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Assessment of coagulase-negative staphylococci isolated from blood cultures of patients with leukemia in the period 2009-2011

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ABSTRACT

Leukemic patients have high probability of developing bacteremia, especially due to the impairment of their immune system and as a consequence of chemotherapy. These infections have been growing significantly in different regions, particularly in university hospitals and are responsible for high rates of morbidity and mortality. We evaluated coagulase-negative staphylococci (CoNS) isolated from blood cultures from patients with leukemia. A retrospective study of blood cultures in the period from 2009 to 2011 was conducted at the University Hospital of Santa Maria. In the period of this study was possible to analyze 282 positive blood cultures, being 46.45% (131/282) caused by CoNS. ***Staphylococcus epidermidis*** **was the prevalent specie. Regarding the hospitalization sectors of patients, the Treatment Center for Children with Cancer showed the highest prevalence, 67.37%. The isolates were predominant in males and in the age group between 0-22 years old. In this study the CoNS represented the most isolated microorganisms. The resistance presented by these microorganisms is a concern since it limits the treatment for bloodstream infections in these patients with compromised immune system. Retrospective studies of prevalence provide us with results for the local epidemiology to be known, considered essential for the antimicrobial treatment, especially when referring to patients with a weakened immune system and admitted in university hospitals.**

Keywords: Bacteria. Blood. *Staphylococcus*. Leukemia.

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INTRODUCTION

Leukemic diseases are malignant tumors that originate in the bone marrow and affect the hematopoietic system. They result from an unregulated proliferation of a cell clone which has changes in the mechanisms of differentiation and apoptosis that ends up replacing normal blood cells by malignant (Santos *et al*., 2003; Ribas & Araújo, 2004; Attman *et al*., 2015).

Bone marrow transplantation is a therapeutic modality, which is used to treat hematologic malignancies such as leukemia and solid tumors to which the patient is exposed to contract bacterial infections (Naoum *et al*., 2002; Oliveira *et al*., 2007). The neutropenia period comprises the first thirty days of treatment and is considered the most dangerous for the patient to get some bacterial hospital infection (Naoum *et al*., 2002; Oliveira *et al*., 2007).

Patients affected by neoplastic and hematological diseases, as well as transplanted, have increased risk and susceptibility to bloodstream infections due to their immune-compromised status. These are caused by the disease itself and/or induced by chemotherapy, repeated hospitalizations and several invasive procedures, which form synergistic risk factors for the increased morbidity and mortality (Naoum *et al*., 2002; Gabe *et al*., 2009; Ahmed *et al*., 2015).

Consensus today is that the bacteremia is among hospital infections with higher morbidity and mortality, contributing to increased hospital costs and length of stay (Alves *et al*., 2012). The gold standard for the diagnosis of an infectious episode of bloodstream remains the blood culture that is significantly increasing in different regions of the world, especially in university hospitals (Dal Forno *et al*., 2005).

Gram-positive bacteria are among the main agents of septic shock in hospitalized patients, followed by Gram-negative, and for neutropenic patients there is a wide range of potential pathogens (Dellinger *et al*., 2013). Staphylococci, especially coagulase-negative Staphylococci (CoNS), which are part of normal human

skin microbiota, have emerged as prevalent pathogens in hospital infections (Mulu *et al*., 2012; Ahmed *et al*., 2015; Roopa, Biradar, 2015). Although CoNS form part of the humans' normal flora, these clinical significances have been increasingly recognized in the recent years, causing a wide variety of infections (Mulu *et al*., 2012; Sheikh & Mehdinejad, 2012).

Normally CoNS are isolated from skin and soft tissue infections, respiratory tract, and specifically in bloodstream infections (Araújo, 2012; Landrum *et al*., 2012; Ahmed *et al*., 2015). Recovery of these organisms from specimens should always be correlated with the clinical condition of the patient and with their role to cause infections. These bacteria usually infect immunocompromised patients, such as newborns and patients with leukemia or other malignant diseases (Sheikh & Mehdinejad, 2012).

