RESEARCH PAPER

Six-Year Surveillance of Acquired Bloodstream Infection in a Pediatric Intensive Care Unit in Israel

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Received: June 06, 2022;
Initial review: June 27, 2022;
Accepted: September 19, 2022

Objectives: We studied the profile of bloodstream infections (BSI) in the pediatric intensive care unit (PICU) and identified predictors of mortality. **Methods**: The study collected data from hospital records for children younger than 18-years who developed BSI during their PICU stay between 2014 and 2019. **Results**: In 114 patients, 136 PICU-acquired BSIs with 152 pathogens were documented. The incidence of BSI was 47.12/1000 PICU admissions and 7.95/1000 PICU hospital days. Gram-negative rods accounted for 75% of isolates, Gram-positive cocci accounted for 21.7% of isolates, and fungi accounted for 3.3% of isolated pathogens. ICU mortality was observed in 25 (21.9%) patients with a BSI compared to 94 (3.1%) patients without a BSI (P<0.001). Hemodynamic instability (P=0.014, OR 4.10, 95%CI 1.33-12.66), higher blood urea nitrogen (BUN) (P=0.044), and lower albumin levels (P=0.029) were associated with increased risk of ICU mortality. **Conclusion**: BSI in the PICU is associated with increased mortality. Early identification and management of risk factors independently associated with poor clinical outcomes in these patients should be aimed to ensure improved survival.

Keywords: *Hypoalbuminemia, Klebsiella spp, Mortality, Nosocomial infection*.

Published online: October 29, 2022; ***PII***: S097475591600464

Bloodstream infections (BSI) acquired in the pediatric intensive care unit (PICU) are the leading cause of hospital morbidity and mortality [1]. Mortality rates attributable to BSI range from 11% to 81.8% [1-3]. A few studies have addressed the epidemiology of BSI in pediatric patients admitted to PICU [1-5], but none of these studies have examined the predictors of mortality. Recognition and treatment of these predictors of mortality may lead to a reduction in the incidence, and consequently, the morbidity and mortality of BSI.

The aim of this study was to determine the characteristics and outcome of BSI in the PICU, and to identify predictors of mortality in these patients.

METHODS

We retrieved hospital records of children younger than 18 years who were admitted to the PICU of Rambam Health Care Campus between January, 2014 and December, 2019, and had acquired BSI. This is a tertiary, university-affliated hospital with a 15-bed PICU with an average of 520 annual PICU admissions, and facilities for respiratory and hemodynamic support, including extracorporeal membrane oxygenation. Cases were identified from monthly reports of positive blood cultures. Clinical and laboratory data of patients with positive blood cultures were obtained from the case sheets. The study was approved by the local ethics committee.

The Centers for Disease Control (CDC) guidelines were used for classification of BSI [6]: PICU-acquired BSI: BSI that occurred after the first 48 hours of hospital admission, when no evidence of infection was present on admission; Primary BSI: BSI that was not due to infection at another body site; Central line-associated BSI (CLABSI): BSI in which a central venous catheter (CVC) is present; Secondary BSI: BSI due to site-specific infection; and, Mucosal barrier injury (MBI): BSI in neutropenic patients or oncologic patients with diarrhea. Hemodynamic instability was defined as need for fluid resuscitation and/or vasopressors, and respiratory deterioration was defined as worsening respiratory status. PICU associated mortality was defined as mortality occurring during the stay in PICU.

Coagulase-negative staphylococci (CoNS) and other commensal bacteria were considered true pathogens only if patients had at least two positive cultures or, alternatively, clinical signs of sepsis and had received targeted antibiotic treatment [6].

Statistical analysis: Data were analyzed using SPSS software (version 26). Univariate analyses were performed using chi square test for categorical variables and independent *t* test for continuous variables. All tests were two-tailed, and $P<0.05$ was considered statistically significant. A binomial regression model was fitted for potential predictors of mortality during PICU stay. In this model, only the last sepsis episode of each patient was considered. Variables were included if the *P* value in the univariate analysis was <0.1; variables with $P<0.05$ were retained.

