Infection and Drug Resistance

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ORIGINAL RESEARCH

Bacterial Epidemiology and Antimicrobial Resistance Profiles of Bloodstream Infections Caused by Negative Bacteria in Children's: A Multicenter Study in China (2016–2022)

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Objective: Aim to investigate the pathogens distribution and drug resistance of gram-negative bacteria causing bloodstream infection (BSIs) in Infectious Disease Surveillance of Pediatric from 2016 to 2022. The prevalence of four important drug resistance phenotypes was studied: difficult-to-treat resistance, fluoroquinolone resistance, carbapenem resistance, and extended-spectrum cephalosporin resistance, and to provide reference basis for preventing and treating BSIs diseases in children.

Methods: Strain identification and antimicrobial susceptibility tests were independently performed at each hospital. Data were analyzed using Whonet 5.6 and GraphPad Prism 8 software. The Mann–Whitney *U*-test was used to examine and compare temporal changes.

Results: A total of 39977 BSIs strains were isolated, with 27.1% of the negative bacteria causing BSIs (10824 strains). The highest bacteria detected were *E. coli* and *S. maltophilia in* the neonatal and pediatric groups. The detection rate of carbapenem-resistant -*K. pneumo*niae (CRKPN) in neonate group was 31.4%, significantly increased compared with pediatric group, whose detection rate was 24.7%. The rates of resistance to levofloxacin and trimethoprim/sulfamethoxazole were significantly lower in neonatal groups than pediatric groups in BSIs caused by *K. pneumoniae*. To imipenem and meropenem were 3.6% and 3.9% among neonatal isolates, which was lower than 4.7% and 5.8 among pediatric BSIs caused by *E. coli*. Isolated from neonatal BSIs caused by *A. baumannii* showed lower resistance ratios to all the agents tested than those from pediatric. However, only the prevalence of piperacillin/tazobactam resistance was statistically lower than that in pediatric BSIs caused by *P. aeruginosa*. The average detection rates of carbapenem resistance, extended-spectrum cephalosporin resistance, and fluoroquinolone resistance for *K. pneumoniae* and *E. coli* were 28.1%,41.4%,11.6% and 4.0%,24.3%,31.1%, respectively.

Received: 3 July 2024
Accepted: 6 September 2024
Published: 20 September 2024

Conclusion: The detection rate of gram-negative pathogens showed an increasing trend among the bloodstream infection. The detection rate of CRKPN assumed a downward trend in 2018. There are differences types of pathogens between the neonatal group and the pediatric group, The detection rate of CRKPN in the neonate group was significantly higher than pediatric group. The first average detection rates for carbapenem resistance, extended-spectrum cephalosporin resistance, and fluoroquinolone resistance were obtained for *A. baumannii, K. pneumoniae*, and *Escherichia coli*, respectively. Those data showed a high level of antimicrobial resistance, which has posed an urgent threat to Children's health, suggested that effective monitoring of antimicrobial resistance and antimicrobial stewardship among children in China are required.

Keywords: bloodstream infection, pathogenic bacterium, difficult-to-treat resistance, carbapenem resistance, extended-spectrum cephalosporin resistance, fluoroquinolone resistance

Introduction

Bloodstream infection (BSIs) refers to the temporary, intermittent, or persistent presence of pathogenic microorganisms in the circulating blood of the body, which can cause damage to all organs and is one of the causes of shock, multiple organ failure, and acute death in patients.[1] The wide execution of invasive treatment and the application of broad-spectrum antibiotics caused a high incident and a trend of increasing in BSIs recent years.[2] High mortality rate of BSIs, the constantly changes of bacterial resistance mechanisms caused experience medication failures occur repeatedly.[3] In children, BSIs carries a high disease burden, higher medical costs, and longer hospital stays, and it requires immediate and appropriate empirical antimicrobial treatment.[4] Therefore, dynamic monitoring of pathogenic bacteria and drug resistance trends in BSIs is greatly significance in clinic. Blood culture is the gold standard for diagnosing BSIs,[5] which can identify the pathogens, analyze drug resistance, guide clinical medications, and be of a certain value in predicting treatment outcomes. As reported that over 50% of the pathogenic bacteria in blood culture are caused by Gram negative bacteria in children,[6] the mortality rate is as high as 11.5%.[7] A report from Malaysia shows that[6] common causes of BSIs were *Staphylococcus aureus, K. pneumoniae, A. baumannii, P. aeruginosa, and E. coli* in the child population. While in the research report of southwest China,[8] top five bacteria for adult bloodstream infections are *E. coli, K. pneumoniae, Staphylococcus epidermidis, Staphylococcus aureus* and *Staphylococcus hominis*, respectively. For Children's are *Escherichia coli, K. pneumoniae, P. aeruginosa, A. baumannii and Enterobacter cloacae*, respectively. From this, we could find differences in the composition of pathogens of BSIs between adults and children.[8] There was a higher incidence of BSIs in newborns and infancy, associated with prolonged hospital stays, higher healthcare costs, and increased patient mortality probably.[9] The distribution and drug resistance of bacteria vary in different regions, making it essential to follow the geographical distribution and age distribution for the initial selection of empirical antibiotics. Knowledge about the pathogen distribution causing pediatric BSI is crucial in providing empirical antimicrobial therapy, tracking resistance patterns, and identifying infection prevention strategies. However, epidemiological data about children's multi-center study of gram-negative bacteria causing BSIs were lacking in China regretfully.

To fill this gap, we launched a 7-year retrospective multicenter study from 2016 to 2022. This study aims to elucidate the longitudinal alterations of pathogen distributions and antibiogram of gram-negative bacteria among pediatric and neonatal BSIs, analyze four important drug-resistance phenotypes. This is the first multicenter study on difference analysis of the species, drug resistance rate and four important drug-resistance phenotypes of bloodstream infection caused by negative bacteria in Children and newborns, which can provide a basis for rational medication for BSIs in children of China.

