

Antimicrobial Resistance in Pathogens Causing Pediatrics Bloodstream Infections in Madinah Maternity and Children's Hospital, Saudi Arabia

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Research Article

ABSTRACT

Background: Bloodstream infection is one of the most common life-threatening condition in hospitalized pediatrics especially if associated with resistant microbes. The aim of the present study was to determine the incidence, predisposing factors, microbiological and antimicrobial resistance patterns in suspected BSI pediatric patients in different wards of Madinah Maternity and Children's Hospital, Saudi Arabia. During one year period from July 1, 2009 to June 30, 2010

Methods: Blood cultures were performed to all cases (n= 11968). Microorganisms were identified by cultural characteristics, Gram stain and biochemical profiles. BD Phoenix™ was used for confirmation of identification of all BSI Gram-negative isolates. Antibiotic susceptibility patterns of isolates was further done by using disk diffusion method.

Results: 728 cases (6%) were diagnosed of bloodstream infection according to positive blood cultures. The overall mortality rate was 11%. Gram-positive, Gram-negative and yeast accounted for 63.8%, 31.6% and 4.6%. Coagulase-negative staphylococci were the most prevalent Gram-positive isolates (44%); while *Serratia marcescens* and *Klebsiella pneumoniae* were the most common Gram-negative isolates. Gram-positive bacteria were mostly sensitive to cephalothin (86.6%) and vancomycin (76.8%), while Gram-negative bacteria were mostly sensitive to piperacillin/tazobactam (92.9%), ciprofloxacin (92.9%) and meropenem (91%).

Conclusion: The incidence rate of BSI is high in ICU infants. So, special attention should be given to the quality of care for these neonates to improve safety. There was appreciable resistance to commonly used antibiotics; and continued monitoring of antibiotic resistance is of great importance to ensure the proper use of antibiotics and to detect any increasing trends in resistance.

Keywords: Bloodstream infections; pediatrics; antimicrobial resistance; Saudi Arabia.

INTRODUCTION

Bloodstream infections (BSIs) are among the most common hospital-acquired infections in pediatric patients, and are responsible for approximately 10% to 30% of the cases (Gray, 2004). BSI is an important cause of death, giving a rate of 25-50% (Gill et al., 2006).

Risk factors for hospital acquired BSI include: prematurity, prolonged hospitalization, intensive care unit (ICU) admission, indwelling catheterization and mechanical ventilation (Babay et al., 2005).

Most of the literature concerning BSI is generated from adult patients that cannot be directly extrapolated to children because of significant differences in age, underlying medical conditions and type, and distribution of pathogens (Yogaraj et al., 2002).

Bacteriological culture to isolate the offending pathogen and knowledge about sensitivity pattern of the isolates remain the core of definitive diagnosis and management of BSI.

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Rates of antimicrobial resistance are increasing rapidly nowadays with patterns of large variations between countries. Thus, knowledge of local antimicrobial resistance patterns is essential to guide empirical and pathogen-specific therapy within any hospital.

Antimicrobial resistance in nosocomial BSIs is a major health care-associated (HA) problem that has a negative impact on patient morbidity and mortality (Foglia et al., 2007). Factors that result in increased resistance in nosocomial pathogens include the inappropriate and high use of antibiotics, limited availability of infection prevention and control programs, limited surveillance systems to measure HA infections and increased use of invasive medical devices and invasive procedures at ICUs (Hsueh et al., 2002, Paskovaty et al., 2005). An important consequence of antimicrobial resistance is treatment failure for serious infections in hospitalized patients, that is often associated with higher rates of morbidity, mortality, longer hospital stays, and increased costs of medical care (Carmeli et al., 2002, Engemann et al., 2003).

Although some studies on the incidence of BSI in pediatric patients have been conducted in Saudi Arabia, information on its incidence is lacking in Madinah Region. Thus, the aim of the present study was to determine the incidence, predisposing factors, microbiological and antimicrobial resistance patterns in pediatric patients in different wards of Madinah Maternity and Children's Hospital (MMCH); so that a guideline can be prepared for empirical antibiotic therapy in the hospital.

