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Research

How Effective are Culture Results in Pediatric Sepsis Survival? A Single-Center Experience

Pediatrik Sepsiste Kültür Sonuçları Sağkalıma Ne Kadar Etkilidir? Tek Merkez Deneyimi

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ABSTRACT

Objective: Sepsis is a clinical syndrome with many faces. For successful treatment of pediatric sepsis, clinicians need a comprehensive understanding of the disease's risk factors, diagnostic procedures, and therapeutic approaches. Our study compared clinical features, laboratory data, and prognostic variables between culture-positive and culture-negative sepsis cases in children admitted to a tertiary pediatric intensive care unit (PICU).

Methods: A total of 57 pediatric patients aged 1-month to 18 years who presented to University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital with suspected or confirmed sepsis between February 2022 and January 2023 were assessed. The study included those who fulfilled the diagnostic criteria for sepsis or septic shock. Demographic data, clinical variables, and outcome measures were analyzed.

Results: Among sepsis cases, 20 (35%) had a positive blood culture, whereas 37 (64.9%) had a negative blood culture. A significantly greater proportion of cases with positive blood cultures required mechanical ventilation (p=0.034) and had longer PICU stays (p=0.004). There were no statistically significant differences between the two groups in treatment modalities, such as therapeutic plasma exchange, renal replacement therapy, and use of inotropic agents. Mortality rates were higher in the culture-positive group, but the difference was not statistically significant (p=0.509).

Conclusion: Although microbiological culture is critical for sepsis diagnosis, culture-negative children may have poor outcomes. Identification of risk factors for mortality and morbidity helps determine which cases should be followed more closely, based on the severity of the disease process, and which require the most appropriate treatment.

Keywords: Culture, infection, organ dysfunction, pediatric, sepsis

ÖZ

Amaç: Sepsis, birçok klinik yüzü olan bir sendromdur. Pediatrik sepsiste başarılı bir tedavi süreci için klinisyenlerin hastalığın risk etmenlerini, tanı sürecini ve tedavi yaklaşımlarını kapsamlı biçimde bilmeleri gerekmektedir. Çalışmamızda, üçüncü basamak pediatrik yoğun bakım ünitesinde (PYBÜ) kültür-pozitif ve -negatif sepsis hastalarının klinik özellikleri, laboratuvar verileri ve prognostik değişkenleri karşılaştırılmıştır.

Gereç ve Yöntem: Şubat 2022 ile Ocak 2023 tarihleri arasında Sağlık Bilimleri Üniversitesi, Sancaktepe Şehit Prof. Dr. İlhan Varank Eğitim ve Araştırma Hastanesi'ne şüpheli ya da kesin sepsis tanısı ile başvuran, 1 ay ile 18 yaş arasındaki toplam 57 pediatrik olgu değerlendirildi. Çalışmaya, sepsis veya septik şok tanı kriterlerini karşılayanlar dahil edildi. Demografik veriler, klinik değişkenler ve sonuç verileri analiz edildi.

Bulgular: Sepsis hastalarının 20'sinde (%35) pozitif kan kültürü varken 37'sinde (%64,9) negatif kan kültürü vardı. Kan kültürü pozitif olan hastalar önemli ölçüde daha fazla mekanik ventilasyona ihtiyaç duydu ve PYBÜ'de daha uzun süre kaldılar (p=0,034; p=0,004). İki grup arasında terapötik plazma değişimi, renal replasman tedavisi ve inotropik ajan kullanımı açısından istatistiksel olarak anlamlı bir fark yoktu. Kültür-pozitif grupta mortalite oranları daha yüksekti ancak istatistiksel olarak anlamlı değildi (p=0,509).

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ÖZ

Sonuç: Kültür sonucunun sepsis tanısında kritik bir yeri olsa da, negatif kültürü olan sepsis hastaları da zayıf tedavi başarısı gösterebilirler. Mortalite ve morbiditeyi etkileyen risk faktörlerinin tanımlaması, hangi hasta grubunun daha kötü seyredeceğini belirleyerek, uygun tedavi yöntemi seçilmesine yardımcı olacaktır.

