Journal of Tropical Pediatrics, 2020, 00, 1–12
doi: 10.1093/tropej/fmaa077
Original Paper

OXFORD

Analysis of Pathogen Distribution and Its Antimicrobial Resistance in Bloodstream Infections in Hospitalized Children in East China, 2015–2018

Cuicui Wang, PhD[1,*], Wei Hao, PhD[2,*], Ruihua Yu, MSc[2], Xiaokang Wang, MSc[2], Jing Zhang, MSc[1] *and* Bo Wang, PhD[1]

[1]Medical Department, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, China
[2]Pediatric Department, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, China
Correspondence: Bo Wang, Medical Department, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Room 117, Renhe Building, No. 324 Jingwu Road, Huaiyin District, Jinan 250021, China. Tel: +86-531-68777020. Fax: +86-531-87030081. E-mail <wangb1688@sina.com>.
*These authors contributed equally to this work.

ABSTRACT

This study analyzed the pathogen distribution in bloodstream-infected (BSI) children hospitalized in Shandong Province from 2015 to 2018, to identify prevention strategies and select empiric antimicrobial therapy for BSI in children. Blood sample data from 14 107 children from 162 hospitals of Shandong Province were obtained from the China Antimicrobial Resistance Surveillance System and analyzed with WHONET 5.6 software. The results of the blood culture test showed the growth of 70.6% Gram-positive and 29.4% Gram-negative bacteria. Of the 14 107 blood isolates, 59.3% were collected from males and 40.7% were from females. Coagulase-negative *staphylococci* (47.1%) were the most commonly distributed pathogens. The distribution of pathogens varied according to age group and season. All *Staphylococcus* isolates were susceptible to vancomycin, teicoplanin and linezolid. Clinically, significant declines in penicillin-resistant *Streptococcus pneumonia* and carbapenem-resistant *Escherichia coli* were observed during the study period; however, detection rates of carbapenem-resistant *Klebsiella pneumoniae* increased over time ($p < 0.05$). Empiric antimicrobial therapy should be prescribed according to corresponding regional pediatric antimicrobial-resistant data.

KEYWORDS: bloodstream infections, pediatric patients, antimicrobial resistance, healthcare-associated infection

INTRODUCTION

Bloodstream infections (BSIs) in children are potentially life-threatening and are associated with higher healthcare costs and more extended hospital stay [1], requiring immediate and appropriate empirical antimicrobial treatment. Knowledge about the pathogen distribution causing pediatric BSIs is important for identifying infection prevention strategies, tracking resistance patterns and informing empiric antimicrobial therapy guidelines [2]. Previous studies

describing the regional epidemiology of BSIs have mainly focused on the adult population [3–5], whereas only a few studies about pediatric populations have been published [6, 7].

The etiology of pediatric BSIs and antimicrobial resistance (AMR) of the pathogens significantly differ in different countries [8]. Coagulase-negative *staphylococci* (CoNS) is the most commonly isolated organism causing BSIs in hospitalized children in the USA [6]. However, in Switzerland, the most frequent pathogens causing pediatric BSIs are *Staphylococcus aureus*, followed by *Escherichia coli*, CoNS, *Streptococcus pneumoniae* and non-*E. coli Enterobacteriaceae* [7]. In the West Africa region, *S. aureus*, *Enterobacteriaceae*, *Salmonella* and *Citrobacter* species are the most common pathogens causing BSIs [9]. In contrast, BSI surveillance in Malawi from 1998 to 2016 indicated that *Salmonella typhimurium*, *S. typhi* and *S. pneumoniae* were the most common causative agents in children [10].

In China, the pathogens responsible for pediatric BSIs vary in different regions. A study of the clinical features of healthcare-associated BSIs in neonates from two hospitals in Henan and Chongqing found that the most prevalent BSI pathogen was *E. coli* in Henan (Middle East of China), whereas it was *Klebsiella pneumoniae* in Chongqing (Southwest China) [11]. However, more supporting data from this study were limited because of its small scope and research population. A gaps in knowledge remain regarding the epidemiology of pediatric BSIs. To bridge this gap and to provide a basis for local empirical treatment of pediatric BSIs, we report pediatric BSI surveillance data obtained from 2015 to 2018 as part of the China Antimicrobial Resistance Surveillance System (CARSS). The CARSS includes 162 microbiological laboratories from 162 hospitals in Shandong Province, East China, a large province with an area of 158 000 square kilometers and a population of 100 million.

METHODS

Study design and data collection

This retrospective surveillance study of healthcare-associated pediatric BSIs was based on blood culture-proven BSI data obtained from Shandong Provincial Antimicrobial Resistance Surveillance System, a branch of the CARSS that includes 162 microbiological laboratories collected from 47 secondary hospitals and 115 tertiary hospitals in Shandong. Each member of the laboratories monitoring the network reports the data regarding bacterial identification and antibiotic sensitivity to the CARSS every quarter.

Bacterial identification and antimicrobial susceptibility

All participating laboratories were instructed to follow standard procedures to perform the blood culture test. Species identification was performed using standard biochemical methodology with Vitek 2 (bioMérieux, Craponne, France), MicroScan WalkAway-96 plus Microbiology System (Siemens, Munich, Germany), Phoenix-100 System (BD Biosciences) and/or matrix-assisted laser desorption/ionization-time of flight mass spectrometry. Antibiotic resistance tests were carried out by the Kirby-Bauer method, minimum inhibitory concentration (MIC) method or *E*-test method and were interpreted by the recommendation of Clinical and Laboratory Standards Institute-M100 S27 [12]. Organisms including *Micrococcus species*, *Bacillus species* and *Diphtheroids* were classified as contaminants. CoNS were judged to be true pathogens or contaminants by confirmation with the clinicians.

