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Outcomes associated with septic shock at admission in a pediatric intensive cara unit

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RESUMO

Objetivo: Analisar a associação entre o diagnóstico de choque séptico na admissão e desfechos negativos em uma UTIP do Sul do Brasil. **Método:** Coorte retrospectiva de internações de crianças de zero a 15 anos, entre 2012 e 2017. A variável dependente foi choque séptico na admissão. Os desfechos foram jejum na admissão, diagnóstico de infecções relacionadas à assistência à saúde (IRAS), tempo de internação em UTIP e óbito. Foi realizada regressão de Poisson com variância robusta, utilizando o Statistical Package for Social Sciences (SPSS®), com ajuste progressivo de variáveis demográficas e clínicas. Foram calculados risco relativo (RR) e intervalo de confiança (IC95%), com significância de 5%. **Resultados:** Das 1068 internações analisadas, 112 (10,5%) tinham diagnóstico de choque séptico na admissão. Parcela significativa era procedente de outros municípios (73,2%, p=0,023), e maiores proporções de necessidade de ventilação pulmonar mecânica invasiva (92,9%, p<0,001) e uso de droga vasoativa (83,0%, p<0,001) foram observados nessa população. O choque séptico foi fator de risco para permanência em jejum após admissão (RR=1,14; IC95%: 1,07-1,21) e para a aquisição de IRAS (RR=1,67; IC 95%: 1,29-2,17). Também se associou com maior tempo de permanência sob cuidados intensivos (RR=1,3; IC 95%:1,09-1,56), considerando a mediana de quatro dias e maior risco de óbito (RR=5,76; IC:95%: 4,39-7,55). **Conclusão:** Reconhecer as características das crianças admitidas com choque séptico permite a identificação do perfil de paciente com maior risco de desfechos desfavoráveis.

Descritores: Unidades de terapia intensiva pediátrica; Choque séptico; Respiração artificial; Drogas vasoativas; Mortalidade hospitalar.

ABSTRACT

Objective: o analyze the association between the diagnosis of septic shock at admission and negative outcomes in a Pediatric Intensive Care Unit (PICU) in Southern Brazil. **Methods:** This was a retrospective cohort study of hospital admissions of children aged 0 to 15 years between 2012 and 2017. The dependent variable was septic shock at admission. The outcomes included fasting at admission, diagnosis of healthcare-associated infections (HAI), length of stay in the PICU, and death. Poisson regression with robust variance was performed using the Statistical Package for Social Sciences (SPSS®), with progressive adjustment for demographic and clinical variables. Relative risk (RR) and 95% confidence intervals (CI) were calculated, with a significance level of 5%. **Results:** Of the 1.068 admissions analyzed, 112 (10.5%) had a diagnosis of septic shock at admission. A significant portion of these patients came from other municipalities (73.2%, p=0.023), and higher proportions of invasive mechanical ventilation (92.9%, p<0.001) and vasoactive drug use (83.0%, p<0.001) were observed in this population. Septic shock was a risk factor for prolonged fasting after admission (RR=1.14; 95% CI: 1.07-1.21) and for the acquisition of HAI (RR=1.67; 95% CI: 1.29-2.17). It was also associated with a longer stay in intensive care (RR=1.3; 95% CI: 1.09-1.56), with a median stay of four days, and a higher risk of death (RR=5.76; 95% CI: 4.39-7.55). **Conclusion:** Recognizing the characteristics of children admitted with septic shock allows for the identification of the patient profile at higher risk of unfavorable outcomes.

Descriptors: Intensive Care Units, Pediatric; Shock, Septic; Respiration, Artificial; Cardiovascular Agents; Hospital Mortality.

