Bloodstream infections in pediatric patients

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ABSTRACT

Objective: Blood stream infection (BSI) is the leading cause of morbidity and mortality in pediatric patients. This study aims to describe the clinical, microbiological characteristics and outcome of BSI in pediatric patients.

Methods: We collected the clinical data from all pediatric patients with positive blood cultures. We identified all isolates from these patients from January 2004 to December 2004 at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, and determined antimicrobial susceptibilities by MicroScan Walk Away 96 (Dade Behring Inc., West Sacramento, CA95691, USA).

Results: Two hundred and twenty pediatric patients had BSI, of whom 147 (67%) were males and 71 (32.2%) were from intensive care units (ICUs). Two hundred and ten (95.4%) had single blood culture isolate. One hundred and seventy-three (78.6%) of the isolates were Gram positive bacteria and included the following: *Staphylococcus epidermidis* (55.4%), *Staphylococcus aureus* (9.5%) of which 14% were methicillin resistant, *Streptococcus pneumoniae* (*S. pneumoniae*) (4.5%), 40% of which were resistant to penicillin and *Enterococcus faecalis* (4%). Gram negative bacteria were 44 (20%) and included *Escherichia coli* and *Klebsiella pneumoniae* (*K.pneumoniae*) (3.6% each). Three isolates (1.3%) were *Candida glabrata*. None of the Gram positive isolates were vancomycin resistant. Three *K.pneumoniae* and one *Pseudomonas spp.* isolates were multiresistant. One hundred and ninety-four (88%) of BSI isolates were hospital acquired. Fever was the most common presentation of pediatric patients (26%) with positive blood culture with no apparent focus of infection. Respiratory tract infections 26 (12%) were the next most common. We seen sepsis in (7.7%) children between 8 days and 6 months of age. Bone and joint infections, cardiac, renal, gastrointestinal diseases, malignancy and surgical cases were other associated clinical diagnoses of BSI in pediatric patients. Patients with immuno-suppressive disorders with BSI had isolates such as *Salmonella spp., S. pneumoniae* and *Pseudomonas spp.* Overall mortality was 13 (6%) ($p<0.005$) and those patients had underlying serious medical conditions with associated risk factors such as prolonged hospital stay, intensive care unit (ICU) admission, indwelling catheterization, mechanical ventilation and prior antimicrobial use.

Conclusion: Bloodstream infection is an important cause of morbidity and mortality in pediatric patients. Risk factors for hospital acquired infection include: prematurity, prolonged hospitalization, ICU admission, indwelling catheterization, mechanical ventilation and prior antimicrobial therapy.

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The presence of bacteria in blood or bloodstream infections (BSI) is a leading cause of significant patient morbidity and mortality. It accounts for 10-15% of nosocomial infections and is the second most frequent infection site representing 20% of all infections and the eighth leading cause of mortality in the United States.[1,2] Blood stream infection may be transient bacteremia, an indication of true systemic infection (endocarditis, osteomyelitis and pneumonia) or otherwise, contamination from skin

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flora.[3,4] Pediatric patients with BSI may present a diagnostic and therapeutic challenge where they often present with fever; however, sometimes they may present with normal or even low body temperature.[3,4] Many studies on BSI have focused on adults and neonatal patients.[4-8] Only a few authors studied BSI in pediatric patients of other age groups, and most originated from the Western countries.[6,9-12] This study aims to describe the clinical, microbiological characteristics and outcome of cases of BSI or presumed cases of bacteremia in pediatric patients at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia.

