



EDITORIAL

Management of septic shock in children with cancer— Common challenges and research priorities[☆]



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Children with cancer frequently develop a critical illness, with up to 40% requiring treatment in a pediatric intensive care unit (PICU) during the course of cancer-directed therapy.¹ Treatment-related mortality, or death related to complications of cancer treatment, remains a major cause of preventable pediatric cancer deaths, representing up to 50% of deaths in some settings.^{2–5} Sepsis and septic shock are among the most common cause of critical illness in children with cancer, with a mortality of 41 to 46%.^{1,6–8} This mortality is significantly higher than the overall PICU sepsis mortality among other pediatric patients of 14 to 24%.^{8–10} Accordingly, an international consensus recently identified sepsis management, outcomes, and costs as a top research priority to improve pediatric onco-critical care outcomes.¹¹

In this issue of *Jornal de Pediatria*, Azevedo et al. present an assessment of the risk factors for mortality among children with malignancy and sepsis.¹² Their study, evaluating 139 pediatric oncology patients with sepsis admitted to a PICU in a dedicated pediatric cancer hospital in Brazil, found a 41% mortality, with 18% of deaths occurring within the first 24 hours of PICU admission. In multivariate analysis, identified risk factors for PICU mortality included the PRISM IV score, number of organs with dysfunction, and relapsed cancer. A positive fluid balance of 2–6% (representing 20–60 ml/kg) was associated with a reduced the relative risk of mortality. This study describes a patient cohort representative of critically ill pediatric oncology patients with sepsis; the most common oncologic diagnosis was leukemia (25%), 28% had a history of hematopoietic stem cell transplantation, and most were neutropenic. Regarding the cause of sepsis, over 40% had culture-confirmed bacteremia with performantly gram-negative bacteria, along with a combination of

other infectious organisms. These patients represent high PICU resource utilization, with nearly 80% requiring mechanical ventilation, 20% using continuous renal replacement therapy, and a long median PICU length of stay of 10 days.

Although this study describes a single-center experience in a dedicated oncology PICU, its findings of risk factors and mortality among children with cancer who develop sepsis and critical illness are likely generalizable to other hospital settings. Importantly, this work highlights several common challenges in managing this high-risk patient population and raises essential questions for future studies. As highlighted by Azevedo et al., high mortality observed in pediatric oncology patients with sepsis is a result of a combination of the host (immunosuppression), disease (cancer and infection), and environmental (hospital) factors.

Children with cancer are typically immunocompromised, either directly from their primary oncologic process involving bone marrow or as the result of cancer-directed therapy. Immunocompromised hosts are inherently at higher risk for infection and have a dysregulated response to infection and inflammation, increasing the severity of sepsis. Additionally, these patients commonly have pre-existing organ dysfunction due to prior chemotherapy toxicity and are more susceptible to developing multiple organ dysfunction syndromes in the setting of inflammation or infection.^{13,14}

In addition to pre-existing risk factors, the current state of a patient's oncologic process similarly impacts outcomes. Relapsed cancer, requiring higher-intensity therapy and carrying a lower chance of survival, is a well-established risk factor in these patients. Similarly, patients with active cancer and infection may experience critical illness due to cancer progression if cancer-directed therapy is held during acute infection treatment. Regarding the cause of sepsis, along with common infections occurring in general pediatric patients, pediatric oncology patients frequently experience

[☆] See paper by Azevedo et al. in pages 127–32.

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prolonged periods of neutropenia, making them at risk for infection from other opportunistic, viral, and fungal organisms.^{15,16} While many pediatric oncology patients with clinical sepsis have an underlying infectious etiology, some do not, representing a subset of patients with dysregulated inflammation as a cause of shock.¹⁷ Differentiating infection from immune-mediated inflammation as the underlying cause of organ dysfunction and shock and choosing appropriate subsequent therapy to address the underlying cause is another major management challenge in children with cancer who present with critical illness and fever.