Materials and Methods

Patients and Enrollment of Bacteria

Gram-negative bacteria were isolated from children clinically diagnosed with BSIs in hospitals participating in the ISPED from 2016 to 2022. Infectious Disease Surveillance of Pediatric (ISPED) is composed of 12 tertiary children's hospitals in nine provinces or autonomous cities in China (Guangdong province, Jiangsu province, Zhejiang province, Shandong province, Shanxi province, Henan province, Jilin province, Shanghai city, and Chongqing city), which intended to monitor the pathogens of infections in Chinese children. Each laboratory member will report the bacterial

identification and antibiotic sensitivity data to the ISPED every year. This study included only gram-negative bacteria isolated from the blood samples of patients. To effectively analyze the accumulated susceptibility data and determine the trend in antimicrobial resistance for the major pathogens, only data from the initial 10 hospitals in 2016, 9 hospitals in 2017, 11 hospitals in 2018–2020, and 12 hospitals in 2021–2022 were analyzed. Contaminating bacteria and duplicate strains detected by the same patient were removed.

Strain Identification

The bacterial isolates were identified using a variety of methods, including the Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, the VITEK2-Compact automatic bacterial identification and drug sensitivity instrument (bio Mérieux, France), the BD Phoenix automatic microbiological identification/drug sensitivity system (USA), the Merier API system.

Antibiotic Sensitivity Testing

Antimicrobial susceptibility testing was performed using the minimum inhibitory concentration (MIC) method, the Kirby–Bauer method, or the E-test method, and the results were interpreted by the breakpoint criteria recommended by the Clinical and Laboratory Standards Institute (CLSI) M100-S32 guidelines from 2022.[10] *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27853) were used as control strains for susceptibility tests.

Definitions

Neonatal patients were defined as those who were no older than 28 days, while pediatric patients were defined as those between 29 days and 14 years old.[11]

DTR is defined as in vitro resistance or intermediate resistance to all β-lactam categories, including carbapenems and fluoroquinolones.[12] Carbapenem resistance (CR) was defined as the resistance to imipenem or meropenem in vitro. Extended-spectrum cephalosporin resistance (ECR) was defined as resistance to ceftazidime, cefotaxime, or cefepime. Fluoroquinolone resistance (FQR) is defined as the resistance to ciprofloxacin or levofloxacin in vitro.

Statistical Analysis

Raw data were first processed using Whonet 5.6 software and then calculated using GraphPad Prism 8. Temporal changes in age distribution and AMR were further determined using the Mann–Whitney *U*-test. Statistical significance was confirmed if the two-tailed P-value was <0.05.

Table 1 Rate of Pathogenic Bacteria in Bloodstream Infections

Year	Pathogens	Pathogens in BSIs	Gram Negative Pathogens	Pathogens in BSIs / Pathogens (%)	Gram Negative Pathogens / Pathogens (%)
2016	57,082	6446	1420	11.3	22
2017	57,881	6372	1569	11	24.6
2018	60,866	6475	1956	10.6	30.2
2019	63,099	6653	1861	10.5	28
2020	41,265	4536	1311	11	28.9
2021	63,508	5211	1418	8.2	27.2
2022	50,399	4284	1289	8.5	30.1
total	394100	39,977	10,824	/	/
average	/	/	/	10.1	27.1

Table 2 Distributions of the Top ten Pathogens from Bloodstream Infections Reported by the ISPED Program from 2016 to 2022

Pathogens	Overall			Neonatal			Pediatric		
	Number of Pathogens (n = 10,824)	Percentage (%)	Rank	Number of Pathogens (n = 2671)	Percentage (%)	Rank	Number of Pathogens (n =8153)	Percentage (%)	Rank
E. coli	2579	23.8	1	982	36.8	1	1597	19.6	2
S. maltophilia	2042	18.9	2	89	3.3	6	1953	24	1
K. pneumoniae	1953	18.0	3	864	32.3	2	1089	13.4	3
A. xylosoxidans	634	5.9	4	134	5	3	500	6.1	5
P. aeruginosa	610	5.6	5	28	1	10	582	7.1	4
A. baumannii	410	3.8	6	58	2.2	7	352	4.3	6
E. cloacae	354	3.3	7	127	4.8	4	227	2.8	8
S. marcescens	278	2.6	8	90	3.4	5	188	2.3	9
Salmonella sp.	266	2.5	9	6	0.2	19	260	3.2	7
S. paucimobilis	117	1.1	10	1	0	61	116	1.4	10

Results

Distribution of Clinical Isolates

From 2016 to 2022, a total of 394100 strains of pathogenic bacteria were isolated from the ISPED project. 39977 bloodstream infection strains among them (10.1%), caused by negative bacteria were 10824 strains (27.1%) (As shown in Table 1). The top 10 negative bacteria in BSIs were *E. coli* (23.8%), *S. maltophilia* (18.9%), *k. pneumoniae* (18.0%), *A. xylosoxidans* (5.9%), *P. aeruginosa* (5.6%), *A. baumannii* (3.8%), *E. cloaca* (3.3%), *S. marcescens* (2.6%), *Salmonella sp*. (2.5%), *S. paucimobilis* (1.1%) (As shown in Table 2). A total of 2671 strains in total isolated from neonate group