2. MATERIALS AND METHODS

2.1 Study location and patients

The present retrospective study was conducted in MMCH, Madinah Munawarah city, located in the western part of Saudi Arabia, during one year period from 1 July 2009 to 30 June 2010. MMCH, which has 500 beds, is the main referral hospital for Madinah region.

Clinical standards of practice in hospitals entail collecting blood for culture from patients exhibiting clinical signs of infection (eg, fever $>38^{\circ}\text{C}$). During the study period, 11968 suspected BSI pediatric patients (new born to 14 years) were involved from different wards at MMCH [Pediatric Intensive Care Unit (PICU), Neonatal Intensive Care Unit (NICU), Minimal Care Unit (MCU), In-Patient Wards (IPWs) and Out-Patient Department (OPD)]. Their mean age was 803.74 $\pm$ 1234.4 days with min. age of 2 days and max. of 14 years.

Data was collected from each patient, eg, age, gender, location (hospital ward), length of hospitalization and risk factor including intravenous devices, urinary catheters, hemodialysis shunt, endotracheal tubes, ventilator support, and previous antibiotic given within the last month. Gestational age and birth body weight was additional data collected for NICU deaths patients.

2.2 Isolation, identification and antibiotic susceptibility testing of microbial isolates from BSI cases

Blood samples for culture were obtained from pediatric patients by venipuncture after preparation of the skin with 70% isopropyl alcohol or from umbilical catheters using aseptic techniques. Pediatric blood culture bottle (Bactec Peds plus/F 40-ml culture vial, aerobic resin) was inoculated aseptically with 1-3 ml of blood from each case in accordance with the manufacturer's instructions. The bottles were then incubated in the Bactec 9240 instrument (Becton Dickinson, USA) for at least 7 days.

Specimens from the positive bottles, were gram stained, sub-cultured on the following media: blood agar, chocolate agar, MacConkey's agar and Sabouraud dextrose agar. Chocolate agar and blood agar plates were incubated in a CO₂ incubator with 5% to 10% CO₂ for up to 48 hours while other culture plates were incubated aerobically overnight at 37 °C.

Identification of blood culture isolates was based on cultural characteristics, results of catalase, coagulase, oxidase, urease, germ tube, optochin, bacitracin and biochemical profiles using API

tests (BioMérieux, France) specific for gram-negative organisms. BD Phoenix™ NMIC/ID panels were also used in confirmation of identification of all BSI Gram-negative isolates.

Furthermore, antibiotic susceptibility testing was done according to National Committee for Clinical Laboratory Standards (NCCLS, 2005).

97 RESULTS AND DISCUSSION

According to positive blood cultures, 728 cases (6%) were diagnosed of BSI out of the 11968 suspected BSI pediatric patients at MMCH during the study period.

Table 100 shows some demographic characteristics of the 728 confirmed BSI pediatric patients. The highest mean duration of hospital stay was reported from MCU (9 months). The overall mortality rate was 11% (80/728) with the most deaths number reported from ICU patients.

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Table 108. Some demographic characteristics of the 728 confirmed BSI pediatric patients

Characteristics	NICU	PICU	MCU	IPWs	OPD	Total
No. of patients	241	138	6	68	275	728
Male	139	70	5	41	160	415
Female	102	68	1	27	115	313
Mean duration of hospital stay	37 days	28 days	9 months	15 days	0	
No. of microbial isolates	280	186	9	74	278	827
Patient deaths	45	30	4	1	0	80
Mortality rate	18.7% (45/241)	21.7% (30/138)	66.7% (4/6)	1.5% (1/68)	0 (0/275)	11% (80/728)

NICU= Neonatal Intensive Care Unit, PICU= Pediatric Intensive Care Unit, MCU= Minimal Care Unit,

IPWs= In-Patient Wards, OPD= Out-Patient Department.

The different microbial isolates from BSI pediatrics were illustrated in table 2. A total of 827 microbial isolates were detected from 728 BSI pediatric patients. Number of microbial isolates were more than number of the total cases because some patients had multiple episodes of BSI with different organisms.

Most BSI cases 720 (98.9%) were monomicrobial, while 8 cases only (1.1%) were polymicrobial (i.e., different organisms were isolated from each case at the same time).

