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Antimicrobial Resistance in Pathogens Causing Pediatrics Bloodstream Infections in a Saudi Hospital

Maha A. Abo-Shadi[1*], Aisha A. Al-Johani[2] and Ahmad A. Bahashwan[3]

[1]Microbiology and Immunology Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.
[2]Biology Department, Faculty of Science, Taibah University, Al-Madinah, KSA.
[3]Laboratory of Madinah Maternity and Children's Hospital, Al-Madinah, KSA.

Authors' contributions

All the authors have made substantial contributions to the intellectual content of the paper. Author MAA planned and designed the study, wrote the protocol, participated in the interpretation of the results and analysis, drafted and critically revised the manuscript for important intellectual content and approval of the version to be published. Author AAA collected the data, performed the practical laboratory activities, participated in the interpretation of the results and drafting of the manuscript. Author AAB participated in the data collection and practical laboratory activities. All authors also read and approved the final manuscript.

Research Article

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ABSTRACT

Background: Bloodstream infection (BSI) is one of the most common life-threatening conditions in hospitalized pediatrics especially if associated with resistant microbes.
Aims: To determine the incidence, predisposing factors, microbiological and antimicrobial resistance patterns in suspected BSI pediatric patients in a Saudi hospital.
Place and Duration of Study: Different wards of Madinah Maternity and Children's Hospital, Saudi Arabia, during one year period from July 1, 2009 to June 30, 2010.
Methodology: Blood cultures were performed to all cases (n= 11968) using Bactec 9240 instrument Blood Culture Systems. Microorganisms were identified by colony morphology, Gram stain and biochemical profiles. BD Phoenix™ was used in confirmation of identification of all BSI Gram-negative isolates. Antibiotic susceptibility pattern of isolates was further done by using disk diffusion method.

**Corresponding author: Email: m_a_shadi@hotmail.com;*

Results: 728 cases (6.1%) were diagnosed with BSI after having a one positive blood culture. The overall mortality rate was 11%. Gram-positive, Gram-negative and yeast accounted for 63.8%, 31.6% and 4.6% of the total isolates, respectively. Coagulase-negative staphylococci were the most prevalent Gram-positive isolates (44%); while *Serratia marcescens* and *Klebsiella pneumoniae* were the most common Gram-negatives. Gram-positive bacteria were mostly sensitive to cephalothin (82.3%) and vancomycin (72.2%), while Gram-negative bacteria were mostly sensitive to ciprofloxacin (93%), piperacillin/tazobactam (92.9%), and meropenem (89.8%).
Conclusion: The incidence rate of BSI is highest in ICU neonates. Therefore, special attention should be given to the quality of care provided for them 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.

1. 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 [1]. Moreover, bacterial sepsis is the seventh leading cause of infant mortality for 2010 in United States [2].

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 or type, and distribution of pathogens [3].

BSI is a serious cause of morbidity and mortality worldwide. Emerging antimicrobial drug resistance among bacterial pathogens causing BSI can limit therapeutic options and complicate patient management [4]. Furthermore, rates of antimicrobial resistance are increasing rapidly nowadays with patterns of large variations between countries.

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

Although some studies on the incidence and epidemiology of BSI in pediatric patients have been conducted in Saudi Arabia, this data 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 suffering from BSI 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. The hospital has 500 beds, and provides primary, secondary and tertiary health care. It is also 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 (e.g., fever >38ºC). During the study period, 11968 suspected BSI pediatric patients (new born to 14 years) 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), were included in the study. Their mean age was 803.83±1234.4 days with min. age of 2 days and max. of 14 years.

The clinical data collected from each patient medical record included: age, gender, hospital ward, clinical diagnosis, length of hospitalization and risk factor including using intravenous devices, urinary catheters, hemodialysis shunts, endotracheal tubes, ventilator support, and previous antibiotic treatment given within the last month. Gestational age and birth body weight was additional data collected for NICU dead patients. The date of death of patients was compiled from the patient administrative system.