RESUMÉN

Objetivo: analizar la asociación entre el diagnóstico de choque séptico al ingreso y los desenlaces negativos en una UCIP del sur de Brasil. **Método:** Cohorte retrospectiva de hospitalizaciones de niños de cero a 15 años, entre 2012 y 2017. La variable dependiente fue el choque séptico al ingreso. Los desenlaces fueron ayuno al ingreso, diagnóstico de infecciones relacionadas con la asistencia sanitaria (IRAS), tiempo de estancia en la UCIP y muerte. Se realizó una regresión de Poisson con varianza robusta utilizando el Statistical Package for Social Sciences (SPSS®), con un ajuste progresivo de variables demográficas y clínicas. Se calcularon el riesgo relativo (RR) y el intervalo de confianza (IC95%), con un nivel de significancia del 5%. **Resultados:** De las 1068 hospitalizaciones analizadas, 112 (10,5%) tenían diagnóstico de choque séptico al ingreso. Una parte significativa procedía de otros municipios (73,2%, p=0,023), y se observaron mayores proporciones de necesidad de ventilación pulmonar mecánica invasiva (92,9%, p<0,001) y uso de fármacos vasoactivos (83,0%, p<0,001) en esta población. El choque séptico fue un factor de riesgo para el mantenimiento del ayuno después del ingreso (RR=1,14; IC95%: 1,07-1,21) y para la adquisición de IRAS (RR=1,67; IC95%: 1,29-2,17). También se asoció con un mayor tiempo de estancia en cuidados intensivos (RR=1,3; IC95%: 1,09-1,56), considerando la mediana de cuatro días, y un mayor riesgo de muerte (RR=5,76; IC95%: 4,39-7,55). **Conclusión:** Reconocer las características de los niños admitidos con choque séptico permite identificar el perfil del paciente con mayor riesgo de desenlaces desfavorables.

Descriptores: Unidades de Cuidado Intensivo Pediátrico; Choque Séptico; Respiración Artificial; Fármacos Cardiovasculares; Mortalidad Hospitalaria.

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Introduction

Pediatric Intensive Care Units (PICUs) provide high-complexity healthcare, typically for patients between 29 days and 14 or 18 years old, depending on the institution[1] . The main conditions leading to PICU admissions include sepsis, respiratory problems, neoplasms, congenital malformations, external causes, and post-operative care, with sepsis being associated with the highest mortality [2].

In terms of frequency and severity, sepsis is a significant pediatric disease and a public health issue. Despite therapeutic advances, it remains one of the leading causes of death worldwide [3-5]. It is estimated that in developing countries, more than 4% of hospitalized patients under the age of 18 are diagnosed with sepsis, and this percentage rises to 8% when considering PICU admissions[6].

Sepsis is a dynamic disease resulting from the body's dysregulated response to infections, being potentially fatal, and involving complex pathophysiological mechanisms that lead to variable and nonspecific clinical presentations. The concept of shock, which includes septic shock, is based on the imbalance between oxygen supply and demand [5]. Clinically, septic shock presents as acute circulatory failure, characterized by persistent hypotension despite fluid resuscitation, unexplained by other causes, or with elevated serum lactate levels, and the need for vasoactive drugs[5,6].

There is a wide epidemiological spectrum regarding pediatric sepsis. Studies point to different prognostic factors for the progression of these patients, as well as variations in mortality rates. An analysis of PICU admissions in Spain showed that preexisting conditions were not determinants of death, while hypotension, purpura or coagulopathy, cardiac dysfunction, renal failure, and hyperglycemia were cited as contributors to this outcome[7] . In contrast, research in Italy indicated that mortality was more significant in patients with pre-existing chronic conditions[8] . Meanwhile, in PICUs in China, there was a significant difference in mortality based on age, with higher rates in preschool-aged patients (one to five years), whereas the presence of preexisting conditions was not a determinant in the clinical evolution of the cases[9].

Recognizing the specific characteristics of admission profiles allows for the development of more effective healthcare strategies, particularly at the national level, where the approach to this issue is more limited compared to other countries[10]. In light of this, the aim of the present study was to analyze the association between the diagnosis of septic shock at admission and negative outcomes in a PICU in Southern Brazil.