The analysis was conducted in singlets. Only the first isolate from each patient was evaluated in this study, considering that blood cultures from multiple isolates of one patient may overestimate the risk of acquiring a resistant strain from several other pathogens of different BSIs during hospitalization [13, 14].

Definitions

Pediatric patients in this study were defined as individuals younger than 14 years old; children were classified as 28 days to14 years old and newborns were classified as less than 28 days. Healthcare-associated infections were defined as infections occurring in patients during their stay in a hospital or a healthcare facility, in whom the infection was neither present nor latent at the time of admission, according to the World Health Organization [15]. Strains such as *K.*

pneumoniae and *E. coli*, which showed resistance to at least any one of the carbapenems such as imipenem, meropenem or ertapenem, were defined as carbapenem-resistant.

Statistical analysis

Antibiotic susceptibility data were analyzed using WHONET 5.6 software. If more than two of the methods were conducted, the results of the *E*-test were chosen, followed by the MIC method and Kirby-Bauer method. Changes in pathogen distribution by age and in AMR over time were determined by the chi-square test or Fisher's exact test using SPSS v.17.0 software. Statistical significance was confirmed if a two-tailed *p*-value was not more than 0.05.

RESULTS

Study population

Between 1 January 2015 and 31 December 2018, 81 189 isolates from blood cultures were collected from patients admitted to the hospitals of Shandong province, of which 14 107 were collected consecutively from children. Table 1 shows the baseline patient characteristics. Pediatric patients included 8365 males (59.3%) and 5742 females (40.7%), with an average age of 1.8 years old. A total of 55.3% of the children were from Linyi, Jinan, Jining and Qingdao. Most of the children were hospitalized in general pediatric wards ($n = 8312$; 58.9%), followed by neonatal units ($n = 3654$; 25.9%), intensive care units (ICUs) (1010; 7.2%), pediatric surgery wards (386; 2.7%) and others (745, 5.3%).

Table 1: Baseline patient characteristics

Variable	HA-pediatric BSI* ($N = 14\,107$[a])
Sex, *n* (%)	
Males	8365 (59.3)
Females	5742 (40.7)
Average age (years)	1.82
Age categories, *n/N* (%)	
−28 days	4362 (30.9)
29 days–1years	5538 (39.3)
1–2years	998 (7.1)
3–5years	1561 (11.1)
6–8years	725 (5.1)
9–11years	521 (3.7)
12–14years	402 (2.8)
Hospitalization unit, *n/N* (%)	
General pediatric wards	8312 (58.9)
Neonatal units	3654 (25.9)
Intensive care unit	1010 (7.2)
Pediatric surgery wards	386 (2.7)
Others	745 (5.3)
Patient's City, *n/N* (%)	
Jinnan	2693 (19.1)
Linyi	2521 (17.9)
Jining	1435 (10.2)
Qingdao	1359 (9.6)
Liaocheng	919 (6.5)
Weifang	815 (5.8)
Zaozhuang	768 (5.4)
Binzhou	728 (5.2)
Taian	543 (3.8)
Rizhao	531 (3.8)
Dongying	445 (3.2)
Yantai	415 (2.9)
Zibo	368 (2.6)
Heze	285 (2.0)
Weihai	274 (1.9)
Dezhou	69 (0.5)

HA-pediatric BSI*, healthcare-associated pediatric bloodstream infection, [a]*N* = denominator used unless otherwise stated

Distribution of common pathogens responsible for BSIs

Table 2 shows the composition of isolated bacteria in pediatric blood culture. There was a high proportion of Gram-positive bacteria (70.6%), whereas Gram-negative bacteria accounted for 29.4%. Excluding 1440 strains that were determined to be contamination, CoNS (47.1%) was the most common pathogen responsible for healthcare-associated BSIs in children, followed by *E. coli* (8.3%), *S. aureus* (7.0%), *S. pneumoniae* (5.9%), *Klebsiella* sp. (5.6%) and *Enterococcus* sp. (4.4%). Figure 1 shows the percentage of main pathogens isolated during 2015–2016 and 2017–2018. The isolation rate of CoNS, *Serratia marcescens* declined ($p < 0.05$), while *E. coli*, *S. aureus*, *S. pneumoniae*, *Enterococcus faecalis* and

Table 2: Causative pathogens of healthcare-associated pediatric BSI in Shandong province

Pathogen	HA-pediatric BSI* (%[a])
Gram-positive	9958 (70.6)
Coagulase-negative *staphylococci*	6648 (47.1)
Staphylococcus aureus	992 (7.0)
Staphylococcus sp.(other)	55 (0.4)
Streptococcus pneumoniae	828 (5.9)
Streptococcus viridan	352 (2.5)
Streptococcus, beta-hem	314 (2.2)
Streptococcus agalactiae	267 (1.9)
Streptococcus pyogenes	29 (0.2)
Streptococcus, beta-hemolytic	18 (0.1)
Enterococcus sp.	625 (4.4)
Enterococcus faecium	384 (2.7)
Enterococcus faecalis	197 (1.4)
Listeria monocytogenes	63 (0.5)
Streptococcus sp.(other)	25 (0.2)
Others	56 (0.4)
Gram-negative	4149 (29.4)
Escherichia coli	1173 (8.3)
Klebsiella sp.	790 (5.6)
Klebsiella pneumoniae	719 (5.1)
Klebsiella oxytoca	63 (0.5)
Serratia sp.	325 (2.3)
Stenotrophomonas maltophilia	319 (2.3)
Enterobacter sp.	248 (1.8)
Salmonella sp.	274 (1.9)
Pseudomonas sp.	267 (1.9)
Acinetobacter sp.	234 (1.7)
Achromobacter sp.	135 (1.0)
Sphingomonas paucimobilis	50 (0.4)
Haemophilus influenzae	38 (0.3)
Burkholderia sp.	34 (0.2)
Citrobacter sp.	17 (0.1)
Aeromonas sp.	16 (0.1)
Proteus sp.	15 (0.1)
Alcaligenes sp.	15 (0.1)
Ralstonia sp.	15 (0.1)
Ochrobactrum sp.	14 (0.1)
Morganella morganii	13 (0.1)
Moraxella sp.	13 (0.1)
Others	144 (1.0)

HA-pediatric BSI*, healthcare-associated pediatric bloodstream infection.
[a] % of all pediatric BSIs (n/N), $N = 14\,107$.