Criteria used for laboratory-confirmed BSI diagnosis should meet at least one of the following criteria: (1) At least one positive blood cultures for a known pathogen, which was not related to an infection at another site; (2) The patient experienced at least one of the following signs or symptoms: fever (> 38ºC), chills, hypotension (systolic blood pressure > 90 mmHg) and a common skin contaminant e.g., diphtheroids (*Corynebacterium* spp.), *Bacillus* spp., *Propionbacterium* spp., coagulase-negative staphylococci CoNS (including *Staph. epidermidis*), viridans group streptococci, *Aerococcus* spp., or *Micrococcus* spp. that was isolated from two or more blood cultures drawn on separate occasions [5]. In neonates, in addition to the above criteria, the criteria included; toxic appearance, lethargy, hypotension, hypoventilation, hyperventilation or cyanosis.

An episode of BSI was defined as isolation of one or more recognised bacterial or fungal pathogens from one or more blood cultures. Only the first isolate per patient is counted, unless at least 14 days has passed without a positive blood culture with the same organism, after which an additional episode is recorded. All significant organisms were reported in a polymicrobial episode.

If a potential skin contaminant was isolated (e.g. CoNS, diphtheroid, etc), and the organism was isolated from two or more blood cultures drawn on separate occasions within 48 hours, the patient must have at least one of the following signs and symptoms within 24 hours of the blood culture being collected: fever (>38ºC), chills, rigors, hypotension (For patients aged >1 year); and fever (>38ºC core), hypothermia (<36ºC core), apnoea or bradycardia (For patients aged ≤1 year).

BSI was considered as community acquired if developed before or within 48 hours after admission (except for isolates with a long incubation period as *Salmonella typh*i) and was not maternally-acquired; and it was considered to be hospital acquired if it occurred more than 48 hours after hospital admission or within 48 hours of discharge and were in-direct relation to medical procedures undertaken in the hospital.

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 sterilization 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 CO_2 incubator with 5% to 10% CO_2 for up to 48 hours while other culture plates were incubated aerobically overnight at 37ºC.

Identification of blood culture isolates was based on colony morphology, test 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 to confirm the identification of all BSI Gram-negative isolates. Furthermore, antibiotic susceptibility testing was done according to National Committee for Clinical Laboratory Standards [6].

3. RESULTS

Positive blood cultures were reported for 728 out of 11968 (6.1%) and were diagnosed as BSI at MMCH during the one year study period.

Table 1 shows Demographic characteristics of the 728 confirmed BSI pediatric patients. The highest mean duration of hospital stay and mortality rate was reported from MCU (9 months). The highest number of BSI microbial isolates was reported from NICU (280 isolate), and OPD (278 isolate), which also had the highest number of patients (241 and 275 patient respectively).

Table 1. 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.

With regard to the place of acquisition of infection, 63% of microbial isolates (521/827) were acquired in the hospital, as compared to 37% (306/827) acquired in the community.

A total of 827 microbial isolates were detected from 728 BSI pediatric patients. The number of microbial isolates was 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 (1.1%) cases only were polymicrobial (i.e., two different organisms were isolated from each case from the same blood culture).

Gram-positive bacteria were the most common BSI causative agents in those pediatric patients. They were 528 (63.8%) of the total isolates, whilst 261 isolates (31.6%) were Gram-negative bacteria. Furthermore, *Candida* spp. (*C. albicans* and other *Candida* spp.) were the only fungal species isolated from 38 (4.6%) of the total BSI cases.

Coagulase-negative staphylococci (CoNS) were the most common pathogens accounting for 44% of the total isolates, followed by *Streptococcus* spp. (10.6%). *Serratia marcescens* (7.5%), *Klebsiella* spp. (5.8%) and *P. aeruginosa* (3.9%) were the most common Gram-negative isolated pathogens (Table 2).

Gram-positive bacteria showed a high level of sensitivity to cephalothin and vancomycin. Methicillin resistant *Staph. aureus* (MRSA) was resistant to all the tested antibiotics except vancomycin (Table 3).

