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ORIGINAL ARTICLE

Epidemiology of bloodstream infections in the paediatric population in a Malaysian general hospital over a 2-year period

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Abstract

Background: Bloodstream infection (BSI) is a major cause of morbidity and mortality. The classification of infection into community-acquired, hospital-acquired, and healthcare-associated infection provides an educated guess on the possible aetiological agents and appropriate empirical antimicrobial therapy to be instituted. This study aims to determine the aetiological agents, the antimicrobial susceptibility patterns, and the classification of infections among the paediatric population. *Materials & Methods*: This study was conducted in Hospital Kuala Lumpur, Malaysia from January 2016 to December 2017. A total of 303 isolates were included in this study which was obtained from 238 patients. The patients' microbiological worksheets and medical notes were reviewed to determine the antimicrobial susceptibility patterns, demographic data, classification of infection, and outcome (survival versus death). *Results:* Most of the patients were in the age group of one to less than five years old (41%) with 58% male and 85% Malay patients. Common causes of BSI were *Staphylococcus aureus* (17%), followed by *Klebsiella pneumoniae* (15%), *Acinetobacter baumanii* (10%), *Pseudomonas aeruginosa* (10%), and *Escherichia coli* (6%). Sixty percent of BSI episodes were caused by gram-negative bacteria, 34% by gram-positive bacteria, and 6% by fungi. Most of the infections were classified as hospital-acquired infections (72%), followed by healthcare-associated (20%) and community-acquired infections (8%). There were 33% of methicillin-resistant *Staphylococcus aureus*, 53% of extended-spectrum beta-lactamase (ESBL) producing *Klebsiella pneumoniae,* and 33% ESBL producing *Escherichia coli*. The overall case fatality rate (CFR) was 27% with the highest CFR caused by *Serratia marcescens* (53.3%). *Conclusions*: The majority of paediatric bloodstream infections are hospital-acquired. Improvement in prevention strategies and revisions in antibiotic policies are important to overcome it.

Keywords: Bloodstream infection, community-acquired infection, healthcare-associated infection, paediatric.

INTRODUCTION

Bloodstream infection (BSI) is a major cause of morbidity and mortality, which is increasing in trend. It is associated with a case fatality rate (CFR) of 2 - 34%.[1-2] BSI may result in septic shock and multiple organ failures. Thus, early identification of pathogens is important in establishing a definitive diagnosis to allow early targeted antimicrobial therapy.[3]

The global epidemiology of BSI is variable depending on different patient populations and co-morbidities. The reported incidence of bloodstream infection in paediatric patients ranges from 9.3 – 12.48%.[4-5] For decades, infections have been classified into two categories according to the timing of their onset into community-acquired (CA) and hospital-acquired (HA) which were used to guide empirical antimicrobial therapy. CA infection (CAI) occurs in the community with no history of previous hospital admission while HA infection (HAI) defined as an infection acquired in the hospital by a patient who was admitted for a

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reason other than that infection.[6-7] The third category of classification is healthcare-associated (HCA) infection (HCAI) which was introduced as there was increasing awareness of patients who present with serious infections from the community but shares characteristics of patients with HAI.[8-12]

The aetiology of BSI and the pattern of antimicrobial resistance is always evolving, and it is different from one institution to the other. These pose a great challenge to medical practitioners. This study is to determine the aetiological agents responsible for BSI in children at Hospital Kuala Lumpur (HKL) and to identify the antimicrobial susceptibility patterns of common pathogens. Besides, infections will be categorised as community-acquired, hospital-acquired, or healthcare-associated, and case fatality rate (CFR) will be determined for each organism. Hospital Kuala Lumpur is the largest hospital under the Ministry of Health of Malaysia and it's a tertiary referral hospital with 2300 beds. Data from this study is expected to empower physicians with the knowledge on local trends of BSI and assist in choosing the appropriate empirical antimicrobial therapy while waiting for the blood culture results.

MATERIALS AND METHODS

Study design and population

This was a retrospective study by reviewing medical notes and microbiology worksheets of children admitted to paediatric and neonatal wards in HKL, a tertiary referral centre in Malaysia, from January 2016 to December 2017. Patients with positive blood culture and fulfilled the inclusion and exclusion criteria were analysed further by collecting their demographic details and outcome (survival versus death) upon discharge. Inclusion criteria were all inpatients whose blood cultures were received within the study period and age ranging from 0 to less than 13 years old. For any given patient during the same hospital admission period, the same isolate recovered multiple times was considered as one isolate. However, in polymicrobial infection, each different organism was considered as one isolate. Those who were not admitted to the ward or transferred out to another hospital were excluded from this study. Organisms that are generally considered contaminants such as *Corynebacterium* spp., *Bacillus* spp. other than *B.anthracis, Propionibacterium acnes* and coagulase-negative *Staphylococcu*s (CoNS) were excluded from this study. However, these isolates were taken as significant isolates if they were obtained from the patients on at least two consecutive blood cultures and treated as pathogenic organisms by clinicians.

