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Healthcare associated infections caused by coagulase-negative *Staphylococci* in a neonatal intensive care unit

Infecções relacionadas à assistência à saúde por Staphylococcus coagulase negativa em unidade de terapia intensiva neonatal

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This study was conducted at the neonatal intensive care unit of Prontobaby-Hospital da Criança - Rio de Janeiro (RJ), Brazil.

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ABSTRACT

Objective: This study sought to evaluate infections related to health care caused by coagulase-negative *Staphylococci* in a neonatal intensive care unit by assessing antimicrobial susceptibility profiles and potentially effective antibiotic regimens.

Methods: This was a retrospective descriptive study performed on a case series of healthcare-associated infections, and the antimicrobial susceptibility profiles were evaluated. Newborns from other hospitals who were admitted to a neonatal intensive care unit in *Rio de Janeiro* between January 1, 2010, and June 30, 2012, were studied.

Results: In total, 765 patients were admitted, totaling 3,051 patient-days, and the incidence density of general infection was 18.9 per 1,000 patient-days. The rate of central venous catheter use was 71.6%, and the positive culture rate for all sites and all infections related to health care were 68.4%. Coagulase-negative *Staphylococci* were identified in 11 (19.2%) of 57 health

care-related infections, and infections with extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* and *Candida* sp. constituted 5 cases each. Of the 11 cases of coagulase-negative *Staphylococci*, 10 (90.9%) were primary bloodstream infections. The sensitivity of the coagulase-negative *Staphylococci* isolates to vancomycin, clindamycin, ciprofloxacin, oxacillin and gentamycin was 100%, 81.8%, 72.7%, 27.2% and 22.2%, respectively. There were no deaths directly attributed to coagulase-negative *Staphylococci* infection.

Conclusion: Coagulase-negative *Staphylococci* was the main agent identified in healthcare-associated infections, with low rates of infections related to central venous catheter. In hospitals with a high oxacillin resistance profile, similar to those included in this study, vancomycin may be used as an initial therapy, although clindamycin represents a viable alternative.

Keywords: Cross-infection; Intensive care, neonatal; *Staphylococcus*

INTRODUCTION

In Brazil, it is estimated that approximately 60% of child mortality occurs during the neonatal period, and most of these deaths are caused by healthcare associated infections (HAI) affect more than 30% of newborns.^(1,2) The term “healthcare-associated infections” is gradually replacing the term “hospital infection” because it includes both care-associated infections and those related to failure in care, prevention, diagnosis and treatment.⁽²⁾

In this context, the group of coagulase-negative *Staphylococci* (CoNS) is of fundamental importance because they are believed to be the main agents of

HAI in neonatology.⁽³⁻⁷⁾ However, the identification of these agents in cultures from patients can be difficult due to the distinction between colonization and infection, as CoNS are typically found on the skin of newborns. Additionally, it can be difficult to determine the best antibiotic regimen for treatment based on the antimicrobial susceptibility profile, and there is the potential for inducing resistance in the treatment unit.^(1,8,9)

Regarding the treatment of infections caused by CoNS, the greatest difficulty in intensive care units is determining whether it is possible to use less potent regimens that spare vancomycin, which is typically the first-choice drug in many units due to the high resistance to oxacillin and aminoglycosides.⁽¹⁰⁻¹²⁾ Recently, the possibility of treatment with other less potent antimicrobial regimens, such as cefazolin, was demonstrated.⁽³⁾

Considering the importance of the agent and the heterogeneous reality of national neonatology services, many of which admit newborns from several maternity wards, it is essential to establish the magnitude of CoNS infections and create a profile for potential antimicrobial regimens to be used when these agents are suspected or isolated in cases of HAI.

Thus, the present study sought to evaluate the importance of CoNS as causative agents for HAI in a neonatal intensive care unit (NICU) in *Rio de Janeiro* as well as to determine the susceptibility of these agents to establish the best treatment possible in this scenario.