Anahtar Kelimeler: Kültür, enfeksiyon, organ disfonksiyonu, pediatrik, sepsis

INTRODUCTION

Sepsis is an infection characterized by immune dysregulation and microcirculatory disorders resulting in life-threatening organ dysfunction. Severe sepsis accounts for more than 8% of all admissions to the pediatric intensive care unit (PICU) (1). It remains a leading cause of morbidity and mortality in children, with an annual mortality rate ranging from 4% to 50%, depending on disease severity, risk factors, and geographic location (2). To achieve the best outcomes, clinicians must be familiar with the risk factors, diagnosis, and treatment of sepsis in children (1).

Over the past two decades, guidelines for the management of sepsis and septic shock have been established and revised. In 2016, the Surviving Sepsis Campaign modified current definitions and protocols for adult patients (3). Despite the enormous burden that sepsis imposes on pediatric healthcare, current definitions of pediatric sepsis and organ dysfunction are based on the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) (4). These definitions are important for clinicians in recognizing and treating critical cases; however, clinical concern for sepsis should not be limited to physiological or laboratory abnormalities. Sepsis in children is difficult to identify and is associated with a high prevalence of febrile infections, challenges in differential diagnosis, stronger physiological compensatory mechanisms than in adults. These shortcomings have been highlighted more frequently since the definitions were developed in 2005 (1,5).

Blood culture is essential for the identification and for guiding further treatment in children with sepsis. However, blood cultures in suspected cases are frequently negative, and pathogen identification remains difficult. Culture-negative sepsis (CNS) refers to sepsis that has not been microbiologically confirmed. Limited data exist on CNS in pediatric cases, whereas it has been identified in 28-49% of severe sepsis cases in adults (6). The relationship between pathogen culture results and clinical outcomes in children is rarely investigated and remains highly controversial. All this conflicting information highlights the need for further studies.

Our study aimed to compare the clinical and demographic characteristics, laboratory parameters, and prognostic factors between CNS and culture-positive sepsis (CPS) cases among children hospitalized in a tertiary PICU.

METHODS

Study Population

This retrospective study was conducted between February 2022 and January 2023 in the PICU of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, affiliated with University of Health Sciences Türkiye. The PICU, which serves children aged 1-month to 18 years, is equipped with 12 beds, 12 ventilators, 5 Prismaflex™ hemofiltration machines (Baxter, USA), and 9 isolation rooms. During the study period, a total of 456 pediatric cases were admitted to the unit. Of these, 57 cases meeting the diagnostic criteria for sepsis or septic shock were included in the study.

We enrolled cases of sepsis defined either by the IPSCC or by the 2020 guidelines for children, or diagnosed by the treating clinician (2,4).

Cases who did not meet these criteria, who were treated with antibiotics before hospitalization, or who died within 24 hours were excluded from the study. Cases with false-positive culture results, primarily due to contamination, were excluded. Some organisms, such as coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp. (other than *Bacillus anthracis*), *Propionibacterium acnes, Micrococcus* spp., viridans group *Streptococci, Enterococci,* and *Clostridium perfringens* were considered contaminants in cases that did not meet the criteria for sepsis (7).

To detect pathogens, blood cultures were obtained from two sites at admission, and other biological samples were collected for culture according to the suspected infection site, including sputum, pleural effusion, ascites, urine, stool, pus. The volume of blood collected was determined based on case weight (6).

Ethics committee approval was received from the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval no: 2023/29, date: 17.02.2023). This study was planned in accordance with the principles of the Declaration of Helsinki. As the study was retrospective and personal data were anonymized, informed consent was not required.

Patient Characteristics

Data were collected using a detailed form recording the case's age, gender, comorbidities, length of stay in the PICU, duration of invasive mechanical ventilation (IMV), requirement for extracorporeal treatment, treatment with inotropic agents, laboratory parameters, treatment outcomes, and mortality. Blood samples for all cases were collected at approximately the same time after onset, and the worst value within the first 24 hours after admission was recorded. Complete blood count, serum albumin, lactate dehydrogenase, procalcitonin, C-reactive protein, and blood gas analysis on admission were retrospectively obtained from our electronic health information system. To calculate the Pediatric Risk of Mortality III (PRISM III) score, data on 16 variables—temperature; systolic blood pressure; heart rate; partial pressure of arterial oxygen; partial pressure of arterial carbon dioxide; Glasgow Coma Scale score; pupillary reaction; prothrombin time and activated partial thromboplastin time; serum creatinine; serum urea nitrogen; serum potassium; blood glucose; serum bicarbonate; white blood cell count; and platelet count—were recorded within 24 hours of PICU admission (8).