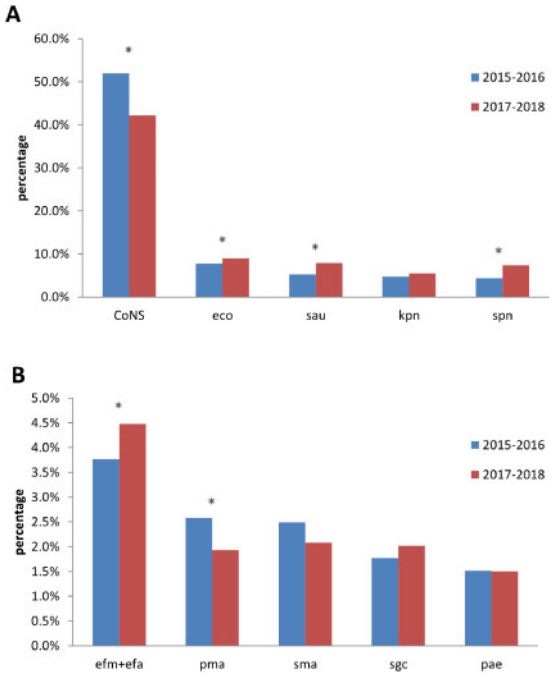

Fig. 1. (A) Percentage of main pathogens isolated at high frequency (>700 isolates totally) during 2015–2016 and 2017–2018. (**B**) Percentage of main pathogens isolated at intermediate frequency (200–700 isolates totally) during 2015–2016 and 2017–2018. Asterisks indicate statistical significance as p-values <0.05.

Enterococcus faecium significantly increased ($p < 0.05$).

Distribution of pathogens in different age groups

A total of 9900 (70.2%) isolates were collected from children aged ≤1 year, of which 4362 (30.9%) were collected from newborns. Gram-positive bacteria (69.0%) were responsible for most cases in neonatal BSIs. CoNS were the most frequently isolated pathogens, accounting for 48.0%, followed by *E. coli* (11.2%) and *K. pneumoniae* (8.3%). Figure 2A–C shows the distribution of main BSI pathogens in different age groups. Given that CoNS were the predominant isolates in all pediatric age groups, the rate of isolated CoNS gradually decreased with an increase in age group, while the rate of *S. aureus* gradually increased with age. Trends in *Streptococcus* BSI revealed that the isolation rate of *S. pneumoniae* and *Viridans streptococcus* peaked at the age of 3–5

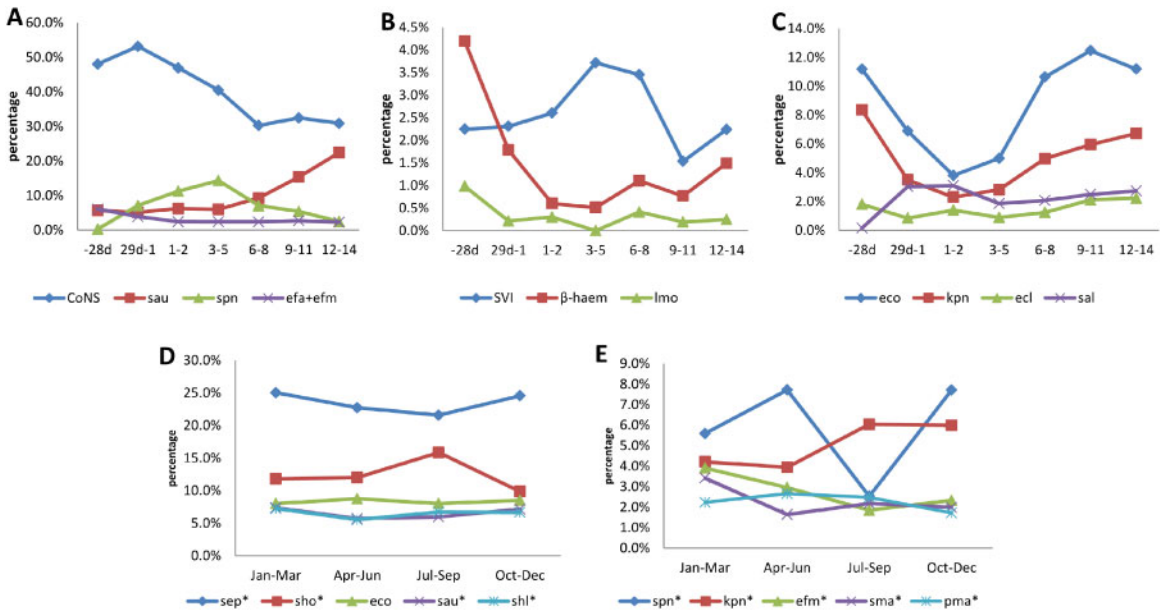

Fig. 2. Distribution of main pediatric BSIs pathogens with age (**A–C**) and season (**D** and **E**). (**A**) Gram-positive bacteria (group 1). (**B**) Gram-positive bacteria (group 2). (**C**) Gram-negative bacteria. (**D**) Percentage of main pathogens isolated at high frequency (>900 isolates totally) with season. (**E**) Percentage of main pathogens isolated at intermediate frequency (300–900 isolates totally) with season. Asterisks marked behind each species in (**D**) and (**E**) indicate statistical significance as *p*-values <0.05.