Gram-positive bacteria were the most common causative agents causing BSI in those pediatric patients. They were 528 isolates accounting for 63.8% of the total isolates, whilst 261 isolates

Microbial isolates	No. of isolates	Total
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(31.6%) were Gram-negative bacteria. Furthermore, candidemia by *Candida* spp. was found in only 11 cases (4.6%) and no other fungi was detected.

Coagulase-negative staphylococci (CoNS) were the most common pathogens accounting for 44% of the total isolates, followed by *Streptococcus* spp. (10.6%). Among the Gram-negative bacteria, *S. maltophilia* (7.5%), *Klebsiella* spp. (5.8%) and *P. aeruginosa* (3.9%) were the most common pathogens.

Gram-positive bacteria showed a high level of sensitivity to cephalothin (86.6%) and vancomycin (76.8%) as in Table 3. All *S. aureus* were resistant to penicillins and ampicillin. CoNS had moderate susceptibility to cephalothin and cotrimoxazole, 42.5% and 51.3%, respectively. 80% of all *Staphylococcus* isolates were sensitive to vancomycin.

While sensitivity of Gram-negative bacteria was (91%) to meropenem and (92.9%) to both piperacillin/tazobactam and ciprofloxacin. Imipenem-resistant *P. aeruginosa* were 55.6% and imipenem-resistant *Acinetobacter* spp. were 25% (Table 4).

All *C. albicans* isolated were susceptible to amphotericin B and fluconazole. 21% of non *C. albicans* were resistant to fluconazole and 18.4% were resistant to amphotericin B.

Table 2. Distribution of the BSI microbial isolates in the different wards of MMCH

	NICU	PICU	MCU	IPWs	OPD	
Gram-positive organism	150	74	4	58	242	528
CoNS	106	53	2	37	166	364
MRSA	22	3	1	5	0	31
<i>S. aureus</i> non MRSA	5	4	0	4	14	27
<i>Streptococcus</i> spp.	14	10	1	9	54	88
<i>Micrococcus</i> spp.	1	1	0	0	1	3
<i>Enterococcus</i> spp.	2	2	0	3	1	8
<i>Corynebacterium diphtheria</i>	0	0	0	0	4	4
<i>Bacillus</i> spp.	0	1	0	0	2	3
Gram-negative organism	112	95	5	14	35	261
<i>Klebsiella</i> spp.	26	11	1	2	8	48
<i>Pseudomonas aeruginosa</i>	25	3	1	0	3	32
<i>Enterobacter</i> spp.	9	18	0	3	4	34
<i>Acinetobacter</i> spp.	6	12	1	2	3	24
<i>E. coli</i>	11	4	0	2	3	20
<i>Salmonella</i> spp.	5	0	0	1	5	11
<i>Stenotrophomonas maltophilia</i>	4	4	1	0	0	9
<i>Chryseobacterium meningosepticum</i>	4	0	0	1	0	5
<i>Citrobacter</i> spp.	1	1	0	1	1	4
<i>Haemophilus influenzae</i>	1	2	0	0	2	5
<i>Moraxella</i> spp.	0	0	0	0	2	2
<i>Brucella</i> spp.	0	0	0	1	3	4
<i>Achromobacter</i> spp.	1	0	0	0	0	1
<i>Serratia marcescens</i>	19	40	1	1	1	62
Fungi	18	17	0	2	1	38
<i>Candida albicans</i>	4	1	0	0	0	5
Non <i>Candida albicans</i>	14	16	0	2	1	33
Total no. of isolates	280	186	9	74	278	827

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CoNS= Coagulase-negative staphylococci, MRSA= Methicillin-resistant *S. aureus*, NICU= Neonatal Intensive Care Unit, PICU= Pediatric Intensive Care Unit, MCU= Minimal Care Unit, IPWs= In-Patient Wards, OPD= Out-Patient Department.

