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Evaluation of Bacteremia in a Pediatric Intensive Care Unit: Epidemiology, Microbiology, Sources Sites and Risk Factors

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A B S T R A C T

Bacteremia is a common cause of morbidity and mortality in children treated in pediatric intensive care unit (PICU). We have investigated the causative agents of bacteremia in our PICU over a one-year period, to determine mortality associated with such infection and identify the dependent predictors for morbidity and mortality. From 1 January till 31 December 2006, 479 patients were admitted in the PICU and 379 blood culture samples were taken. Samples were incubated in the BACTEC 9050 System, and isolates identified by routine microbiological methods. A pair of samples taken for aerobic and anaerobic culture were statistically regarded as one sample. Data collected from the medical records of each patient were recorded onto standardized collections sheets and included demographic information, predisposing conditions, source(s) of infection, important clinical and laboratory parameters at the time of infection, and microbiological data. Based on these data, positive blood cultures were classified as either contaminants or true bacteremias. During a year period, 117 episodes of bacteremia were documented in 72 patients. The most frequent isolates were the coagulase-negative staphylococci 32.2% (39), followed by Candida spp. 30.5% (36). The mean white blood cell count (WBC) on the day of bacteremia was 15.2 × 10^9/L (range 0.1–48.0 × 10^9/L), and 3.3% of episodes occurred in neutropenic (WBC count <1 × 10^9/L) children. The mean temperature on the day of infection was 38.2±1.1 °C (range, 34–41 °C). Some newborns 23% (n=5) had a significantly lower mean temperature (p<0.02) and lower mean WBC count (p<0.05) than older children. Hemodynamic instability was noted in 11% of bacteremic episodes. Among all bacteremias, intravascular catheters were implicated in 22.6%, pneumonia in 20.4%, genitourinary tract in 14.2%, surgical wounds in 11.7% and, gastrointestinal tract in 9.8%. Seven patients died because of sepsis. Early diagnosis, prompt blood culture reports, followed by appropriate antibiotic treatment is essential in reducing mortality in such patients. Short hospital stay and restricted use of invasive devices should be the aims to reduce the risk of bacteremia during the stay in the PICU.

***Key words**: bacteremia, pediatric intensive care unit, epidemiology, surveillance*

Introduction

In hospitals the incidence of infection is highest in the intensive care units, adult and children, and these would seem suitable areas for targeting efforts to reduce bacteremia[1–3]. Although the number of cases of bacteremia in hospital is small in comparison with urinary and respiratory tract infections, the morbidity and mortality rates are high[4–7]. Identification of those at risk could help focus efforts on prevention and early diagnosis should lead to earlier and more appropriate therapy for those in whom the diagnosis is suspected. Blood culture remains the gold standard in diagnosing causative pathogens; however, the average time to detection of positive cultures is

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TABLE 1
THE SYSTEMIC INFLAMMATORY SYNDROME (SIRS)

Clinical manifestations	Underlyng cause
Any two or more of the following:	Any of the following:
Body temperature >38 °C or <36 °C	infection
Heart rate > p bpm	intestinal endotoxin
Respiratory rate >20	ischemia
Hyperventilation ($PaCO_2$ <32 mmHg)	multiple trauma
WBC > 12.000/mm^3 or <4.000 mm^3	noxious substances
Immature neutrophils >10%	pancreatitis
	shock
	thermal injury

From ACCP/SCCM Consensus Conference on Sepsis and Organ Failure, American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference Committee, Chest, 101 (1992) 1644.

16 hours and may be as long as 24 to 48 hours[8], increasing the risk of complications.

During a year period, 117 episodes of bacteremia were documented in 72 patients. The aim of the study was to: 1) assess the incidence of bacteremia in our pediatric intensive care unit (PICU), 2) describe their epidemiologic and microbiologic characteristics, and 3) determine other risk factors for developing bacteremia.

Materials and Methods

Setting

Children in the intensive care unit were chosen for this prospective study because of the accurate documentation of blood culture results in their files. Children's Hospital is a 230-bed teaching hospital in Zagreb, Croatia, University of Zagreb, School of Medicine. From January 1 to December 31, 2006, 479 children were admitted in the PICU and 379 blood culture samples were taken. The mean age of children was 5.4 years (min. 1 day, max. 15 years), and the median length of PICU stay was 7.5 days (range, 2–273). There were 39 newborns (8.1%), 269 boys and 210 girls.