Methods

This was a retrospective cohort study using data from children admitted between January 1. 2012. and December 31. 2017. in a PICU of a university hospital in northern Paraná. The hospital is a referral center for several clinical-surgical specialties, as well as for emergency care. In pediatrics, the hospital stands out for its work in pediatric surgery, neurosurgery, nephrology, and specialized burn care, as it houses one of the only two Burn Treatment Centers (BTC) in the state

The PICU is classified as a mixed unit, attending children aged between zero and 15 years. Currently, this age range has been extended to 17 years. During the study period, the unit had seven beds according to the National Registry of Health Facilities. However, with the increased demand for children with Severe Acute Respiratory Syndrome (SARS) due to the COVID-19 pandemic, the number of beds was increased to 19 in 2020. given the hospital's referral status for municipalities in the 17th Health Region of Paraná and other parts of the state. Today, the unit has ten beds following bed reductions after epidemic control in the region.

The study data were obtained from medical records made available by the hospital's Medical Records and Statistics Service (SAME). The study also used a computerized system to obtain laboratory test results and cultures for the diagnosis of healthcare-associated infections (HAIs).

Data collection was conducted using a standardized form with variables grouped into sociodemographic characteristics, personal and family history, admission and hospitalization conditions, details of ventilatory support, and hospital outcomes. Data entry was performed by nursing and medical professors specialized in pediatric intensive care, as well as by undergraduate and graduate students in nursing and medicine who had received prior training. The training consisted of expository and interactive classes covering the contents of the data collection form, delivered by specialist professors, totaling five initial sessions, in addition to follow-up meetings whenever requested by the data collection team. The undergraduates were in their second year or higher in medical and nursing programs. The postgraduates were residents in child health nursing and pediatric medicin.

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The research data were obtained from medical records provided by the hospital's Medical Records and Statistics Service (SAME). Additionally, a computerized system was used to obtain laboratory test results and cultures for the diagnosis of Healthcare-Associated Infections (HAIs).

After collection and verification, the data were entered into the Epi Info™ software, version 3.5.4. with subsequent correction of inconsistencies.

The primary independent variable of the study was the diagnosis of septic shock at admission, characterized by infections associated with arterial hypotension, and/or elevated serum lactate, and/or the use of vasoactive drugs to maintain adequate blood pressure for the specific age group [5].

Fasting at admission (yes and no), diagnosis of HAIs (yes and no), length of stay in the PICU based on the median duration of hospitalization in the unit in days (≤ 4 and > 4), and death (yes and no) were the outcomes analyzed. For the diagnosis of HAIs, infections identified after 48 hours of hospitalization were considered, with the information

recorded in the medical chart or through culture results.

Other variables, considered potential confounders, were used in the adjustments of the analyses, such as age in years (< 1 and ≥ 1), sex (male and female), origin (local municipality and other municipalities), and diagnosis of chronic disease (yes and no), and malnutrition at admission (yes and no). The need for invasive mechanical ventilation (IMV) (yes and no) and the use of vasoactive drugs (VAD) (yes and no) were also analyzed. For IMV, children who remained connected to a mechanical ventilator via orotracheal intubation or tracheostomy were classified as "yes." Nutritional status was classified using the weight-for-age z-score, with children having scores lower than -2 being classified as malnourished.

The Statistical Package for Social Sciences (SPSS®), version 19.0. was used for the statistical analysis of the data. To understand the relationship between septic shock at admission and the outcomes studied, Poisson regression with robust variance was performed, adjusted by progressive insertion of demographic (model 1) and clinical variables (model 2) that were associated with these outcomes, with a p-value < 0.2. Relative risk (RR) and confidence intervals (95% CI) were calculated, considering a 5% significance level. The project was approved by the Research Ethics Committee, approval number: 2.568.388. and CAAE: 83069418.7.0000.5231.

Results

Between 2012 and 2017. there were 1.223 hospital admissions, of which 155 were not analyzed due to missing records, representing a 12.6% loss. Of the remaining 1.068 admissions, 112 (10.5%) had a diagnosis of septic shock at admission.

Regarding demographic variables, just over half of the children were aged one year or older (51.0%), with a median age of 11 months, and the majority were male (54.0%) and from other municipalities (63.4%).