Antimicrobial resistance is a serious public health problem worldwide. Pathogens resistant to antibiotics are a growing concern, and for healthcare professionals it has become a challenge, since the therapeutic options to treat some infections caused by resistant microorganisms are becoming more restricted (Paiano & Bedendo, 2009; Patel & Saiman, 2010; Roopa & Biradar, 2015). Thus, it is important to know the resistance pattern of each group of patients treated at each hospital, monitoring the evolution of bacteria resistance (Paiano & Bedendo, 2009).

Typically, CoNS infections are acquired in hospitals and have resistance to many antibiotics. The most common resistance by these microorganisms is the resistant to methicillin/oxacillin that are a serious clinical problem, since it prevents any other therapy with antibiotics from the classes of beta-lactams, leaving few alternatives for the treatment (Hussain *et al*., 2000; Ferreira *et al*., 2003; Palazzo & Darini, 2006).

Due to the significant increase of the different mechanisms of resistance, it is necessary to isolate the etiologic agents in culture to assess the sensitivity profile against the antimicrobial agents so that the effective antimicrobial therapy is instituted as soon as possible (Michelim *et al*., 2005). The knowledge of the local hospital epidemiology allows clinicians the election of the empirical antimicrobial therapy, which would be reverted in a satisfactory outcome, contributing to the control of the bacterial resistance, reversing in the reduction of hospital costs. This way this study aimed to evaluate CoNS isolated from blood cultures from patients with leukemia in the period from 2009 to 2011 admitted at University Hospital of Santa Maria.

MATERIALS AND METHODS

We conducted a retrospective study of the positive blood cultures isolated from patients with myeloid leukemia, lymphoid leukemia and from patients who had undergone bone marrow transplantation admitted at University Hospital of Santa Maria for a period of three years (2009 to 2011).

The University Hospital of Santa Maria is located in Santa Maria, Rio Grande do Sul (RS), Brazil and is a regional reference, with outpatient care and hospitalization in several specialties. This hospital is the Reference Center in compliance with Oncology. In this hospital are performed bone marrow transplants, leukemia treatment, as well as major surgery, urgency and emergency.

The hospital units, where the patients who took part of this study were hospitalized, consisted of Center for Treatment of Children with Cancer, Center for Bone Marrow Transplantation, Medical Clinic, Pediatric Intensive Care Unit, First Aid Post, Hematology and Oncology Clinic and Pediatric Emergency Care.

Samples were processed according to Standard Operating Procedure of the Clinical Laboratory of Analyses (LAC). Blood cultures were required whenever some clinical sign was present, such as increased body temperature (>38°C) or hypothermia (<36°C), leukocytosis (>10.000 leukocytes/mm3, especially with left deviation) or absolute granulocytopenia (<1000 leukocytes/mm3); two or more blood cultures were always required. All blood culture samples received from patients suspected of having blood stream infections were incubated in the automatized system BACTEC 9240® (Becton Dickson, Spark, MD) and were considered positive when both samples showed CoNS development.

Then a direct bacterioscopy of the broth culture (Gram staining method) and sowing on plates containing sheep blood agar base Mueller Hinton 90x15mm (NewProv, Paraná, BR) were performed from the bottles flagged as positive. Later, the sowed plates were incubated in a bacterial incubator at 35°C ± 2°C for 18 to 24 hours for bacteria isolation.

After that, the bacterial inoculum was prepared in sterile solution; the turbidity was adjusted to McFarland standard 0.5 and 300 µl was dropped in the panels for identification of the isolated bacteria and the sensitivity profiles against antimicrobials. These tests were performed with the automatized system MicroScan® (Siemens

Healthcare Diagnostics INC, USA) using B1017-209 Panel 156.

The sensibility profiles of all CoNS identified were analyzed following recommendations by the Clinical and Laboratory Standard Institute effective at the time of the study (CLSI, 2009, 2010, 2011).

This study was approved by the Ethics Committee at the Federal University of Santa Maria, under number 0235.0.243.000-08.

RESULTS

In the period covered by this study, there were 282 positive blood cultures. From these cultures, 64.18% (181/282) comprised Gram-positive and 35.82% (101/282) Gram-negative. The organism most predominantly isolated was CoNS (131/282 – 46.45%). Significant variation in the percentages of CoNS isolated in each year of the study was not noticed (Figure 1).

Figure 1 – Percentage of positive blood cultures for CoNS according to year of study in University Hospital of Santa Maria.