Definitions

1. Community-acquired infection – positive blood culture obtained at the time of hospital admission or within 48 hours after hospital admission for patients who did not fit the criteria for a healthcare-associated infection.
2. Hospital-acquired infection - positive blood culture obtained from patients who had been hospitalized for 48 hours or longer.
3. Healthcare-associated infection - positive blood culture obtained from a patient at the time of hospital admission or within 48 hours of admission if the patient fulfilled any of the following criteria:
   a. Received intravenous therapy in the 30 days before the BSI.
   b. Haemodialysis in 30 days before the BSI.
   c. Hospitalized in the previous 90 days for 2 or more days.

These definitions are based on the CDC definition[6] and the initial definition of healthcare-associated infection by Friedman *et al*.[12]

Bacteriology

All blood cultures received were incubated for a maximum of 5 days. Once positive, a gram stain was done and then the blood was inoculated on suitable culture plates as per protocol. The culture plate was read after 24 hours and appropriate further tests were undertaken. The identification of microorganisms was based on the Analytical Profile Index (API) (bioMérieux, France) and the VITEK identification system (bioMérieux, France). Certain microorganisms were identified based on a variable combination of tests such as gram stain, colony characteristics, biochemical reactions, antimicrobial resistance patterns, growth requirements, and rapid latex system without using the API or VITEK systems. These include *S. aureus, P. aeruginosa, A. baumanii, E. coli, K. pneumoniae,* CoNS, *S. pneumoniae, S. pyogenes, S. agalactiae, Micrococcus, P. mirabilis,* and *P. vulgaris*. If diagnostic challenges arose by these methods, then further tests using API or VITEK was done. For an organism identified by API or VITEK, it was excluded from this study if the percentage of identification was less than 90%. The antimicrobial susceptibility testing was performed according to the Clinical Laboratory

Standards Institute guideline.[13] In the event of the CLSI has no interpretive criteria, then the interpretive criteria used were based on either Zone Diameter Interpretive Chart, BD BBL ™ Sensi-disc Antimicrobial Susceptibility Test Discs Product Insert (OXOID)[14] or the European Committee on Antimicrobial Susceptibility Test[15] guidelines.

Ethical approval

This study was registered with the National Medical Research Register of Malaysia (NMRR) (NMRR-17-3159-38940). It was approved by Universiti Kebangsaan Malaysia (UKM) Medical Research and Ethics Committee (FF-2018-119), and HKL Clinical Research Centre (CRC) Ethical Committee (HCRC.IIR-2018-04-074). Ethical approval for this study was also obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

Data collection and analysis

All data were entered and analyzed using statistical software, IBM SPSS version 26. Descriptive and univariable analyses were done for different age groups. Fisher's Exact Test was used to determine the patient's case fatality rate (survival versus death). Level of significance was taken at 0.05 ($p < 0.05$).

RESULTS

A total of 5,549 blood cultures were received from paediatric inpatients from January 2016 to December 2017. A total of 1,015 blood cultures were positive. There were 309 blood cultures with poor identification, missing data, or repetitive isolates which were excluded. A further 403 isolates were excluded as contaminant organisms. A total of 303 isolates were included in this study and these were obtained from 238 patients. Among these 238 patients, the major group of patients was in the age group of one to less than five years old (41%, 97/238). The majority were male (58%, 139/238) and Malay (85%, 202/238) patients (Table 1). The study population consisted of 25% of patients with underlying haematological malignancy.

Of these 238 patients, there were 303 BSI episodes. Sixty percent of BSI episodes were caused by gram-negative bacteria, 34% by gram-positive bacteria, and 6% by fungi. The most commonly isolated organisms were *Staphylococcus aureus* (17%), *Klebsiella pneumoniae* (15%), *Acinetobacter baumanii* (10%), *Pseudomonas aeruginosa* (10%), and *Escherichia coli* (6%) (Table 2). The commonest isolated fungus was *Candida parapsilosis* (28%, 5/18) of which 60% was HA and 40% was HCA.