Regarding demographic variables, just over half of the children were aged one year or older (51.0%), with a median age of 11 months, and the majority were male (54.0%) and from other municipalities (63.4%). In relation to the diagnosis of septic shock at admission, a statistically significant difference was observed only in the place of origin, where patients with the diagnosis were more frequently from other cities (73.2%) compared to those without the diagnosis (62.2%), with a p-value of 0.023. Regarding clinical conditions in the general population, 46.4% had chronic diseases; 29.0% were malnourished, and around 59.0% required invasive mechanical ventilation (IMV). The use of vasoactive drugs (VAD) occurred in almost a quarter of the cases, and 44.5% remained hospitalized in the Pediatric Intensive Care Unit (PICU) for more than four days. Children with a diagnosis of septic shock at admission had higher proportions of needing IMV (92.9%, p<0.001) and VAD (83.0%, p<0.001) (Table 1).

Table 1: Demographic characteristics and clinical conditions according to the diagnosis of septic shock at admission in a Pediatric Intensive Care Unit (PICU), 2012-2017.

Variables	Total		Septic Shock at Admission				p-value
			Yes		No		
	N	%	N	%	n	%	
Age (years)							
< 1	523	49,0	50	44,6	473	49,5	0,333
≥ 1	545	51,0	62	55,4	483	50,5	
Gender*							
Male	577	54,0	57	50,9	520	54,4	0,482
Female	491	46,0	55	49,1	436	45,6	
Place of Origin							
Other municipalities	677	63,4	82	73,2	595	62,2	0,023
Own municipalities	391	36,6	30	26,8	361	37,8	
Chronic Disease							
Yes	496	46,4	49	43,8	447	46,8	0,546
No	572	53,6	63	56,2	509	53,2	
Malnutrition*†							
Yes	296	29,0	30	29,4	266	29,0	0,927
No	724	71,0	72	70,6	652	71,0	
Need for IMV							
Yes	622	58,2	104	92,9	518	54,2	< 0,001
No	446	41,8	8	7,1	438	45,8	
Need for VPD							
Yes	244	22,8	93	83,0	151	15,8	< 0,001
No	824	77,2	19	17,0	805	84,2	

* Excluded records with missing information; † Based on z-score weight-for-age < -2; IMV: invasive mechanical ventilation; VPD: vasopressor drugs.

Regarding the outcomes analyzed, in the crude analysis, it was observed that the diagnosis of septic shock was associated with fasting ($p < 0.001$), healthcare-associated infections (HAI) ($p < 0.001$), length of stay in the PICU greater than four days ($p = 0.004$), and death ($p < 0.001$). Other variables, such as sex and malnutrition, were also associated with all outcomes, considering a p-value of < 0.20. Age was not associated with death. Both origin and chronic disease did not present statistical significance with length of stay in the PICU exceeding four days (Table 2).

Table 2: Bivariate analysis of septic shock and adjustment variables with the outcomes of interest in the Pediatric Intensive Care Unit (PICU), 2012-2017.

Variables	Outcomes							
	Fasting		HAI		PICU Stay > 4 days		Death	
	n(%)	p-value	n(%)	p-value	n(%)	p-value	n(%)	p-value
Septic Shock								
Yes	104 (92,9)	<0,001	43 (38,4)	<0,001	63 (56,2)	0,004	64 (54,5)	<0,001
No	779 (81,5)	-	219 (22,9)	-	412 (43,1)	-	92 (9,6)	-
Age (years)								
< 1	421 (80,5)	0,066	142 (27,2)	0,052	284 (54,3)	<0,001	76 (14,5)	0,851
≥ 1	462 (84,8)	-	120 (22,0)	-	191 (35,0)	-	77 (14,1)	-
Gender*								
Female	397 (80,9)	0,150	136 (27,7)	0,027	229 (46,6)	0,189	78 (15,9)	0,180
Male	486 (84,2)	-	126 (21,8)	-	246 (42,6)	-	75 (13,0)	-
Place of Origin								
Other municipalities	552(81, 5)	0,184	186 (27,5)	0,004	303 (44,8)	0,808	109 (16,1)	0,032
Reference city	331 (84,7)	-	76 (19,4)	-	172 (44,0)	-	44(11,3)	-
Chronic Disease								
Yes	386 (77,8)	<0,001	144 (29,0)	0,002	221 (44,6)	0,961	92 (18,5)	<0,001
No	497 (86,9)	-	118 (20,6)	-	254 (44,4)	-	61 (10,7)	-
Malnutrition *†								
Yes	132 (55,9)	0,070	88 (37,3)	0,003	144 (61,0)	<0,008	29 (12,3)	0,119
No	279 (48,8)	-	156 (27,3)	-	255 (44,6)		56 (9,8)	-

