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> ACESSE AQUI A REVISTA ONLINE

ORIGINAL ARTICLE

Multidrug-Resistant Bacteria colonization as a risk factor for catheter-related Infections in children with cancer

Colonização de bactérias multirresistentes como fator de risco para infecções relacionadas a cateter em crianças com câncer

La colonización de bacterias resistentes a múltiples fármacos como factor de riesgo de infecciones relacionadas con el catéter en niños con cáncer

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BACKGROUND

Objectives: The aim of the current study is to analyse which factors are associated to Central-Line associated Bloodstream Infection in children during cancer treatment. **Methods:** A prospective study was conducted with children admitted to the university hospital of the Federal University of Minas Gerais. All children and adolescents, up to 18 years of age, with cancer and with a central venous catheter placed were included and followed from March to December 2017. A multivariate logistic regression was performed to check if sex, age, neutrophils and platelet count, hemoglobin levels, type of neoplasia (hematologic versus solid), local of care, recent use of antibiotic and duration of catheter are predictors of Central Line-Associated Bloodstream Infection, according to Center for Disease Control and Prevention criteria. **Results:** In the 100 eligible patients (36% girl; median age 8 years), the incidence of infection was 6.01 cases in 1000 catheter-days. The most common isolated microorganisms were Moraxella catarrhalis (3 patients), E. coli (2 patients), S. epidermidis (2 patients). Univariate and multivariate analysis showed a positive association between catheter infections and colonization by multidrug-resistant organisms (OR: 43, CI 95% 7.86–240.6, $p < 0.001$ and OR: 2.92, CI 95% 9.46–347.41, $p = 0.001$, respectively). **Conclusions:** The colonization by these microrganism at the time of insertion of the central venous catheter might be an important risk factor of catheter infections in children undergoing cancer treatment.

RESUMO

Objetivos: O objetivo do presente estudo é analisar quais fatores estão associados à infecção da corrente sanguínea associada à linha central em crianças durante o tratamento do câncer. **Métodos:** Estudo prospectivo realizado com crianças internadas em hospital universitário da Universidade Federal de Minas Gerais. Todas as crianças e adolescentes, até 18 anos, com câncer e com cateter venoso central colocado foram incluídos e acompanhados de março a dezembro de 2017. Foi realizada regressão logística multivariada para verificar se sexo, idade, neutrófilos e contagem de plaquetas, hemoglobina níveis, tipo de neoplasia (hematológica versus sólida), local de atendimento, uso recente de antibiótico e duração do cateter são preditores de infecção da corrente sanguínea associada ao cateter, de acordo com os critérios do Center for Disease Control and Prevention. **Resultados:** Nos 100 pacientes elegíveis (36% meninas; idade mediana de 8 anos), a incidência de infec-

ção foi de 6,01 casos em 1000 cateter-dias. Os microrganismos isolados mais comuns foram Moraxella catarrhalis (3 pacientes), E. coli (2 pacientes), S. epidermidis (2 pacientes). A análise univariada e multivariada mostrou uma associação positiva entre infecções de cateter e colonização por organismos multirresistentes (OR: 43, IC 95% 7,86–240,6, p <0,001 e OR: 2,92, IC 95% 9,46-347,41, p = 0,001, respectivamente) **Conclusões:** A colonização por esses microrganismos no momento da inserção do cateter venoso central pode ser um importante fator de risco para infecções do cateter em crianças em tratamento oncológico.