Table 3. Antibacterial resistance rate of BSI Gram-positive isolates understudy (n= 112)

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Antibacterials	Antibacterial resistance rates No. (%)				
	CoNS n = 80	<i>S. aureus</i> n = 10	<i>Streptococcus</i> spp. n = 15	<i>Enterococcus</i> spp. n = 4	<i>Micrococcus</i> spp. n = 3
PG	74 (92.5)	10 (100)	11 (73.3)	4 (100)	3 (100)
E	69 (86.3)	1 (10)	4 (26.7)	4 (100)	3 (100)
AP	73 (91.3)	10 (100)	10 (66.7)	4 (100)	3 (100)
KF	8 (10)	0 (0)	3 (20)	4 (100)	0 (0)
CD	34 (42.5)	1 (10)	5 (33.3)	3 (75)	0 (0)
TS	41 (51.3)	1 (10)	11 (73.3)	2 (50)	0 (0)
VA	21 (26.3)	2 (20)	3 (20)	0 (0)	0 (0)

PG= Penicillins G, E= Erythromycin, AP= Ampicillin, KF= Cephalothin, CD= Clindamycin, TS= Cotrimazole, VA= Vancomycin.

Table 4. Antibacterial resistance rate of BSI Gram-negative isolates under study (n= 112)

Antibacterials	Antibacterial resistance rates No. (%)										
	<i>Klebsiella</i> spp. n = 30	<i>E. coli</i> n = 10	<i>S. marcescens</i> n = 25	<i>Enterobacter</i> spp. n = 13	<i>P. aeruginosa</i> n = 18	<i>Salmonella</i> spp. n = 3	<i>Citrobacter</i> spp. n = 2	<i>Acinetobacter</i> spp. n = 4	<i>Chryseobacterium</i> <i>meningosepticum</i> n = 3	<i>S. maltophilia</i> n = 3	<i>Moraxella</i> spp. n = 1
Beta-lactams											
CTX	11 (36.7)	1 (10)	0 (0)	0 (0)	18 (100)	0 (0)	1 (50)	1 (25)	3 (100)	3 (100)	0 (0)
CAZ	11 (36.7)	1 (10)	1 (4)	0 (0)	1 (5.6)	2 (66.7)	1 (50)	1 (25)	3 (100)	2 (66.7)	0 (0)
CRO	13 (43.3)	1 (10)	9 (36)	0 (0)	11 (61.1)	3 (100)	1 (50)	2 (50)	2 (66.7)	3 (100)	1 (100)
CPD	11 (36.7)	1 (10)	5 (20)	0 (0)	18 (100)	2 (66.7)	1 (50)	3 (75)	3 (100)	3 (100)	0 (0)
KF	17 (56.7)	7 (70)	25 (100)	12 (92.3)	18 (100)	3 (100)	1 (50)	4 (100)	3 (100)	3 (100)	1 (100)
CXM	10 (33.3)	1 (10)	25 (100)	13 (100)	18 (100)	2 (66.7)	1 (50)	3 (75)	3 (100)	3 (100)	0 (0)
FOX	7 (23.3)	0 (0)	25 (100)	12 (92.3)	18 (100)	2 (66.7)	1 (50)	4 (100)	3 (100)	3 (100)	1 (100)
FEP	11 (36.7)	1 (10)	0 (0)	0 (0)	1 (5.6)	1 (33.3)	1 (50)	1 (25)	3 (100)	3 (100)	0 (0)
AMP	30 (100)	10 (100)	25 (100)	12 (92.3)	18 (100)	2 (66.7)	2 (100)	4 (100)	3 (100)	3 (100)	0 (0)
PIP	17 (56.7)	8 (80)	1 (4)	0 (0)	1 (5.6)	2 (66.7)	1 (50)	3 (75)	3 (100)	3 (100)	0 (0)
ATM	11 (36.7)	1 (10)	5 (20)	0 (0)	4 (22.2)	2 (66.7)	1 (50)	4 (100)	3 (100)	3 (100)	0 (0)
IMI	0 (0)	0 (0)	0 (0)	0 (0)	10 (55.6)	0 (0)	0 (0)	1 (25)	3 (100)	3 (100)	0 (0)
MEM	0 (0)	0 (0)	1 (4)	0 (0)	2 (11.1)	0 (0)	0 (0)	1 (25)	3 (100)	3 (100)	0 (0)
β-lactams/β-lactamase inhibitors											
AUG	17 (56.7)	2 (20)	25 (100)	11 (84.6)	18 (100)	0 (0)	1 (50)	4 (100)	3 (100)	3 (100)	0 (0)
TZP	0 (0)	0 (0)	1 (4)	0 (0)	1 (5.6)	0 (0)	0 (0)	1 (25)	3 (100)	2 (66.7)	0 (0)
non β-lactams											
GM	8 (26.7)	0 (0)	1 (4)	0 (0)	3 (16.7)	3 (100)	0 (0)	1 (25)	3 (100)	3 (100)	0 (0)
AK	1 (3.3)	0 (0)	1 (4)	0 (0)	3 (16.7)	3 (100)	0 (0)	1 (25)	3 (100)	3 (100)	0 (0)
CIP	2 (6.7)	0 (0)	0 (0)	0 (0)	3 (16.7)	0 (0)	0 (0)	1 (25)	0 (0)	2 (66.7)	0 (0)
TS	13 (43.3)	6 (60)	2 (8)	1 (7.7)	18 (100)	2 (66.7)	1 (50)	4 (100)	3 (100)	1 (33.3)	1 (100)

