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

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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 pneumoniae 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 *Staphylococcus* (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 to 14 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 8,365 males (59.3%) and 5,742 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=8,312; 58.9%), followed by neonatal units (n=3,654; 25.9%), intensive care units (ICUs) (1,010; 7.2%), pediatric surgery wards (386; 2.7%) and others (745, 5.3%).

**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 1,440 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 1: Baseline patient characteristics**

| Variable                                      | HA-pediatric BSI* (N = 14,107a) |
|-----------------------------------------------|----------------------------------|
| Sex, n (%)                                    |                                  |
| Males                                         | 8,365 (59.3)                     |
| Females                                       | 5,742 (40.7)                     |
| Average age (years)                           | 1.82                             |
| Age categories, n/N (%)                       |                                  |
| – 28 days                                     | 4,362 (30.9)                     |
| 29 days–1years                                | 5,538 (39.3)                     |
| 1–2years                                      | 998 (7.1)                        |
| 3–5years                                      | 1,561 (11.1)                     |
| 6–8years                                      | 725 (5.1)                        |
| 9–11years                                     | 521 (3.7)                        |
| 12–14years                                    | 402 (2.8)                        |
| Hospitalization unit, n/N (%)                 |                                  |
| General pediatric wards                       | 8,312 (58.9)                     |
| Neonatal units                                | 3,654 (25.9)                     |
| Intensive care unit                           | 1,010 (7.2)                      |
| Pediatric surgery wards                       | 386 (2.7)                        |
| Others                                        | 745 (5.3)                        |
| Patient’s City, n/N (%)                       |                                  |
| Jinan                                         | 2,693 (19.1)                     |
| Linyi                                         | 2,521 (17.9)                     |
| Jining                                        | 1,435 (10.2)                     |
| Qingdao                                       | 1,359 (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, aN = denominator used unless otherwise stated
**Table 2: Causative pathogens of healthcare-associated pediatric BSI in Shandong province**

| Pathogen                        | HA-pediatric BSI* (%a) |
|---------------------------------|------------------------|
| **Gram-positive**               |                        |
| Coagulase-negative *staphylococi* | 9958 (70.6)            |
| *Staphylococcus aureus*         | 6648 (47.1)            |
| *Staphylococcus* sp.(other)     | 992 (7.0)              |
| *Streptococcus pneumoniae*      | 55 (0.4)               |
| *Streptococcus viridan*         | 828 (5.9)              |
| *Streptococcus*, beta-hem       | 352 (2.5)              |
| *Streptococcus*, beta-hemolytic | 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**               |                        |
| *Escherichia coli*              | 4149 (29.4)            |
| *Klebsiella* sp.                | 1173 (8.3)             |
| *Klebsiella pneumoniae*         | 790 (5.6)              |
| *Klebsiella oxytoca*            | 719 (5.1)              |
| *Serratia* sp.                  | 63 (0.5)               |
| *Stenotrophomonas maltophilia*  | 325 (2.3)              |
| *Enterobacter* sp.              | 319 (2.3)              |
| *Salmonella* sp.                | 248 (1.8)              |
| *Pseudomonas* sp.               | 274 (1.9)              |
| *Acinetobacter* sp.             | 267 (1.9)              |
| *Achromobacter* sp.             | 234 (1.7)              |
| *Sphingomonas paucimobilis*     | 135 (1.0)              |
| *Haemophilus influenzae*        | 50 (0.4)               |
| *Burkholderia* sp.              | 38 (0.3)               |
| *Citrobacter* sp.               | 34 (0.2)               |
| *Aeromonas* sp.                 | 17 (0.1)               |
| *Proteus* sp.                   | 16 (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.  
* % of all pediatric BSIs (n/N), N = 14107.