METHODS

A retrospective, descriptive study of a case series of HAI attributed to CoNS in a NICU in the city of *Rio de Janeiro* (RJ), Brazil was performed, and the antimicrobial susceptibility profiles were evaluated.

The NICU evaluated in this study contains 11 beds and is part of 1 of the 4 ICUs associated with *Prontobaby-Hospital da Criança*, a private hospital located in the northern part of the municipality of *Rio de Janeiro*. This hospital does not have its own maternity unit, and all hospitalized patients are referred from the emergency department or from other hospitals (public and/or private).

Surveillance of HAI was performed daily by an infectious disease physician or nurse, both of whom were specialists in hospital infection control. The diagnostic criteria adopted for HAI in neonatology were those

recommended by the National Agency for Sanitary Surveillance (*Agência Nacional de Vigilância Sanitária - ANVISA*) published in 2010.⁽²⁾ Briefly, infections were classified according to the presence or absence of invasive devices and the specific topographical involvement.

Regarding laboratory confirmed bloodstream infection (LCBI), CoNS were considered the causative agent when grown in at least 2 blood cultures collected at 2 different locations (with a maximum interval of 48 hours between collections) or when isolated from a peripheral blood culture of patients with central venous catheters (CVCs). Additionally, the presence of at least 1 of the signs and symptoms for the diagnosis of infection was necessary, including thermal or hemodynamic instability, apnea, food or glucose intolerance, respiratory distress, hemodynamic instability or underactivity/lethargy. The growth of the infectious agent within 48 hours after collection was considered clinically significant. If the culture of the tip of the catheter detected a growth >15 CFU/mL (in a semiquantitative technique) or if there was pus at the site of catheter insertion, the infection was associated with a CVC.

The tabulation of infection rates also followed the criteria established by ANVISA. The incidence density measure was used for both infections detected by weight range and for invasive devices. A minimum of 50 patient-days or device-days was required to calculate the rates. When this value was not reached during the year, a grouping was made to reach this value.

Newborns that were admitted between January 1, 2010, and June 30, 2012, and spent more than 24 hours in the NICU were included in the study. Children who remained less than 24 hours in the unit were excluded.

The identification of CoNS in clinical specimens was performed at the microbiology laboratory of the hospital, as requested by the assistant doctors. Sample analysis was performed using the MicroScan autoScan-4 Siemens® device for identification and determination of the minimum inhibitory concentration (MIC), according to a semi-automated method. In some situations, the manual processing of cultures and analysis of the antimicrobial susceptibility profile through the disk-diffusion testing method, according to the standards outlined by the Clinical and Laboratory Standard Institute (CLSI), were performed.⁽¹³⁾

Clinical variables such as gender, age at infection, birth weight, antimicrobial regimen used, length of hospital stay, type of invasive device used and clinical outcome were analyzed. Mortality that occurred within 14 days after the positive culture was attributed to infection, whereas deaths that occurred after 30 days of infection were considered general mortality.

This study was approved by the Ethics Committee of the *Hospital Universitário Clementino Fraga Filho* on July 19, 2012, under number 58,636. The term of consent was considered unnecessary given the observational nature of the study. The study was registered in a research Brazil National Platform under the number 00678912.0.0000.5257.

RESULTS

During the study period, 765 patients were admitted, totaling 3,051 patient-days. All patients were referred from other units or from the *Prontobaby* emergency unit. Table 1 shows the number of patient-days, according to the time period and the weight range.

Table 1 - Patient-days admitted to the neonatal intensive care unit according to the time period and weight range

Weight (g)/Year	2010	2011	2012	Total
<1,500	102	55	19	176
1,501-2,500	423	174	316	913
>2,500	478	605	879	1,962
Total	1,003	834	1,214	3,051

Regarding invasive devices, there was an overall utilization rate of 71.6% for CVCs and 38.8% for mechanical ventilators. In total, 57 HAI were recorded, totaling an overall incidence density of 18.9 per 1,000 patient-days and an incidence of 7.5%. Figure 1 shows the incidence density of HAI according to the year and weight range.