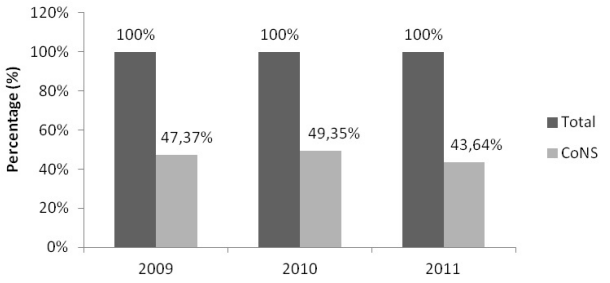
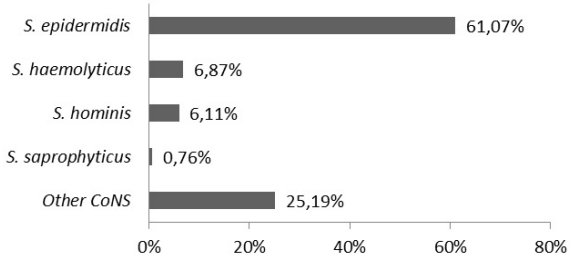


Figure 2 – Distribution of the species of CoNS isolated from the blood cultures of the hospitalized patients in the Units that serve onco-hematological patients in the period 2009-2011 at University Hospital of Santa Maria.



The prevalent microorganism was *Staphylococcus epidermidis*, with a percentage of 61.07% (80/131) (Figure 2). The Center for Treatment of Children was the hospital unit where there was the highest percentage of isolation of the CoNS (66.41%), followed by the Center for Bone Marrow Transplantation (19.08%) (Table 1).

Regarding the gender of the patients involved in this study, the male was the most affected with bloodstream infections (60.30%) and the highest positivity occurred in the age group 0-22 years old (77.10%).

Table 2 shows the sensitivity profile against the antimicrobials of 131 samples of CoNS of this study.

DISCUSSION

In this study the Gram-positive bacteria were prevalent (64.18%). Compared to the study realized by Velasco *et al*., in 2004, at the Cancer Hospital in Rio de Janeiro, Brazil, in which blood cultures were evaluated in patients with malignancies and post-transplanted of bone marrow, 56% of the bacteria isolated from the blood cultures were Gram-negative, and only 32% were represented by Gram-positive (Velasco *et al*., 2004). Two years later (2006), these researchers conducted another study in the same hospital, but analyzing positive blood cultures for results from adult patients with hemato-oncological diseases and neutropenia, finding similar results to their previous study, predominance of Gram-negative (Velasco *et al*., 2006). Oliveira *et al*., in 2007, analyzing data from blood cultures taken from patients in 13 hospitals in Brazil, who had undergone bone marrow transplantation, found similar percentages between Gram-positive (47%) and Gram-negative (37%), and 16% were polymicrobial (Gram-negative + Gram-positive) (Oliveira *et al*., 2007). In the study carried out by Ortega *et al*., in

Table 1 – Distribution of the blood cultures in which there was the isolation of CoNS and respective sectors in the period from 2009 to 2011 at University Hospital of Santa Maria.

Sector	Percentage
CTCriaC	66,41%
CTMO	19,08%
4 ° A	8,40%
UTI PED	0,76%
AMB	0,76%
OH	3,82%
PA PED	0,76%

CTCriaC = Center for Treatment of Children with Cancer; CTMO = Center for Bone Marrow Transplantation; 4o A = Medical Clinic; UTI PED = Pediatric Intensive Care Unit ; AMB = First Aid Post; OH = Hematology and Oncology Clinic; PA PED = Pediatric Emergency Care.

Table 2 – Sensitivity profile to the antimicrobials of the 131 isolates of CoNS from the positive blood cultures of the hospitalized patients in the onco-hematological units in the period from 2009 to 2011, at University Hospital of Santa Maria.