Methods. This study was conducted over a one-year period from January 2004 to December 2004 on positive blood culture specimens received at the microbiology laboratory from all pediatric patients seen at KKUH, which has 700 beds, and 5 different intensive care units (ICUs). It provides primary, secondary and tertiary health care for all patients from the region of Riyadh, the capital of Saudi Arabia. Clinical data collected from each patient record included: age, gender, whether inpatient or outpatient, or ICU patient, clinical diagnosis, presence of vascular or respiratory catheters and the outcome. Two to five milliliters (mls) of peripheral blood were aseptically collected from neonates and children up to 10 years of age and 10 mls from children more than 10 years of age and inoculated into blood culture bottles. Blood culture bottles were then incubated aerobically in BacT/Alert 3 D (Organon Teknika, USA). Bottles showing positive growth index were Gram stained and subcultured on sheep blood agar, chocolate agar and MacConkey agar plates. Blood and chocolate agar plates were then incubated aerobically for 24-48 hours. MacConkey agar plates were incubated aerobically for 24 hours. Identification and susceptibility testing were carried out by MicroScan Walk Away 96 (Dade Behring Inc., West Sacramento, CA95691, USA). Rapid Gram negative panels were inoculated from MacConkey agar plates, and other panels were inoculated from blood agar plates according to manufacturer's directions. Specimens that appear to contain more than one organism were isolated and identified separately. Only one isolate was included from each patient with recurrent infection with the same bacterial species. All aerobic and facultative anaerobic bacteria were identified by the MicroScan except *Haemophilus influenzae* (*H.influenzea*), *Streptococcus pneumoniae* (*S. pneumoniae*) and yeasts that were identified by standard methods. The correlation between variables such as bacterial isolates, and clinical diagnosis and mortality with different underlying medical conditions and bacterial isolates were computed by Chi-square. A $p<0.005$ was considered significant.

Results. **Table 1** depicts the characteristics of pediatric patients with BSI during the 12-month period. Two hundred and twenty patients had positive blood cultures, of which 173 (78.6%) of the isolates were Gram-positive bacteria, 44 (20%) were Gram-negative bacteria while 3 (1.3%) were *Candida glabrata*. **Figure 1** illustrates the most common bacterial isolates. Seven organisms accounted for the majority of isolates. These were: *Staphylococcus epidermidis* (*S. epidermidis*) 122 (55.4%), *Staphylococcus aureus* (*S. aureus*) 21 (9.5%), *S. pneumoniae* 10 (4.5%), *Enterococcus*

Table 1 - Characteristics of pediatric patients with bloodstream infections (BSI).

Characteristics	n	(%)
Gender		
Males	147	(67)
Females	73	(33)
Age range		
1-30 days	43	(19.5)
31 days - 24 months	91	(41.3)
3 - 15 years	86	(39)
Location		
Intensive care units	71	(32.2)
Non-intensive care units	100	(45.4)
Out patients	49	(22.2)
Single isolate BSI	210	(95.4)
Polymicrobial BSI	8	(3.6)
S. epidermidis + Bacillus spp	1	(0.45)
S. pneumoniae + diphtheroids	1	(0.45)
S. epidermidis + E. faecalis	3	(1.4)
Acinetobacter spp. + Pseudomonas spp.	1	(0.45)
Moraxella catarrhalis + Streptococcus spp. + S. epidermidis	1	(0.9)
S. aureus + S. epidermidis + Streptococcus spp.	1	(0.9)

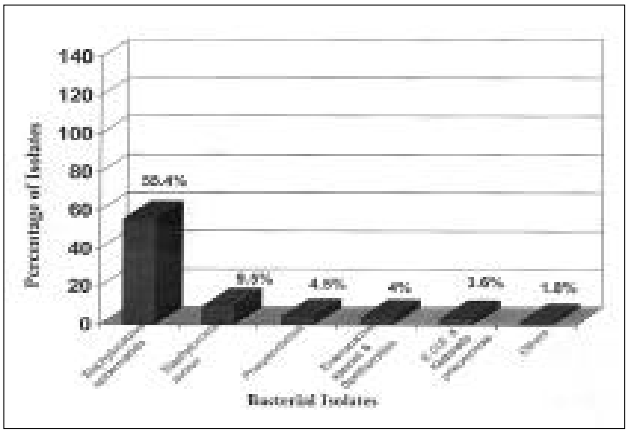

Figure 1 - Histogram representing common bacterial isolates of bloodstream infection.

Table 2 - Bacterial isolates from commonly encountered clinical syndromes.