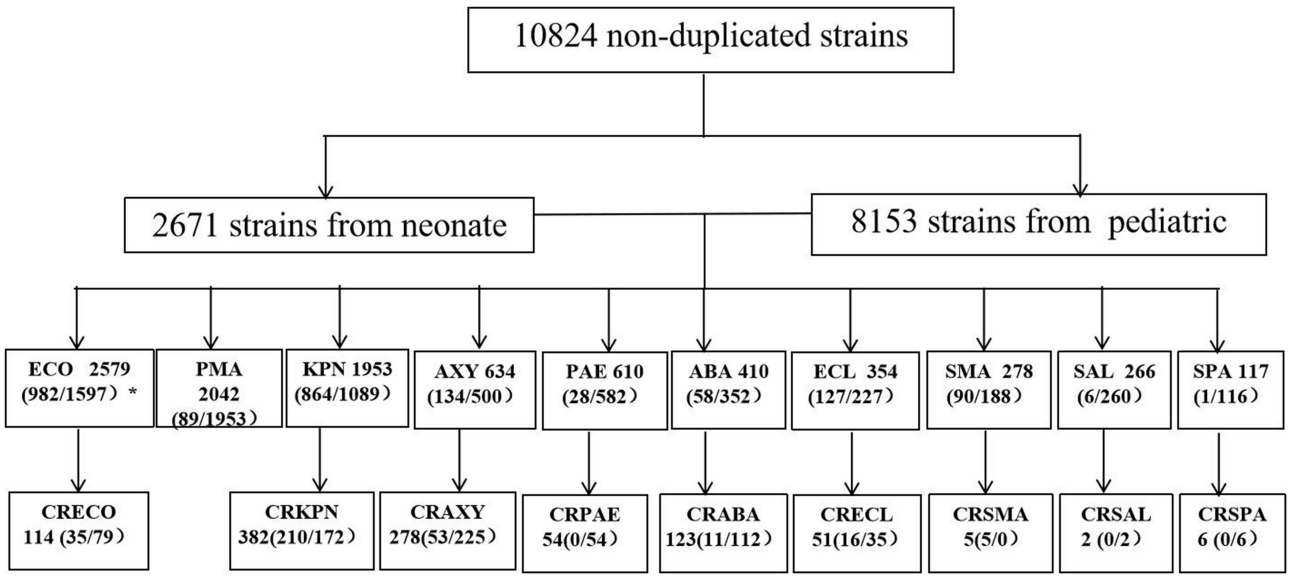

Figure 1 ISPED program pathogens encountered in BSIs in this present study.
Note: N (A/B) * "N" means the total number of strains in the BSIs. "A" stands up the number of strains isolated from neonatal BSIs, "B" is the number of strains isolated from Pediatric BSIs.
Abbreviations: ECO, *E. coli*; PMA, *S. maltophilia*; KPN, *K. pneumoniae*; AXY, *A. xylosoxidans*; PAE, *P. aeruginosa*; ABA, *A. baumannii*; ECL, *E. cloacae*; SMA, *S. marcescens*; SAL, *Salmonella sp.*; SPA, *S. paucimobilis*; CRECO, carbapenem-resistant *E. coli*; CRKPN, carbapenem-resistant *K. pneumoniae*; CRAXY, carbapenem-resistant *A. xylosoxidans*; CRPAE, carbapenem-resistant *P. aeruginosa*; CRABA, carbapenem-resistant *A. baumannii*; CRECL, carbapenem-resistant *E. cloacae;* CRSMA, carbapenem-resistant *S. marcescens*; CRSAL, carbapenem-resistant *Salmonella sp.*; CRSPA, carbapenem-resistant *S. paucimobilis*.

(24.7%), 8153 strains in pediatric group (75.3%), There were discrepancies in the top 10 pathogens distribution between two groups. The detection rate of CRKPN in neonate group was 31.4%, which was significantly increased compared with that in pediatric group, 24.7% ($P < 0.05$) (As shown in Figure 1).

Antimicrobial Resistance (AMR) Trends of ISPED Program Pathogens in Neonatal and Pediatric BSIs

Through analyzing the AMR of the top eight pathogenic bacteria for *K. pneumoniae* in BSIs, we found that the rates of resistance to ciprofloxacin, levofloxacin, amikacin, gentamicin, and trimethoprim/sulfamethoxazole in neonatal BSIs were lower than those in pediatric, especially for levofloxacin and trimethoprim/sulfamethoxazole. The prevalence of piperacillin/tazobactam, imipenem, and meropenem resistance in neonatal BSIs was higher than that in pediatric (31.5% vs 20.1%, 25.1% vs 16.3%, and 31.4% vs 24.7%, respectively), while no significant difference between them. Among the other antimicrobial resistance tests, the resistance rates of the first, second, third, and fourth-generation cephalosporins all were over 50%, and the resistance rate of ampicillin/sulbactam was as high as 72.4%. The number of newborns was significantly higher than that in the pediatric group (As shown in Figure 2A).

In contrast to *K. pneumoniae, E. coli* showed a different AMR profile between the two groups. The prevalence of imipenem and meropenem resistance were 3.6% and 3.9%, respectively, in neonatal isolates, which was lower than the 4.7% and 5.8% in pediatric BSIs. The prevalence of ceftazidime, cefepime, and ampicillin/sulbactam resistance in neonatal BSIs (17.3%,17.6% and 30.6%, respectively) was notably lower than that in pediatric (28.5%,27.0% and 49.1%) ($P < 0.0001$). The prevalence of ciprofloxacin and levofloxacin resistance was higher than that in pediatric BSIs (37.5% vs 35.0% and 37.9% vs 37.8%) (Shown in Figure 2B).