Antimicrobials tested	Number of samples tested	Sensitive	Intermediate	Resistant
Amikacin	45/131	42 (93,30%)	0	3 (6,70%)
Chloramphenicol	5/131	5 (100%)	0	0
Clindamycin	68/131	35 (51,47%)	5 (7,35%)	28 (41,18%)
Cefepime*	69/131	19 (27,54%)	0	50 (72,46%)
Daptomycin	43/131	43 (100%)	0	0
Erythromycin	70/131	25 (35,70%)	1 (7,16%)	44 (57,14%)
Ertapenem*	69/131	19 (27,54%)	0	50 (72,46%)
Gentamicin	113/131	79 (69,90%)	1 (0,90%)	33 (29,20%)
Imipenem*	69/131	19 (27,54%)	0	50 (72,46%)
Levofloxacin	104/131	74 (71,15%)	9 (8,66%)	21 (20,19%)
Linezolid	49/131	49 (100%)	0	0
Meropenem*	69/131	19 (27,54%)	0	50 (72,46%)
Oxacillin*	69/131	19 (27,54%)	0	50 (72,46%)
Penicillin	70/131	8 (11,27%)	0	64(90,22%)
Rifampicin	58/131	49 (84,88%)	0	9 (15,12)
Sulfamethoxazole / trimethoprim	108/131	46 (42,60%)	0	62 (57,40%)
Tetracycline	20/131	12 (60,00%)	1 (5,00%)	7 (35,00%)
Tobramycin	37/131	34 (91,89%)	0	3 (8,11%)
Vancomycin	64/131	64 (100%)	0	0

*Resistance to the antimicrobial oxacillin makes strains resistant to all other beta-lactam antimicrobials and also the beta-lactam with inhibitor of beta-lactamase (CLSI, 2009, 2010, 2011).

2015, at a hospital in Barcelona, Spain, evaluating blood cultures in neutropenic patients, was found the prevalence of Gram-positive, corroborating the data obtained in our study. Likewise, Piukovics *et al*. in 2015, found 67.1% of Gram-positive bacteria in blood culture (Ortega *et al*., 2015; Piukovics *et al*, 2015).

The CoNS represent the human microflora bacteria most involved in blood cultures isolates, representing potential pathogens, especially in immunocompromised patients (Michelim *et al*., 2005). In our study we found the involvement in 46.45% (131/282) of CoNS, and their relationship to invasive devices is noteworthy (Gohel *et al*., 2014).

In the research carried out by Velasco *et al*., in 2000 (Rio de Janeiro, RJ, Brazil), CoNS were the prevalent agents of bloodstream infections, and 32% of these patients had hematologic diseases and 34.7% of solid tumors (Velasco *et al*., 2000). Piukovics *et al*. found CoNS as the most frequent isolates among Gram-positive bacteria, 65% (Piukovics *et al*., 2015). Attman *et al*. in this study carried out in Tampere University Hospital, Finland, during the periods from 1999 to 2001 and from 2005 to 2010, evaluating bloodstream infections from patients with hematological malignancy found 23% of CoNS (Attman *et al*., 2015).

Among the species of CoNS, the *S. epidermidis* is the most prevalent in bacteremias, found in a range of 74 to 92% of these *Staphylococcus* spp (Hudome *et al*., 2001). In our study, *S. epidermidis* was the predominant, with 61.07% (80/131). In one of the studies previously mentioned, by Velasco *et al*., the *S. epidermidis* was also the most frequent among the Gram-positive isolates (73.2%). (Velasco *et al*., 2004) Naoum *et al*., in 2002 evaluating results of surveillance cultures of patients who had undergone bone marrow transplantation, also found the *S. epidermidis* as the most frequent agent (30% among the Gram-positive) (Naoum *et al*., 2002).

S. epidermidis is the most clinically relevant CoNS associated infections related to health care; *S. saprophyticus* are presented as one of the main urinary tract infection agents in women; while other CoNS are related to osteomyelitis, endorcadite, abscess formation and sepsis, especially in immunocompromised patients (Roopa & Biradas, 2012; Sheikh & Mehdinejad, 2012).

In our study, males were the most affected with the blood stream infections (60.30%). This percentage was similar to that found in other studies, which ranged from 52% to 59% (Velasco *et al*., 2004; Ortega *et al*., 2015; Sano *et al*., 2015).