RESUMEN

Objetivos: El objetivo del presente estudio es analizar qué factores están asociados con la infección del torrente sanguíneo asociada a la vía central en niños durante el tratamiento del cáncer. **Métodos:** Se realizó un estudio prospectivo con niños ingresados en el hospital universitario de la Universidad Federal de Minas Gerais. Todos los niños y adolescentes, hasta los 18 años de edad, con cáncer y con catéter venoso central colocado fueron incluidos y seguidos de marzo a diciembre de 2017. Se realizó una regresión logística multivariante para verificar si sexo, edad, recuento de neutrófilos y plaquetas, hemoglobina Los niveles, el tipo de neoplasia (hematológica versus sólida), el lugar de atención, el uso reciente de antibióticos y la duración del catéter son predictores de infección del torrente sanguíneo asociada a la vía central, según los criterios del Centro para el Control y la Prevención de Enfermedades. **Resultados:** En los 100 pacientes elegibles (36% niñas; mediana de edad 8 años), la incidencia de infección fue de 6,01 casos en 1000 catéteres-días. Los microorganismos aislados más comunes fueron Moraxella catarrhalis (3 pacientes), E. coli (2 pacientes), S. epidermidis (2 pacientes). El análisis univariado y multivariado mostró una asociación positiva entre las infecciones del catéter y la colonización por organismos resistentes a múltiples fármacos (OR: 43, IC 95% 7,86-240,6, p <0,001 y OR: 2,92, IC 95% 9,46-347,41, p = 0,001, respectivamente). **Conclusiones:** La colonización por estos microorganismos en el momento de la inserción del catéter venoso central podría ser un factor de riesgo importante de infecciones del catéter en niños sometidos a tratamiento oncológico.

INTRODUÇÃO

Neutropenic children undergoing cancer treatment often require central venous catheters (CVC) for the safe administration of chemotherapy, blood components, antibiotics or bone marrow transplant. They are also relevant in emergency settings where larger intravenous (i.v) fluid volumes and vasoactive drugs are required to be infused. An important clinical consideration are Central Line-associated Bloodstream Infection (CLABSI) and Catheter-related Bloodstream Infection (CRBSI), recognized as causes of high morbidity and mortality in children.[1,2] These infections increase costs to the healthcare system, length of hospital stay, delayed administration of chemotherapy and can reduce the chance of cure for affected children.[3,4]

About 14% to 51% of central venous catheters implanted in children with cancer may complicate with bacteremia[5] from August, 1988 to April, 1989, a total number of 4328 hospitalized pediatric patients at the Department of Child Health, Padjadjaran University, Hasan Sadikin General Hospital Bandung, were observed to identify skin and soft tissue nosocomial infections (not included postoperative, mainly due to agents present on the skin and mucous membranes, such as Staphylococcus aureus, coagulase-negative Staphylococcus, Gram-negative Bacillus and Candida species, which may vary according to social economical level and between health facilities.[6] Less frequent etiological agents, such as A. defective, have also been identified and can cause serious infections.[7] Previous studies demonstrated a slightly predominance of bloodstream infections in males (57.4%), with a median age of 56 months.[8,9] Some risk factors for CLABSI alterady reported were reported, such as prematurity and the presence of an intra-adominal disease.[10]

Epidemiological data on factors that predispose catheter-related infections are scarce, mainly in developing countries. In children, most studies investigate the efficacy of strategies for prevention and treating infections related to devices.[5,11,12] The aim of this study was to evaluate relevant risk factors for central line-associated bloodstream infection (CLABSI) in chidren with a device placed for cancer treatment.

MÉTODOS

Design and loca

A prospective cohort study was conducted including all children with cancer admitted to a brazilian tertiary university hospital in Belo Horizonte, Brazil, from March to December 2017.

Patient selection

All children under 18 years of age with cancer diagnosis who required a central venous catheter placement.

Exclusion criteria

Children with bone marrow aplasia or bone marrow transplantation were excluded from this study.

Data collection

Demographic and relevant clinical data were collected and registered in a record file during the follow up of each case. Date and site of insertion condition, catheter type, neutrophils at the time of insertion, the reason for removal, blood cultures and complications were also obtained. All data were collected by trained professionals of Hospital Infection Control Committee and medical students, supervised by a master's student and university professors. Blood tests results were interpreted by pediatric and resident oncologists togheter in meetings at the institution.

Definitions

The classification of bloodstream infection was based on Infectious Disease Society of America (IDSA), Centers for Disease Control and Prevention (CDC) and the National Health care Safety Network (NHSN) criteria.[13,14]

A definitive diagnosis of catheter-related bloodstream infection (CRBSI) requires that the same organism grows from at least 1 percutaneous blood culture and from a culture of the catheter tip or 2 blood samples be taken (one from a catheter hub and the other from a peripheral vein). The cultured microorganism meets CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP).