The commonest organisms isolated from those less than five years old were *Staphylococcus aureus* (16%), *Klebsiella pneumoniae* (16%), *Acinetobacter baumanii* (10%). On the other hand, the commonest organism isolated from those five years old and above were *Staphylococcus aureus* (20%), *Pseudomonas aeruginosa* (14%), followed equally by *Escherichia coli* and *Klebsiella pneumoniae* at 8% each (Table 3).

The majority of BSI were classified as HAI (72%, 218/303) followed by HCAI (20%, 61/303) and CAI (8%, 24/303). Hospital-acquired infection was caused by *Klebsiella pneumoniae* (18%) followed by *Staphylococcus aureus* (15%). The commonest organisms causing CAI were *Staphylococcus aureus* and *Escherichia coli* at 25% each. The majority of HCAI were caused by *Staphylococcus aureus*

TABLE 1: Sociodemographic characteristics of patients (n=238 patients)

Sociodemographic data		Frequency (%)
Age	<1m	37 (15)
	1m - <1y	69 (29)
	1y - <5y	97 (41)
	5y - <13y	35 (15)
Gender	Male	139 (58)
	Female	99 (42)
Ethnic	Malay	202 (85)
	Chinese	14 (6)
	Indian	13 (5)
	Others	9 (4)

TABLE 2: Organisms isolated (n=303)

Organisms	Frequency (%)
Gram-positive bacteria	
Staphylococcus aureus	51 (16.8)
Coagulase-negative Staphylococcus	15 (5.0)
Streptococcus viridans	14 (4.6)
Streptococcus species	10 (3.3)
Enterococcus species	6 (2.0)
Other gram-positive organisms	8 (2.6)
Gram-negative bacteria	
Klebsiella pneumoniae	45 (14.9)
Acinetobacter baumannii	29 (9.6)
Pseudomonas aeruginosa	29 (9.6)
Escherichia coli	18 (5.9)
Serratia marcescens	15 (5.0)
Stenotrophomonas maltophilia	13 (4.3)
Enterococcus species	11 (3.6)
Salmonella species	5 (1.7)
Pseudomonas species	4 (1.3)
Other gram-negative organisms	12 (4.0)
Fungsi	
Candida parapsilosis	5 (1.7)
Candida albicans	3 (1.0)
Candida glabrata	3 (1.0)
Candida tropicalis	2 (0.7)
Others	5 (1.7)

(20%), followed by *Pseudomonas aeruginosa* and CoNS at 11% each.

Antibiotic susceptibility patterns of *Staphylococcus aureus* showed that 33% of the isolates in this study were methicillin-resistant *Staphylococcus aureus* (MRSA) (Figure 1). Those with HAI had 39% MRSA cases while those with HCAI had 33% MRSA cases. There were no MRSA isolates from community-acquired infection.

Antibiotic susceptibility patterns of *Klebsiella pneumoniae* showed that there were 51 to 56% isolates that were non-susceptible to 2nd, 3rd, and 4th generation cephalosporin. There were

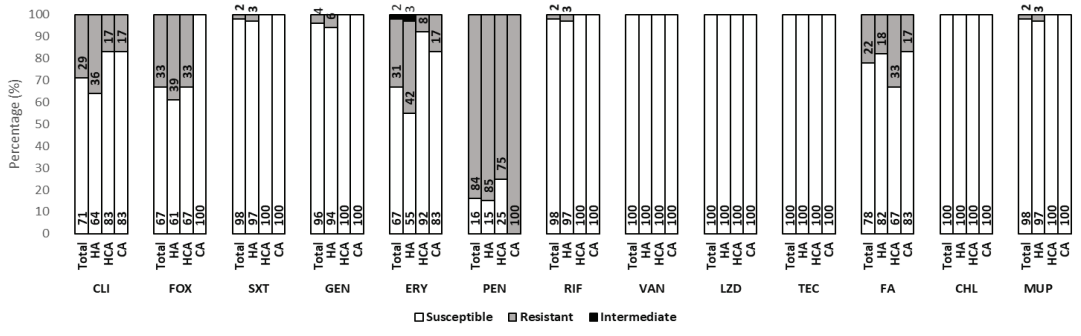

FIG. 1: Antibiotic susceptibility patterns among *Staphylococcus aureus* isolates (Total, n=51), (Hospital-acquired (HA), n=33), (Healthcare-associated (HCA), n= 12) and (Community-acquired (CA), n=6). CLI clindamycin, FOX cefoxitin, SXT trimethoprim/sulfamethoxazole, GEN gentamicin, ERY erythromycin, PEN penicillin, RIF rifampin, VAN vancomycin, LZD linezolid, TEC teicoplanin, FA fusidic acid, CHL chloramphenicol, MUP mupirocin