(14.3% and 3.7%, respectively), while the isolation rate of *β-hemolytic streptococcus* was the highest in the 0–28 days (newborn) group (4.2%), of which *Streptococcus agalactiae* was the main pathogen (85.0%). The rate of isolated *E. faecium* and *E. faecalis* declined after peaking (6.1%) in newborns. The isolation rate of *Listeria monocytogenes* was highest in the newborn group (1.0%). Regarding the Gram-negative pathogens, *E. coli* and *K. pneumoniae* BSI tended to significantly decline from the 0–28 days group to the 13 months–2 years group, but increased from the 13 months–2 years group to the older than 9 years old age group. *Salmonella* sp. fluctuated and peaked in the 13 months–2 years group (3.1%).

Seasonal distribution of pediatric BSI pathogens

Figure 2D and E show the seasonal distribution of pediatric BSI pathogens with more than 300 isolates. The total isolation rate was higher in the third and fourth quarters (26.1% and 26.5%, respectively) than in the first and second quarters (23.2% and 24.3%, respectively) ($p < 0.05$). The isolation rate of *E. coli* was relatively stable across all four seasons, whereas the isolation rates of *S. epidermidis, S. hominis, S. aureus, S. haemolyticus, S. pneumoniae, K. pneumoniae, E. faecium, S. marcescens* and *Stenotrophomonas maltophilia* were statistically different in the four quarters ($p < 0.05$). The isolation rates of *S. epidermidis, S. aureus, S. haemolyticus* and *S. marcescens* were higher in the first and fourth quarters than in the second and third quarters, while the rate of *S. maltophilia* was just the opposite. Most *S. pneumoniae* isolates were identified from October to December and from April to June, and the lowest number observed in a quarter was from July to September. Most *K. pneumoniae* isolates were collected from July to December. The isolation rates of *E. faecium* and *S. marcescens* were highest in this period from January to March.

Antimicrobial susceptibility changes in Gram-positive pathogens by time

Variations in AMR profiles of main pathogens were analyzed between the periods of 2015–2016 and 2017–2018 (Table 3). All *Staphylococcus* isolates were susceptible to vancomycin, teicoplanin or

Table 3: The AMR fluctuations in main pathogens from 2015–2016 to 2017–2018

Pathogen	Antibiotic agent	Resistant rate (%)			Change (%)[a]	*p*-Value
		Pooled	2015–2016	2017–2018		
S. aureus ($n = 922$)	PEN	95.3	94.4	95.8	1.5	0.319
	OXA	35.6	35.6	35.5	−0.3	0.971
	GEN	15.4	17.6	14.0	−20.5	0.146
	RIF	1.9	1.6	2.0	25.0	0.673
	LVX	7.7	8.7	6.9	−20.7	0.328
	SXT	22.2	23.7	21.3	−10.1	0.399
	CLI	58.7	60.9	57.4	−5.7	0.301
	ERY	77.1	74.1	79.2	6.9	0.075
	LNZ	0.0	0.0	0.0	0.0	–
	VAN	0.0	0.0	0.0	0.0	–
	TEC	0.0	0.0	0.0	0.0	–
CoNS ($n = 6648$)	PEN	94.1	94.6	93.5	−1.2	0.083
	OXA	76.6	75.7	77.7	2.6	0.067
	GEN	18.5	17.7	19.4	9.6	0.095
	RIF	7.4	7.1	7.7	8.5	0.349
	LVX	28.3	27.9	28.9	3.6	0.383
	SXT*	50.5	51.8	49.1	−5.2	0.044
	CLI	48.2	47.9	48.5	1.3	0.642
	ERY*	80.8	79	82.9	4.9	0.000
	LNZ	0.0	0.0	0.0	0.0	–
	VAN	0.0	0.0	0.0	0.0	–
	TEC	0.0	0.0	0.0	0.0	–
S. pneumonia ($n = 828$)	PEN*	4.0	6.6	2.4	−63.6	0.008
	CRO*	5.1	7.9	3.5	−55.7	0.029
	LVX	1.4	2.1	1.0	−52.4	0.197
	MFX	0.5	0.0	0.7	–	0.356
	SXT	58.8	62.4	57.1	−8.5	0.175
	CLI	92.5	90.4	93.7	3.7	0.190
	ERY	96.2	94.5	97.2	2.9	0.052
	LNZ	0.0	0.0	0.0	0.0	–
	VAN	0.0	0.0	0.0	0.0	–
	CHL	8.0	9.5	7.2	−24.2	0.371
	TCY	68.1	83.5	86.0	3.0	0.390
V. streptococcus ($n = 352$)	PEN	25.2	20.0	27.8	39.0	0.163
	CRO	29.6	25.8	31.5	22.1	0.426
	FEP	19.1	21.1	18.1	−14.2	0.648
	LVX	10.1	8.8	10.7	21.6	0.607
	CLI*	60.4	46.4	68.4	47.4	0.000
	ERY*	71.0	57.8	77.7	34.4	0.000
	LNZ	0.0	0.0	0.0	0.0	–
	VAN	0.0	0.0	0.0	0.0	–

(continued)

Table 3:. (continued)