The culture positivity for all sites for all HAI was 68.4% (39 isolated bacteria). Regarding etiological agents, CoNS were implicated in 11 (19.2%) of the 57 HAI; infections with extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Candida* sp. were detected in 5 cases each. Other bacteria were isolated in 18 episodes, and the causative agent was not identified in 18 cases.

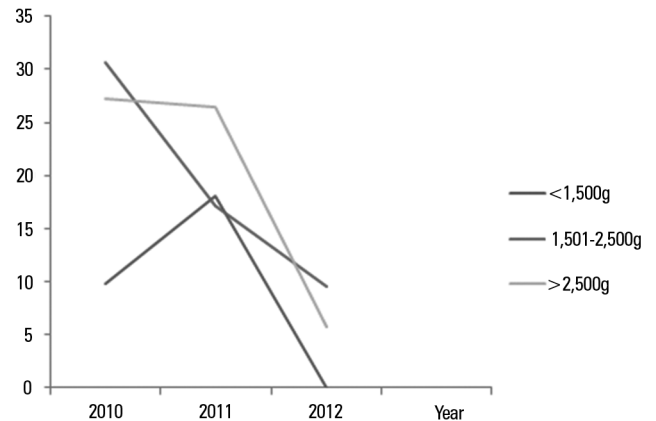


Figure 1 - Incidence density of infections related to nosocomial late healthcare, according to weight range. Incidence density of infection (per 1,000 patient-days).

Of the 11 CoNS infections, 6 (54.5%) occurred in male newborns, 1 occurred in a newborn with a birth weight <1,500g, 5 occurred in newborns weighing between 1,500 and 2,500g, and 5 occurred in newborns with a birth weight >2,500g. The age of the infants at the time of diagnosis of infection varied between 7 and 103 days (mean of 39 days). The mean time to diagnosis of HAI by CoNS after hospitalization was 15 days (range from 1 to 50 days), and the mean hospital stay was 33 days (range from 11 to 133 days). Additionally, 63.6% of the cases were submitted to antimicrobial regimens before the diagnosis of infection, and ampicillin and gentamycin were the most frequently administered antimicrobials in 4 cases (36.3%). The other antibiotics used included cefazolin, amikacin, oxacillin, vancomycin and cefepime.

Regarding the type of intravenous catheter used for newborns before or during infection, 5 were deep venous punctures, 3 were umbilical venous catheters, 1 utilized venous dissection and 1 utilized peripheral access. Only 1 newborn had no catheter access before or at the time of infection.

The overall mortality rate was of 45.4% (5 deaths), although none were directly attributed to infection with CoNS. In 8 (72.7%) cases, there was a preexisting primary disease, and congenital heart defects were present in 6 (54.5%) patients.

Table 2 shows the HAI attributed to CoNS according to the month and year of occurrence, site and typing of the species. Table 3 shows the antimicrobial susceptibility profile of the CoNS isolates, for which it was possible to test at least 70% of the samples for each antibiotic.

Table 2 - Infections related to nosocomial late health care attributed to coagulase-negative *Staphylococci*, according to the month and year of detection, site of infection and species typing

Month/year of infection	Site of infection	Identification of coagulase-negative <i>Staphylococci</i> isolated
January/2010	BI CVC-associated	<i>S. epidermidis</i>
March/2010	LCBI	<i>S. hominis</i>
September/2010	LCBI	<i>S. epidermidis</i>
December/2010	LCBI	<i>S. hominis</i>
December/2010	LCBI	<i>S. epidermidis</i>
April/2011	LCBI	coagulase-negative <i>Staphylococci</i>
May/2011	LCBI	coagulase-negative <i>Staphylococci</i>
September/2011	LCBI	coagulase-negative <i>Staphylococci</i>
October/2011	LCBI	coagulase-negative <i>Staphylococci</i>
January/2012	LCBI	<i>S. hominis</i>
January/2012	LCBI	coagulase-negative <i>Staphylococci</i>

BI - bloodstream infection; LCBI - laboratory confirmed bloodstream infection; CVC - central vascular catheter.