Antibacterial resistance rate of BSI Gram-negative isolates is represented in Table 4. All *Candida albicans* isolated were susceptible to amphotericin B and fluconazole; while 21% of non *Candida albicans* were resistant to fluconazole and 18.4% were resistant to amphotericin B (Not shown in a table).

4. DISCUSSIONS

BSI still carries high morbidity and mortality in hospitalized patients despite the availability of current sophisticated therapeutic modalities [7].

In the present investigation, we analyzed clinical and microbiological characteristics of BSI pediatric patients in a Saudi hospital (MMCH); and results showed that 6.1% (728/11968) of pediatric patients had at least one episode of BSI. Previous studies from Saudi Arabia have documented widely varying pediatric infection rates between individual institutions depending on the age group and the hospital ward. The observed incidence of BSI in NICU was 9% at King Khalid University Hospital [8], and 40.9% at Abha general hospital [9]. In contrast to our finding, a higher positivity rate (between 36-55%) in pediatric patients was reported [10,11].

In the current study, 415/728 (57%) of the confirmed BSI pediatric patients were males and 313 (43%) were females. Similar finding have been reported by Al-Zamil [12], where 58.7% of the total 259 pediatric patients with bacteremia were males and 41.3% were females.

Out of the total 11968 admitted pediatrics, 6558 (54.8%) were males and the rest were females. Thus, the rate of BSI in males (6.3%, 415/6558) was higher than females (5.8%, 313/5410). This is in accordance to data of Meyer et al. [13] in their investigation of a total of 1699 patients in 20 hospitals, where male patients had a significantly higher risk of acquiring BSI than female patients (p=0.002). This slight difference could be attributed to a higher admission rate of males compared to females.

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

Microbial isolates	No. of isolates					Total (%)
	NICU	PICU	MCU	IPWs	OPD	
Gram-positive organisms (total)	**150**	**74**	**4**	**58**	**242**	**528(63.8)**
CoNS	106	53	2	37	166	364
MRSA	22	3	1	5	0	31
MSSA	5	4	0	4	14	27
Streptococcus spp.	14	10	1	9	54	88
Micrococcus spp.	1	1	0	0	1	3
Enterococcus spp.	2	2	0	3	1	8
Corynebacterium diphtheria	0	0	0	0	4	4
Bacillus spp.	0	1	0	0	2	3
Gram-negative organisms (total)	**112**	**95**	**5**	**14**	**35**	**261(31.6)**
Klebsiella spp.	26	11	1	2	8	48
Pseudomonas aeruginosa	25	3	1	0	3	32
Enterobacter spp.	9	18	0	3	4	34
Acinetobacter spp.	6	12	1	2	3	24
E. coli	11	4	0	2	3	20
Salmonella spp.	5	0	0	1	5	11
Stenotrophomonas maltophilia	4	4	1	0	0	9
Chryseobacterium meningosepticum	4	0	0	1	0	5
Citrobacter spp.	1	1	0	1	1	4
Haemophilus influenzae	1	2	0	0	2	5
Moraxella spp.	0	0	0	0	2	2
Brucella spp.	0	0	0	1	3	4
Achromobacter spp.	1	0	0	0	0	1
Serratia marcescens	19	40	1	1	1	62
Fungi (total)	**18**	**17**	**0**	**2**	**1**	38**(4.6)**
Candida albicans	4	1	0	0	0	5
Non Candida albicans	14	16	0	2	1	33
Total no. of isolates	**280**	**186**	**9**	**74**	**278**	**827**

CoNS = Coagulase-negative staphylococci, MRSA = Methicillin-resistant S. aureus, MSSA = Methicillin-sensitive 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= 521*)