Central line-associated BSI (CLABSI) defined by CDC as a recovery in a single blood culture sample of a pathogen rarely encountered on the skin or a recovery, in at least two samples, of a microrganism which commonly is found on the human skin. It is also required that the central line has been placed for over 2 calendar days on the date of the infection. If a central line was in place for over 2 calendar days and then removed, the date of the event of the LCBI must be the day of discontinuation or the next day to be a CLABSI.[15]

In this study, the outcome considered was both CRBSI and CLABSI. Multidrug-resistant organisms were considered being bacteria resistant to one or more class of antimicrobials, acording to the antimicrobial mechanism of action, as defined by the CDC.[16, 17]

Leukemia and lymphoma were considered as hematological, and the remaining diseases were considered as solid tumors. Recent use of antibiotics was considered positive if the child received the medication for less than 14 days. Type of CVC were considered as Broviac, Porth-a-cath or short term CVC.

Statistical analysis

All analysis were performed using RStudio statistics (V3. 1.1, Boston, MA). Basic descriptive statistics were used to describe patients children demographics, including frequency for categorical variables and mean and standard deviation for quantitative variables. Comparative P-values were obtained using Fisher exact test, with a α-level of 5%. Multivariate logistic regression was used to test if sex, age (in years), neutrophils and platelet count, hemoglobin levels, type of neoplasia (hematologic and solid), local of care, recent use of antibiotic and duration of catheter are predictors of any infection in patients with CVC.

Ethics consideration

This study was approved by Intitutional Review Board of Ethics Committee (report number: CAAE number 52792715.5.0000). An informed consent was obtained from all patients for being included in this study.

RESULTS

A total of 100 eligible patients who had a CVC placed were enrolled. The patients whose CVC was a long-term catheter were followed for 10 months after its placement. At the end of follow-up, the overall incidence rate of infection was 6.01 cases in 1000 days of catheter (catheter-days). Table 1 summarizes the characteristics of the population studied. The most common isolated microorganisms were Moraxella catarrhalis (3 patients), *E. coli* (2 patients), *S. epidermidis* (2 patients).

The overall mean age of children at the catheter insertion day was 7.6 years old. Most of the neoplasms were hematological. In children with CDC's criteria for CLABSI or CRBSI, the median age was 4.6 years old, and eight of nine children (88.9%) were admitted to the ward. Acute Lymphoblastic Leukemia (ALL) was present in 56.0% of cases; only one child was diagnosed with a Central Nervous System (CNS) tumor (11.0%); lymphoma was diagnosed in two children (22.0%). Finally, there was only one case of osteosarcoma.

The source of the infection could be detected only in three children (33.33%). These individuals had typhlitis, mucositis and pneumonia. The most common diagnosis in children with CLABSI or CRBSI was ALL, present in five of nine children (44.44%). Cefepime, a fourth-generation cephalosporin, was the most frequent antimicrobial (five cases, 55.55%) as first-choice. The child diagnosed with mucositis received Polymyxin. Meropenem was used for the management of a febrile neutropenia episode in a patient with osteosarcoma. This scholar had a diagnosis of osteosarcoma and had blood cultures positive for *S. maltophilia*. Figure 1 shows the distri-

Table 2. Distribution of most common isolated bacteria. *E. coli* was frequently found in blood, followed by *S. maltophilia, H. influenzae* and *K. pneumoniae*. Gram – negative bacteria were more common than Gram – positive organisms in the sample children.

	Infection		p value	OR (IC95%)
	Yes	No		
Context				
Elective	78	6	0.154	3.00 (0.67,13.51)
Urgency	13	3		
Type of neoplasia				
Hematologic	60	7	0.714	1.75 (0.34, 8.94)
Solid tumor	31	2		
Sex				
Female	32	4	0.719	1.52 (0.38, 6.08)
Male	59	5		
Age				
Mean (SD)	7.4 (5.20)	9.22 (4.15)	0.312	0.93 (0.81,1.07)
Central venous catheter days				
Mean (SD)	22.7 (47.61)	47.11 (39.42)	0.194	0.99 (0.98-1.00)
Absolute neutrophil count at insertion (/mm^3)				
Median	2320	2120	0.907	1.00 (0.99,1.00)
Platelet count at insertion (/mm^3)				
Median	213000	258000	0.612	1.00 (0.9,1.1)
Multidrug Resistant Bacteria				
No	87	3	< 0.001*	43.0 (7.86 - 240.59)
Yes	4	6		
Type of Catheter				
Broviac	1	2	0.03*a	0.34
Short term	66	6		
Port-a-Cath	24	1		
Recent use of antibiotics (< 90 days)				
Negative	51	4	0.728	2.94 (0.25,34.57)
Positive	40	5		