TABLE 3: Distribution of organisms according to age (n=303)

Organisms		<5 years old	5 - <13 years old
Gram-positive bacteria			
Staphylococcus aureus	Number of isolate, N % within age group (n)	41 (16.2)	10 (20.0)
Coagulase-negative *Staphylococcus*	Number of isolate, N % within age group (n)	14 (5.5)	1 (2.0)
Streptococcus viridans	Number of isolate, N % within age group (n)	12 (4.7)	2 (4.0)
***Streptococcus* species**	Number of isolate, N % within age group (n)	8 (3.2)	2 (4.0)
***Enterococcus* species**	Number of isolate, N % within age group (n)	4 (1.6)	2 (4.0)
Other gram-positive organisms	Number of isolate, N % within age group (n)	7 (2.8)	1 (2.0)
Gram-negative bacteria			
Klebsiella pneumoniae	Number of isolate, N % within age group (n)	41 (16.2)	4 (8.0)
Acinetobacter baumanii	Number of isolate, N % within age group (n)	26 (10.3)	3 (6.0)
Pseudomonas aeruginosa	Number of isolate, N % within age group (n)	22 (8.7)	7 (14.0)
Escherichia coli	Number of isolate, N % within age group (n)	14 (5.5)	4 (8.0)
Serratia marcescens	Number of isolate, N % within age group (n)	14 (5.5)	1 (2.0)
Stenotrophomonas maltophilia	Number of isolate, N % within age group (n)	11 (4.3)	2 (4.0)
***Enterobacter* species**	Number of isolate, N % within age group (n)	8 (3.2)	3 (6.0)
***Salmonella* species**	Number of isolate, N % within age group (n)	4 (1.6)	1 (2.0)
***Pseudomonas* species**	Number of isolate, N % within age group (n)	2 (0.8)	2 (4.0)
Other gram-negative organisms	Number of isolate, N % within age group (n)	10 (4.0)	2 (4.0)
Fungi			
Candida parapsilosis	N(%) % within age group	4 (1.6)	1 (2.0)
Candida albicans	N(%) % within age group	2 (0.8)	1 (2.0)
Candida glabrata	N(%) % within age group	2 (0.8)	1 (2.0)
Candida tropicalis	N(%) % within age group	2 (0.8)	0 (0)
Others		5 (2.0)	0 (0)
Total		253 (100)	50 (100)

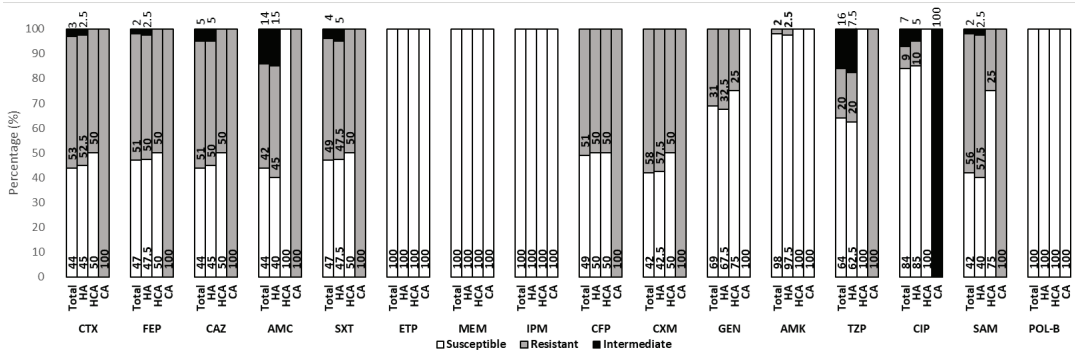

FIG. 2: Antibiotic susceptibility patterns among *Klebsiella pneumoniae* isolates (Total, n=45), (Hospital-acquired (HA), n=40), (Healthcare-associated (HCA), n= 4), and (Community-acquired (CA), n=1). CTX cefotaxime, FEP cefepime, CAZ ceftazidime, AMC amoxycillin/clavulanic acid, SXT trimethoprim/sulfamethoxazole, ETP ertapenem, MEM meropenem, IPM imipenem, CFP cefoperazone, CXM cefuroxime, GEN gentamicin, AMK amikacin, TZP piperacillin/tazobactam, CIP ciprofloxacin, SAM ampicillin/sulbactam, POL-B polymyxin B

53% isolates that were ESBL producers and 2% isolates that were multidrug-resistant organisms (MRO). However, there were no carbapenem-resistant isolates seen (Figure 2). Also, the susceptibility towards amoxycillin/clavulanic acid and ampicillin/sulbactam were both less than 50%. For *Klebsiella pneumoniae* causing HAI, there were 52.5% ESBL isolate and 2.5% MRO isolates. Only one isolate caused a CAI and it was ESBL positive. In those isolates causing HCAI (n=4), 50% of isolates were ESBL positive.