Antibiotic	CoNS n=364	MRSA n=31	MSSA n=27	*Streptococcus* n=88	*Enterococcus* n=8	*Micrococcus* n=3
PG (10 IU)	337 (92.6)	31 (100)	27 (100)	65 (73.4)	8 (100)	3 (100)
E (15 µg)	313 (86.3)	31 (100)	3 (10)	23 (26.1)	8 (100)	3 (100)
AP (10 µg)	332 (91.2)	31 (100)	27 (100)	58 (65.9)	8 (100)	3 (100)
KF (30 µg)	36 (9.9)	31 (100)	0 (0)	17 (19.3)	8 (100)	0 (0)
CD (2 µg)	154 (42.3)	30 (96.8)	3 (11.1)	29 (33)	6 (75)	0 (0)
TS (25 µg)	186 (51.1)	31 (100)	3 (11.1)	67 (76.1)	4 (50)	0 (0)
VA (30 µg)	96 (26.4)	25 (80.6)	5 (18.5)	19 (21.6)	0 (0)	0 (0)

MRSA = methicillin-resistant S. aureus; MSSA = methicillin-sensitive S. aureus; PG = Penicillins G; E= Erythromycin; AP = Ampicillin; KF = Cephalothin; CD = Clindamycin; TS = Cotrimoxazole; VA = Vancomycin;
**Seven isolates of Bacillus & corynebacterium spp. were not tested.*

Table 4. Antibacterial resistance rate of BSI Gram-negative isolates under study (n= 256*)

	Antibacterial resistance rates No. (%)										
	Klebsiell n=48	***E. coli n=20***	***S. marcescens n=62***	***Enterobacter n=34***	***P. aeruginosa n=32***	***Salmonella n=11***	***Citrobacter n=4***	***Acinetobacter n=24***	***C. meningosepticum n=5***	***S. maltophilia n=9***	***Moraxella n=2***
Beta-lactams											
CTX,30 µg	17 (35.4)	2 (10)	0 (0)	4 (11.8)	32 (100)	0 (0)	2 (50)	6 (25)	5 (100)	9 (100)	0 (0)
CAZ,30 µg	17 (35.4)	2 (10)	3 (4.8)	5 (14.7)	2 (6.3)	7 (63.6)	2 (50)	6 (25)	5 (100)	6 (66.7)	0 (0)
CRO,30 µg	20 (43.3)	2 (10)	22 (35.5)	5 (14.7)	20 (62.5)	11 (100)	2 (50)	12 (50)	3 (6)	9 (100)	2 (100)
CPD,10 µg	18 (36.7)	2 (10)	13 (21)	3 (8.8)	32 (100)	7 (63.6)	2 (50)	18 (75)	5 (100)	9 (100)	0 (0)
KF,30 µg	27 (56.3)	14 (70)	62 (100)	31 (91.1)	32 (100)	11 (100)	2 (50)	24(100)	5 (100)	9 (100)	2 (100)
CXM,30 µg	16 (33.3)	2 (10)	62 (100)	34 (100)	32 (100)	7 (63.6)	2 (50)	18 (75)	5 (100)	9 (100)	0 (0)
FOX,30 µg	11 (22.9)	0 (0)	62 (100)	31 (91.1)	32 (100)	7 (63.6)	2 (50)	24(100)	5 (100)	9 (100)	2 (100)
FEP,30 µg	17 (35.4)	2 (10)	0 (0)	0 (0)	2 (6.3)	4 (36.4)	2 (50)	6 (25)	5 (100)	9 (100)	0 (0)
AMP,10µg	48 (100)	20 (100)	62 (100)	31 (91.1)	18 (100)	7 (63.6)	4 (100)	24 (100)	5 (100)	9 (100)	0 (0)
PIP,100 µg	27 (56.3)	16 (80)	3 (4.8)	0 (0)	2 (6.3)	7 (63.6)	2 (50)	18 (75)	5 (100)	9 (100)	0 (0)
ATM,30 µg	17 (35.4)	2 (10)	13 (21)	3 (8.8)	7 (21.9)	7 (63.6)	2 (50)	24(100)	5 (100)	9 (100)	0 (0)
IMI, 10 µg	0 (0)	0 (0)	0 (0)	0 (0)	18 (56.3)	0 (0)	0 (0)	6 (25)	5 (100)	9 (100)	0 (0)
MEM,10µg	0 (0)	0 (0)	2 (3.2)	0 (0)	4 (12.5)	0 (0)	0 (0)	6 (25)	5 (100)	9 (100)	0 (0)
β-lactams/β-lactamase inhibitors											
AUG,30 µg	27 (56.3)	4 (20)	62 (100)	28 (82.4)	32 (100)	0 (0)	2 (50)	24 (100)	5 (100)	9 (100)	0 (0)
TZP100/10 µg	0 (0)	0 (0)	3 (4.8)	0 (0)	2 (6.3)	0 (0)	0 (0)	4 (25)	5 (100)	6 (66.7)	0 (0)
Non β-lactams											
GM,10 µg	12 (25)	0 (0)	3 (4.8)	0 (0)	5 (15.6)	11 (100)	0 (0)	4 (25)	5 (100)	9 (100)	0 (0)
AK,30µg	2 (4.2)	0 (0)	3 (4.8)	0 (0)	5 (15.6)	11 (100)	0 (0)	4 (25)	5 (100)	9 (100)	0 (0)
CIP, 5 µg	3 (6.3)	0 (0)	0 (0)	0 (0)	5 (15.6)	0 (0)	0 (0)	4 (25)	0 (0)	6 (66.7)	0 (0)
TS, 25 µg	21 (43.8)	12 (60)	5 (8.1)	3 (8.8)	32 (100)	7 (63.6)	2 (50)	24 (100)	5 (100)	3 (33.3)	2 (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 = Ciprofloxacin, TS = cotrimoxazole,