CTX= Cefotaxime, CAZ= Ceftazidime, CRO= Ceftriaxone, CPD= Cefpodoxime, KF= Cephalothin, CXM= Cefuroxime, FOX= Cefoxitin, FEP= Cefepime, AMP= Ampicillin, PIP= Piperacillin, ATM= Aztreonam, IMI= Imipenem, MEM= Meropenem, AUG= amoxicillin-clavulanic acid, TZP= Piperacillin/tazobactam, GM= Gentamicin, Ak= Amikacin, CIP= Ciprolfloxacin, TS= cotrimoxazole.

BSI carries high morbidity and mortality in hospitalized patients despite the availability of current sophisticated therapeutic modalities (Blomberg et al., 2007).

In the present investigation, we analyzed clinical and microbiological characteristics of BSI pediatric patients in a Saudi hospital (MMCH), 6% (728/11968) of pediatric patients were having BSI. In contrast to our finding, some studies show higher positivity rate in pediatric patients. In India, it is reported to be between 36-55 percent (Jain et al., 2003, Mahapatra et al., 2002).

Nosocomial BSI, in neonatal, adult, and pediatric patients, was 38% in ICUs in three large university hospitals in Egypt (Saied et al., 2011). The lower rate in our study may be explained by the fact that most patients received good clinical care, including antimicrobial agents.

In the current study, BSI was confirmed in 728 BSI pediatric patients (new born to 14 years) with various diseases. Of them, 415 (57%) were male and 313 (43%) female. Similar findings have been reported by Al-Zamil (Al-Zamil, 2008) in Riyadh, where 152 (58.7%) were male and 107 (41.3%) female of the total 259 pediatric patients (1 month to 15 years) with bacteremia.

We tried also to assess the risk factors associated with BSI. Of which, the duration of hospitalization prior to the occurrence of BSI is a factor reported in the literature for cases of multidrug resistance nosocomial BSIs (Hedenbach et al., 2004). In the present study, the highest duration of hospital stay was reported from ICU followed by NICU and PICU.

Most BSI pediatric patients in this study were from ICU (379 patients, 52%) and stayed for longer duration with continuous use of intravascular and central venous catheterization. Central venous catheterization was reported to be the most common risk factor for BSI and attributed with 4-37% of mortality (Rosenthal et al., 2006). Central line associated BSIs in pediatric ICUs extend the length of stay and increase the cost of hospitalization (McLaughlin et al., 2012).

The overall mortality among our patients was 11%. This mortality was higher than that reported from other study done in an English children's hospital by Gray (Gray, 2004) where, the overall mortality rate directly attributable to infection was 2.4%. In addition, the mortality rate in NICU was 18.7% in our investigation, which is comparable (13.4%) to infants in a study performed previously in four main hospitals in Makkah (Asghar, 2006).

Due to the diversity of clinical conditions, it was not possible to attribute BSI as a cause of mortality in all our patients. As, mortality could be attributed to different factors such as the causative organisms, age, underlying diseases and ICU admission (Babay, 2007). With respect to the organisms, the most commonly isolated organisms in patients who died of BSI in this work were CoNS, *Klebsiella* spp. and *Candida* spp. In a study by Babay (Babay, 2007), CoNS, *S. aureus* and *Enterococcus* spp. were the most leading to death. In study of Martin et al. (Martin et al., 1989), mortality due to CoNS was reported to be 14%.