*Initially, a binary logistic logistic regression was performed to identify possible editors (p value <0.2). OR: Odds ratio. CI 95%: confidence interval at 95%. a: Likelihood-ratio test. * P < 0.05.*

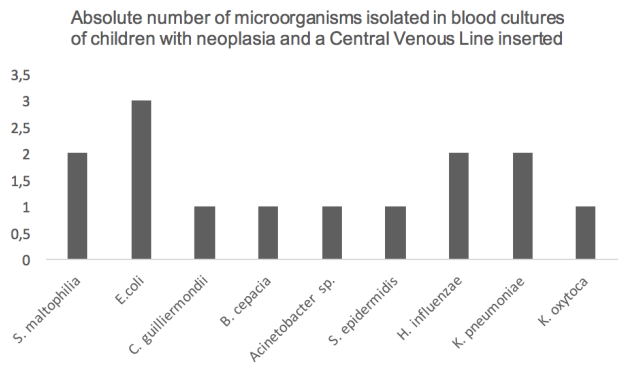

Figure 1. Distribution of most common isolated bacteria. *E. coli* was frequently found in blood, followed by *S. maltophilia, H. influenzae* and *K. pneumoniae*. Gram – negative bacteria were more common than Gram – positive organisms in the sample children.

bution of bacteria isolated from blood of patients that meet criteria for CLABSI or CRBSI.

There was one patient with a diagnosis of ALL and CLABSI, initially admitted to the ward, who needed a closer care in pediatric Intensive Care Unit (ICU). Of note, his blood culture were positive for *S. epidermidis*, which was not a Multidrug-resistant bacteria. The other individuals with CLABSI or CRBSI had a complete response do antimicrobial therapy. A non-neutropenic male child, undergoing chemotherapy due to ALL, died after pneumonia during the follow-up period. He presented to the emergency department and was then admitted to ICU, where received prompt antimicrobial therapy. Half of the patients had a positive history for antimicrobial use within 90 days of device insertion.

Univariate analysis showed that the context of hospitalization (urgent versus elective), isolated from Multidrug-resistant (MDR) bacteria, catheter type and recent use of antibiotics could be predictors of infection. Neutrophil count was not associated with the infection outcome (Table 2). In multivariate analysis (Table 3), however, only isolation of MDR bacteria was a significant factor (odds ratio = 57.3, CI 95: 9.46 – 347.41; p < 0.001).

Table 3. Predictors of Central Line-Associated Blood Stream Infection in children with oncological diseases in multivariated analysis.

Multivariate parameters	B	OR (CI 95%)	*p value*
Context	-1.075	2.92 (0.65 – 13.17)	0.30
Multidrug Resistant Bacteria	-3.754	57.33 (9.46 - 347.41)	< 0.001*
Central venous catheter days	0.005	0.99 (0.98 – 1.00)	0.50
Type of Catheter	3.427		0.28
Broviac		1	
Short-term		2.12 (0.24 – 18.58)	
Port-a-cath		0.05 (0 – 0.59)	

*Multivariate analysis of risk factors for catheter related infections in neutropenic children assisted in aa referral center, Minas Gerais, Brazil, March to December 2017. OR: odds ratio. CI 95%: confidence interval at 95%. B Standardized coefficients. OR Odds ratio. * p < 0.05.*