Statistical Analysis

SPSS version 20.0 for Windows was used to perform statistical analyses. Descriptive statistics included counts, frequencies (%), ratios, medians, and standard deviations. The distributions of the variables were assessed using the Kolmogorov-Smirnov test. During the analysis of quantitative data, t-tests and Mann-Whitney U tests were used. The chi-square test was used to compare categorical variables, and the Fisher's exact test was used when chi-square test assumptions were not met.

RESULTS

During the study period, 57 of 456 cases were admitted to the PICU with a diagnosis of sepsis. The sex distribution was approximately equal. The cases' median ages were 41 (3-98) months and 21 (1-194) months in the blood culture-positive and blood culture-negative groups, respectively. There were no statistically significant differences in age, gender, or PRISM III score. Of the total cases, 20 (35%) had positive bacterial blood cultures, whereas 37 (64.9%) had negative bacterial blood cultures (Table 1). The pathogens isolated from positive cultures are shown in Table 2. The most frequent bacterium was *Pseudomonas aeruginosa* (24.3%).

Significantly more cases with positive blood cultures required mechanical ventilation and had longer PICU stays (p=0.034; p=0.004). There were no statistically significant differences between the two groups in treatment modalities, including therapeutic plasma exchange (TPE), continuous renal replacement therapy (CRRT), and inotropic agents. Mortality rates were higher in the CPS group, but the difference was not statistically significant (p=0.509) (Table 1).

Table 1. Demographics, clinical characteristics of children with septis according to the culture results.

		Sepsis		p
		Culture-positive sepsis (n=20)	**Culture-negative sepsis (n=37)**	
Gender, (%)	Male	10 (50%)	22 (59.5%)	0.492
	Female	10 (50%)	15 (40.5%)	
Age (month), mean (range)		41 (3-98)	21 (1-194)	0.219
PRISM III score		12.0 (0.0-30.0)	10.0 (0.0-40.0)	0.255
Mortality, (%)		6 (30.0)	7 (18.9)	0.509
Length of stay (day)		14.5 (4-90)	6.0 (2-59)	**0.017**
Length of stay >7 days, (%)		16 (80.0)	22 (59.5)	**0.004**
Requirement of IMV, (%)		16 (80.0)	19 (51.4)	**0.034**
Duration of IMV, days		8.0 (1-90)	7.0 (2-49)	0.683
Requirement of TPE, (%)		10 (50%)	11 (29.9%)	0.448
Requirement of CRRT, (%)		7 (35%)	16 (43.2%)	0.545
Requirement of inotropic agents, (%)		15 (75%)	18 (48.6)	0.054
Pathogens	Gram-positive bacteria	2 (10.0%)		-
	Gram-negative bacteria	12 (60.0%)		
	Fungus	2 (10.0%)		
	Multipl pathogens	4 (20.0%)		

Bold values indicate statistically significant results (p<0.05)
CRRT: Continuous renal replacement therapy, IMV: Invasive mechanical ventilation, PRISM III: Pediatric Risk of Mortality III, TPE: Therapeutic plasma exchange

Univariate analyses were performed on cases of sepsis. Statistically significant associations were observed between prolonged length of stay, requirement for IMV, inotropic agent use, CRRT, TPE, and mortality. In addition, the analysis showed that levels of leukocytes, lymphocytes, and albumin, as well as the lactate/albumin ratio, were significantly associated with mortality in septic cases (Tables 3 and 4).

DISCUSSION

In the diagnosis and treatment of sepsis, standard practice is to identify pathogens by culture. However, culture positivity in children is uncommon, and the impact of positive versus negative culture results on the prognosis of children with sepsis remains unclear. In our study, only 35% of children admitted to the PICU with a diagnosis of sepsis had a positive blood culture on admission. Although this rate is similar to the 30% positive culture rate of Hazwani et al. (6), it is lower than that reported in most other studies (9).