Table 3 - Susceptibility profile of coagulase-negative *Staphylococci* agents that cause nosocomial late infections related to health care

Antibiotics	Number of susceptible/ tested samples	Susceptibility (%)
Clavulin	2/9	22
Ciprofloxacin	8/11	72.7
Clindamycin	9/11	81.8
Erythromycin	1/8	12.5
Gentamycin	2/9	22.2
Oxacillin	3/11	27.2
Vancomycin	10/10	100

DISCUSSION

HAI represent an important cause of morbidity and mortality in newborns admitted to NICUs, with the rates reported in the national literature varying from 18.9 to 57.7%, depending on the unit studied.⁽¹⁴⁻¹⁷⁾ In most studies, both national and foreign, CoNS are reported as the main type of bacterial agent involved in HAI, as these bacteria are identified in 33.3 to 60% of culture isolates.^(7,8,10,18-21) Mortality caused by this type of infection can reach 16%, mainly in preterm infants and those with a very low birth weight.^(20,21) However, no deaths were related to infections with CoNS in the current study, although the majority of included cases had other comorbidities, mainly congenital heart diseases.

The overall incidence density of infection was found to be lower in the current study than that reported in the literature,⁽²²⁻²⁵⁾ most likely because all children were referred from other units and most newborns weighed >1,500g, which implies a lower probability of the acquisition of infection when compared to low-weight neonates.⁽²⁶⁾ Despite the high rate of CVC use, which was greater than that reported by the American surveillance system (National Healthcare System Network - NHSN) in 2010 as well as that reported by the surveillance system of nosocomial infections of the State of *São Paulo* in 2011 for NICUs,^(25,27) only 1 episode of infection associated with CVCs was recorded. This low number of infections associated with CVCs may be explained by the Infection Control Committee (ICC) as this institution works in this sector to observe and correct potential inadequacies related to the use of invasive devices. Other measures employed by the ICC that may have contributed to these rates include the checklist of medical and nursing procedures during insertion; the maintenance and removal of CVCs in neonates; the direct discussion of the need for exchange of antimicrobials with the medical staff; the measurement of the change of antibiotics adequacy index in the institution (ideally close to 100%); the training of all professionals working in the sector after admission to the institution regarding the prevention and control of infections; and the on-line identification (intranet) of all patients with multidrug-resistant infections.

The positive culture rate for microbial agents causing HAI varies between hospital services, and our study found an overall positivity rate higher than that previously reported by Freitas et al.⁽²⁸⁾ (17.1%) and Dal-Bó et al.⁽⁷⁾ (27.1%).

In this study, CoNS were most commonly implicated as the agent of HAI, which is consistent with the results of hospital services that possess a maternity unit⁽²⁹⁾ and demonstrates the importance of these agents in services that only receive outpatients.

One limitation of this study was that CoNS typing was only performed in 6 (54.5%) of the 11 isolates, with results demonstrating a prevalence of *Staphylococcus hominis* and *S. epidermidis*. HAI due to *S. epidermidis* are generally caused by strains that exhibit high resistance to oxacillin, as demonstrated in a study conducted in the ICU of the *Hospital Universitário de*