Pathogen	Antibiotic agent	Resistant rate (%)			Change (%)[a]	*p*-Value
		Pooled	2015–2016	2017–2018		
E. faecalis ($n = 197$)	PEN	10.1	10.3	9.9	−3.9	0.934
	AMP	6.5	6.2	6.7	8.1	0.896
	GEH*	27.8	38	20.4	−46.3	0.012
	CIP	12.1	11.2	12.8	14.3	0.76
	LVX	8.1	8.5	7.8	−8.2	0.876
	ERY	62.8	62.3	63.2	1.4	0.904
	LNZ	0.0	0.0	0.0	0.0	–
	VAN	0.0	0.0	0.0	0.0	–
E. faecium ($n = 384$)	PEN	86.3	87.1	85.6	−1.7	0.79
	AMP	84.7	84.2	85.1	1.1	0.822
	GEH*	37.6	49	28.2	−42.4	0.000
	CIP	74.3	76.9	71.8	−6.6	0.277
	LVX	55.7	59.6	52	−12.8	0.147
	ERY	80.8	82.3	79.5	−3.4	0.495
	LNZ	0.0	0.0	0.0	0.0	–
	VAN	0.0	0.0	0.0	0.0	–
E. coli ($n = 1173$)	AMP	81.1	79.0	82.9	4.9	0.101
	CSL	4.1	5.5	3.2	−41.8	0.219
	TZP*	2.9	4.8	1.3	−72.9	0.001
	CZO	60.0	64.6	58.2	−9.9	0.132
	CXM	49.5	49.0	49.7	1.4	0.885
	CAZ	16	16.6	15.5	−6.6	0.621
	CRO	49.4	51	48.2	−5.5	0.39
	FEP	16.3	15.6	16.8	7.7	0.587
	FOX	7.5	9.2	5.9	−35.9	0.144
	ATM	26.4	26.4	26.3	−0.4	0.968
	IPM	2.0	2.5	1.6	−36.0	0.303
	MEM	2.6	3.7	1.7	−54.1	0.113
	AMK	1.4	1.7	1.1	−35.3	0.426
	GEN	40.5	42.8	38.6	−9.8	0.159
	CIP*	33.6	36.8	30.9	−16.0	0.037
	LVX*	32	35.5	29.0	−18.3	0.02
	SXT	59.0	58.0	59.7	2.9	0.565
K. pneumonia ($n = 719$)	CSL	14.6	9.9	17.0	71.7	0.117
	TZP*	16.2	10.9	20.9	91.7	0.000
	CZO*	69.1	62.2	71.9	15.6	0.046
	CXM	69.0	66.9	70.0	4.6	0.553
	CAZ	38.4	39.2	37.7	−3.8	0.702
	CRO	59.3	56.6	61.5	8.7	0.234
	FEP*	34.9	24	42.9	78.8	0.000
	FOX	26.8	23.2	30.4	31.0	0.112

(continued)

Table 3:. (continued)

Pathogen	Antibiotic agent	Resistant rate (%)			Change (%)[a]	*p*-Value
		Pooled	2015–2016	2017–2018		
	ATM*	41.8	32.7	48.0	46.8	0.000
	IPM*	11.3	5.5	16.4	198.2	0.000
	MEM	10.9	7.7	13.4	74.0	0.076
	AMK*	3.5	0.9	5.8	544.4	0.000
	GEN	29.2	30.3	28.2	−6.9	0.526
	CIP	10.1	8.6	11.5	33.7	0.205
	LVX*	6.1	3.3	8.8	166.7	0.003
	SXT	48.1	46.9	49.2	4.9	0.551
E. cloacae ($n = 183$)	CSL	6.9	10.8	2.9	−73.1	0.358
	TZP	10.4	11.9	9.2	−22.7	0.55
	CAZ*	30.7	41.7	22.0	−47.2	0.007
	CRO	36.2	37.7	35.1	−6.9	0.755
	CTX	35.3	38.1	33.3	−12.6	0.726
	FEP	10.1	10.6	9.7	−8.5	0.848
	ATM	30.1	34	27.8	−18.2	0.436
	IPM	6.1	7.2	5.1	−29.2	0.551
	MEM	6.2	8.6	3.6	−58.1	0.105
	AMK	1.6	3.6	0.0	−100.0	0.096
	GEN	11.8	13.6	10.3	−24.3	0.501
	CIP	2.8	4.9	1.1	−77.6	0.184
	LVX	2.8	6.0	0.0	−100.0	0.021
	SXT	16.8	20.8	13.5	−35.1	0.205
Salmonella sp. ($n = 274$)	AMP	58.5	56.0	61.2	9.3	0.412
	CRO	13.9	19.2	9.8	−49.0	0.070
	FEP	7.7	9.1	6.6	−27.5	0.577
	CIP	18.5	20.4	15.8	−22.5	0.577
	LVX	2.6	11.7	11.9	1.7	0.976
	SXT	13	8.9	17.1	92.1	0.055

AMK, amikacin; AMP, ampicillin; ATM, aztreonam; CAZ, ceftazidime; CHL, chloramphenicol; CIP, ciprofloxacin; CLI, clindamycin; CRO, ceftriaxone; CSL, cefoperazone/sulbactam; CTX, cefotaxime; CXM, cefuroxime; CZO, cefazolin; ERY, erythromycin; FEP, cefepime; FOX, cefoxitin; GEH, gentamicin-high; GEN, gentamicin; IPM, imipenem; LNZ, linezolid; LVX, levofloxacin; MEM, meropenem; MFX, moxifloxacin; OXA, oxacillin; PEN, penicillin G; RIF, rifampin; SXT, trimethoprim/sulfamethoxazole; TCY, tetracycline; TEC, teicoplanin; TZP, piperacillin/tazobactam; VAN, vancomycin.

[a] Difference of resistant rates between 2017–2018 and 2015–2016.

*Statistical significance as *p*-values <0.05.

linezolid. An increase in the isolation of methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS) was found during the study periods, from 74.8% to 77.0%. The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) changed slightly (34.2% and 34.7% in 2015–2016 and 2017–2018, respectively). The resistance rates of *V. streptococcus* to all β-lactam agents slightly increased, while the resistance rates to clindamycin and erythromycin significantly increased during the two study periods ($p < 0.05$). By contrast, *S. pneumoniae* exhibited descending resistance to penicillin and ciprofloxacin ($p < 0.05$), while its resistance to clindamycin and erythromycin increased to some extent. The resistance rates of *E. faecalis* and *E. faecium* to all agents tested did not significantly vary over time, except the

reduced resistance of *E. faecalis* and *E. faecium* to the high concentration of gentamicin (decreased by 17.6% and 20.8%, respectively).