**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
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. pneumon-iae, 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 (%) | p-Value |
|----------------|------------------|--------------------|------------|---------|
|                | Pooled           | 2015–2016          | 2017–2018  |         |
| S. aureus (n = 922) | PEN             | 95.3               | 94.4       | 1.5     | 0.319  |
|                | OXA              | 35.6               | 35.6       | -0.3    | 0.971  |
|                | GEN              | 15.4               | 17.6       | -20.5   | 0.146  |
|                | RIF              | 1.9                | 1.6        | 25.0    | 0.673  |
|                | LVX              | 7.7                | 8.7        | -20.7   | 0.328  |
|                | SXT              | 22.2               | 23.7       | -10.1   | 0.399  |
|                | CLI              | 58.7               | 60.9       | -5.7    | 0.301  |
|                | ERY              | 77.1               | 74.1       | 6.9     | 0.075  |
|                | LNZ              | 0.0                | 0.0        | 0.0     | -      |
|                | VAN              | 0.0                | 0.0        | 0.0     | -      |
|                | TEC              | 0.0                | 0.0        | 0.0     | -      |
| CoNS (n = 6648) | PEN              | 94.1               | 94.6       | -1.2    | 0.083  |
|                | OXA              | 76.6               | 75.7       | 2.6     | 0.067  |
|                | GEN              | 18.5               | 17.7       | 9.6     | 0.095  |
|                | RIF              | 7.4                | 7.1        | 8.5     | 0.349  |
|                | LVX              | 28.3               | 27.9       | 3.6     | 0.383  |
|                | SXT              | 50.5               | 51.8       | -5.2    | 0.044  |
|                | CLI              | 48.2               | 47.9       | 1.3     | 0.642  |
|                | ERY              | 80.8               | 79         | 4.9     | 0.000  |
|                | LNZ              | 0.0                | 0.0        | 0.0     | -      |
|                | VAN              | 0.0                | 0.0        | 0.0     | -      |
|                | TEC              | 0.0                | 0.0        | 0.0     | -      |
| S. pneumonia (n = 828) | PEN*            | 4.0                | 6.6        | -63.6   | 0.008  |
|                | CRO              | 5.1                | 7.9        | -55.7   | 0.029  |
|                | LVX              | 1.4                | 2.1        | -52.4   | 0.197  |
|                | MFX              | 0.5                | 0.0        | 0.7     | -0.356 |
|                | SXT              | 58.8               | 62.4       | -8.5    | 0.175  |
|                | CLI              | 92.5               | 90.4       | 3.7     | 0.190  |
|                | ERY              | 96.2               | 94.5       | 2.9     | 0.052  |
|                | LNZ              | 0.0                | 0.0        | 0.0     | -      |
|                | VAN              | 0.0                | 0.0        | 0.0     | -      |
|                | CHL              | 8.0                | 9.5        | -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     | -      |
|                | VAN              | 0.0                | 0.0        | 0.0     | -      |

(continued)
### Table 3: (continued)

| Pathogen    | Antibiotic agent | Resistant rate (%) | Change (%)<sup>a</sup> | 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<sup>*</sup> | 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<sup>*</sup> | 33.6            | 36.8               | 30.9                    | -16.0   | 0.037  |
| LVX<sup>*</sup> | 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<sup>*</sup> | 16.2            | 10.9               | 20.9                    | 91.7    | 0.000  |
| CZO<sup>*</sup> | 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<sup>*</sup> | 34.9            | 24                 | 42.9                    | 78.8    | 0.000  |
| FOX         | 26.8            | 23.2               | 30.4                    | 31.0    | 0.112  |

(continued)
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

### 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)**

| Pathogen          | Antibiotic agent | Resistant rate (%) | Change (%)$^a$ | $p$-Value |
|-------------------|------------------|--------------------|---------------|-----------|
| CSL               | 6.9              | 10.8               | 2.9           | −73.1     | 0.358    |
| TZP               | 10.4             | 11.9               | 9.2           | −22.7     | 0.55     |
| CAZ$^1$           | 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             | −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             | −100.0    | 0.021    |
| SXT               | 16.8             | 20.8               | 13.5          | −35.1     | 0.205    |

**Salmonella sp. (n = 274)**

| Pathogen          | Antibiotic agent | Resistant rate (%) | Change (%)$^a$ | $p$-Value |
|-------------------|------------------|--------------------|---------------|-----------|
| 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, ceftazidine; CHL, chloramphenicol; CIP, ciprofloxacin; CLI, clindamycin; CRO, ceftriaxone; CSL, cefoperazone/sulbactam; CTX, cefotaxime; CXM, cefuroxime; CZO, cefazolin; ERY, erythromycin; FEP, cepime; 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.
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.
Goudie A, Dynan L, Brady PW, University Ethics Committee for Research in Health, and the Provincial Hospital Affiliated to Shandong First Medical of Helsinki and had been approved by the Shandong The study was performed in accordance with the Declaration content. All authors read and approved the final manuscript.

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