Uberlândia, which reported a rate of oxacillin resistance of 81.8%.⁽⁸⁾ The study by Qu et al. analyzed CoNS isolates in neonates with a very low birth weight and identified oxacillin resistance rates of 91.7%.⁽³⁰⁾ In addition, Loureiro et al. studied the susceptibility of 255 positive-culture cases of neonatal sepsis in *Rio de Janeiro* and detected CoNS in 17.3% of cases and rates of oxacillin and cephalothin resistance of 58.8% and 13%, respectively.⁽¹⁸⁾ Furthermore, the study by Cunha and Lopes analyzed the susceptibility of CoNS infections in newborns in the NICU of the *Hospital de Clínicas de Botucatu* (SP) and found an overall resistance rate of 50.4%.⁽¹⁰⁾

Another problem associated with CoNS infections is the determination of antimicrobial susceptibility. This knowledge is critical to establish the best treatment possible and to avoid the indiscriminate use of broad-spectrum antibiotics. In this study, the susceptibility to antibiotics such as oxacillin, gentamycin and clavulanate was low, and vancomycin was the only drug with a susceptibility of 100%. One of the factors that may have contributed to this pattern of resistance was that in most infections with CoNS, the children had previously received antibiotics.

Regarding the CoNS neonatal infection treatment period, recent studies have demonstrated safe time periods of 3 and 5 days, as compared to the traditional regimens of 7 to 10 days.^(24,31)

CONCLUSION

In hospitals similar to the one studied here, in which the neonatal intensive care unit receives outpatients and has a high prevalence of coagulase-negative *Staphylococci* infections related to health care with a high resistance profile to oxacillin, vancomycin can be used as an initial therapy in suspected cases, although clindamycin represents a viable alternative. Further studies are needed to determine the appropriate treatment duration for each patient.

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RESUMO

Objetivo: Avaliar as infecções relacionadas à assistência à saúde, em unidade de terapia intensiva neonatal, causadas pelo *Staphylococcus* coagulase negativa, verificando o perfil de sensibilidade antimicrobiana e possíveis esquemas antibióticos eficazes.

Métodos: Estudo descritivo retrospectivo de uma série de casos de infecções relacionadas à assistência à saúde tardias de origem hospitalar atribuída ao *Staphylococcus* coagulase negativa, avaliando o perfil de sensibilidade antimicrobiana. Foram estudados os recém-nascidos internados entre 1º de janeiro de 2010 a 30 de junho de 2012 em uma unidade de terapia intensiva neonatal da cidade do Rio de Janeiro, sendo todos os pacientes oriundos de outras unidades.

Resultados: Foram admitidos 765 pacientes, totalizando 3.051 pacientes-dia e uma densidade de incidência de infecção geral de 18,9 por 1.000 pacientes-dia. A taxa de utilização de cateteres venosos centrais foi de 71,6% e a positividade das culturas de todos os sítios para todas as infecções relacionadas à assistência à saúde foi de 68,4%. O *Staphylococcus* coagulase

negativa foi implicado em 11 (19,2%) das 57 infecções relacionadas à assistência à saúde e *Klebsiella pneumoniae* produtor de *betalactamase* de espectro estendido e *Candida* sp em 5 ocasiões cada. Das 11 infecções, 10 (90,9%) foram atribuídas a infecções primárias de corrente sanguínea. A sensibilidade dos isolados de *Staphylococcus* coagulase negativa em relação à vancomicina, clindamicina, ciprofloxacina, oxacilina e gentamicina foi de 100%, 81,8%, 72,7%, 27,2%, 22,2%, respectivamente. Não houve óbito atribuído diretamente à infecção por *Staphylococcus* coagulase negativa.

Conclusão: O *Staphylococcus* coagulase negativa foi o principal agente encontrado nas infecções relacionadas à assistência à saúde tardias de origem hospitalar, sendo baixas as taxas de infecções relacionadas a cateter venoso central. Em hospitais semelhantes ao aqui estudado, com elevado perfil de resistência à oxacilina, a vancomicina pode ser utilizada como terapêutica inicial, sendo também a clindamicina uma alternativa viável.

Descritores: Infecção hospitalar; Terapia intensiva neonatal; *Staphylococcus*

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