Antibiotic susceptibility patterns of *Acinetobacter baumanii* showed that the isolates were 65 – 66% susceptible to ampicillin/sulbactam and cefoperazone/sulbactam. Higher susceptibility was seen towards ciprofloxacin and gentamicin (69%). For imipenem and meropenem, susceptibility was 66% and 62%, respectively (Figure 3). In HAI, susceptibility towards ampicillin/sulbactam, cefoperazone/sulbactam, imipenem, and meropenem were 58% each. Susceptibility towards ciprofloxacin and gentamicin was 62.5%. There was only one isolate from CAI, which was susceptible to cefoperazone/sulbactam, ampicillin/sulbactam, and imipenem; resistant towards ceftazidime; and intermediate susceptibility towards trimethoprim/sulfamethoxazole and meropenem. There were 4 isolates from HCAI which showed susceptibility to all the antibiotics tested except chloramphenicol.

Antibiotic susceptibility patterns among *Pseudomonas aeruginosa* showed the highest non-susceptibility (resistant and intermediate susceptibility) seen towards piperacillin/tazobactam (24%) followed by meropenem

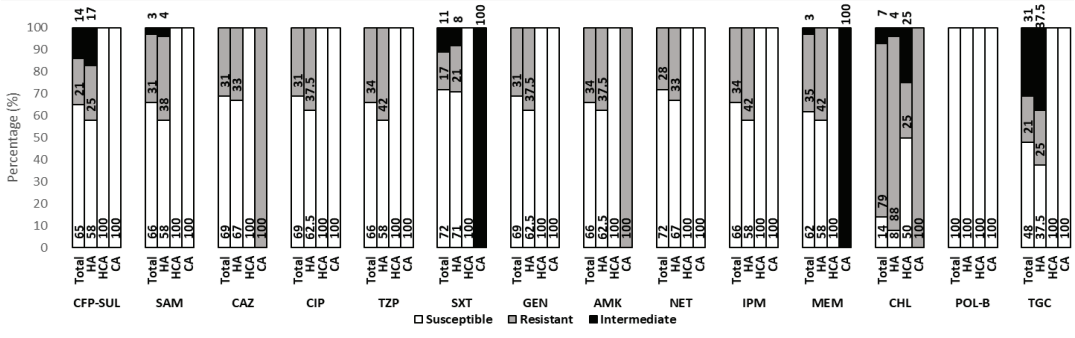

FIG. 3: Antibiotic susceptibility patterns among *Acinetobacter baumanii* isolates (Total, n=29), (Hospital-acquired (HA), n=24), (Healthcare-associated (HCA), n= 4) and (Community-acquired (CA), n=1). CFP-SUL cefoperazone/sulbactam, SAM ampicillin/sulbactam, CAZ ceftazidime, CIP ciprofloxacin, TZP piperacillin/tazobactam, SXT trimethoprim/sulfamethoxazole, GEN gentamicin, AMK amikacin, NET netilmicin, IPM imipenem, MEM meropenem, CHL chloramphenicol, POL-B polymyxin B, TGC tigecycline