** Five isolates of Brucella & Achromobacter spp. were not tested.*

The overall hospital-acquired BSI (521 microbial isolates, 63%) were relatively higher than the community-acquired. Different hospital-acquired BSI rates (90% [14]; 43% [15]; 53% [16]) were previously reported.

The assessment of the risk factors associated with BSI revealed that the duration of hospitalization prior to the occurrence of BSI is an important factor especially for cases of multidrug resistance nosocomial BSIs [17]. In the present study, the highest duration of hospital stay in MMCH (9 months) and mortality rate (4/6 patients, 66.7%) were reported from the MCU (Table 1), whereas some patients had polymicrobial infections. MCU is used for hospice-type patients who are terminally ill or incurably ill. Most of those patients were mechanically ventilated or under continuous use of intravascular and central venous catheterization. Central venous catheterization was reported to be the most common risk factor for BSI that extends the length of stay, increases the cost of hospitalization; and attributed to 4-37% of mortality [18,19].

Surprisingly, mortality rate was higher in PICU than NICU. This may explained by the higher infection rate in PICU (186/138, 1.34) than NICU (280/241, 1.16). There is of course a problem in infection control of this unit, and this problem is now in concern of the infection control department of MMCH.

The overall mortality among our patients was (80/728, 11%) (Table 1). Similar mortality rates were reported by other Saudi pediatric studies [14,15,20]. The 11% mortality rate in the current study was higher than that reported by Gray [1] where, the overall mortality rate directly attributable to infection was 2.4%. In addition, the mortality rate in the NICU was 18.7% in our investigation, which is comparable to a study performed previously in four main hospitals in Makkah (13.4%) [21]. Recently, Ballot et al. [22] reported a mortality rate of 6.3% in the early-onset sepsis and 19.6% in the late-onset sepsis groups.

Due to the diversity of clinical conditions and wards, it was not possible to attribute the cause of death to BSI in all our patients. As, mortality could be attributed to different factors such as the causative organisms, age, underlying diseases and ICU admission [14]. The most commonly isolated organisms in our patients who died of BSI were CoNS, *Klebsiella* spp. and *Candida* spp. CoNS, *S. aureus* and *Enterococcus* spp. were the most leading to death reported in another study [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 [9].