RESULTS

Over the six-year study period, 114 patients [61 males; median (IQR) age, 0.92 (0.12,11.53) years] were diagnosed with 136 episodes of BSI, with isolation of 152 pathogens (**Web Fig. 1**). The BSI incidence rate in the PICU was 47.12 per thousand PICU admissions, and 7.95 per thousand PICU hospitalization days (**Fig. 1**).

About half of the patients with BSI were younger than 1 year, compared with 29.1% of all patients admitted to the PICU during the study period ($P<0.001$). A CVC was documented in 99 (72.8%) cases, and 60 (60.6%) episodes of these were defined as CLABSI. Mean (SD) time from CVC insertion to BSI in patients with CLABSI was 14.45 (13.08) days (**Table I**).

A total of 152 isolates were identified from blood cultures. Most, 114 (75%), were Gram-negative rods (GNR).

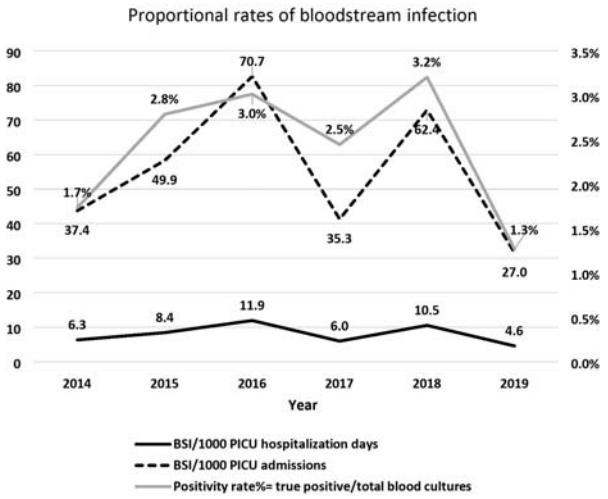

Fig. 1 Rates of bloodstream infections in children in a pediatric intensive care unit in Haifa, Israel (2014-2019).

Table I Characteristics of Children With Bloodstream Infection in the Pediatric Intensive Care Unit (*N*=114)

Characteristic	*Number (%)*
Age	
0-28 d	22 (19.3)
29 d - 1 y	36 (31.6)
1-5 y	19 (16.7)
>5 y	37 (32.5)
Jewish ethnicity	35 (30.7)
Diagnosis on admission	
Medical	73 (64)
Surgical	25 (21.9)
Trauma/burns	15 (13.2)
Underlying condition	
No underlying condition	25 (21.9)
Cardiac	33 (28.9)
Genetic/metabolic	15 (13.2)
Neurologic	11 (9.6)
Oncologic/immune deficiency	11 (9.6)
Renal	6 (5.3)
Gastrointestinal	6 (5.3)
Prematurity	4 (3.5)
Pulmonary	3 (2.6)
Carriage of multidrug resistant organisms at time of BSI[a]	
Extended spectrum beta-lactamases	45 (39.5)
Enterobacteriaceae	
Methicillin-resistant *Staphylococcus aureus*	8 (7)
Vancomycin resistant *Enterococcus*	3 (2.6)
Clinical presentation	
Fever	99 (72.8)
Hemodynamic instability	35 (25.7)
Respiratory deterioration	53 (39)
Acute renal failure	20 (14.7)
CVC type (>2 d)	
No CVC	37 (27.2)
Subclavian	11 (8.1)
Femoral	30 (22.1)
Jugular	35 (25.7)
Multiple	23 (16.9)
Classification	
CLABSI	60 (44.1)
Secondary BSI	42 (30.9)
Primary BSI	29 (21.3)
Mucosal barrier injury BSI	5 (3.7)
Secondary BSI	
PVAP/PNEU	24 (57.1)
Surgical site infection	6 (14.3)
CAUTI/SUTI	8 (19)
Other sources	4 (9.6)

Values in no. (%) [a]*One child had carbapenem resistant Acinetobacter. CVC-central venous catheter, CLABSI-central line associated blood stream infection, BSI-bloodstream infection, PVAP/PNEU-ventilator associated pneumonia, CAUTI/SUTI-catheter associated urinary tract infection.*