Clinical syndromes	n	(%)	Bacterial isolates
Fever	57	(26)	*Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis, Streptococcus* group B, *diphtheroids, Escherichia coli, Brucella spp., Haemophilus influenzae*
Respiratory tract infection	26	(12)	*Staphylococcus epidermidis, Streptococcus pneumoniae, Moraxella catarrhalis, Enterococcus faecalis, Methicillin-resistant Staphylococcus aureus, Pseudomonas spp.*
Sepsis	17	(7.7)	*Staphylococcus epidermidis, Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Enterobacter spp.*
Preterm	38	(17)	*Staphylococcus epidermidis, Staphylococcus aureus, Klebsiella pneumoniae, Enterococcus faecalis, Serratia marcescens, Escherichia coli*
Bone and joint infections	9	(4)	*Staphylococcus epidermidis, Staphylococcus aureus, Salmonella spp.*
Cardiac diseases	6	(2.7)	*Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis*
Renal diseases	6	(2.7)	*Staphylococcus epidermidis, Klebsiella pneumoniae, Enterococcus faecalis, Pseudomonas spp.*
Gastrointestinal tract diseases	8	(4)	*Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae*
Malignancy	7	(3)	*Staphylococcus epidermidis, Staphylococcus aureus*
Surgical intervention	11	(5)	*Staphylococcus epidermidis, Bacillus spp., Enterococcus faecalis, Acinetobacter spp., Pseudomonas aeruginosa, Candida glabrata*
Other*			

*includes uncommon cases such as: burn, metabolic disorders, convulsion, sickle cell disease, drowning, hydrocephalus, congenital anomalies and hepatitis C.

Table 3 - Data of fatal cases of bloodstream infections (N=13).

Age	Gender	Diagnosis	Intensive care unit/ none intensive care unit	Bacteria isolated*
3 days	Female	Preterm	Intensive care unit	*Escherichia coli*
7 days	Female	Preterm	Intensive care unit	*Escherichia coli*
8 days	Male	Sepsis	Intensive care unit	*Staphylococcus epidermidis*
1 month	Male	Hypoglycemia	None intensive care unit	*Staphylococcus epidermidis*
74 days	Male	Sepsis	Intensive care unit	*Stenotrophomonas maltophilia*
4 months	Male	Sepsis and failure to thrive	Intensive care unit	*Klebsiella pneumoniae*
7 months	Male	Nephrotic syndrome	Intensive care unit	*Enterococcus faecalis*
7 months	Female	Acute respiratory distress syndrome	Intensive care unit	*Enterococcus faecalis and Staphylococcus epidermidis*
7 months	Male	Pneumonia	None intensive care unit	*Pseudomonas aeruginosa*
9 months	Female	Immune deficiency	None intensive care unit	*Pseudomonas spp.*
4 years	Male	Neuroblastoma	None intensive care unit	*Staphylococcus aureus,*
14 years	Male	Systemic lupus erythematosus	None intensive care unit	*Pseudomonas spp .*
15 years	Female	Rheumatic heart disease	Intensive care unit	*Enterococcus faecalis* and *Staphylococcus epidermidis*