Patient data

Clinical parameters recorded on the day of bacteremia included the patient's white blood cell count and maximal or lowest temperature if the patient was hypothermic (<36.0 °C). Also noted was any evidence of hemodynamic instability or shock, manifest as hypotension, requirement for vasopressor medications to maintain adequate end-organ perfusion, or oliguria (<1mL/kg urine output over a hour period). The source(s) of each episode were also recorded. These included the lower respiratory tract, gastrointestinal tract, hepatobiliary tract, peritoneum, genitourinary tract, intravascular catheter, urinary catheter, bone or joint, skin or soft tissue, surgical wound, endocarditis, and other.

TABLE 2
MICROBIOLOGICALCHARACTERISTICS

Microorganisms	Number	Isolates %
Coagulase negative staphyloccoci (CNS)	39	32.2
Staphylococus aureus (MRSA)	2	2
Candida	36	30.5
Enterobacteria	20	17.3
E. coli (11)		
Serratia spp. (4)		
Enterobacter spp. (4)		
K. pneumoniae (1)		
Non-fermentative gram-negative bacteria	13	11.6
P. aeruginosa (8)		
Acinetobacter spp. (4)		
Xanthomonas maltophilia (1)		
Streptococci	5	4.4
S. pneumoniae (1)		
S. viridans (2)		
Enterococcus (2)		
Corynebacterium Sp.	1	1
Anaerobes	1	1
Total	117	100%

Data collected from the medical records of each patient were recorded onto standardized collection sheets and included demographic information, predisposing conditions, source of infections, important clinical parameters at the time of infection, and microbiologic data. Based on this data, positive blood cultures were classified as either contamination or bacteremia. We use the term bacteremia to mean either bacteremia or fungemia, unless otherwise specified. Copy isolates, defined as the same organism isolated from multiple blood cultures from the same patient within 48h were excluded. An episode of polymicrobial bacteremia referred to the isolation

of more than one presumed pathogenic organism from blood cultures from the same individual taken within the 48 h period. The probable source of infection was determined by the physician reviewer, and was based on objective clinical evidence, microbiologic data, and the physician's clinical judgment.

The clinical signs and parameters that promoted a blood culture to be taken were:

1. Signs of a systemic inflammatory response syndrome (SIRS) (Table 1).
2. Body temperature above 38 °C or lower than 36 °C in high-risk patients (patients with wound infection, pneumonia, endocarditis, pericarditis, perforated ulcer, pancreatitis, sinusitis, catheter sepsis, translocation, enterocolitis, bowel infractions, urosepsis).

Epidemiology

Precise definitions have been largely debated in the literature, but those proposed by the full name (CDC) in 1988[9,10] have been validated and are now widely used. The aim of the study was to determine microbiological characteristics (incidence of microorganismus causing) bacteremia in our PICU, to determine mortality associated with such infection and indentify the dependent predictor for morbidity and mortality over a year period.

Microbiology

Blood culture samples were incubated in the BACTEC 9050 System[11], and isolates identified by routine microbiological methods. A pair of samples taken for aerobic and anaerobic culture was statistically regarded as one sample. The blood sample for the culture was drawn through a new venipuncture performed and through an already placed (usually subclavia or jugular vein) at the same time. A low or moderate probability of bacteremia, such as that expected from a pneumonia or urinary tract infection merits two sets of cultures. A high probability of bacteremia, as expected in catheter-related sepsis, requires at least three sets of blood cultures.

Statistics

Univariate analysis of categorical variables was performed using either an X^2 or Fisher's exact test (when an expected cell frequency was less than five), and Student's *t* test was used for comparison of continuous variables. Estimates of relative risk from exposures of interest, expressed as odds ratios (OR), were calculated along with 95% confidence intervals derived via maximum likelihood estimation. Potential covariates were examined individually for their association with mortality and P values less than 0,05 were considered statistically significant.