Antimicrobial susceptibility changes in Gram-negative pathogens by time

Escherichia coli showed decreased resistance rate to all agents tested except ampicillin, cefepime and trimethoprim/sulfamethoxazole (Table 3). The isolation rate of ceftriaxone/cefotaxime (CRO/CTX)-resistant *E. coli* decreased from 50.7% to 48.7%. Similarly, the detection rate of carbapenem-resistant *E. coli* decreased from 4.9% to 1.6% ($p < 0.05$). By contrast, *K. pneumoniae* exhibited markedly increased resistance to piperacillin/tazobactam, cefazolin, cefepime, aztreonam, imipenem, amikacin and levofloxacin ($p < 0.05$) (Table 3). The resistant rates of *K. pneumoniae* to the fourth-generation cephalosporin were increased from 24.0% in 2015–2016 to 42.9% in 2017–2018, while the rates to piperacillin/tazobactam and cefoperazone/sulbactam were increased from 10.9% to 20.9% and from 9.9% to 17.0%, respectively (Table 3). The detection rate of CRO/CTX-resistant *K. pneumoniae* rose from 56.5% to 62.7%. Notably, the detection rate of carbapenem-resistant *K. pneumoniae* (CRKP) increased from 7.8% to 17.6% ($p < 0.05$). The resistance rate of *E. cloacae* to all of the agents tested decreased to some extent, especially the resistance rate to ceftazidime ($p < 0.05$). The resistance rate of *Salmonella* sp. to ampicillin is high and increased from 56.0% to 61.2%, and the resistance rate to ceftriaxone was lower than 20% (Table 3).

DISCUSSION

Enhancing surveillance of antimicrobial-resistant organisms is one of the most effective ways to decrease the spread and alleviate the adverse effects of resistant bacteria [16]. Of the 14 107 patients in our research, 9900 (70.2%) were children aged <1 year. This result suggests that the occurrence of BSIs peaks in the first year of life. Changes in pathogen distribution within different age groups and the resistance of pathogen over time were identified, indicating that age group is an important factor in pathogen distribution and changes in the resistant pattern within certain time period [2].

Studies conducted in the USA and Finland [6, 17] have found that CoNS is the most commonly isolated organism in children hospitalized in this region. Diagnosis of CoNS sepsis is challenging, because its isolation from a single blood culture may mean central line colonization or culture contamination. Also, collecting blood samples multiple times from precarious infants may affect adherence to clinical guidelines [18, 19]. However, the disease-causing CoNS represents a pathogenic subgroup that has acquired genetic elements and related phenotypes leading to the development of infection [20]. A single positive blood culture is sometimes considered sufficient for the presence of signs and symptoms of sepsis or laboratory results indicating infection.

The possibility of eliminating the contaminating bacteria has been discussed among clinicians. The isolation rate of MRSA was stable in this region, which is different from the rising trends of MRSA prevalence in children (from 18.0% in 2005 to 29.8% in 2017) in China Antimicrobial Surveillance Network data [21], whereas the MRCNS isolation rate increased from 74.8% in 2015–2016 to 77.0% in 2017–2018. The increasing trend in children may be related to the increasing ICU beds in pediatric hospitals, indicating that effective infection prevention strategies were important to delay the AMR. Limited choices of antimicrobials compared with adults may also result in the increasing trend of resistant organism prevalence [21].

Our research indicated that the constituent ratios of pathogens varied with age groups. The isolation rate of *S. aureus* gradually increased with age. The isolation rate of *S. pneumoniae* and *V. streptococcus* peaked at the age of 3–5. The isolation rate of *S. agalactiae* and *L. monocytogenes*, which play an important role in severe materno-neonatal infections [22], was the highest in the 0–28 days group. Understanding the distribution of pathogens in different age groups can direct physicians to prescribe more specific antibiotics in the future.

Seasonal trends should be considered for healthcare-associated infections [23]. Of the Gram-positive bacteria, the isolation rate of *S. epidermidis*, *S. aureus* and *S. haemolyticus* were higher in winter months, consistent with previous research on both

adults and children [24]. It was previously proven that Gram-negative BSI incidence increases proportionately to an increase in temperature [25]. However, no difference in the seasonal distribution of *E. coli* was found in our study. Most *K. pneumoniae* isolates were collected from summer and autumn months, whereas the isolation rates of *S. marcescens* were highest in winter months. Further studies are needed to determine if pediatric BSIs have seasonal trends.

The resistance rate of Gram-positive bacteria to most antibiotics detected changed slightly. Among Gram-negative bacteria, the resistant rate of *E. coli* to most antibiotics tested declined to some extent, while antibiotic resistance in *K. pneumoniae* is of great concern. An increase in resistant rates to fourth-generation cephalosporin (42.9% in 2017–2018), β-lactamase inhibitor complex (20.9% of piperacillin/tazobactam and 17.0% of cefoperazone/sulbactam in 2017–2018) and carbapenems (17.6% in 2017–2018) was observed among *K. pneumoniae* causing pediatric BSIs. Similar trends were also observed by Tian, *et al.* and Yang, *et al.* [4, 26]. Hematologic malignancies and previous cephalosporin applications are associated with the development of CRKP BSIs, while mechanical ventilation, septic shock and CRKP infection are independent predictors of mortality caused by *K. pneumoniae* BSIs [27]. Recent studies in China and abroad have showed that the increased usage of carbapenems accelerates the production of carbapenemase [28–30]. Therefore, the appropriate medical prescription of carbapenems to fight against pediatric CRKP BSIs is promoted. Nationwide surveillance of carbapenem-resistant *Enterobacteriaceae* (CRE) in China has confirmed that the prevalence of CRE strains producing carbapenemase increased in the last 10 years, especially among *K. pneumoniae* and *E. coli* [31]. The mobile-resistance genes, especially those encoding bla KPC-2, play an important role in CRKP transmission [32, 33]. However, in pediatric patients, several studies have reported the predominance or outbreak of bla NDM-1 among CRKP in Beijing, Shanghai, Shandong and Chongqing [34–38]. Thus, more studies are in progress to discover the potential molecular mechanisms of the high prevalence of CRKP in pediatric BSIs.