*$p<0.005$

faecalis (*E. faecalis*) 9 (4%), *Escherichia coli* (*E.coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) 8 (3.6%) each, and diphtheroids 9 (4%). Other isolates included: *Pseudomonas aeruginosa, Pseudomonas spp., Enterobacter spp., Serratia marcescens, Salmonella spp., Brucella spp., Moraxella catarrhalis, Acinetobacter spp., Stenotrophomonas maltophilia, Bacillus spp.* and *Viridans streptococci*. One hundred and ninety-four (88%) of the BSIs were considered of nosocomial origin, including most of those caused by *S. epidermidis, K. pneumoniae, Pseudomonas spp., Enterobacter spp.* and *Candida glabrata*. Most of the BSI caused by *S. epidermidis* (91 [75%]) as well as those caused by diphtheroids and *Bacillus spp*. were considered to be due to skin contaminants. Three (14%) of the *S. aureus* isolates were methicillin resistant (MRSA). For the *S. pneumoniae*, 4/10 (40%) were resistant to penicillin. Only one of the *E. faecalis* was ampicillin resistant. None of the Gram positive bacteria were resistant to vancomycin. Among Gram negative bacteria, 3/8 (38%) *K. pneumoniae* from ICU were multiresistant to ampicillin, ceftriaxone, cefotaxime, ceftazidime, cefepime, gentamicin, amikacin and aztreonam but were sensitive to imipenem, meropenem, tazobactam-clavulanic acid and ciprofloxacin. One *Pseudomonas spp.* was also multiresistant to ceftazidime, cefepime, aztreonam, gentamicin, amikacin, and ciprofloxacin but was sensitive only to meropenem. With regard to the symptoms of patients with BSI, fever with no apparent source of infection was the most common diagnosis (58 [26%]). Cases with fever had *S. aureus, S. pneumoniae, E. coli, E. faecalis, Streptococcus* group B and *Brucella spp*. BSIs. Fever was more common in ages from 10 days up to 9 years which was statistically significant. Respiratory tract infection was the common focus of infection in 26 (12%) of patients and occurred mainly between one month and 8 years of age. Only 2 patients had community- acquired pneumonia that was caused by *S. pneumoniae* and *Moraxella catarrhalis* and one case had hospital acquired pneumonia caused by MRSA. Other patients with clinical pneumonia but negative blood cultures were presumed to be viral infections of the respiratory tract.

Table 2 demonstrates bacterial isolates from the most commonly encountered clinical syndromes and the age groups. *Salmonella spp*. was isolated from a sickle cell disease patient with osteomyelitis, and 2 *S. aureus* isolates were from blood of patients with arthritis and osteomyelitis. Patients with cardiac diseases accounted for 6 (2.7%) and were seen after the first year of life: *S. aureus* was isolated from a case of valvular disease, *S. pneumoniae* from another with congenital heart defect and *E. faecalis* plus *S. epidermidis* were isolated from one case of rheumatic heart disease. Six (2.7%) cases had renal diseases. In these, *E. coli* and *K. pneumoniae* were isolated from 3 patients with urinary tract infection, *E. faecalis* from one with nephrotic syndrome, *Pseudomonas spp.* from one with hydronephrosis and *S. epidermidis* from a patient with renal failure on renal dialysis. Regarding patients who presented with signs and symptoms related to gastrointestinal tract, *S. epidermidis* was isolated early on admission from the majority of those complaining of vomiting, abdominal pain and gastroenteritis. In 3 patients with Crohn's disease, one had *S. aureus* and the other had *K. pneumoniae* and the third had *S. epidermidis* isolated at late onset of the disease. In 2 patients with short bowel syndrome, one had MRSA and the other had *E. coli*. Six cases of acute leukemia had late onset *S. epidermidis* BSI. A case of neuroblastoma had *S. aureus*. Nosocomial BSI of children in different age groups was seen after such surgical procedures as appendectomy, craniotomy, road traffic accident and laparotomy. The isolates included *Candida glabrata, Bacillus spp.* and *E. faecalis.* One child had polymicrobial isolates (*Acinetobacter spp.* and *Pseudomonas aeruginosa*). Interestingly, one newborn had *H. influenzae* and another had *Gardnerella vaginalis.* The mortality rate was 13 (6%).

Table 3 shows the data on the pediatric patients who died of BSI. Five (38.5%) were neonates and 8 (61.5%) were males. In seven (53.8%) of the patients who died, the isolates were Gram-negative bacteria. Most of the patients who died had serious underlying medical conditions, 8 (61.5%) of them were from ICU and had vascular, respiratory and urinary catheters or had stayed for long periods in the hospital in addition to being on antimicrobial therapy. There was a significant correlation between underlying conditions and bacteria isolated from fatal cases of BSI ($p<0.005$).