Table II Predictive Factors for Mortality in the Intensive Care Unit (ICU) in Children With Bloodstream Infection

Factors	*ICU survivors (n=89)*	*ICU non-survivors (n=25)*
Age (y)[a]	4.82 (6.16)	5.43 (6.94)
Male gender	50 (56.2)	11 (44)
Arab ethnicity	60 (67.4)	19 (76)
Admission cause		
Medical	55 (62.5)	18 (72)
Surgical	20 (22.7)	5 (20.0)
Trauma/burns	13 (14.8)	2 (8.0)
Associated serious comorbid condition[c]	65 (73.0)	23 (92.0)
Hemodynamically unstable[c]	19 (21.3)	12 (48.0)
Consciousness deterioration	6 (6.8)	2 (8)
Acute kidney injury	12 (13.6)	6 (24)
Laboratory		
White blood count (10^9/L)[a]	14.07 (11.56)	15.96 (15.44)
Hemoglubin (g/dL)[a]	10.22 (2.69)	10.35 (2.26)
Albumin (g/dL)[a,c]	2.75 (0.69)	2.43 (0.54)
CRP (mg/dL)[a]	0.53 (0.41)	0.74 (0.72)
Lactate (mmol/L)[a]	1.56 (0.64)	2.68 (1.41)
Creatinine (mg/dL)[a]	0.53 (0.42)	0.74 (0.72)
BUN (mg/dL)[a,c]	17.9 (14.2)	34.87 (29.39)
Gram-positive organisms	23 (26.7)	5 (20.8)
CLABSI	38 (42.7)	12 (48.0)
ICU stay before BSI (d)[a]	17.9 (15.42)	17.60 (17.26)
ICU stay after BSI (d)[a]	25.1 (28.93)	21.08 (31.40)
Carriage of resistant bacteria[b]	43 (48.3)	15 (60.0)
Carriage of ESBL	31 (34.8)	14 (56.0)
Inappropriate empiric antibiotics	13 (12)	5 (11.6)

All values in no. (%) or [a]mean (SD). [b]Resistant bacteria-ESBL, CRE, MRSA, VRE or CRAB. CLABSI-central line-associated bloodstream infection, ESBL-extended-spectrum beta-lactamase Enterobacteriaceae, CRE-carbapenem resistant enterobacteriaceae, MRSA-methicillin resistant staphylococcus, VRE-vancomycin resistant enterococcus, CRAB-carbapenem resistant Acinetobacter baumani. [c]P<0.05.

Klebsiella spp. were most frequently identified in 37 (24.3%) cultures. Gram-positive cocci (GPC) were detected in 33 (21.7%) cultures. *Staphylococcus aureus* was most frequently isolated GPC in 13 (8.6%) cultures.

Fifty-eight (50.9%) patients were carriers of multi-drug resistant organisms (MDRO) at the time of bacteremia, detected by screening or clinical specimens. ESBL producing enterobacteriaceae were isolated from blood cultures of 36 (31.6%) patients and MRSA was isolated from blood cultures of 4 (3.5%) patients. Carbapenem-resistant enterobacteriaceae (CRE) were not detected during the study period. GNR resistance to amikacin was detected in 6 (5.8%), to piperacillin-tazobactam in 20 (20.6%) and to ceftazidime in 36 (40.9%) patients (**Table I**).

Mortality occurred during stay at PICU was documented in 25 (21.9%) patients with BSI compared with 94 (3.1%) patients without BSI. Mean age, sex, and ethnicity were similar in survivors and non-survivors. Bacteria group (GNR vs GPC) was not associated with higher mortality (P=0.557). Inappropriate empiric antibiotic treatment administered within 2 hours of clinical or laboratory evidence of bacteremia occurred in 12% of survivors and 11.6% of non-survivors (P=0.944) (**Table II**).