Unlike *E. coli* and *K. pneumoniae*, no significant differences in the AMR profiles of *E. cloacae, S. marcescens*, and *S. maltophilia* were found between the neonatal and pediatric BSIs (Shown in Figure 2C–E). The carbapenem resistance rate of *E. cloacae* in both the groups were over 10%. The rates of resistance to aztreonam, ceftazidime, ceftriaxone, cefotaxime, and cefuroxime were higher in neonatal than in pediatric BSIs. All AMR rates for *S. marcescens* were less than 25.0%. Notably, the AMR of imipenem, meropenem, cefepime, and cefoperazone/sulbactam in neonatal BSIs was higher than that in pediatric BSIs. However, the AMR of minocycline, trimethoprim/sulfamethoxazole, and levofloxacin was less than 5% in *S. maltophilia*, and the AMR in neonatal BSIs was lower than that in pediatric. The prevalence of cefepime resistance in neonatal BSIs (11.2%) was notably lower than that in pediatric (27.4%) for *A. xylosoxidans* ($P < 0.05$, shown in Figure 2F).

For non-fermenters, The AMR of all the Antibiotics was lower than 45.0% in *A. baumannii* isolated from neonatal BSIs, which showed lower resistance ratios to all the agents tested than those from pediatric ($P < 0.05$, shown in Figure 2G). The AMR of ciprofloxacin, amikacin, ceftazidime, and cefepime were higher than those in neonatal BSIs in *P. aeruginosa*; only the prevalence of piperacillin/tazobactam resistance was significantly lower than that in pediatric BSIs ($P < 0.05$, shown in Figure 2H).

Trends in Specific Drug Resistance Phenotypes in Main Gram-Negative Bacteria

The CR detection rate ranged from 10.7% to 30.9%, the CR, ECR, and FQR meanwhile decreased significantly after 2018 from 30.9% to 17.6%, 55.7% to 30.9%, and 18.8% to 9.7% (shown in Figure 3A). The detection rate of *E. coli* for CR was less than 6%, for ECR and FQR ranged from 18.1% to 32.9%, and 26.7% to 37.6% severally (shown in Figure 3B). *P. aeruginosa* increased significantly after 2020, and the ECR as well as FQR showed clear downward trends after 2021 instead (shown in Figure 3C). *A. baumannii* for the CR decreased significantly after 2021 and the FQR ranged from 9.6% to 34.2% (shown in Figure 3D).

The Distribution of Special Antimicrobial Resistance Phenotypes by Time

For *K. pneumoniae, E. coli, P. aeruginosa* and *A. baumannii*, the detection rates for DTR were 0% between 2016 and 2022. The detection rates of CR in *E. coli* and *A. baumannii* manifested downtrend from 2021. CR in *P. aeruginosa* performed a rising trend at the same time. The average CR detection rate in *E. coli* (4.0%) was clearly lower than that in

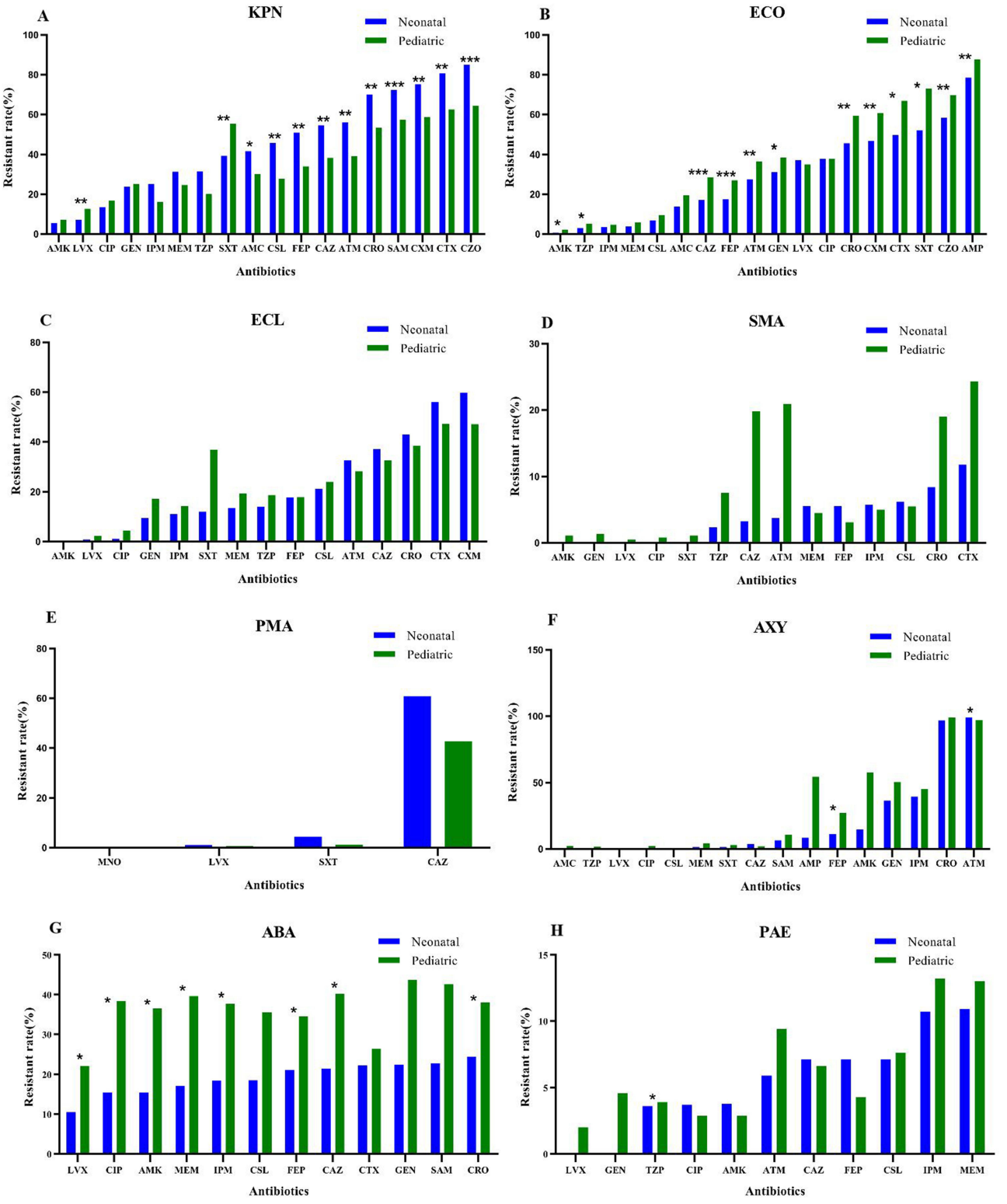

Figure 2 (**A**–**H**) Antimicrobial resistance profiles of ISPED program pathogens in Neonatal and Pediatric BSIs.