Results

During a year period, 117 episodes of bacteremia were documented in 72 patients (Table 2). The mean WBC count on the day of bacteremia was 15.2×10^9/L (range $0.1–48.0 \times 10^9$/L), and 3.3% of episodes occurred in neutropenic (WBC count $<1 \times 10^9$/L) children. The mean temperature on the day of infection was 38.2±1.1 °C. Some newborns 23% (n=5) had a significantly lower mean temperature ($p<0.02$) and lower mean WBC count ($p<0.05$) than older children. Hemodynamic instability was noted in 11% of bacteremic episodes, and this did not vary according to age.

As shown in Table 2 the most frequent isolates were the coagulase-negative staphylococci 32.2% followed by *Candia* spp. 30.5%. Enterobacteria were isolated in 17.3% episodes of bacteremia, and non-fermentative gram-negative bacteria in 11.6%. Streptococci were isolated in 4.4% patients, methicillin-resistant *S. aureus* (MRSA) in 2%, and corynebacteria and anaerobes in 1% blood culture each. Saprophytic corinebacterium species and two viridans group streptococci isolates were regarded as contaminants.

The different causes for admission in the PICU and the incidence of bacteremia according to the cause of admission are shown in Table 3.

In 72 patients bacteremia was documented. Thirteen of these patients suffered from multiple episodes of bac-

TABLE 3
THE INCIDENCE OF BACTEREMIA ACCORDING TO THE CAUSES OF ADMISSION

Causes for admission in the PICU	Precentage (%)	Incidence of bacteremia according to the cause of admission (%)
Trauma	20.2	6.9 ± 1.2
Elective postoperative care	41.9	3.2 ± 0.4
Emergency postoperative care	11.1	4.7 ± 0.9
Burns	3.9	25.4 ± 3.1
Neurologic disease	5.6	6.2 ± 0.7
Malignancy	3.7	13.3 ± 1.3
Haematological disease	1.9	18 ± 2.1
Renal failure	3.2	5.9 ± 1.7
Respiratory disease	18.5	16 ± 2.1

teremia caused by different agents. With the exception of one patient with *Streptococcus pneumoniae* and one with *Actinomyces viscosus* isolate in their blood, all the others were considered to have bacteremia as a complication of the treatment in the ICU.

Fifteen patients suffered from candidemia, but in nine of them it was associated with one or multiple episodes of bacteremia with different other microorganisms.

Rate of bacteremia

26.1 *per* 100 admissions

3.5 *per* 1000 patient days

5.9 *per* 100 catheter days

The sources of bacteremias leading to bacteremias are listed in Table 4. Intravascular catheter were the most commonly associated with bacteremias 22.6%. The lower respiratory tract and genitourinary tract where the second and third most frequent primary sites of infections, respectively. Among all bacteremias, intravascular catheters were implicated 22.6%, pneumonia in 20.4%, genitourinary tract in 14.2%, surgical wounds in 11.7% and, gastrointestinal tract in 9.8%. The most common causes of S. aureus bacteremia were bone/joint and skin soft tissue infections (burns), which together accounted for 5.9% of episodes.

The episodes for which a source could not be identified were caused by a variety of organisms, with aerobic gram-positive organisms and aerobic bacilli isolated from 38% and 51% of episodes, respectively.

The most common pathogens isolated from bacteremic patients with pneumonia were *Pseudomonas aeruginosa* (42%) and *Streptococcus* spp. (28%). In patients with urinary tract infections, the most common organisms were *Escherichia coli* (37%) and enterococci (26%). Intraabdominal infections resulted most often in monomicrobial gram-negative bacteremias (69%) with polymicrobial bacteremias occurring in 16%. Anaerobes were isolated from 1% episodes.

There were seven deaths among 117 patients with first episodes of bacteremia (5.9%). Mortality was significantly higher in children with septic shock (OR, 4.1; $p< 0.001$). The highest rates of death by organism were observed among children with fungemia (31.7%) and bacteremia due to *P. aeruginosa* (22.1%) and *Acinetobacter calcoaceticus* (17.3%). Patients who had more than one source of infection were more likely to die than those with only a single source of infection (OR, 2.7; $p<0.004$).