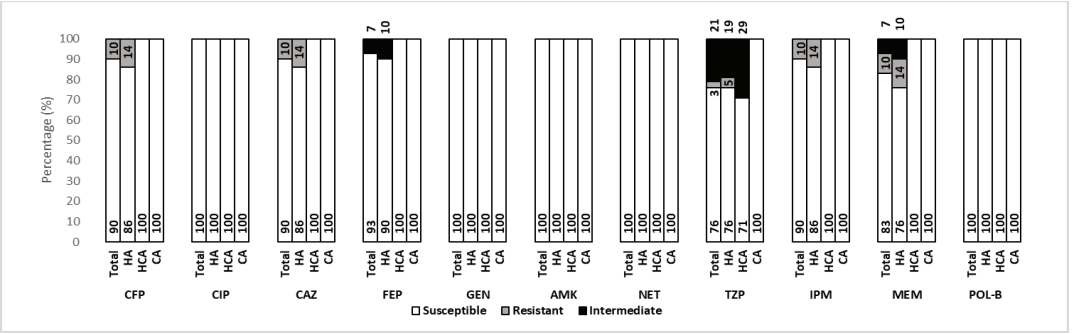

FIG. 4: Antibiotic susceptibility patterns among *Pseudomonas aeruginosa* isolates (Total, n=29), (Hospital-acquired (HA), n=21), (Healthcare-associated (HCA), n= 7) and (Community-acquired (CA), n=1). CFP cefoperazone, CIP ciprofloxacin, CAZ ceftazidime, FEP cefepime, GEN gentamicin, AMK amikacin, NET netilmicin, TZP piperacillin/tazobactam, IPM imipenem, MEM meropenem, POL-B polymyxin B

(17%) (Figure 4). Susceptibility towards 3rd and 4th generation cephalosporin ranges from 90 – 93% while susceptibility towards ciprofloxacin and gentamicin was 100% (Figure 4). In HAI, 24% non-susceptibility seen towards piperacillin/tazobactam and meropenem. The susceptibility towards ceftazidime was 86 %. There was only one isolate from CAI which was susceptible to all the antibiotics tested. For HCAI, the isolates were susceptible to all the antibiotics tested except for piperacillin/tazobactam which had only 71% susceptibility.

The antibiotic susceptibility patterns among *Escherichia coli* showed there were 28% to 33% isolates resistant to 3rd and 4th generation cephalosporins (Figure 5). The isolates were most resistant to ampicillin (72%). No carbapenem-resistant isolates were seen. There were 33% ESBL and 6% MRO isolates seen. In HAI, the isolates showed 50% to 62.5% resistance to 2nd, 3rd, and 4th generation cephalosporins. It was also 87.5% resistant to ampicillin and had 62.5% ESBL isolates. In CAI, there were no ESBL or MRO isolates seen. Resistance was seen towards ampicillin (67%), trimethoprim/sulfamethoxazole (50%), and intermediate susceptibility towards ampicillin/sulbactam (17%). There were only 4 isolates from HCAI with 1 ESBL and 1 MRO isolate.

Overall case fatality rate (CFR) was 27% with the highest bacterial cause due to *Serratia marcescens* (53.3%) followed by *Klebsiella pneumoniae* (44.4%) (Table 4). Overall, the number of fungemia cases in this study was small and CFR for fungus was 38% and not statistically significant (7 out of 18 patients died, p=0.280). Fisher's Exact test showed statistical significance for CFR of *Serratia marcescens* (p=0.034) and *Klebsiella pneumoniae* (p=0.010).

DISCUSSION

From this study, it was found that the commonest type of BSI is HAI (72%), followed by HCAI (20%), while CAI has the lowest incidence (8%). Not many studies have used similar classification

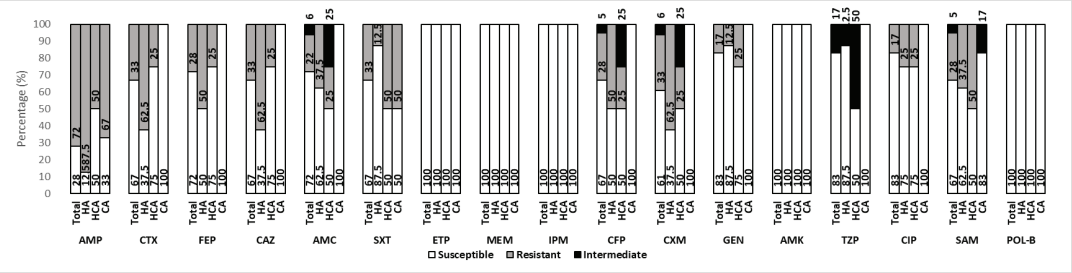

FIG. 5: Antibiotic susceptibility patterns among *Escherichia coli* isolates (Total, n=18), (Hospital-acquired (HA), n=8), (Healthcare-associated (HCA), n= 4) and (Community-acquired (CA), n=6). AMP ampicillin, CTX cefotaxime, FEP cefepime, CAZ ceftazidime, AMC amoxycillin/clavulanic acid, SXT trimethoprim/sulfamethoxazole, ETP ertapenem, MEM meropenem, IPM imipenem, CFP cefoperazone, CXM cefuroxime, GEN gentamicin, AMK amikacin, TZP piperacillin/tazobactam, CIP ciprofloxacin, SAM ampicillin/sulbactam, POL-B polymyxin B