Notes: *indicate statistical significance with P < 0.05, **indicate statistical significance with P < 0.01, ***indicate statistical significance with P < 0.001.

Abbreviations: ECO, *E coli*; KPN, *K pneumoniae*; ECL, *E cloacae*; SMA, *S marcescens*; PMA, *S maltophilia*; AXY, *Axylosoxidans*; ABA, *Abaumannii*; PAE, *P aeruginosa*; IMP, Imipenem; MEM, Meropenem; AMP, Ampicillin; CZO, Cefazolin; CXM, Cefuroxime; CRO, Ceftriaxone; CAZ, Ceftazidime; CTX, Cefotaxime; FEP, Cefepime; AMC, Amoxicillin/Clavulanic acid; SAM, Ampicillin/Sulbactam; TZP, Piperacillin/Tazobactam; CLS, Cefoperazone/Sulbactam; CIP, Ciprofloxacin; LEV, Levofloxacin; AMK, Amikacin; GEN, Gentamicin; SXT, Trimethoprim/Sulfamethoxazole; ATM, Aztreonam; MON, Minocycline.

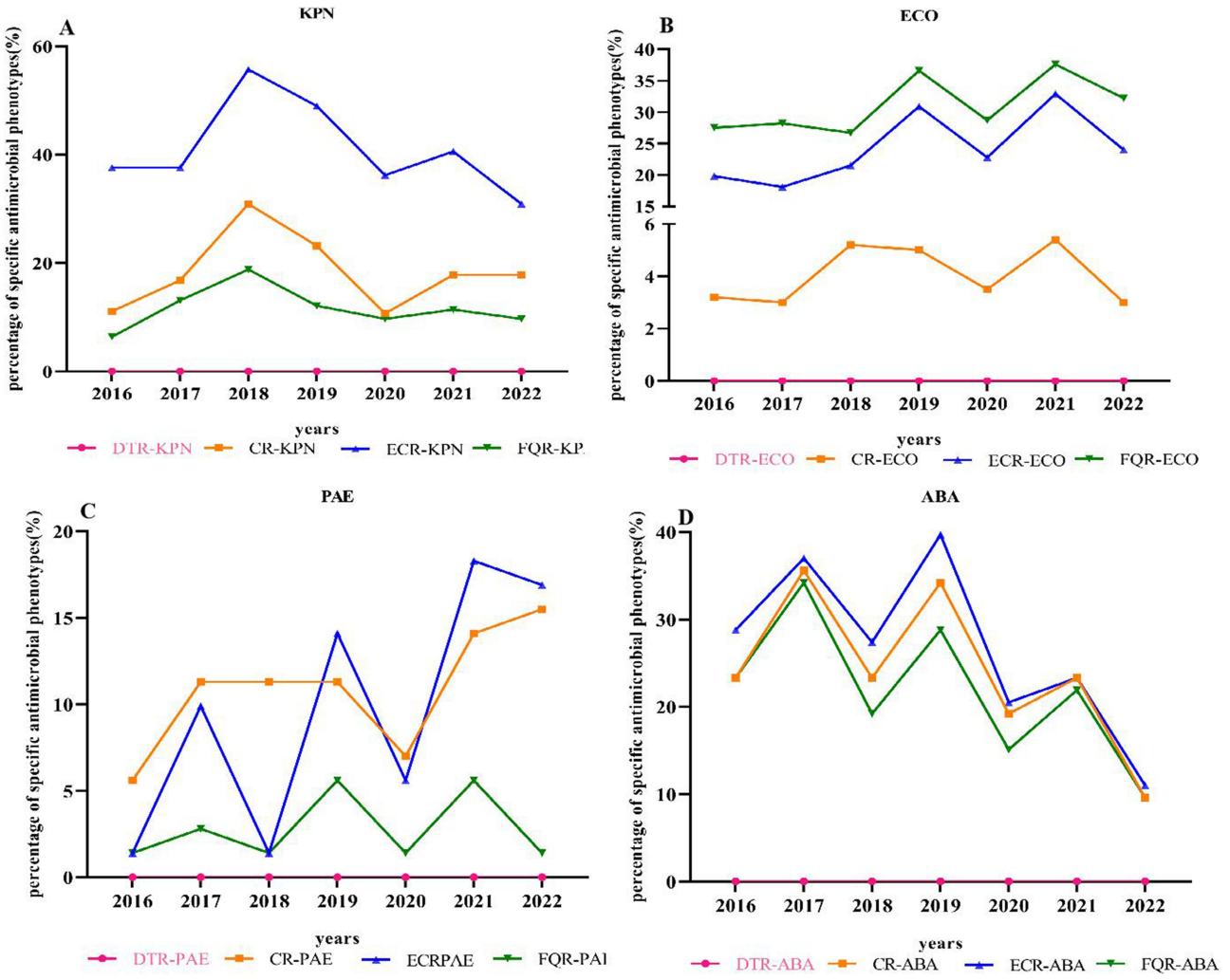

Figure 3 (**A**–**D**) Trends in special antimicrobial resistance phenotypes from 2016 to 2022.
Abbreviations: KPN, *K pneumoniae*; ECO, *E coli*; PAE, *P aeruginosa*; ABA, *A baumannii.*