While host and disease risk factors are often fixed and immutable to clinicians at the bedside, there are multiple modifiable environmental, or hospital/practice, factors that impact outcomes in pediatric oncology patients with sepsis. Late identification of critical illness, with delays in PICU transfer and initiation of organ-supporting therapy, is a major challenge in the care of children with cancer.^{18,19} This is highlighted by funding from Azevedo et al. demonstrating increased mortality among patients with delayed initiating vasoactive medications and more organ dysfunction at sepsis identification.¹² Multiple studies have noted the effectiveness of quality improvement initiatives to promote proactive identification and management of critical illness, such as Pediatric Early Warning Systems (PEWS), to improve hospital outcomes in children with cancer.^{20–28} Hospital and provider experience managing children with cancer are also important, with high-volume centers typically having lower PICU mortality for these patients.^{18,29} Finally, strong interdisciplinary (oncology, intensive care, etc.) and interprofessional (physician, nurses, etc.) collaboration is integral to improving the quality of care and outcomes for high-risk pediatric oncology patients. Multidisciplinary guidelines to manage pediatric sepsis,^{30,31} treating fever and neutropenia,³² preventing central line infections and other complications of therapy^{33,34} are vital to improving care. Recent work has identified global hospital indicators to assess the quality and capacity of pediatric onco-critical care services;^{35,36} using such assessments can aid hospitals to identify opportunities to improve patient care and outcomes. A greater systems-level focus on these modifiable factors will improve global survival for children with cancer who develop sepsis and critical illness.

The majority of available literature describes outcomes of sepsis in children with cancer comes from high-resource settings. Most children with cancer, however, live in low- and middle-income countries (LMICs), which account for more than 90% of childhood cancer deaths worldwide.^{37,38} Resource-limited hospitals face a range of challenges in providing acute and critical care to children, including limited staff, equipment, and medications.^{39,40} These hospitals also face additional barriers to implementing and sustaining quality improvement interventions designed to improve patient quality of care and outcomes.^{41–44} While few studies evaluate the outcome of critical illness in children with cancer in resource-limited hospitals, available data from Latin America suggest mortality is higher than in high-resource settings and increases with the severity of sepsis and organ dysfunction.^{18,45} Recent work has demonstrated, however, that excellent outcomes for critically ill children with cancer are possible in resource-limited hospitals utilizing effective quality improvement strategies and multidisciplinary

collaboration to proactively improve care for these high-risk patients.⁴⁶ Guidelines for the management of critical illness,⁴⁷ pediatric sepsis^{31,48} and febrile neutropenia³² tailored to local contextual factors and resources are integral to improving care in these settings.

The study by Azevedo et al. highlights multiple urgent research priorities to improve outcomes for children with cancer who develop sepsis. Strategies for early identification of critical illness²⁸ and novel diagnostic techniques to rapidly identify infectious etiology⁴⁹ and distinguish infection from inflammation¹⁷ remain a priority. Management approaches for children with cancer who develop sepsis, including risk stratification, appropriate contextually informed antimicrobial, and supportive care protocols are also essential. As emphasized by findings from Azevedo et al., appropriate fluid resuscitation targets remain a question for these patients, particularly ones with co-occurring respiratory dysfunction, where fluid overload has been linked to higher mortality.⁵⁰ Similarly, there is a need to identify clinically pragmatic biomarkers for early bedside identification of organ dysfunction syndrome phenotypes and develop novel targeted therapies to reduce morbidity and mortality from organ failure in these patients.¹³ Finally, the global epidemiology, outcomes, and resource utilization of children with cancer and sepsis must be described in multi-center studies that include diverse, variably-resourced settings.^{51,52} Regional and global research collaborations, such as LARed (Red Colaborativa Pediátrica de Latinoamérica),^{53,54} POKER (PICU Oncology Kids in Europe Research Group),^{11,55} PALISI Global Health (Pediatric Acute Lung Injury and Sepsis Investigators),^{56,57} WHO GICC (World Health Organization Global Initiative for Childhood Cancer),⁵⁸ and St. Jude Global Critical Care Program,⁵⁹ which address critical illness in children are needed to take on these pressing research questions.

Sepsis resulting in critical illness in children with cancer remains a major clinical challenge and cause of preventable cancer-related mortality. Addressing this challenge will require multidisciplinary and multinational collaborations across the fields of basic science, clinical research, quality improvement, and implementation science. This work must systematically focus on the unique characteristics of this patient population as well as local contextual factors that impact their care and management. There is an urgent need for global collaboration to systematically address sepsis in children with cancer to improve survival and long-term outcomes worldwide.

Conflicts of interest

The author declares no conflicts of interest.

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