Most BSI cases in this work were monomicrobial (98.9%), and the polymicrobial BSI was caused by *S. viridians*, CoNS, *Klebsiella* spp., *Acinetobacter, Candida* spp., *Enterobacter* spp. and *S. marcescens*. Polymicrobial bacteremia was reported in 5.2% in a previous study by Al-Zamil [12]. The causative agents involved in the polymicrobial bacteremia included *E. coli, P. aeroginosa, K. pneumoniae, K. oxytoca, S. marcesceus, E. cloacae* and *A. baumannii* [23].

Many studies were in accordance to our results as Gram-positive bacteria were more prevalent than Gram-negatives [1,6,14,21,24,25,26]. Furthermore, Wisplinghoff et al. [27] detected Gram-positive, Gram-negative and yeast in 65%, 24% and 11% of isolates in the

US prospective surveillance for nosocomial BSI in pediatric patients at 49 hospitals during a 6-year period. On the other hand, some earlier studies [4,15,28] revealed a high occurrence of Gram-negative compared with Gram-positive bacteria.

Gram-positive cocci started reemerging as predominant pathogens in BSI in the early 1980s and it has been suggested that this change is due to evolution of medical care [29,30].

CoNS was the most frequent isolate in this study, which could be due to the increasing use of intravascular devices in the medical care of MMCH. 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 [31], where biofilm production plays a role in pathogenesis [32]. Furthermore, the increased isolation of CoNS in blood cultures; its association with higher mortality and prolongation of the length of hospital stay may reflect a change from regarding these organisms as normal skin flora to viewing them as clinically significant [33,34].

CoNS was the most common isolate overall accounting for 43% of the total isolates in study of Wisplinghoff et al. [27]. Recently, Ballot et al. [22] reported the most common isolate overall was CoNS accounting for 19.1% of the total isolates, while Saied et al. [35] reported CoNS as the second most frequent isolate accounting for 25.5% of the total isolates recovered from nosocomial BSI, only exceeded by *K. pneumonia* (26.7%).

The second most causative agents after CoNS in the cases under study were *Septococcus* spp., of whom (1.7%) were *S. pneumonia,* which was also previously reported [36]. Al-Zamil [12] 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 MRSA from children is increasing [37]. Furthermore, Bacteraemia due to MRSA is associated with high mortality compared with methicillin sensitive *S. aureus* bacteraemia [34].

Worldwide, MRSA rates vary widely, from <1% in Denmark, Sweden, and The Netherlands to >40% in the United Kingdom, Greece, and Italy [38]. In our study, we encountered 31/58 (53.45%) isolates of MRSA of the total *Staph. aureus* isolates, with the highest proportion in NICU (22/31, 71%). MRSA infections in MMCH was higher than reported by Gray [1] which was 15.5%., and that reported by Khairuldin et al. [37] (13.1%); but lower than a study from USA by Wisplinghoff et al. [27] (29%) & a study from Egypt by Saied et al. [35] (64%).

Increasing MRSA infection rates have been reported in tertiary care centers in Saudi Arabia between 2000 and 2004 [39]. MRSA constituted 5.9% of the Gram-positive bacteria recovered from blood cultures of our patients. This is opposed to much higher rate reported from Iran, 79% [4]. Promoting hand hygiene and isolation precautions are important measures to prevent the spread of MRSA.

No vancomycin-resistance was detected among Enterococcus isolates. However, Wisplinghoff et al. [27] saw vancomycin-resistance in 1% of *Enterococcus faecalis* and in 11% of *Enterococcus faecium* isolates.

BSI with Gram-negative bacteria are one of the most serious infections in the hospital setting, a situation compounded by the increasing antibiotic resistance of Gram-negative bacteria causing BSI [40]. The most frequently isolated Gram-negative bacteria were *S.*

marcescens. (62 isolate, 23.7%), which is a well-recognised cause of outbreaks of hospital-acquired infections, particularly in NICUs [41].

P. aeruginosa rate was 3.9% in this setting, which is in agreement with the 3.5% reported by Al-Zamil [12]. *P. aeruginosa* BSI in immunocompromised patients can lead to death within the first 72 hours [42]. On contrary to our results, Wendt et al. [43] and Weinstein et al. [44] reported *P. aeruginosa* as the commonest Gram-negative pathogen isolated from BSI cases.