K. pneumoniae (28.1%) (p<0.0001, shown in Figure 4A and D). For *K. pneumoniae, A. baumannii, E. coli*, and *P. aeruginosa*, the detection rates for ECR and FQR decreased from 2021 (shown in Figure 4B and C). The average detection rate for CR in *P. aeruginosa* (10.9%) was obviously not a patch on *A. baumannii* (24.1%) (p<0.001), and for ECR in *E. coli* and *P. aeruginosa* (10.9%) were visibly inferior to those in *K. pneumoniae* and *A. baumannii* (24.3% vs 41.1,9.7% vs 26.8%) (p<0.001). FQR in *P. aeruginosa* (2.8%) was notably lower than *A. baumannii* (21.7%) (p<0.0001), and the average detection rate of FQR in *E. coli* (31.6%) distinctly exceeder than *K. pneumoniae* (11.6%) (shown in Figure 4D). The initial average detection rates for CR, ECR, and FQR were 24.1%, 41.1%, and 31.1% for *A. baumannii, K. pneumoniae*, and *E. coli*, respectively (24.1%, 41.1% and 31.1%) (shown in Figure 4D).

Discussions

BSIs is one of the life-threatening systemic infectious diseases and has a high morbidity and mortality in children, which has become an important cause of neonatal death. Gram negative bacteria is a common cause of BSIs in newborns and young children. Although studies have investigated these isolates in adults, there is a lack of equivalent data in the pediatric population. This multicenter study confirmed the distribution of pathogens causing BSIs from 2016 to 2022, AMR patterns, changes in four specific drug resistance patterns in Chinese children, as well as demonstrated the increasing antibiotic resistance rate of most gram-negative bacterial BSIs, the unique AMR pattern in neonatal and

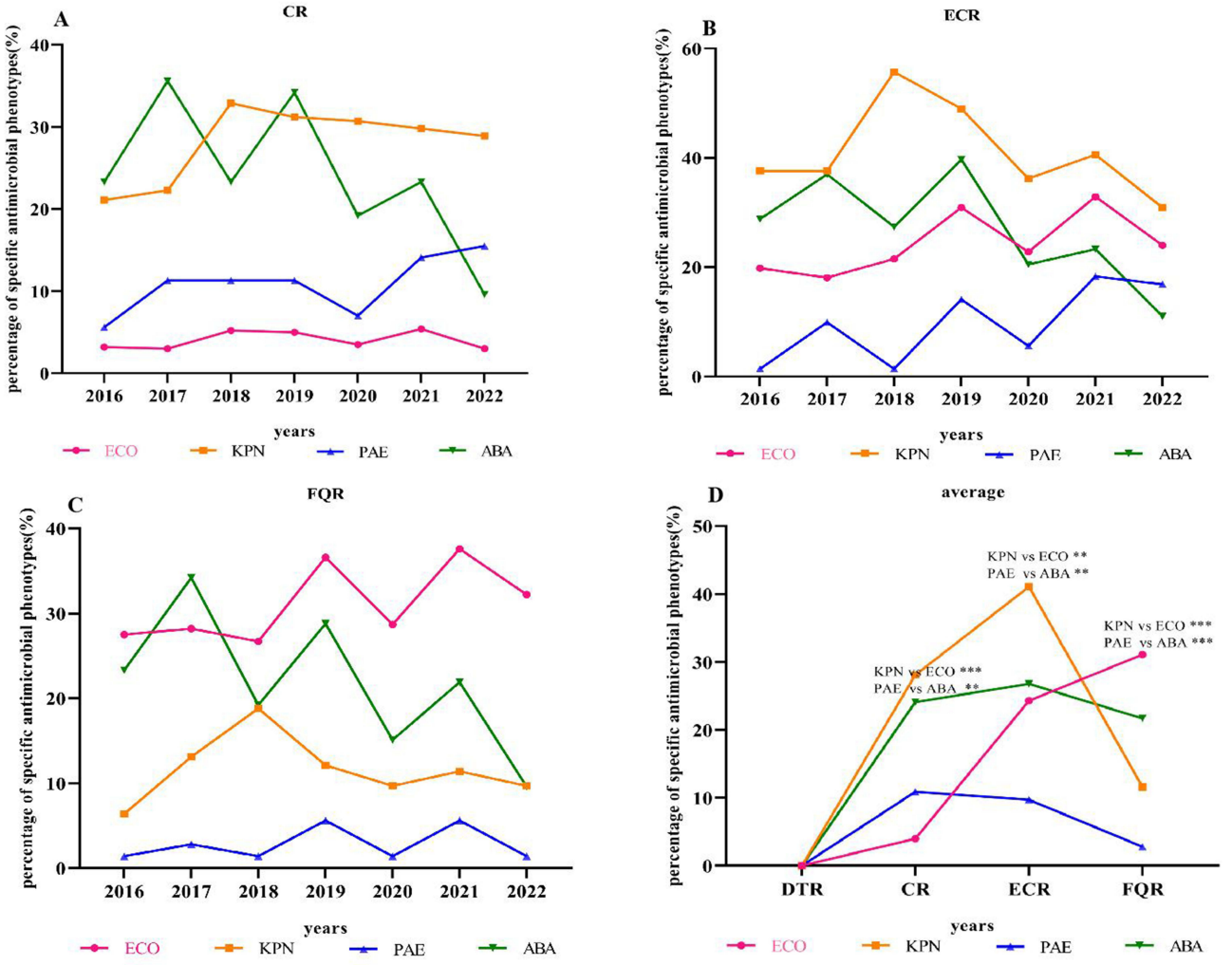

Figure 4 (**A**–**D**) Time trend and age distribution of special antimicrobial resistance phenotypes from 2016 to 2022.
Note: **indicate statistical significance with P < 0.01, ***indicate statistical significance with P < 0.001.
Abbreviations: CR, carbapenem resistance; ECR, extended-spectrum cephalosporin resistance; FQR, fluoroquinolone resistance; average, average detection rate from 2016 to 2022.