In univariate analysis, presence of serious comorbid condition, hemodynamic instability, low albumin level and higher blood urea nitrogen (BUN) levels were significantly more prevalent in non-survivors (P=0.046, 0.008, 0.035 and 0.010, respectively). These variables were included in the multivariate analysis in addition to carriage of ESBL (P=0.056). In the multivariate analysis, hemodynamic instability resulted in a 4-fold increase in ICU mortality. Each one-unit increase in BUN level was associated with a 1.026-fold increase in ICU mortality, whereas each one-unit decrease in albumin level was associated with a 2.6-fold increase in ICU mortality (**Table II**). The logistic regression model was statistically significant (P<0.001), and fitted the data well, as shown by Hosmer and Lemeshow test (P=0.317).

DISCUSSION

We found a high proportion of BSI among children in PICU, comparable to rates of 56 and 63/1,000 PICU admissions [2,3] and to 7 and 31.2/1,000 patient days [2,5]. During the study period, the incidence of BSI varied between 27 and 70.7/1,000 PICU admissions. This change in incidence may be related to the changing workload and intermittent reinforcement of infection prevention measures taken to reduce BSI in ICUs, such as reimplementation of CVC insertion and maintenance policies, surveillance of BSI, and debriefing of BSI events. The significant proportion of patients younger than one year and patients with complicated underlying diseases may explain the broad use of invasive devices, such as a CVC in this cohort.

The ICU mortality rate in patients who developed BSI was consistent with that reported by Gray, et al. [7], but significantly lower than in previous studies (40.7 -55.9%) [2,3]. In the current study and in another Israeli study [3], ICU mortality was 7-fold higher in patients with BSI than in patients without BSI. This difference in ICU mortality was less pronounced in other studies worldwide [5,7].

Hemodynamic instability, as also noted by Pillon, et al. [8], increased BUN, and decreased albumin levels were identified as predictors of PICU-associated mortality. Diagnostic tools based on biomarkers such as albumin and urea have been successfully used to predict mortality

WHAT THIS STUDY ADDS?

- Profile of bloodstream infections and associated factors of mortality in the pediatric intensive care unit are presented.

[9,10]. Critical illness often results in altered cellular energy metabolism and protein catabolism. Whether albumin levels or nutritional status have a direct adverse effect on survival or reflect severe disease and catabolic state remains to be determined [11]. The predictors of ICU mortality found in this study may reflect in some way the severity of illness at the onset of bacteremia and the compromise to vital organs.

Similar to previous studies [2,3,5], GNR pathogens were responsible for the majority of BSI events [2,3,5], but they were not associated with greater mortality. We found a much lower rate of fungemia in this study, compared to 7.8-15% in previous studies [3,5].

The main limitation of the study was its retrospective design, which may affect the quality of the data and follow-up. However, most of the data were collected as part of a national monthly surveillance of BSI in intensive care units in Israel, which masks this limitation. Although, a single study, it was conducted in a large referral center that enrolls patients with complicated conditions, which may mitigate this limitation and even overestimate the mortality rate. Although data on comorbidities and disease severity parameters were presented in the current study, no well-known disease severity scores were used to standardize severity, and no severity data were collected from patients who were admitted to the PICU but had not developed BSI, making it difficult to determine whether patients with BSI had higher severity compared with patients without BSI. Moreover, the fact that low albumin levels were associated with mortality makes it necessary to assess overall nutritional status in future studies.

In conclusion, the high incidence of BSI, the high mortality in patients with BSI, and the uncontrolled factors predicting mortality found in this study underscore the need for continuous surveillance and infection prevention interventions to all patients to reduce the incidence of BSI. These predictors may indicate severe disease and catabolic state, and clinicians should be aware of these predictors and provide optimal supportive and nutritional care.