The incidence of BSI caused by *K. pneumoniae* in this investigation was 5.6%, which is comparable to that reported previously by Haddon et al. [36] (7.4%); Al-Zamil [12] (6.6%).

Candida BSI contributes to increased length of hospital stay, increased hospital costs, and most importantly, increased morbidity and mortality [45]. *Candida* spp. was implicated in 4.6% of all BSI episodes representing the fifth most common etiologic agent in this study. Previous studies indicated that *Candida* spp. represent the fourth to seventh most common etiologic agent causing septicemia [25,46,47]. However, the infections with *Candida* spp. in our study was more than what had been reported by Babay et al. [26] and Saied et al. [35] but less than that of Gomaa et al. [48].

The three departments generating the greatest number of microbial isolates in MMCH were NICU, OPD and PICU. 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 the critically ill or immunocompromised patients requiring mechanical support and indwelling devices [49].

Increases in neonatal septicemia have been linked to increased use of prosthetic devices in hospitals in recent years [50]; or to better methods of detection of organisms in blood with more sensitive equipment such as the Bactec 9240 instrument [48], 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 [51].

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 bacterial isolates showed a very low level of resistance to cephalothin and vancomycin. Babay et al. [26] reported none of the Gram-positive bacteria were resistant to vancomycin. Our results also showed resistance of a large proportion of Gram-positives to penicillin G (90.4%) and ampicillin (73.1%). In a study of Al-Zamil [12], 95% of *S. aureus* and 38% of S. *pneumonae* was resistant to penicillin G.

An important observation was noted which is the high resistance pattern of *S. maltophilia and C. meningosepticum isolates* to most antibiotics used. Treatment of *S. maltophilia* is problematic owing to its high level of intrinsic resistance to multiple classes of antibiotics [52]. A number of factors, including multidrug efflux pumps and outer membrane impermeability, likely contribute to the intrinsic antibiotic resistance of Cullmann [53], Alonso and Martinez [54].

C. meningosepticum exists in water systems and wet surfaces of the hospital environment [55]. *C. meningosepticum* is also resistant to multiple antibiotics [56].

All our *C. albicans* isolated were susceptible to amphotericin B and fluconazole as Babay et al. [26] reported the sensitivity of all their fungal isolates to all antifungal agents tested.

The high resistance rates for the commonly used antibiotics in this study could be explained by the fact that resistance develops wherever antibiotics are abused, overused, misused and dispensed at levels lower than the suggested treatment guidelines. This means that antibiotics kill only the non-resistant organisms, while leaving behind their tougher counterparts to replicate and spread resistance genes.

Resistance to β-lactams, especially third-generation cephalosporins and non β-lactams, among clinical isolates of Gram-negative bacteria is increasing worldwide [57,58]. The Gram-negative isolates among the studied patients demonstrated a high level of resistance towards cefpodoxime (41.4%), cefotaxime (30%), ceftriaxone (40.2%) and aztreonam (34.8%). This type of resistance is a marker for the presence of extended-spectrum β-lactamases (ESBL) [59]. Thus, phenotypic screening of beta-lactamases should be performed; and *bla* genes identified.

5. CONCLUSION

BSIs are 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. and *Serratia marcescens*. The incidence rate of BSI is high in ICUs (PICU & NICU). So, special attention should be given to the quality of care for those patients to improve safety. This could be done through training, proper selection of catheters and sites, standardization of central venous catheter insertion and maintenance processes and use prophylactic antimicrobial lock solution in patients who have a history of multiple catheter-related BSI. Furthermore, empowerment of team members to enforce adherence to best practices will help prevent and control hospital acquired infection.

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 hospitals. It is also very important to define the potential of resistant organism's colonization surveillance in all ICU patients to predict etiology of subsequent infection and improve adequacy of empiric antimicrobial treatment.

ETHICAL APPROVAL

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

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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