (33.3)	1 (25)	
Total	36 (100)	28 (100)	8 (100)	7 (100)	6 (100)	4 (100)	3 (100)

*Frequency (percentage).
CSF: cerebrospinal fluid; PF: peritoneal fluid.

factors change according to the type of patients cared for in each unit and to the sociodemographic characteristics of each country, and even each region, and that is why it is important to have local studies establishing which factors are associated with the development of infectious complications in NICU-admitted neonates.

In the analyzed patients, five independent risk factors were found to be associated with the development of NI. Similar to reports by other authors[17,23-26,31], CVC was one of the main risk factors. Catheter colonization can occur at the moment of insertion owing to inadequate disinfection of the skin, to manipulation and/or contamination of the insertion site, or to insufficient care once the catheter is inserted, and thus it can the way for bacteria growing in the skin of the patient to enter along the catheter or at the insertion site[18].

Another NI-independently associated factor was the administration H_2 blockers. The use of H_2 blockers and proton pump inhibitors has significantly increased in NICUs; they are used for empirical management of gastroesophageal reflux and stress ulcer prophylaxis and treatment in operated patients and in those seriously ill and for the management of feeding intolerance in very low weight NBs[34]. Gastric fluid proteolytic activity significantly decreases with increasing pH (≥ 4), with subsequent stomach colonization by gram-negative bacilli, which may contribute to the development of pneumonia (by gastric content aspiration) and sepsis by gram-negative bacteria[29]. Dinsmore et al.[35] demonstrated a higher incidence of bacteria translocation to mesenteric lymph nodes, spleen and liver after gastric pH increase with a H_2 blocker in a NB rabbit model. Bianconi et al.[36] reported that the use of ranitidine in NICU-hospitalized NBs increased nearly 7-fold the risk for the development of late sepsis (OR: 6.99; 95% CI: 3.78-12.94; $p < 0.0001$). In more recent studies, the use of ranitidine in premature NBs has been found to be associated with necrotizing enterocolitis, infections and death[37,38].

In most patients of the present study, the employed antacid was ranitidine, although some subjects received omeprazole. Although the literature mentions that ranitidine is associated with infection and other

Table 7. Risk factors associated with NI in the univariate analysis

	Cases (n = 188)	Controls (n = 192)	OR	95% CI	p*
CVC	184	126	24.1	8.5-68.0	< 0.001
MV	184	152	16.2	4.9-53.5	< 0.0001
MV duration (days)	157	96	5.0	3.1-8.1	< 0.0001
Days of stay (> 14 days)	143	40	12.1	7.4-19.5	< 0.001
Parenteral nutrition	169	85	11.2	6.4-19.5	< 0.001
Antacids	136	48	7.8	5.0-12.3	< 0.0001
Fasting	182	155	7.2	3.0-17.6	< 0.001
Vesical catheter	128	60	4.7	3.0-7.2	< 0.001
Postnatal steroid	104	44	4.1	2.7-6.5	< 0.0001
Chest tube	49	19	3.2	1.8-5.7	< 0.0001
Surgery	137	89	3.1	2.0-4.8	< 0.0001
Number of surgeries (≥ 2)	56	6	13.1	5.5-31.4	< 0.0001
Intraventricular hemorrhage	47	27	2.0	1.2-3.4	0.005
Congenital malformation	61	39	1.8	1.2-2.9	0.008
Orogastric tube	176	168	2	1.0-4.3	0.03
Heart disease	51	39	1.4	0.9-2.3	0.07
Gestational age (< 37 weeks)	134	136	1.0	0.6-1.6	0.5
Birth weight (< 1,500 g)	72	87	0.7	0.5-1.1	0.1
Sex (male)	100	109	0.8	0.5-1.3	0.2
Previous antibiotics	106	103	1.1	0.7-1.1	0.3

*Mantel-Haenszel chi-square test.

adverse events, omeprazole, through a different mechanism, increases gastric pH as well and may cause an intestinal flora alteration that can result in sepsis. This is why ranitidine avoidance and careful omeprazole use in NICU-admitted NBs is recommended.

Rojas et al.[29] reported on the postnatal steroid and H_2 blockers combination as being a NI-associated factor. In the present study, only the use of H_2 blockers was associated with NI.

One of the characteristics of the NICU where the study was conducted is that nearly 60% of admitted patients required surgical treatment, especially due to heart and gastrointestinal tract malformations. This explains why NBs who required 2 or more surgeries had 3-fold higher risk for acquiring some NI. It is expected for a patient undergoing surgery for a second occasion, especially major surgery such as heart or abdominal surgery, to have an increased risk for infectious complications, since this implies more exposure of tissue and large surgical wounds that are manipulated again. Carrier et al.[23] have reported that neonates

Table 8. Independent risk factors associated with NI in the NICU by means of logistic regression multivariate analysis

Variable	OR	95% CI	p*
CVC	7.3	2.3-22.8	0.001
Hospital stay (> 14 days)	3.4	1.7-6.7	< 0.0001
Surgeries (≥ 2)	3.0	1.1-7.9	0.02
Gastric acid inhibitors†	2.3	1.2-4.2	0.008
MV (> 7 days)	2.1	1.1-4.2	0.03

*Mantel-Haenszel chi-square test.
†Ranitidine and omeprazole.

undergoing any surgical intervention have twice the risk for developing late sepsis than those who have not undergone surgery, but the number of surgeries is not mentioned.

Some devices, such as MV, are part of the technological advances for the treatment of NBs in the NICU, which has brought as a result a survival increase for these patients, especially for premature NBs. However, it is well known that these tools, which can be beneficial, may cause infectious complications as well, such as ventilator-associated pneumonia. In this report, the fact of having received MV for a prolonged period (> 7 days) was independently associated with NI. Carrieri et al.[23] reported MV duration longer than a week as an independent risk factor for late and very late sepsis (relative risk [RR]: 4.0; 95% CI: 2.6-6.0). Couto et al.[13] also reported that MV prolonged duration was associated with NI.

As previously reported by Shankar et al.[39], in patients analyzed in this study, prolonged hospital stay (> 14 days) was an independent risk factor for the development of NI. This can be explained by the type of patients that are cared for in the NICU: most are patients with congenital malformations warranting surgery, MV, long fasting periods, etc., i.e., patients with several comorbidities that require longer hospitalization and, the longer the hospital length of stay, the higher the risk of infection. The characteristics of the patients included in the study by Shankar et al. were similar to those of the subjects in this report; the diagnoses were mainly congenital malformations and most (93%) required at least one surgical procedure. Maraga et al.[40] reported that for each 10 days of NICU stay, the risk of methicillin-resistant *S. aureus* infection increased by 1.32-fold. Carrieri et al.[23] and Couto et al.[13] also reported that the longer the hospital stay, the higher the probability of sepsis.

In this study, some NI-associated risk factors were found, some already reported in previous studies and others not, such as the number of surgeries, but there are many other factors that also play an important role in the development of NI and that may not have been identified. Some can be modified, such as the use of antacids and MV time, but others not so much, such as the number of surgeries, and for this reason we consider relevant recommending for hygiene measures not to be overlooked, including hand washing, skin antisepsis during intravascular catheter insertion and care of the device according to the catheter management guidelines, in addition to rational use of drugs such as antacids and trying to reduce the length of MV use and NICU stay as much as possible in order to reduce NIs in NICU-admitted neonates.

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