TABLE 4: Case fatality rate based on organisms isolated (n=303)

Organisms	Survived (n)	Died (n)	Total (N)	CFR (n (Died)/N%)	Fisher's Exact test
Gram-positive bacteria					
Staphylococcus aureus	42	9	51	17.6	0.120
Coagulase-negative *Staphylococcus*	10	5	15	33.3	0.564
Streptococcus viridans	12	2	14	14.3	0.365
Streptococcus species	10	0	10	0	0.067
Enterococcus species	4	2	6	33.3	0.667
Other gram-positive organisms	7	1	8	12.5	0.454
Gram-negative bacteria					
Klebsiella pneumoniae	25	20	45	44.4	0.010
Acinetobacter baumanii	18	11	29	37.9	0.193
Pseudomonas aeruginosa	17	12	29	41.4	0.083
Escherichia coli	16	2	18	11.1	0.171
Serratia marcescens	7	8	15	53.3	0.034
Stenotrophomonas maltophilia	11	2	13	15.4	0.526
Enterobacter species	11	0	11	0	0.039
Salmonella species	5	0	5	0	0.328
Pseudomonas species	4	0	4	0	0.578
Other gram-negative organisms	10	2	12	16.7	0.522
Fungi					
Candida parapsilosis	4	1	5	20	1.00
Candida albicans	2	1	3	33	1.00
Candida glabrata	1	2	3	66	0.183
Candida tropicalis	1	1	2	50	0.473
Others	3	2	5	40	0.617
Total	220	83	303	27	-

criteria. A study done by Laupland *et al*.[16] with similar classification has shown there was 48% CAI, 26% HCAI, and 27% HAI while Lochan *et al*.[17] found 53.5% HA, 35.8% CA, and 10.7% HCA-BSI. These findings are quite different from our study. The differences reflect the variations of the background of the study population. The majority of BSI was caused by gram-negative bacteria and this was quite consistent with other studies.[18-19] The majority of the study population were male (58%) and Malay (85%) and this reflects Malaysia's general population distribution where male gender and Malay ethnicity predominates.

The commonest aetiological agents of BSI were *Staphylococcus aureus* (17%), followed by *Klebsiella pneumoniae* (15%), *Acinetobacter baumanii* (10%), *Pseudomonas aeruginosa* (10%), and *Escherichia coli* (6%). *Staphylococcus aureus* as the commonest organism causing BSI in the paediatric population is similar to other studies.[18,20-21]

According to the classification of infection, the commonest organisms causing HAI were *Klebsiella pneumoniae* (18%), *Staphylococcus aureus* (15%), and *Acinetobacter baumanii* (11%), while CAI was caused by *Staphylococcus aureus* (25%), *Escherichia coli* (25%) and *Streptococcus* species (13%). The commonest organisms causing HCAI were *Staphylococcus aureus* (20%), *Pseudomonas aeruginosa* (11%) and CoNS (11%). The commonest organisms isolated

based on each classification criteria were different except for *Staphylococcus aureus*. Patients with *Staphylococcus aureus* bacteremia (SAB) mainly had gastrointestinal disease (25.5%), followed by respiratory disease (13.7%). There were 9.8% thrombophlebitis and 4% catheter-related bloodstream infection (CRBSI) cases associated with SAB. *Staphylococcus aureus* is known to be the 2nd most common leading cause of nosocomial bloodstream infection.[22] Although CoNS is a common contaminant organism, it was isolated as the second cause of HCA BSI together with *Pseudomonas aeruginosa*. Those with CoNS associated HCAI were relatively immunocompromised with 71% had underlying malignancy and 29% had a CRBSI which could have been associated with a longer hospital stay. It was found that risk factors for CoNS bacteraemia include previous antibiotic use and catheter-related complications.[23]

Among *Staphylococcus aureus*, 33% of isolates were MRSA and both HAI and HCAI had 39% and 33% of MRSA isolates respectively, while no MRSA was seen from CAI. This shows that HCAI isolates susceptibility patterns are similar to HAI isolates. However, our study showed a higher resistance rate compared to data from Malaysian National Surveillance on Antimicrobial Resistance (NSAR) reports in 2017 which showed 19.8% of *Staphylococcus aureus* were MRSA.[24]

There were 53% *Klebsiella pneumoniae* isolates that were ESBL producers and 2% of the isolates were MRO. Based on NSAR (2017)[24], there were 30.1% - 37.8% of isolates that were resistant to 3rd and 4th generation cephalosporins (ceftazidime, cefotaxime, and cefepime). According to a study done by Sharma *et al*.[25], the prevalence of *Klebsiella* spp. with ESBL production is higher (67%). Among *Acinetobacter baumanii*, resistance was seen towards ampicillin/sulbactam (31%), cefoperazone/sulbactam (21%), imipenem (34%) and meropenem (35%). The resistance towards carbapenem seems to be the highest. The incidence of carbapenem-resistant *Acinetobacter baumanii* (CRAB) is on the rise as shown by NSAR (2017)[24] which increased from 54.8% (2013) to 61.7% (2017).