Concerning the age of the patients involved in our study, 77.10% were in the age between 0 to 22 years old. Velasco *et al*., found a higher age group (43 years old); for Oliveira *et al*. and Attman *et al*., the prevalence was in the range of 57 years old (Velasco *et al*., 2004; Oliveira *et al*., 2007; Attman *et al*., 2015). The differences in the data found in our study may be attributed to the fact that we have evaluated only blood cultures from leukemic patients, with the majority of leukemias occurring in this lower age range, especially acute leukemia (Gabe *et al*., 2009).

The analysis of the sensitivity profile of the bacteria isolated from blood cultures provides an important contribution to reduce morbidity and mortality by providing decisive subsidies for the establishment of a rational drug therapy (Leão, 2007). The selection of the antibiotics therapy is a factor directly correlated to the survival of immunocompromised patients, by the fact that the bacteria, currently, beyond the vertical endurance, acquire the horizontal one, developing multi-resistance to several classes of antimicrobials (Cabral *et al*., 2008).

The CoNS isolated in this study had a significant resistance against oxacillin (72.46%) and 100% of sensitivity to daptomycin, linezolid, chloramphenicol and vancomycin. Studies show that there has been a steady increase in CoNS resistant to methicillin/oxacillin and the isolation rates in hospital infections are among 50-80% (Hussain *et al*., 2000; Ferreira *et al*., 2003; Palazzo & Darini, 2006). Sano *et al*. in his analysis of blood cultures of adolescents with hematologic and malignant diseases hospitalized at Sapporo Hokuyu Hospital, Japan, found more than 52.9% Gram-positive cocci resistant to β-lactam antibiotics, but 100% susceptible to vancomycin (Sano *et al*.,2015).

The virulence of CoNS associated with immune system deficiency exposes patients to severe clinical complications, especially cancer patients and those who had under bone marrow transplantation (Naoum *et al*., 2002; Hsueh *et al*., 2009). Additionally, the indiscriminate use of antibiotics combined with the use of characterized as a broad spectrum favors the selection of resistant bacteria, which requires the use of more powerful antibiotics, creating a vicious circle of bacterial resistance (Gales *et al*., 2012).

In this study, about 50% samples of CoNS were isolated. Thus, the involvement of this bacterium in bacteremia was established in immunocompromised patients, in this hospital. The resistance presented by these microorganisms are causes for concern as they may reduce the therapeutic options for the treatment of bloodstream infections that are hard for these patients due to their impaired immune system.

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RESUMO

Avaliação de *Staphylococcus* coagulase negativo isolados de hemoculturas de pacientes com leucemia no período compreendido entre 2009 a 2011

Pacientes leucêmicos possuem grande probabilidade de desenvolver bacteremia, especialmente devido ao acometimento de seu sistema imune e como consequência da quimioterapia. Esse tipo de infecção vem aumentando significativamente em diferentes regiões, principalmente nos hospitais universitários, e são responsáveis por altas taxas de morbidade e mortalidade. Foram avaliados *Staphylococcus* **coagulase negativos isolados de culturas de sangue de pacientes com leucemia. Realizou-se a avaliação de** *Staphylococcus* **coagulase negativo (SCoN) isolados de hemoculturas de pacientes com leucemia. Efetuou-se um estudo retrospectivo das hemoculturas realizadas no período de 2009 a 2011 no Hospital Universitário de Santa Maria. No período deste estudo foi possível analisar 282 hemoculturas positivas, sendo 46,45% (131/282) causadas por SCoN.** *Staphylococcus epidermidis* **foi a espécie prevalente. Em relação aos setores de internação dos pacientes, o Centro de Tratamento da Criança com Câncer mostrou a maior prevalência, 67,37%. Os isolamentos predominaram em pacientes do sexo masculino e na faixa etária compreendida entre 0 a 22 anos. Neste estudo os SCoN representaram os microrganismos mais isolados. A resistência apresentada por estes microrganismos constitui preocupação, uma vez que limita as opções de tratamento por infecções de corrente sanguínea neste tipo de pacientes com o sistema imune comprometido. Estudos retrospectivos de prevalência nos fornecem resultados para que seja conhecida a epidemiologia local, considerada essencial para o tratamento antimicrobiano, principalmente quando se refere aos pacientes com o sistema imune debilitado e internados em hospitais universitários.**

Palavras-chave: Bactérias. Sangue. *Staphylococcus*. Leucemia.

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