This study showed the picture of pediatric BSI trend in Shandong Province, a province with the second largest population in China. CoNS, *E. coli*, *S. aureus*, *S. pneumoniae* and *E. faecium* were the main pathogens causing pediatric BSIs in this region, while the main pathogens in Hubei Province were *S. aureus*, *Enterococcus* sp., *S. pneumoniae* and *E. coli* [4], and the main pathogens in Chongqing were *E. coli*, *S. aureus*, *K. pneumoniae* and *S. pneumoniae* [26]. Regional differences can be attributed to environmental and climatic factors [39] and differences in managing hospitals such as infection control measures, visitation strategies and distribution of bed [40]. Further research on the element of potential diversities among pediatric BSI patients is proportional.

The limitations of this study were the inability to perform a detailed chart review for each episode and to characterize the clinical severity in each case of bacteremia. In addition, the rates of AMR may be overestimated because microbiology in this region tends to be a diagnostic tool within hospitals with more antibiotic pressure, and part of the samples were drawn from patients who were admitted for treatment failure and/or after receiving empirical antibiotics elsewhere. More strict studies and prospective trials are needed for broader coverage to avoid this potential bias.

CONCLUSION

The pathogen growth and distribution pattern in pediatric BSIs change with time and regions and should be regularly re-evaluated to proceed with empirical treatment. The findings of this study indicated that CoNS, *E. coli*, *S. aureus*, *S. pneumoniae* and *E. faecium* were the most common pathogens responsible for healthcare-associated pediatric BSIs in Shandong province. The detection ratios of pathogens varied with age group and season. The resistance rate of Gram-positive bacteria to most antibiotics detected changed slightly. The resistance rate of *E. coli* to CRO/CTX and carbapenem declined, whereas the resistance rate of *K. pneumonia* to CRO/CTX and carbapenem was increased. Further studies are required to analyze the stimulators of potential AMR diversities among pediatric BSI patients.

ACKNOWLEDGEMENTS

The authors thank all members of Antimicrobial Surveillance Resistance System of Shandong Province for providing bacterial data.

FUNDING

This study was supported by a research grant from the Science and Technology Project of Jinan, Shandong Province, P.R China [201805018].

AVAILABILITY OF DATA AND MATERIALS

All datasets in this manuscript are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

C.W. and W.H. made contributed equally to the study conception and design, acquisition of data, interpretation of data and wrote the manuscript; R.Y. and X.W. analyzed the data; J.Z. participated in the study design and coordination; B.W. revised the manuscript by providing important intellectual content. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was performed in accordance with the Declaration of Helsinki and had been approved by the Shandong Provincial Hospital Affiliated to Shandong First Medical University Ethics Committee for Research in Health, and the approval number is LCYJ: NO. 2019-157.

REFERENCES

1. Goudie A, Dynan L, Brady PW, *et al.* Attributable cost and length of stay for central line-associated bloodstream infections. Pediatrics 2014;133:e1525–32.
2. Spaulding AB, Watson D, Dreyfus J, *et al.* Epidemiology of bloodstream infections in hospitalized children in the United States, 2009-2016. Clin Infect Dis 2019;69: 995–1002.
3. Anderson DJ, Moehring RW, Sloane R, *et al.* Bloodstream infections in community hospitals in the 21st century: a multicenter cohort study. PLoS One 2014;9:e91713.
4. Tian L, Sun Z, Zhang Z. Antimicrobial resistance of pathogens causing nosocomial bloodstream infection in Hubei Province, China, from 2014 to 2016: a multicenter retrospective study. BMC Public Health 2018;18:1121.
5. Magill SS, O'Leary E, Janelle SJ, *et al.* Changes in prevalence of health care-associated infections in U.S. hospitals. N Engl J Med 2018;379:1732–44.
6. Larru B, Gong W, Vendetti N, *et al.* Bloodstream infections in hospitalized children: epidemiology and antimicrobial susceptibilities. Pediatr Infect Dis J 2016;35: 507–10.
7. Buetti N, Atkinson A, Kottanattu L, *et al.*; the Swiss Centre for Antibiotic resistance (ANRESIS). Patterns and trends of pediatric bloodstream infections: a 7-year surveillance study. Eur J Clin Microbiol Infect Dis 2017;36: 537–44.
8. Dat VQ, Vu HN, Nguyen The H, *et al.* Bacterial bloodstream infections in a tertiary infectious diseases hospital in Northern Vietnam: aetiology, drug resistance, and treatment outcome. BMC Infect Dis 2017;17:493.
9. Obeng-Nkrumah N, Labi AK, Addison NO, *et al.* Trends in paediatric and adult bloodstream infections at a Ghanaian referral hospital: a retrospective study. Ann Clin Microbiol Antimicrob 2016;15:49.
10. Musicha P, Cornick JE, Bar-Zeev N, *et al.* Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998-2016): a surveillance study. Lancet Infect Dis 2017;17:1042–52.
11. Wang S, Chen S, Feng W, *et al.* Clinical characteristics of nosocomial bloodstream infections in neonates in two hospitals, China. J Trop Pediatr 2018;64:231–6.
12. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Seventh Informational Supplement. CLSI Document M100-S27. Wayne, PA: Clinical and Laboratory Standards Institute, 2017.
13. Zhang Z, Chen M, Yu Y, *et al.* Antimicrobial susceptibility among gram-positive and gram-negative blood-borne pathogens collected between 2012-2016 as part of the Tigecycline Evaluation and Surveillance Trial. Antimicrob Resist Infect Control 2018;7:152.
14. Clinical and Laboratory Standards Institute. Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data: 4th Approved Guideline. CLSI Document M39-A4. Wayne: CLSI, 2014.
15. World Health Organization. Department of Communicable Disease, Surveillance and Response, Prevention of Hospital-Acquired Infections. Geneva: World Health Organization, 2002. Publication WHO/CDS/CSR/EPH/2002.12.
16. Marston HD, Dixon DM, Knisely JM, *et al.* Antimicrobial resistance. JAMA 2016;316:1193–204.
17. Huttunen R, Attman E, Aittoniemi J, *et al.* Nosocomial bloodstream infections in a Finnish tertiary care hospital: a retrospective cohort study of 2175 episodes during the years 1999-2001 and 2005-2010. Infect Dis (Lond) 2015; 47:20–6.
18. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309–32.
19. Struthers S, Underhill H, Albersheim S, *et al.* A comparison of two versus one blood culture in the diagnosis and