Discussion. In the current study, *S. epidermidis* was the most common BSI isolate (55.4%). Its significance is difficult to determine. *S.epidermidis* was the most common nosocomial BSI isolate in studies from Western countries and it is considered mostly as a blood contaminant.[13,14] Haimi-Cohen et al[14] suggested quantitative culture to aid interpretation and determining whether it is vascular related.[14] But this is not performed in most laboratories since many including ours use automated, continuously monitored blood culture systems. In addition to *S.epidermidis, Bacillus spp.*, diphtheroids and *Viridans streptococci* were considered as contaminants in the absence of clinical features of sepsis. Diphtheroids are normal flora of mucous membranes and gastrointestinal tract, some as well have environmental origins.[15,16] Therefore, we have speculated that these organisms are probably derived from the skin following extraction of blood or from the respiratory tract following intubations or

catheter insertion due to barrier breakdown. *Bacillus spp.* may have originated from the environment.[15] These contaminants have been noticed to be common in pediatric patients since it is difficult to take blood samples from very young infants due to much skin manipulation leading to contamination. In addition, only single samples are usually taken from these patients and this adds to the difficulty of interpretation. However, it needs to be pointed out that *S. epidermidis* and other coagulase negative staphylococci can cause sepsis particularly in preterm infants, immunosuppressed patients and patients with intravascular devices.[14,16] Furthermore, it has been found that the leading sources for *S. epidermidis* in blood are intravenous catheters, respiratory and genitourinary tracts and intra-abdominal foci.[16,17] A number of publications have associated diphtheroids with human infections including bacteremia.[18,19] In our case, the 2 isolates of diphtheroids from sickle cell disease patients were considered insignificant. Most studies on BSI have concentrated on the neonatal period, since this age group is most vulnerable for infection due to their developmental status and physical examination findings are usually less reliable in neonates.[4-8] In Nigerian infants, *E. coli* and *S. aureus* were more predominant.[4] In Kenya, *E. coli,* and group B streptococci predominated among infants under 60 days old while *S. pneumoniae,* non-typhoid *Salmonella spp., H. influenzae* and *E. coli* predominated among infants 60 days or older.[6] In one study from Saudi Arabia, 60% of neonatal BSIs were caused by Gram-negative organisms such as *Klebsiella spp., E. coli, Pseudomonas spp., Serratia spp.* and *Enterobacter spp*.[5] Surprisingly, in another local study, *Salmonella spp.* were the most common isolates from neonatal BSI.[20]