* Records with missing information were excluded; †Based on weight-for-age z-score < -2; PICU: Pediatric Intensive Care Unit; HAI: Healthcare-Associated Infection.

After adjusting for all confounding variables, using regression models that considered demographic characteristics (model 1) and clinical characteristics (model 2), the associations between septic shock and fasting (RR=1.16; 95%CI=1.10-1.23), HAI (RR=1.66; 95%CI=1.26-2.19), PICU stay > 4 days (RR=1.37; 95%CI=1.15-1.63), and death (RR=5.76; 95%CI=4.39-7.55) remained significant (Table 3).

Table 3: Crude and Adjusted Relative Risk (RR) and 95% Confidence Interval for Outcomes in Children Diagnosed with Septic Shock in Pediatric Intensive Care Unit (PICU), 2012-2017.

Outcomes	Crude analysisRR (CI95%)	Adjusted analysis (Model 1) RR (CI 95%)	Adjusted analysis (Model 2) RR (CI 95%)
Fasting	**1,14 (1,07-1,21)**	1,14 (1,07-1,21)*	1,16 (1,10-1,23) †
HAI	**1,67 (1,29-2,17)**	1,63 (1,25-2,13)*	1,66 (1,26-2,19) †
PICU stay > 4 days	**1,30 (1,09-1,56)**	1,33 (1,11-1,59) ‡	1,37 (1,15-1,63) §
Death	**5,66 (4,37-7,32)**	5,51 (4,25-7,14) ‖	5,76 (4,39-7,55) ¶

PICU: Pediatric Intensive Care Unit.
HAI: Healthcare-Associated Infections.
*Adjusted for age, sex, and origin.
†Adjusted for age, sex, origin, chronic illness, and malnutrition.
‡Adjusted for age and sex.
§Adjusted for age, sex, and malnutrition.
‖Adjusted for sex and origin.
¶Adjusted for sex, origin, chronic illness, and malnutrition.

Discussion

This study identified that the prevalence of septic shock in children admitted to the PICU was 10.3%, regardless of age and sex. Most admissions with this diagnosis came from other municipalities and required invasive mechanical ventilation (IMV) and the use of vasoactive drugs (VAD). Regarding the analyzed outcomes, septic shock was associated with a longer fasting period upon admission and a higher incidence of healthcare-associated infections (HAIs). Additionally, these children had a greater risk of extended stays in the PICU, with hospitalization exceeding four days and a fivefold increase in the incidence of mortality within this population.

In a North American study, pediatric sepsis was shown to account for 8% of PICU admissions (11). Regarding septic shock, a multicenter study conducted in Italian PICUs reported a prevalence of 2.1%[8]. These values were lower than those observed in this research (10.3%). It is believed that the analyzed period, the child's age, the diagnostic criteria used, and the sociodemographic conditions of the population may have influenced the result.

Regarding demographic characteristics, no differences were found concerning age and sex. However, a significant portion of children with septic shock came from other municipalities. In an Italian study, sepsis was more common in infants (32.8%) and preschool-aged children (31.5%), with no difference in mortality rates across age groups[8].