treatment of coagulase-negative staphylococcus in the neonatal intensive care unit. J Perinatol 2002;22:547–9.
20. Meric G, Mageiros L, Pensar J, *et al.* Disease-associated genotypes of the commensal skin bacterium Staphylococcus epidermidis. Nat Commun 2018;9:5034.
21. Hu F, Zhu D, Wang F, *et al.* Current status and trends of antibacterial resistance in China. Clin Infect Dis 2018;67: S128–34.
22. Arora N, Sadovsky Y, Dermody TS, *et al.* Microbial vertical transmission during human pregnancy. Cell Host Microbe 2017;21:561–7.
23. Paul M. Seasonality in infectious diseases: does it exist for all pathogens? Clin Microbiol Infect 2012;18:925–6.
24. Kolonitsiou F, Papadimitriou-Olivgeris M, Spiliopoulou A, *et al.* Trends of bloodstream infections in a University Greek Hospital during a three-year period: incidence of multidrug-resistant bacteria and seasonality in gram-negative predominance. Pol J Microbiol 2017;66:171–80.
25. Schwab F, Gastmeier P, Meyer E. The warmer the weather, the more gram-negative bacteria—impact of temperature on clinical isolates in intensive care units. PLoS One 2014;9:e91105.
26. Yang S, Xu H, Sun J, *et al.* Shifting trends and age distribution of ESKAPEEc resistance in bloodstream infection, Southwest China, 2012-2017. Antimicrob Resist Infect Control 2019;8:61.
27. Zhang Y, Guo LY, Song WQ, *et al.* Risk factors for carbapenem-resistant K. pneumoniae bloodstream infection and predictors of mortality in Chinese paediatric patients. BMC Infect Dis 2018;18:248.
28. Yang P, Chen Y, Jiang S, *et al.* Association between antibiotic consumption and the rate of carbapenem-resistant Gram-negative bacteria from China based on 153 tertiary hospitals data in 2014. Antimicrob Resist Infect Control 2018;7:137.
29. Zhang D, Hu S, Sun J, *et al.* Antibiotic consumption versus the prevalence of carbapenem-resistant Gram-negative bacteria at a tertiary hospital in China from 2011 to 2017. J Infect Public Health 2019;12:195–9.
30. Meyer E, Schwab F, Schroeren-Boersch B, *et al.* Dramatic increase of third-generation cephalosporin-resistant E. coli in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. Crit Care 2010;14:R113.
31. Zhang R, Chan EW, Zhou H, *et al.* Prevalence and genetic characteristics of carbapenem-resistant Enterobacteriaceae strains in China. Lancet Infect Dis 2017;17:256–7.
32. Li H, Zhang J, Liu Y, *et al.* Molecular characteristics of carbapenemase-producing Enterobacteriaceae in China from 2008 to 2011: predominance of KPC-2 enzyme. Diagn Microbiol Infect Dis 2014;78:63–5.
33. Zhang R, Liu L, Zhou H, *et al.* Nationwide surveillance of clinical carbapenem-resistant Enterobacteriaceae (CRE) strains in China. EBioMedicine 2017;19:98–106.
34. Jin Y, Shao C, Li J, *et al.* Outbreak of multidrug resistant NDM-1-producing Klebsiella pneumoniae from a neonatal unit in Shandong Province. PLos One 2015;10: e0119571.
35. Zhang X, Chen D, Xu G, *et al.* Molecular epidemiology and drug resistant mechanism in carbapenem-resistant Klebsiella pneumoniae isolated from pediatric patients in Shanghai, China. PLoS One 2018;13:e0194000.
36. Huang X, Cheng X, Sun P, *et al.* Characteristics of NDM-1-producing Klebsiella pneumoniae ST234 and ST1412 isolates spread in a neonatal unit. BMC Microbiol 2018; 18:186.
37. Yan J, Pu S, Jia X, *et al.* Multidrug resistance mechanisms of carbapenem resistant Klebsiella pneumoniae strains isolated in Chongqing. Ann Lab Med 2017;37:398–407.
38. Tian X, Sun S, Jia X, *et al.* Epidemiology of and risk factors for infection with extended-spectrum beta-lactamase-producing carbapenem-resistant Enterobacteriaceae: results of a double case-control study. Infect Drug Resist 2018; 11:1339–46.
39. Fisman D, Patrozou E, Carmeli Y, *et al.*; the Geographical Variability of Bacteremia Study Group. Geographical variability in the likelihood of bloodstream infections due to gram-negative bacteria: correlation with proximity to the equator and health care expenditure. PLoS One 2014;9: e114548.
40. Oztoprak N, Cevik MA, Akinci E, *et al.* Risk factors for ICU-acquired methicillin-resistant Staphylococcus aureus infections. Am J Infect Control 2006;34:1–5.