Ethics clearance: Local Ethics Committee; No.0053-19-RMB, dated Jan 24, 2019.
Contributors: HDY,IK,KH: designed the study, analyzed the data and edited the manuscript; MA,RDS: gathered the data and reviewed the manuscript; JBA,AH, YSM,TA: helped in gathering the data and revising the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding; None*; Competing interests*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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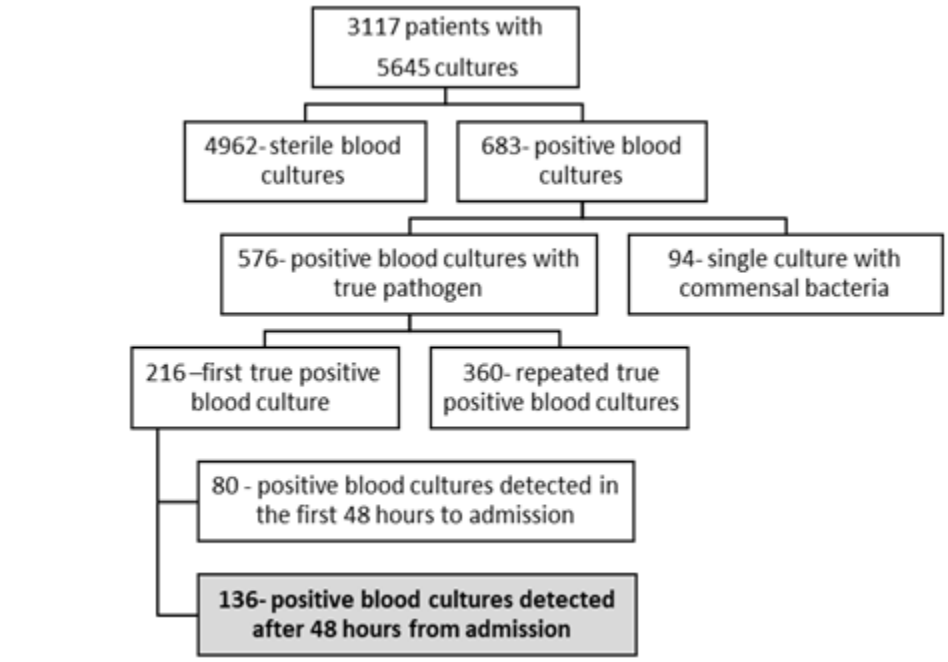

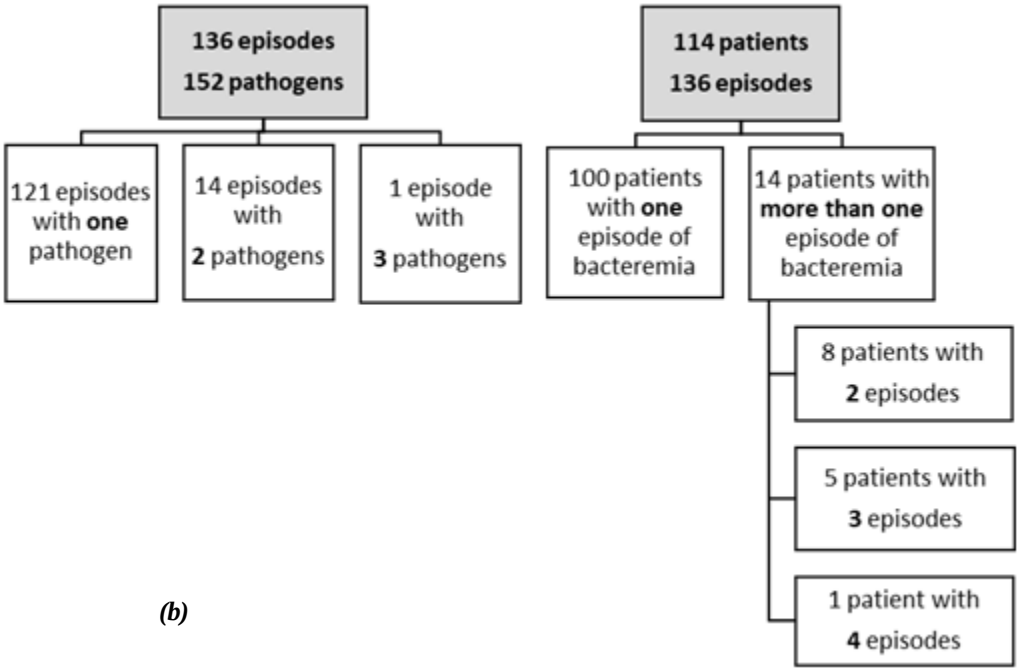

Web Fig. 1. (*a*) The total number of patients and blood cultures identified in the study. (*b*) Flowchart of patients, episodes and pathogens included in the study.