In this investigation, 33 cases (73%) were preterm among neonates deaths. Premature neonates are at especially high risk of infection because of their lack of protective maternal antibodies, underdeveloped innate immunity and their fragile, easily damaged skin. However, while the newborn intrinsically faces an increased risk of infection, failures at critical points in the system of care can greatly increase this risk (Mahfouz et al., 2010).

In this study, the most common reasons for NICU admission were respiratory distress syndrome, intrauterine growth retardation, premature rupture of membranes, congenital heart defect, hyaline membrane disease, very low birth weight, sepsis, septic shock, hydrocephalus and prematurity. In a study carried out in NICU in Abha general hospital by Mahfouz et al. (Mahfouz et al., 2010), the five primary reasons for admission to the NICU were preterm & hyaline membrane disease, transient tachypnoea of newborn, meconium asphyxia syndrome, birth asphyxia and congenital anomaly.

Most BSI cases 720 (98.9%) in this work were monomicrobial while 8 cases only (1.1%) were polymicrobial. Polymicrobial BSI was caused by *S. viridians*, CoNS, *Klebsiella* spp., *Acinetobacter*, *Candida* spp., *Enterobacter* spp. and *S. marcescens*. Polymicrobial bacteremia was found in 13 cases (5.2%) in a previous local study by Al-Zamil (Al-Zamil, 2008). Polymicrobial bacteremia was previously

reported to be caused by *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *K. oxytoca*, *S. marcescens*, *E. cloacae* and *A. baumannii* (Emori and Gaynes, 1993).

In our study, Gram-positive, Gram-negative and yeast accounted for 63.8%, 31.6% and 4.6%, respectively. Similarly, they were 66.2%, 31.3% and 2.2% of isolates, respectively in a study at Birmingham children's hospital over 7 years (Gray, 2004).

Babay (2007) found Gram-positive bacteria were the most common isolates accounting for 50% (61% of the total isolates whilst 31 (38%) were Gram-negative bacteria in King Khalid University Hospital, Riyadh. Also, in Kuwait, Gram-positive organisms and Gram-negative organisms were cultured from 70% and 25% of the total microbial isolates (Gomaa et al., 2001). Babay et al. (2005) reported 78.6% of the total isolates were Gram-positive bacteria, 20% Gram-negative bacteria while 1.3% were *S. glabrata*. In another local study done in Makkah hospitals by Asghar (2006), comprising elderly patients and pediatric patients, Gram-positive organisms, Gram-negative organisms and *Candida* spp. were involved in 56.6%, 37.5% and 5.9% of cases. All the above literature were in accordance to our results. Gram-positive bacteria were more prevalent than Gram-negative bacteria. Also, this finding is in agreement with the general concept reported in some international studies that noting the increase in septicemic cases among Gram-positive bacteria compared with Gram-negative (NCCLS, 2005, Haddad et al., 2004, Karchmer, 2000). On the other hand, some studies performed in Saudi Arabia revealed a high occurrence of Gram-negative compared with Gram-positive organisms (Al-Orainey et al., 1989, Bashier et al., 1998).

Gram-positive cocci have begun to reemerge as predominant pathogens in BSI in the early 1980s and it has been suggested that this change is due to evolution of medical care (Warran et al., 2001). Possibly in Europe and USA for similar reasons, blood culture is more likely to yield Gram-positive growth (Siefert and Wiplinghoff, 2005).

CoNS is the most frequent isolate accounting for 44% of the total isolates in this study. This could be due to the increasing use of intravascular devices in medical care (Ahmed et al., 2009). CoNS are one of the most common causes of nosocomial BSI and also the most common blood culture contaminant (Haddon et al., 1999). 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 (Babay et al., 2005). However, it needs to be pointed out that *S. epidermidis* and other CoNS can cause sepsis particularly in preterm infants, immunosuppressed patients and patients with intravascular devices (Haimi-Cohen et al., 2002). Thus, the increased isolation of CoNS in blood culture may reflect a change from regarding these organisms as normal skin flora to viewing them as clinically significant (Ahmed et al., 2009).