pediatric BSIs in particular. To our knowledge, this is the first multicenter study on gram-negative bacteria in pediatric BSIs in China, which can provide a theoretical basis for rational drug use in pediatric bloodstream. Also, it should be noted that current study is completely different from our previously published research 10 [13] terms in research objectives, research content, research conclusions and even time span, whose research content mainly focused on the distribution and drug sensitivity data of pathogens isolated from all ISPED samples from 2016 to 2020, including: respiratory tract (53.9%), followed by blood (10.4%) and urine (10.0%). The main sample types were respiratory tract (53.9%), which makes it difficult to exclude interference from normal bacterial communities.

The data from ISPED indicates that the proportion of gram negative bacteria causing BSIs ranges from 22.0% to 30.1% from 2016 to 2022, the average detection rate is 27.1%, which was lower than that in 23 other centers with positive blood culture: The mean fraction of bacteremia associated with Gram-negative bacteria was 48.4% (range 26.4% to 61.8%),[14] were lower than the 55.4% which reported by Tehran 55.4%,[15] higher than the 22% by Zhi-yong Lyu[16] in the area of Beijing of China nevertheless, but that's in line with the 29.4% reported by Cuicui Wang in East China.[17] The top five pathogens isolated from overall group in this study were *E. coli, S. maltophilia, K. pneumoniae, A. xylosoxidans, P. aeruginosa* in turn, which differed from the report in East China (*E.coli, Klebsiella sp, Serratia sp., S.maltophilia, Enterobacter sp*).[17] The top five pathogens isolated from the neonatal groups in our study were *E. coli, K. pneumoniae,*

A. xylosoxidans, E. cloacae and *S. marcescens*, which differed from a cross-sectional study (*K. pneumoniae, A. baumannii, E. coli, S. marcescens* and *E. cloacae*),[18] yet as the same as H Crichton.[18] The reason we speculate may be due to differences in economic, climate, medical conditions, and the distribution of pathogens causing BSIs varied from region to region across the whole world.[19,20] In the meantime, detection rate of *S. maltophilus was* same with some other correlative studies.[21] The detection rate of non-fermenting bacteria causing infections in children takes up the highest proportion, accounting for 24.0% in gram-negative bacteria, significantly higher than the other non-fermenting bacteria such as *P. aeruginosa* (7.1%) and *A. baumannii* (4.3%), which differs from the studies reported in hospitalized children in East China and Ghanaian referral hospital.[17,22] It is perhaps related to the higher detection rate of *S. maltophilia* in two-member units. The detection rate of *A. xylosoxidans* colorless bacteria (6.1%) ranks fifth among gram-negative bacteria in pediatric BSIs, which may be relevant to the isolation of a significant number of *A. xylosoxidans* colorless bacteria from the blood culture of children with pulmonary cystic fibrosis, immune system damage, and chronic underlying diseases.

Notably, our study found that the mean detection rate of CRKPN was 28.2%, which is lower than the 50.8% reported by Zhi-yong Lyu [16] in a tertiary pediatric hospital in Beijing. Especially, the detection rate of CRKPN in the neonate group (31.4%) was significantly higher than pediatric group (24.7%). The neonatal patients were associated with poor physical conditions, low immunity, prolonged use of broad-spectrum antibiotics, indwelling catheters, deep venous intubation and indwelling catheters. They are risk factors of carbapenem resistant Enterobacteriaceae (CRE) acquisition.[23] The prevalence of carbapenem-resistant *E. coli* was 4.0%, which was lower than that as Zhi-yong Lyu reported[16] in a tertiary pediatric hospital in Beijing (12.9%), Yan Zhou reported[24] in Jiangxi Region of China (6.0%). This finding may be associated with the strategies of our hospital implemented to controlling the transmission of MDR infections, which has been actively implemented national policies on the rational use of antibiotics and strengthened hospital infection control. The high prevalence may be due to the heterogeneity of resistant elements among the strains and the dissemination of conservative mobile elements. The crucial mechanism of CRE is the production of carbapenemase, the components of ISKpn27 *blaKPC-2-ISKpn2* play a fatal role in CRKPN transmission.[25] However, several studies have reported that *blaNDM* dominates in CRKPN.[26–29] Therefore, we are also conducting more research to reveal the potential molecular mechanisms underlying the high prevalence of CRKPN in children with BSIs and advocate for the cautious use of carbapenems for the treatment of CRKPN causing BSIs in children.