Contradictorily, other findings showed a relationship between male sex and sepsis, with an estimated ratio of 2:1 compared to females[7,9]. The hospital in this study is a regional reference for critically ill children, frequently admitting patients with sepsis-related complications. Access to the PICU may be delayed due to transport issues or originating service inefficiencies, leading to increased severity and worse prognoses for these children at admission, alongside challenges in establishing homogeneous and precise diagnostic criteria, in line with varying international recommendations[5,6,12].

Chronic illness and malnutrition were not associated with a diagnosis of septic shock in this study. The majority of the population diagnosed with septic shock had no comorbidities (56.2%). However, Pérez et al., in a study of seven PICUs in tertiary hospitals in Spain between 2011 and 2012, identified a high prevalence of comorbidities among the population diagnosed with sepsis[7]. Another multicenter study from Southwest China (9) found that 24.1% of children with septic shock had moderate or severe malnutrition, a percentage similar to that found in this study (29.3%), although the association was not significant in this case. Malnutrition in these children from developing countries has been viewed as a contributing factor to the progression of sepsis into septic shock, leading to increased severity[13].

In this study, the need for invasive mechanical ventilation (IMV) and vasopressor drugs (DVA) was 92.9% and 83.0%, respectively. High percentages were also identified in other studies, ranging from 69% to 75% for IMV and 57% to 100% for DVA[11,14]. Although guidelines do not specifically recommend obtaining a definitive airway, intubation should be considered for children with volume-refractory shock and DVA[15]. The risk of gastric content The use of vasoactive drugs (VAD) is well established in these cases. The updated Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children, published in 2020, supports this recommendation. It is considered reasonable to initiate VAD after 40-60 mL/kg of fluid resuscitation in patients who remain with poor perfusion, or even earlier if there are signs of fluid overload. However, there is no defined threshold at which shock is classified as volume-refractory[6,17]. Therefore, the precise timing for initiating VAD is not clear, despite its importance in therapeutic management. It is worth noting in this context that excessive fluid administration can lead to fluid overload, a situation associated with increased mortality in critically ill children[15].

After adjusting for confounding variables, the outcomes of fasting upon admission, healthcare-associated infections (HAIs), prolonged stay in the pediatric intensive care unit (PICU) exceeding four days, and mortality remained associated with the diagnosis of septic shock. The understanding of these associations stems from the greater severity of the cases, also marked by hemodynamic instability. Fasting contributes to poorer prognosis and predisposes patients to the development of HAIs, which, combined with the admission diagnosis of sepsis and septic shock, leads to prolonged hospitalization under intensive care[18]. It is important to emphasize that the development of HAIs in children has a greater impact on morbidity and mortality due to intrinsic factors in this population, such as immunological immaturity, the presence of immunodeficiencies, pre-existing diseases, the use of immunosuppressants, prolonged hospital stays, and invasive

procedures such as securing the airway and catheterization[5,18].

Conclusions

This research found a high prevalence of septic shock among children admitted to the PICU, particularly those from other municipalities. The use of invasive mechanical ventilation (IMV) and vasoactive drugs (VAD) was frequent in this population. Additionally, septic shock was associated with prolonged fasting at admission, a higher incidence of healthcare-associated infections (HAI), an extended stay in the PICU for more than four days, and increased mortality.

Pediatric sepsis remains one of the leading causes of mortality in PICUs. The challenges in recognizing and managing septic shock delay timely interventions, especially in certain Brazilian regions due to a lack of specialized resources. In this context, analyzing the characteristics of children in intensive care with this diagnosis and the related negative outcomes helps to identify the profile of patients at higher risk for unfavorable outcomes.

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Author Contributions

Fruzeto, FA: contributed to data collection, data analysis and interpretation, manuscript writing, and critical manuscript revision for intellectual content. Linck Junior, A: contributed to research design and conception, data collection, data analysis and interpretation, and critical manuscript revision for intellectual content. Vieira, AA: contributed to manuscript writing and critical manuscript revision for intellectual content. Gabani, FL: contributed to research design and conception, data collection, data analysis and interpretation, statistical analysis, manuscript writing, and critical manuscript revision for intellectual content.

Conflict of Interest

The authors certify that no commercial or associative interest presents a conflict of interest regarding the manuscript.

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