In this study, fever (axillary temperature greater than 38^{0}C) was the most common presentation and predictor of BSI in 33 infants (1-12 months) and 20 children (1-15 years) as in other studies.[4,6] Preterm infants commonly presented with sepsis (bacteremia with evidence of systemic invasive infection). The bacterial isolates in these patients included *S. epidermidis, K. pneumoniae, E. coli, Serratia spp.* and *Enterobacter spp.* These patients also had long hospital stay and invasive procedures. It needs to be pointed out that it is the standard practice to initiate a septic work up in any child presenting with fever or sepsis, or suspected bacteremia in afebrile immunosuppressed patients. Consequently, some of these blood isolates may be coincidental. However, Ayoola et al[4] reported that fever, age <6 months, restlessness and white cell count more than 15,000/mm^3 were associated with increased risk of bacteremia in Nigerian infants.[4] Some cases of clinically diagnosed sepsis may have negative blood culture results. This could be explained, among others, by the bacteremia being intermittent, small number and volume of blood drawn, and most importantly patients receiving broad-spectrum antimicrobial drugs that will decrease the sensitivity of the test.[2] Although *H. influenzae* is rarely isolated from neonates, it was isolated from a 15 days old infant in our study. *Staphylococcus aureus* was the second most common isolate constituting 9.5% of our study. It was associated with a foci of infections in 6 (28.5%). The foci were osteomyelitis and septic arthritis. This compares with the study of Ladhani et al.[3] which had an incidence of 5% of *S.aureus* with foci in 53.6% of the cases.[3] Some of the cases of so-called 'no-focus' could be related to cardiac lesion since Friedland et al[21] reported 36% of children with silent endocarditis had *Staphylococcus* septicaemia or pericarditis and therefore, echocardiography should be considered in cases of staphylococcal BSI without a focus.[21] Fourteen percent of the cases of *S. aureus* BSI were due to MRSA. This compares with the 13.1% reported by Khairuldin et al[22] in 2000. Although the majority of infections in children who present with symptoms of respiratory tract infections and high temperature are presumed to be of viral etiology it is a common practice to take blood specimen for culture from such children. This is why most of these cultures are usually negative. In our study, *S. pneumoniae* was isolated from a sickle cell disease patient, *Pseudomonas spp.* from immunodeficient and systemic lupus erythematosus patients and *Salmonella spp.* from a patient with osteomyelitis and immune defect disorder. In another study, 26% of the reported cases with invasive pneumococcal infections in children and adults had underlying immunocompromising conditions.[23-25] On the other hand, *Salmonella spp.* other than *Salmonella typhimurium* was reported more often in patients with sickle-cell disease, alcoholism, and liver disease.[26] It is recommended that the recovery of unusual bacterium from blood culture such as *S. pneumoniae*, *Pseudomonas spp*. and *Salmonella spp*. should necessitate a search for the possibility of underlying conditions.[26] The *E. faecalis* in our study was associated with long hospital stay, endocarditis and septic preterm infants. It was reported that enterococcal BSI is more common in older age group children with instrumentation and prior to or with current antimicrobial therapy.[27] In our study, we encountered only one strain of *E. faecalis* which was resistant to ampicillin and none with high level resistance to gentamicin. This agrees with the report by Madani et al.[27] With regards to the enteric Gram-negative bacilli, *E. coli, K. pneumoniae* and *Enterobacter spp.* were the most common isolates. This is in agreement with the results of Cordero et al.[28] Urinary tract infection has been reported to occur in 7-8% of boy infants younger than 6 months and 8% of girls younger than 2 years with fever and bacteremia.[12] In our study, *E. coli* and *K. pneumoniae* were the cause of urinary tract infec-

tions in 2 girls aged 7 months and 5 years and a 13 years boy with BSI. None of our 3 children with multi-resistant *K. pneumoniae* died, and all of them had risk factors which included prior hospitalization and use of oxyimino-cephalosporins, and ICU admission with venous catheter and ventilator as had been reported in other studies.[30,31] Three patients had fungemia in our study. One of them, a neonate, had recurrent episodes of *Candida glabrata* following corrected urology surgery. This patient had been in hospital for a long period and had urinary and vascular catheters. All our fungal isolates were sensitive to all antifungal agents tested and none of them was a consequence of break through infection as has been reported in another study.[31] Among the genuine cases of polymicrobial BSI in this report, 2 cases had *E. faecalis* and *S. epidermidis*, both were from patients in the ICU and both of them died. Caballero-Granado et al[31] reported that a polymicrobial etiology and nosocomial acquisition of enterococcal bacteremia have been the independent risk factors for a long hospital stay. The isolation of *Gardnerella vaginali*s from a newborn infant suggested maternal origin. Beebe and Koneman[26] reported perinatal factors as predisposing for the entry of this organism into the bloodstream. Among the 13 (6%) fatality cases in this study, those attributable to BSI were 7/220 (3%), which is much lower than that reported by Elbasheir et al[5] but comparable to that reported by Gray.[9] In Kenya, community-acquired BSI was responsible for one third of death in infants and one quarter of deaths in children over one year of age.[6] Mortality due to hospital acquired Gram-negative bacteria was reported to be higher than that due to Gram-positive organisms. Such results were similar to ours (64%, 36%).[7,29] The Gram-negative related mortality rates were significantly associated with the following underlying conditions: sepsis, immune deficiency and systemic lupus erythe-matosus and pneumonia (**Table 3**).

In conclusion, BSI is an important cause of morbidity and mortality in our pediatric patients. Risk factors for hospital-acquired infection include: prematurity, prolonged hospitalization, ICU admission, indwelling catheterization, mechanical ventilation and prior antimicrobial use.

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