TABLE 4
THE SOURCES OF BACTEREMIAS

Sources of bacteremia	percentage (%)
Intravascular catheter	22.6
Respiratory tract	20.4
Genitourinary tract	14.2
Surgical wound	11.7
Gastrointestinal tract	9.8
Bone/joint	5.9
Endocarditis	0.8
Others	2.6
Unknown	12.0
Total	100.0

Discussion

Bacterial infections are major causes of morbidity and mortality in PICU. The detection, identification, and susceptibility testing of a causative species of bacteremia is essential for the proper treatment, and better prognosis of the child. The mean mortality related to bacteremia has usually been reported 9–62 %[12–16]. In that studies the most common sources of mortality were sepsis, intravenous access devices, surgical and trauma patients.

In our study of bacteremias among children admitted to the PICU over a year period coagulase-negative staphylococci (CoNS) were the leading pathogen and caused one-third of episodes. CoNS accounted for 32.2% of the blood culture obtained from clinically defined infections. Our results are in agreement with other studies that reported CoNS as the most common bacteria isolated from children[17]. Henesy and al.[8] described the rise in incidence as coincident with change in skin desinfection usage and general use of third-generation cephalosporin to which the CoNS were resistant. The increase in the incidence of coagulase negative staphylococcal bacteremia is likely related to increased use of intravascular catheters in PICU. In fact, vascular catheters were identified as one of the leading causes of bacteremia in our study (22.6%). This finding is similar to that reported by Lark and colleagus[18] who documented a substantial increase in rate of bacteremias due to intravascular devices. Steinberg at all.[19] documented increase in the rate of bacteremias due to intravascular devices – from 0% in 1980–1983 to 22% in 1990–1993. Growing evidence has suggested repeatedly[20–22] that central lines inserted into jugular site are more likely to be colonised than those inserted by the subclavian route. Sheretz at al.[22] recently reported that educational program for physicians in training also can decrease the risk of catheter-related infection from 3.3 to 2.4 per 1.000 CVC-days.

The second most common organism causing bacteremia in our PICU was *Candida* spp., confirming the findings of Makhoul et al.[23]. There are reasons for that: first, children who had significantly longer hospitalizations, and second, mechanical ventilation and antibacterial agent are significant risk factors, especially previous treatment with broad-spectrum antibacterial agents (amikacin, vancomycin, ceftazidime or imipenem). Candida infections are high among immunocompromised patients, especially when these patients receive broad-spectrum antimicrobials or parenteral nutrition. A special risk group of patients with increased susceptibility for fungal infections are very low birth weight infants resulting from their impaired specific and non-specific defence mechanisms[24].

The most common pathogens isolated from bacteremic patient with pneumonia were *P. aeruginosa* (42%) and streptococci (8%). Research for effective measures to prevent ventilator-associated pneumonia have been recently reviewed elswehre[25–27]. A large proportion of cases of ventilator-associated pneumonia are related to the continuous aspiration of contaminated oropharyngeal secretions and/or possibly of gastric content. The simplest measure to decrease the aspiration of gastric content in mechanically ventilated patients is to place them in a semirecumbent position (i.e. a 45° angle)[27].

Several randomized studies[28] have found that sucralfate which does not lower gastric pH, is associated with lower rates of ventilator-associated pneumonia than histamine H_2-receptor antagonists, but some data[29] suggest that it may be less efficient in stress ulcer prophylaxis, and this field continues to be controversial[26–29]. Nosocomial sinusitis is probably underestimated in critically ill children who are receiving mechanical ventilation, in whom it may be viewed as a direct consequence of impaired drainage of the sinus cavities due to devices placed in the nose[30]. Its prevention would include the avoidance of nasotracheal intubation and the systemic use of the orotracheal route, which is the current practice in many PICU.

The urinary tract remains the third important single source of bacteremia in our PICU. A large proportion of these infections (14.2%) occurred in children with indwelling urinary catheters in our study (Table 4). Most episodes were asymptomatic, and their treatment is not recommended for most PICU patients[31,32]. However, this point needs to be reviewed in the case of immunosuppressed child. A quantitative culture of $\geq 10^5$ CFU/mL is the threshold admitted for a diagnosis of catheter-associated bacteriuria[33,12]. Risk factors include the duration of catheterization, the absence of systemic antibiotic treatment and renal failure[34,35].

The group in whom gram-negative organisms caused bacteremia episodes (Enterobacteria 17% and non-fermentative gram-negative bacteria 11%) is very similar to that found by others, with reports varying between 11% and 26%[35]. In our setting gram-negative bacteria dominate over gram-positive bacterema.