The resistance rates of *K. pneumoniae* to ceftazidime, ceftriaxone, and cefepime were 38.5%,53.5%and 34.1%, respectively, in the pediatric group, which were significantly lower than those reported for ZY L.[16] The resistance rates of *K. pneumoniae* to imipenem and meropenem in the neonatal and pediatric groups continue to increase, while the ceftriaxone, ceftazidime, cefotaxime, and cefepime decrease instead, which is similar reported by Lei Tian.[30] A possible explanation for this change is the widespread use of imipenem or meropenem. Owing to severe BSIs in children, most empirical antibiotic treatments for BSIs rely on imipenem or meropenem rather than third or fourth-generation cephalosporins, leading to antibiotic selection pressure. Recent domestic and international studies as well have shown that the increasing use of carbapenems can accelerate the production of carbapenemases, which increases the production of CRKPN in turn.[31–33]

The ISPED data showed that *K. pneumoniae* was detected in overall group from 2016 to 2022, with imipenem resistance rate was 16.8% to 34.6%, meropenem 29.5% to 56.0%, significantly higher than the other 23 centers with positive blood culture reported: imipenem sensitivity (99% to 88%; $p = 0.030$) and meropenem sensitivity (98% to 89%; $p = 0.033$), but significantly higher than what reported by L Dong[34] and Cuicui Wang.[17] The former resistance rates of *K. pneumoniae* to carbapenems was under 10% in Wenzhou of China, the latter to imipenem as well as meropenem were 11.3% and 10.9% in East China. Between 2016 and 2022, the amikacin resistance rate decreased from 15.2% to 0, which was opposite to what had been reported that was a substantial reduction in susceptibility of *K. pneumoniae* isolates to amikacin (89% to 76%; $p = 0.051$).[35] Low resistance to amikacin is associated with its reduced clinical use in children. Amikacin is ototoxic which may cause hearing impairment; however, once the phenomenon appears that clear indications of clinical indication has been equipped and no other antimicrobial agents are available, this drug may be considered under strict understanding of the indications and close monitoring of adverse reactions. The resistance rates to amikacin,

levofloxacin, ciprofloxacin, gentamicin, and trimethoprim/sulfamethoxazole in the neonatal group were significantly lower than those in the pediatric group, which was associated with the lower use of these drugs in newborns.

This study showed that the resistance rate to various antibiotics such as ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, and levofloxacin to *P. aeruginosa* were lower than 15% in the pediatric group, which is consistent with other interiorly research,[16] indicating that these drugs can be used as first-line drugs for the treatment of pediatric BSIs caused by *P. aeruginosa*. The resistance rate of *A. baumannii* to these drugs has increased significantly. At present, the treatment for multidrug-resistant baumannii mainly relies on a combination therapy regimen of sulbactam, polymyxin, and tigecycline. The average resistance rates of *P. aeruginosa* to imipenem and meropenem in the pediatric group were 13.1% and 10.8%, respectively, lower than those of *A. baumannii* (37.8% and 40.1%, respectively): a similar trend was reported by Zhi-yong Lyu.[16] Interestingly, the average resistance rate of *P. aeruginosa* to carbapenem has been on the rise since 2020, whereas *A. baumannii* declined on the contrary.

DTR is also a public health threat that contributes to the international spread of plasmids, antibiotic overuse, and the need for expensive infection control measures in healthcare facilities. DTR is a very practical value indicator, whose emergence indicates when deciding a clinical treatment, antibacterial drugs that are less effective and/or toxic should be considered.[36]

The emergence of DTR poses a threat to clinical anti-infection treatment and hospital infection prevention, hence DTR has now been closely monitored in the field of public health services. Validation on large patient cohorts has made it clear that this new definition is promising in better defining the correlation with clinical outcomes, designing and evaluating clinical trials on the therapeutic management of antibiotic resistant gram-negative infections.[37] No negative bacteria for DTR had been found in our study, lower than the multicenter surveillance report over 20 years monitoring report.[38] The proportion of strains of special antimicrobial resistance phenotypes including CR, ECR and FQR in *K. pneumoniae* were 18.3%, 41.1%, 11.6% while in *E. coli* were 4.4%, 24.3%, 31.1%, respectively, which were different from the multicenter surveillance report over 20 years (14.00%, 31.91%, 11.40%,0.26% and 13.95%, 22.78%). [12,38,39]

Our study manifested that the detection rates of FQR-KPN (11.6%) was significantly lower than FQR-ECQ (31.1%). FQR-PAE (2.8%) was obviously lower than FQR-ABA (21.1%). The main mechanism underlying CRKPN resistance is the production of *DNM* carbapenemases. Our previous research indicated that the main genotype in our hospital was *bla-DNM5*, in the meantime, the detection rates of CR-PAE and CR-ABA were 10.9% and 24.1%, respectively, which were significantly lower than the 26.9% and 54.5% reported by Beijing Children's Hospital.[16] There were significant differences in medication habits and drug resistance among different regions.

Conclusions

Our 7-year study revealed the characteristics of BSIs, antibiotic resistance patterns, and four important drug-resistance phenotypes in 12 tertiary pediatric hospital in China. *E. coli* was the most primary pathogens causing children's BSIs in gram-negative bacteria, followed by *S. maltophilia, K. pneumoniae, A. xylosoxidans, and P. aeruginosa*. The resistance rates of *K. pneumoniae, E. coil, A. baumannii, and P. aeruginosa* to carbapenems were 28.1%, 4.0%, 24.1%, and 10.9% respectively. The average detection rates of ECR and FQR for *K. pneumoniae* and *E. coli* were severally 41.4%,11.6% and 24.3%,31.1%. Disclosure of the distinct resistance profiles could help to avoid their rational use of antibiotics and reduce antimicrobial resistance.

Ethics Approval and Consent to Participate

We confirm that we have read the Editorial Policy pages. We confirm that a parent or legal guardian of patients under 18 years of age provided has provided informed consent. This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University in accordance with the Helsinki Declaration of the World Medical Association and the ethical principles formulated by the Chinese GPC. Written informed consent was obtained from all participants.

Acknowledgments

We thank the ISPED (Infectious Disease Surveillance of Pediatrics) group for their support with this study.

Funding

This work was funded by the Chongqing Natural Science Foundation Joint Fund for Innovation and Development (Municipal Education Commission/Key Project) (Grant Number: CSTB2022NSCQ-LZX0045).

Disclosure

The authors declare that they have no conflicts of interest in this work.

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