DISCUSSION

Identification of the risk factors for infection in children with cancer is of great relevance. This study showed an incidence of 6.0 cases in 1000 days of catheter (catheter-days) of infection among children hospitalized for chemotherapy. We also demonstrate a relationship between colonization by multi-resistant microorganisms and CLABSI. This result is plausible since resistant organisms are isolated in patients with cancer and CVC.[18] Colonization rates for MDR organisms in patients with cancer reach up to 36% in some studies.[19]

One study conducted at Children's Hospital at Montefiore, New York, compared rates of outpatient and in-hospital CLABSIs and found a result of 0.65 infections per 1000 central catheter days in outpatient settings and 2.2 cases per 1000 central line days at the hospital level.[20] Another cancer center in Israel studied 419 children admitted with central venous catheters. They found an incidence of 4.66 events per 1000 catheter days in those Hickman catheter patients and 1.45 infections per 1000 catheter days in patients with long-term catheters.[21] The rate of infections in our institution was higher than those found by these authors. Coagulase-negative Staphylococci, S. epidermidis and S. aureus appear to be the most isolated microorganisms and infection responds for the main reason of catheter removal.[22] Gram-positive infections make up 70% of cases.[23] In our institution, gram-negative infections were more common, in contrast to most studies. A multicentric study showed that gram-negative microrganisms tended to be more common in patients with a tunneled CVC with external lines in comparison to children with non-tunneled (47% vs 20%, P = 0.06), although there was no statistical significance. A retrospective cohort study with 143 records had a higher frequency of Gram-negative microbe isolated in blood cultures (52.1%) in their institution.[24] Hord et al[25] found that Gram-negative organisms were the most common cause of CLABSI in children with tunneled externalized catheter ocurring in ambulatory setting, while Gram-positive infections were the main etiology of these events in inpatient setting.

Although previous studies consider low neutrophil count a risk factor for catheter-related bloodstream infections, in the present report neutropenia was not associated with a higher incidence of infections, regardless of its definition.[26,27] A recent retrospective study of 179 children affected by ALL found no association between severe neutropenia at the time of implantable catheter insertion and higher catheter infection rates.[22] Another work with 117 children tested whether CVC implantation, since cancer diagnosis without considering neutrophil counts, affects the incidence of device removal within 30 days. The removal occurred in 12 children (10.2%) and has not been influenced by neutropenia, but by age below 2 years.[28] In our results, age was not a relevant factor for this outcome.

The first step in preventing multidrug-resistant organisms is to identify risk factors such as prolonged hospitalization, recent exposure to antimicrobials, lung disease, diabetes mellitus, and patients with transplants.[29, 30] The next step comprises aseptic measures, using gloves and a mask to manipulate children, controlling air quality, suppressing endogenous flora through antibiotic therapy.[31]

Central venous catheter bundles include a series of actions that prevent CLABSI when adopted by the health team.[32] A study conducted at the Johns Hopkins School of Medicine showed a decrease from 2.25 CLABSIs per 1000 central line days to 1.79 infections per 1000 central line days using a standardized central line maintenance care bundle.[33] In an outpatient setting, this strategy still proved useful in reducing CLABSIs over a 1-year interval.[34] As far as the authors know, this study was the first to prospectively investigate the association between neutrophil count in the moment of catheter placement and infectious outcomes. A cross-sectional study at Jai Prakash Narain Apex Trauma Centre investigated 530

patients admitted to the intensive care unit after trauma and showed a high prevalence of resistance among device-isolated microorganisms in patients with CLASBIs.[35]

Data on catheter-related infection are best established in adults. In the pediatric cancer population, knowledge of risk factors for catheter infections is even rarer. In addition to the lack of evidence in this field, there are doubts about the need for catheter removal, optimal coverage of antibiotics for treatment, duration of treatment, and about the use of catheter lock. Our study attempted to demonstrate possible risk factors in the pediatric population to address this deficiency.[5] This work has some limitations. One of them is the limited sample size, which can hinder the statistical analysis and the distribution of the considered groups. The university hospital of the Federal University of Minas Gerais is a reference center for cancer treatment and for complex cases of the state, which may influence the incidence of the outcome. The effect size is inaccurate because of the relatively small sample size. However, this result reinforces the current concern about the incidence of MDR organisms in the pediatric population.[36]

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