Streptococci were isolated in five samples. Due to database limitations, we could not evaluate the impact of antimicrobial therapy on the outcome of patients with bacteremia.

Conclusion

This study provides an analysis of the epidemiology and microbiology of bacteremia in the PICU Children's Hospital Zagreb, Croatia in 2006. Coagulase-negative staphylococci and *Candida* spp. were identified as the leading pathogens causing bacteremia, and the sources most frequently implicated were intravascular catheters, respiratory and genitourinary tracts. It is noteworthy that a substantial proportion of children in our study had indwelling intravascular or urinary tract catheters. This finding emphasizes the need for appropriate and judicious use of such devices. Fortunately, many of these device-related infections are potentially avoidable through adherence to the established infection control practices used to prevent bacteremia.

Early diagnosis, prompt blood cultures reports, followed by appropriate antibiotic treatment are essential in reducing mortality in such patients. Given the morbidity and mortality of bacteremia, we decided to better describe this important clinical problem. We thus provide a detailed and comprehensive analysis of bacteremia occurring at a single institution over a recent a year period.

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PROCJENA BAKTEREMIJE U PEDIJATRISKOJ JEDINICI INTENZIVNOG LIJEČENJA: EPIDEMIOLOGIJA, MIKROBIOLOGIJA IZVORI INFEKCIJE I RIZIČNI ČIMBENICI

S A Ž E T A K

Bakteremija je česti uzrok morbiditeta i mortaliteta u djece koja se zbrinjavaju u pedijatriskoj jedinici intenzivnog liječenja (PICU). U radu smo ispitivali mikroorganizme koji dovode do bakteremije u našem PICU tijekom jedne godine, kako bi ustanovili smrtnost koja je povezana sa takovim infekcijama i otkrili čimbenike koji najčešće dovode do morbiditeta i mortaliteta. Od 1. siječnja do 31. prosinca 2006. god., 479 bolesnika je zaprimljeno u PICU, izvađeno je 379 uzoraka hemokulture. Uzorci su smješteni u BACTEC 9050 System a izolati identificirani rutinskim mikrobiološkim metodama. Uzorci uzeti za aerobnu i anaerobnu kulturu smatrani su u statističkoj obradi kao jedan uzorak. Podaci su sakupljani iz medicinske dokumentacije svakog bolesnika na standardnim dokumentima naše bolnice a uključivali su demografsku informaciju, predisponirajuća stanja, izvore infekcija, važne laboratorijske i kliničke parametre u vrijeme infekcije kao i mikrobiološke podatke. Bazirano na tim podacima pozitivne hemokulture su klasificirane kao kontaminirane ili kao bakteremija. Tijekom jedne godine, dokumentirano je 117 epizoda bakteremije u 72 bolesnika. Najčešći izolati su bili koagulaze-negativni stafilokoki 32,2% (39), zatim slijedi Candida spp. 30,5% (36). Srednja vrijednost bijele krvne slike (WBC) na dan bakteremije iznosila je $15{,}2 \times 10^9$/L (niz, 0,1–$48{,}0 \times 10^9$/L). Srednja vrijednost temperature na dan infekcije iznosila je 38,2±1,1 °C (niz, 34–41 °C). Neka novorođenčad 23% (n=5) su imala signifikantno nižu temperaturu ($p<0{,}02$) i niže WBC ($p<0.05$) nego starija djeca. Hemodinamska nestabilnost je zamijećena u 11% bakterijskih epizoda. Bakteremija je u 22.6% slučajeva izazvana intravaskularnim kateterima, 20,4% pneumonijom, genitourinarnim traktom 14,2%, kirurškim ranama u 11,7% i gastrointestinalnim traktom u 9,85% slučajeva. Sedam bolesnika umrlo je zbog sepse. Rana dijagnoza, promptno dobivanje rezultata hemokulture, koje prati odgovarajući antibiotski tretman će značajno smanjiti mortalitet u takovih bolesnika. Što kraće vrijeme boravka u bolnici, restriktivna uporaba invazivnih monitoringa i tehnika bitno će smanjiti rizik bakteremije za vrijeme boravka u PICU.