Saied et al. (2011) reported CoNS as the second most frequent isolate accounting for 25.5% of the total isolates recovered from nosocomial BSI, exceeded by *K. pneumoniae* accounting for 26.7% of the total isolates.

The second most causative agents after CoNS in BSI pediatrics under study were *Streptococcus* spp. (10.6%), of whom (1.7%) were *S. pneumoniae*. *S. pneumoniae* was reported previously as the most common pathogen in children with bacteremia (Haddon et al., 1999). Al-Zamil (2008) reported that the most common Gram-positive isolates from pediatric BSI were *S. aureus* (18.7%) and *Streptococcus* spp. (16.3%).

The proportion of blood culture isolates of *S. aureus* from children that are methicillin-resistant is increasing (Khairulddin et al., 2004). Bacteraemia due to MRSA is associated with high mortality compared with methicillin sensitive *S. aureus* bacteraemia (Ahmed et al., 2009).

Worldwide, MRSA rates vary widely, from <1% in Denmark, Sweden, and The Netherlands to >40% in the United Kingdom, Greece, and Italy (Tiemersma et al., 2004). MRSA in the study of Gray (2004) reached 15.5%. In our study, we encountered 31 isolates of MRSA of the total 58 *S. aureus* isolates (53.4%), with the highest proportion in NICU (22/31, 71%) suggesting a high dissemination in the hospital. This ratio was higher than 13.1% reported by Khairulddin et al. (2004) in children < 15 years; but lower than 64% in study of Saied et al. (2011) from Egypt.

Increasing MRSA rates have been reported in tertiary care centers in Saudi Arabia, from 0.8 to 2.3 per 1,000 admissions between 2000 and 2004 (Balkhy et al., 2007). Promoting hand hygiene and isolation precautions are important measures to prevent the spread of MRSA and should be implemented and enforced to control the spread of these highly resistant isolates.

Gram-negative bacteria were lower in this study. The most frequently isolated were *S. marcescens* accounting for 7.5% of the total isolates. *S. marcescens* is a well-recognised cause of outbreaks of nosocomial infection, particularly in NICUs (Madani et al., 2011).

Several international studies showed that *E. coli* and *Pseudomonas* spp. were the most common isolates among Gram-negative organism from blood culture (Anthony et al., 2000, Diekema et al., 1999, Lark et al., 2005). Gray (2004) showed that *E. coli* accounted for a greater proportion of neonatal BSI (9.8%). In some previous local studies, the most common Gram-negative organisms were *E. coli* (9.1%) and *Pseudomonas* spp. (8.7%) (Asghar, 2006); *Pseudomonas* spp. (7.3%) and *E. coli* (6%) (Babay, (2007).

In our investigation, the incidence of BSI caused by *K. pneumoniae* was 5.6%. The rate is comparable to that reported previously 7.4% by Haddon et al. (Haddon et al., 1999) and 6.6% by Al-Zamil (2008).

P. aeruginosa BSI in immunocompromised patients can lead to death within the first 72 hours (Munson et al., 2003). Wendt et al. (1998) and Weinstein et al. (1995) found that *P. aeruginosa* was the commonest Gram-negative pathogen. On contrary, *P. aeruginosa* was isolated from 3.9% of all BSI cases in this study. This rate concurs with Al-Zamil (2008), who found that 3.5% of cases were *P. aeruginosa*.

Risk factors for acquisition of fungal nosocomial BSIs include extended ICU stay, exposure to different classes of antibiotics, and multiple invasive procedures (Marchetti et al., 2004). *Candida* BSI contributes to increased length of hospital stay, increased hospital costs, and most importantly, increased morbidity and mortality (Garey et al., 2006). *Candida* spp. was implicated in 4.6% of all BSI episodes representing the most common etiologic agent in this study. Previous studies indicated that *Candida* spp. represent the fourth to seventh most common etiologic agent causing septicemia, which are in comparable to our findings (Lark et al., 2000, Hadziyannis et al., 2004, Rangel-Frausto et al., 1999). However, the rate of *Candida* isolates in our study is more than what has been reported by Babay et al. (2005) who detected *C. glabrata* 1.3%. On the other hand, Gomaa et al. (Gomaa et al., 2001) detected candidemia in 14% of the neonates which may be attributed to the large number of antibiotics used and the immune status of the neonates. The proportion of nosocomial BSIs due to budding yeast in study of Saied et al. (2011) was (3.8%).