Among *Pseudomonas aeruginosa*, 10% isolates were resistant to ceftazidime, meropenem, and imipenem. Three percent of the isolates were resistant while 21% isolates had intermediate susceptibility towards piperacillin/tazobactam. According to NSAR (2017)[24], the resistance rate to all antibiotics has reduced in 2017 compared to 2016 with resistance towards ceftazidime, imipenem and meropenem were 6.9%, 7.8%, and 6.6% respectively. The national resistance rate shows <10% resistance for all antibiotics tested. Data from our study has shown that the resistance rate is higher than the national data.

For *Escherichia coli*, there were 33% ESBL and 6% MRO isolated. These rates are lower compared to a study done by Sharma *et al*.[25] that showed 57% of *Escherichia coli* were ESBL producers. *Escherichia coli* showed the highest resistance towards ampicillin (72%) which is slightly higher from NSAR (2017)[24] report that showed 65.5% resistance towards ampicillin. From this, it is noted that ampicillin is not an ideal choice of empirical treatment if *Escherichia coli* bacteraemia is suspected.

The case fatality rate (CFR) overall was 27% with the highest CFR caused by *Serratia marcescens* (53.3%). The overall CFR is similar to the adult population in Malaysia with a mortality rate of 27%.[19] The CFR caused by *Serratia marcescens* is generally higher than other studies which ranged from 22.4% to 44%.[26-28] *Serratia marcescens* BSI caused 87% of HAI and 13% of CAI. Age group one-month-old to less than one year old was the main group (53.3%) with *Serratia marcescens* BSI. S*erratia marcescens* is a well-known cause of outbreaks in paediatric units.[29] However, there were no outbreaks during the study period. Knowing that the mortality rate is high, an aggressive and efficacious approach is necessary to prevent transmission to other patients. Interestingly, there were 11 cases of *Enterobacter* species with no mortality that had a significant statistical test for CFR with p=0.039. This shows that in comparison to other organisms isolated from this study, cases of *Enterobacter* species BSI had a statistically significant survival chance.

From this study, it was found that HAI causes the majority of BSI. This perhaps was associated with progress in healthcare systems where more invasive procedures such as intravascular devices and ventilation are performed. The study population was from a tertiary referral centre, where 25% of patients from this study had an underlying haematological malignancy which predisposes them to more invasive procedures and more susceptible to HAI. Further improvements in HAI prevention strategies such as reinforcement on hand hygiene, environmental hygiene, and antimicrobial stewardship will assist in reducing the incidence of HAI. The

continuous surveillance of the rate of infection and compliance to HAI prevention strategies that is already established in this centre is expected to reduce the incidence of HAI. Future similar studies will be helpful in monitoring the trend of infection. The national antibiotic guideline has been followed, however adaptation based on local antibiogram pattern helps to prevent the increasing resistance rates of antibiotics.

This study was done at a single centre and may not significantly represent the other hospitals or the whole country because of differences in the study populations. In view of the retrospective nature of this study, some data could have been missed during data collection. Future studies involving multiple healthcare centres including private and public sectors from each state in the country would be more beneficial to get an overview of the situation in the whole country. This information will be helpful for policymakers to allocate resources where more active interventions are needed.

CONCLUSIONS

From this study, common causes of BSI in paediatric patients were *Staphylococcus aureus* (17%), followed by *Klebsiella pneumoniae* (15%), *Acinetobacter baumanii* (10%), *Pseudomonas aeruginosa* (10%), and *Escherichia coli* (6%). Most of the infections were hospital-acquired infections (72%), followed by healthcare-associated (20%) and community-acquired infections (8%). There were 33% of MRSA, 53% of ESBL *Klebsiella pneumoniae* and 33% of ESBL *Escherichia coli* cases. The overall case fatality rate (CFR) was 27% with the highest CFR caused by *Serratia marcescens* (53.3%). Hospital-acquired infection is a major growing concern and improvement in prevention strategies is important to overcome it.

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