An important question is why the microorganisms can be identified in some cases of sepsis but not in others. Possible explanations for CNS exist. First, according to the Surviving Sepsis Campaign Guidelines, broad-spectrum antibiotics should be administered as soon as possible to improve outcomes in children (2). In recent years, broad-spectrum antibiotics have been administered early in suspected cases as a result of increased diagnostic vigilance. In our study, we addressed the first factor by excluding all patients who had received antibiotics before hospitalization. This methodological choice strengthens the validity of our findings regarding the CNS.

Another possibility is an the increasing prevalence of non-bacterial sepsis, such as viral or fungal sepsis, which is difficult to detect using conventional methods. Hazwani et al. (6) reported that the incidence of CNS was higher than that of CPS in the presence of respiratory tract infections. This finding supports the possibility of viral sepsis in some cases within the CNS group and may partially explain the lower rate of culture positivity. However, we did not

Table 2. Frequency of pathogens for the positive cultures

	Frequency (%)	Blood	Tracheal aspirate	Urine	Cerebrospinal fluid
Gram-positive, n (%)	6 (16.2%)				
Enterococcus species	3 (8.1%)	2	1	-	-
Methicillin-resistant *Staphylococcus aureus*	2 (5.4%)	-	2	-	-
Streptococcus pyogenes	1 (2.7%)	-	-	-	1
Gram-negative, n (%)	23 (62.1%)				
Pseudomonas aeruginosa	9 (24.3%)	4	5	-	-
Escherichia coli	4 (10.8%)	1	1	2	-
Klebsiella species	3 (8.1%)	3	-	-	-
Acinetobacter baumannii	3 (8.1%)	1	2	-	-
Stenotrophomonas maltophilia	3 (8.1%)	-	3	-	-
Neisseria meningitidis	1 (2.7%)	1	-	-	-
Fungus, n (%)	8 (21.6%)				
Candida species	8 (21.6%)	4	4	-	-

Table 3. Treatment modalities according to sepsis outcomes

	Outcome		p
	Mortality (%), (n=13)	Survival (%), (n=44)	
Length of stay >7 days	7 (22.6)	24 (77.4)	0.965
Requirement of IMV	13 (37.1)	22 (62.9)	**<0.001**
Requirement of CRRT	11 (47.8)	12 (52.2)	**<0.001**
Requirement of TPE	8 (38.1)	13 (61.9)	**0.036**
Requirement of inotropic agents	13 (39.4)	20 (60.6)	**<0.001**

Bold values indicate statistically significant results (p<0.05)
CRRT: Continuous renal replacement therapy, IMV: Invasive mechanical ventilation, TPE: Therapeutic plasma exchange

Table 4. Relationship between laboratory parameters and outcomes of sepsis patients

	Outcome		p
	Mortality (%), (n=13)	**Survival (%), (n=44)**	
Leukocyte	7850 (100-28050)	12565 (50-86300)	**0.036**
Neutrophil	4720 (70-24100)	8070 (0-76700)	0.073
Lymphocyte	860 (0-6180)	2165 (0-9720)	**0.010**
Platelet	111000 (55000-446000)	224500 (8000-680000)	0.227
RDW	15 (13-19.4)	14.3 (11.9-22.0)	0.151
CRP	62.59 (6.27-313.6)	62.41 (0.60-349.10)	0.581
Procalcitonin	7.16 (0.37-334.24)	18.44 (0.07-593.50)	0.732
Lactate	2.17 (1.3-10.0)	1.84 (0.8-16.6)	0.135
LDH	365 (206-3340)	384 (173-5316)	0.879
Albumin	2.74 (2.03-3.62)	3.31 (1.68-5.00)	**0.012**
Lactate/albumin ratio	0.77 (0.36-3.03)	0.54 (0.18-4.44)	**0.035**
Neutrophil/lymphocyte ratio	5.09 (1.60-28.02)	4.01 (0.32-102.13)	0.566
CRP/albumin ratio	23.79 (2.43-109.65)	18.58 (0.18-114.46)	0.458
PCT/albumin ratio	2.50 (0.14-92.33)	4.91 (0.01-201.18)	0.924
LDH/albumin ratio	139.50 (72.03-1403-36)	146.86 (53.35-2150.0)	0.621

Bold values indicate statistically significant results ($p<0.05$)
CRP: C-reactive protein, LDH: Lactate dehydrogenase, PCT: Procalcitonin, RDW: Red cell distribution width

routinely perform viral respiratory panels for all cases, which is a limitation of the study. Some CNS cases may have represented viral sepsis, particularly in the presence of upper or lower respiratory tract involvement. Future studies should include molecular viral diagnostics to clarify this issue.