The departments generating the greatest number of microbial isolates in this study which were; NICU with 33.9% of the total isolates, OPD with 33.6% and PICU with 22.5%. In agreement with other international studies, our results confirmed that ICU is the most important department generating the greatest number of positive cultures, which is quietly normal, since most of the patients in the ICU are those who are critically ill or immunocompromised requiring mechanical support and indwelling devices (Una et al., 2004).

In our study, the highest number of BSI microbial isolates was reported from NICU than other departments. Previous studies from Saudi Arabia have documented widely varying infection rates between individual institutions. The observed incidence of BSI in NICU was 9% at King Khalid University Hospital, Riyadh (Haq et al., 1990), and 40.9% at Abha general hospital (Mahfouz et al., 2010).

Increases in neonatal septicemia have been linked to increased use of prosthetic devices in hospitals in recent years (Brodie et al., 2000); or to better methods of detection of organisms in blood with more sensitive equipment such as the Bactec 9240 instrument (Gomaa et al., 2001), that was used in the present study. The Bactec 9240 instrument facilitates the early detection of microorganisms from blood cultures of newborn infants when compared with other blood culture methods (Garcia-Prats et al., 2000).

Periodic testing and analysis of antibiotic resistance would enable physicians to detect trends in the resistance pattern to commonly prescribed antibiotics in a given organism.

Gram-positive bacteria isolated in this work, showed a very low level of resistance to cephalothin (13.4%) and vancomycin (23%). Babay et al. (2005) reported none of the Gram-positive bacteria were resistant to vancomycin. Our results also showed resistance of a large proportion of isolates to penicillin G (91.1%) and ampicillin (89.3%), eg. 100% of *S. aureus* and 73.3% of *Streptococcus* spp. were resistant to penicillin G. In a study of Al-Zamil (2008), 95% of *S. aureus* and 38% of *S. pneumoniae* was resistant to penicillin G.

All *Candida* isolates were susceptible to amphotericin B and fluconazole in our study. Babay et al. (2003) reported the sensitivity of all fungal isolates to all antifungal agents tested.

Resistance to β -lactams, especially third-generation cephalosporins and non β -lactams, among clinical isolates of Gram-negative bacteria is increasing worldwide (Andrews, 2001). Previous use of more than two different families of antimicrobials in patients with BSI increased the risk for ESBL-producing strains (Quirante et al., 2011). The 112 Gram-negative isolates in this study demonstrated a high level of resistance, 40% towards cefpodoxime, cefotaxime, ceftazidime, ceftriaxone and aztreonam. This type of resistance is a marker for the presence of extended-spectrum β -lactamases (ESBL) (Nathisuwan et al., 2001). Phenotypic screening of beta-lactamases should be performed. Moreover, bla genes could be identified.

A limitation of this study is that antibiotic sensitivity was done for only 27.09% (224/827) of the total isolates.

CONCLUSION

BSI is a major cause of morbidity and mortality in pediatrics. The pathogen distribution was different from those in the developed countries with a predominance of CoNS, *Streptococcus* spp. & *Serratia marcescens*. The incidence rate of BSI is high in ICU infants. So, special attention should be given to the quality of care for these neonates to improve safety.

There was appreciable resistance to commonly used antibiotics. Physicians should receive regularly updated antibiograms to be familiar with trends for the antimicrobial agents used frequently in their hospital. This information is crucial for clinical care management and for improving antimicrobial prescribing habits and performance-based infection prevention and control practices.

COMPETING INTERESTS

AUTHORS HAVE DECLARED THAT NO COMPETING INTERESTS EXIST.

ETHICAL CLEARANCE

Ethical Committee of the Madinah Maternity and Children's Hospital & the Scientific Committee of Taibah University approved the study

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