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Predictors of 7- and 30-day mortality in pediatric intensive care unit patients with cancer and hematologic malignancy infected with Gram-negative bacteria

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ABSTRACT

Background: Infection with Gram-negative bacteria is associated with increased morbidity and mortality. The aim of this study was to evaluate the predictors of 7- and 30-day mortality in pediatric patients in an intensive care unit with cancer and/or hematologic diseases and Gram-negative bacteria infection.

Methods: Data were collected relating to all episodes of Gram-negative bacteria infection that occurred in a pediatric intensive care unit between January 2009 and December 2012, and these cases were divided into two groups: those who were deceased seven and 30 days after the date of a positive culture and those who survived the same time frames. Variables of interest included age, gender, presence of solid tumor or hematologic disease, cancer status, central venous catheter use, previous *Pseudomonas aeruginosa* infection, infection by multidrug resistant-Gram-negative bacteria, colonization by multidrug resistant-Gram-negative bacteria, neutropenia in the preceding seven days, neutropenia duration ≥3 days, healthcare-associated infection, length of stay before intensive care unit admission, length of intensive care unit stay >3 days, appropriate empirical antimicrobial treatment, definitive inadequate antimicrobial treatment, time to initiate adequate antibiotic therapy, appropriate antibiotic duration ≤3 days, and shock. In addition, use of antimicrobial agents, corticosteroids, chemotherapy, or radiation therapy in the previous 30 days was noted.

Results: Multivariate logistic regression analysis resulted in significant relationship between shock and both 7-day mortality (odds ratio 12.397; 95% confidence interval 1.291–119.016; $p = 0.029$) and 30-day mortality (odds ratio 6.174; 95% confidence interval 1.760–21.664; $p = 0.004$), between antibiotic duration ≤3 days and 7-day mortality (odds ratio 21.328; 95% confidence interval 2.834-160.536; $p = 0.003$), and between colonization by multidrug resistant-Gram-negative bacteria and 30-day mortality (odds ratio 12.002; 95% confidence interval 1.578–91.286; $p = 0.016$).

Conclusions: Shock was a predictor of 7- and 30-day mortality, and colonization by multidrug resistant-Gram-negative bacteria was an important risk factor for 30-day mortality.

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Introduction

Children undergoing treatment for malignancy have an excellent chance of survival, with an overall survival rate approaching 75%.[1] In most cases, children who die following treatment for cancer do so as a result of their disease. However, despite significant improvements in supportive care, approximately 16% of the deaths within five years following diagnosis are due to complications of therapy.[1] Infection continues to be one such life-threatening complication in immunocompromised children.[1]

With recent advances in cancer treatments and improvements in critical care, an increasing number of patients with hematologic malignancies are being admitted to intensive care units (ICU).[2] Despite the associated improvements in outcomes, mortality remains high in critically ill patients with hematologic malignancies, particularly in the presence of ICU-acquired nosocomial infections.[2] In addition, infection results in ICU admission in cancer patients.

Oncologic patients are at a greater risk of developing sepsis and nosocomial infections as a consequence of a number of mechanisms, including immunosuppression related to the disease itself and to aggressive treatments, such as combined regimens of chemotherapy and radiation therapy, high dose steroids, and hematopoietic stem cell transplantation.[3] Moreover, despite recent improvements in survival rates, sepsis in patients with cancer remains associated with high morbidity, mortality, costs, and use of ICU resources, and information on this topic is limited.[3]

Research has previously focused on adult patients with cancer. Little is known regarding the predictors of 7- and 30-day mortality related to Gram-negative bacterial (GNB) infection in children with cancer who are hospitalized in the ICU. Therefore, this study aimed at evaluating the predictors of 7- and 30-day mortality risk in children with cancer and/or hematologic diseases who were also infected with GNB.

Patients and methods

Study design

We performed a case–control study in the pediatric ICU of the National Cancer Institute (INCA), Rio de Janeiro, Brazil, which is an exemplary tertiary oncology public hospital. The 6-bed pediatric ICU admits only patients with solid tumors and hematologic malignancies. Admission to the ICU is not generally permitted for palliative care. However, some patients may be admitted while a full assessment of the extent of their cancer and therapeutic options is still ongoing.

We collected data related to all GNB episodes that occurred between January 2009 and December 2012 in patients aged less than 18 years, who were hospitalized for >24 h in the pediatric ICU. The study was approved by the ethics committee of the Fluminense Federal University.

GNB infections were divided into two groups by time and survival status: patients who were deceased and those who survived seven and 30 days after the date of a positive culture. At each time period, the patients were from the same unit and had infections that occurred at the same time and at the same sites.

The following data were collected: age, gender, presence of solid tumor or hematologic disease, cancer status, central venous catheter use, previous *Pseudomonas aeruginosa* infection, healthcare-associated infection, infection by multi-drug resistant (MDR)-GNB, colonization by MDR-GNB (assessed using a rectal swab or stool culture), neutropenia in the preceding seven days, neutropenia duration ≥3 days, length of stay before ICU admission, length of ICU stay >3 days, appropriate empirical antimicrobial treatment, definitive inadequate antimicrobial treatment, appropriate antibiotic duration ≤3 days, the time to initiate adequate antibiotic therapy, and shock (within two days before or after the date of a positive culture). In addition, the use of any of the following in the previous 30 days was noted: antimicrobial agents, corticosteroids, chemotherapy, or radiation therapy. Colonization with antibiotic-resistant GNB was detected *via* weekly routine surveillance (nasal and rectal swabs).

Definition of terms

Death within seven days or 30 days after the date of a positive culture was considered as 7- and 30-day mortality, respectively. An episode of infection was defined as the isolation of GNB from three days before the date of pediatric ICU admission to the last day of hospitalization in the pediatric ICU, from cultures of blood, urine, stools, broncho-alveolar lavage, tracheal aspirate, cerebrospinal fluid, or catheter tip, in the presence of associated, compatible clinical signs or symptoms. The tracheal aspirate was collected from endotracheal tubes and tracheostomies of patients who underwent mechanical ventilation. The diagnostic criteria for pneumonia included purulent tracheobronchial secretion and new pathogenic bacteria isolated from tracheal aspirate or broncho-alveolar lavage in addition to two or more of the following criteria: fever >38 °C; leukocytes >12,000 cells/mL or <4000 cells/mL; a new and persistent (>48 h) infiltrate on chest radiograph; new onset or worsening cough, dyspnea, or tachypnea; and declining gas exchange. Catheter cultures were performed when a catheter was removed for suspected intravascular catheter-related infection, if the patient had unexplained sepsis or erythema overlying the catheter insertion site, or if there was purulence at the catheter insertion site. The end of the infection episode was the date when the infection was considered to be resolved by the medical team.

The presence of extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*; microorganisms with intrinsic resistance mechanisms such as *S. maltophilia* and *Elizabethkingia meningoseptica*; carbapenem-resistant GNB; or strains of *A. baumannii* were considered as MDR-GNB infection. Polymicrobial infection involved the isolation of more than one pathogen from a culture sample.

Neutropenia was defined as an absolute neutrophil count <500 neutrophils/mm^3 in blood samples. Shock was defined as arterial hypotension requiring vasoactive drugs.

Initial antimicrobial treatment was considered inappropriate if the treatment regimen did not include at least one antibiotic active *in vitro* against the microorganism. It was also considered inappropriate when the antibiotic treatment was