Sepsis is a highly heterogeneous clinical syndrome with complex and variable manifestations. Non-infectious conditions, such as hematologic diseases or chronic inflammatory disorders, may clinically mimic sepsis and contribute to lower culture positivity rates. In the study by Huang et al. (9), no significant difference was found between the CNS and CPS groups in terms of overall comorbidities. However, in our study we did not perform a subgroup analysis comparing the CNS and CPS groups regarding chronic inflammatory conditions or immunodeficiencies. This limitation suggests that non-bacterial causes or sterile inflammatory processes may be more prevalent among culture-negative cases and highlights an important gap in understanding the clinical similarities and differences between the two groups.

In our study, CNS and CPS cases showed similar IMV duration, use of inotropic agents, need for TPE, and need for renal replacement therapy. The CPS group, on the other hand, had longer hospital stays and required mechanical ventilation more often than the CNS group. One possible explanation for this result is that children with culture-positive results typically require prolonged antibiotic therapy, particularly in cases of bacteremia and meningitis, and are more likely to develop extrapulmonary pediatric respiratory distress syndrome. Huang et al. (9) showed that children with CPS had a significantly longer length of stay than in our study. However, unlike in our study, the requirement for IMV was similar. Cases with CNS were not significantly different from cases with CPS in terms of inotropes, length of PICU stay, or hospital stay, according to Hazwani et al. (6). It is possible that variations in case demographics, organ dysfunctions, and bacterial resistance to antibiotics all play a role in these dissimilarities.

Several studies have examined the impact of microbiological culture results on the prognosis of patients with sepsis over the past decade. In meta-analyses of adult populations, no statistically significant correlation was found between culture results and mortality (10,11). Our findings revealed comparable mortality rates for the CNS and CPS groups, in accordance with the literature. However, Hazwani et al. (6) demonstrated that among pediatric cases, the CPS group had a higher mortality rate than the CNS group. Changes in diagnostic criteria and in the definition of sepsis over time may explain the differences in these results. Moreover, excluding cases with non-bacterial infections from the studies may contribute to these differences.

With advances in pediatric critical care, it is increasingly crucial to understand which aspects are most relevant to mortality in children with sepsis, as this will aid in risk classification and the better allocation of healthcare

resources. Numerous clinical and laboratory parameters were investigated for their prognostic value in studies (12-14).

The survivor group required statistically significantly fewer interventions, including mechanical ventilation, inotropic agents, TPE, and renal replacement support. Cases with high leukocyte counts and high lactate/albumin ratios, as well as low lymphocyte counts and low albumin levels upon admission, were statistically associated with poor prognosis. In our opinion, cases with the aforementioned risk factors can be monitored and treated more aggressively.

Study Limitations

The main limitations of this study were the small number of cases compared with sepsis studies in adults and the inclusion of patients from only one tertiary center. The inclusion of multiple centers could provide additional information and identify other prognostic factors in sepsis among children. Second, low culture positivity and the lack of standardized timing for culture collection may have affected the results of pathogen identification.

CONCLUSION

In conclusion, sepsis is a clinical syndrome with multiple manifestations. Although culture is important for diagnosis, it should not be forgotten that the prognosis may be poor in culture-negative cases. Identification of risk factors for mortality and morbidity helps determine which cases should be followed more closely according to the severity of the process and the most appropriate treatment.

ETHICS

Ethics Committee Approval: Ethics committee approval was received from the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval no: 2023/29, date: 17.02.2023).

Informed Consent: As the study was retrospective and personal data were anonymized, informed consent was not required.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: K.B.G., C.D., Concept: K.B.G., Design: E.G.Ş., C.D., Data Collection or Processing: Y.Y.C., Analysis or Interpretation: A.S., Literature Search: E.G.Ş., F.V., Writing: E.G.Ş., C.D., F.V.

Conflict of Interest: No conflict of interest was declared by the authors.

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