Infection and Drug Resistance

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ORIGINAL RESEARCH

Monitoring of *Klebsiella pneumoniae* Infection and Drug Resistance in 17 Pediatric Intensive Care Units in China from 2016 to 2022

Panpan Fan[1,*], Pan Fu[2,3,*], Jing Liu[1,*], Chuanqing Wang[2,3], Xiaolei Zhang[1], Yixue Wang[1], Yingying Zhang[1], Ting Zhu[1], Caiyan Zhang[1], Guoping Lu[1], Gangfeng Yan[1] On behalf of the China Paediatric Intensive Care Unit Pathogen Surveillance Network (CHIPS) Study Group

[1]Department of Pediatric Intensive Care Unit, Children's Hospital of Fudan University, National Center for Children's Health, Shanghai, People's Republic of China; [2]Lab of Microbiology, Department of Clinical Laboratory, Children's Hospital of Fudan University, National Center for Children's Health, Shanghai, People's Republic of China; [3]Nosocomial Infection Control Department, Children's Hospital of Fudan University, National Center for Children's Health, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guoping Lu; Gangfeng Yan, Email 13788904150@163.com; gangfeng_yan@fudan.edu.cn

Objective: To investigate the characteristics and drug resistance patterns of Klebsiella pneumoniae (*K. pneumoniae*) infection in pediatric intensive care unit (PICU).

Methods: *K. pneumoniae* strains from 17 domestic PICUs were analyzed for overall condition and drug resistance using WHO-NET software.

Results: From 2016 to 2022, there was a linear increase in the detection rate of *K. pneumoniae* ($P<0.05$), with a total of 2591 (9.7%) strains detected. The primary sites of *K. pneumoniae* detection were the respiratory tract (71.1%), blood (8.6%), and urinary tract (7.1%). *K. pneumoniae*'s resistance to penicillin drugs exceeded 90%, and are over 50% to cephalosporins. Resistance to cefoperazone-sulbactam decreased from 51.7% to 25.7%, and ranged from 9.1% to 20.8% for ceftolozane-tazobactam. Carbapenem-resistant *K. pneumoniae* strains constituted 32.3%. Resistance to imipenem and meropenem have decreased to 33.8% and 40.2%, while increased to 35.2% for ertapenem. Levofloxacin and amikacin resistance rates have decreased to 25.7% and 9.1%, but remain high at 63.8% for moxifloxacin and 44.6% for ciprofloxacin. *K. pneumoniae* demonstrated the lowest resistance rates to polymyxin B (0.9%), tigecycline (2.2%), and polymyxin E (3.1%). No strain of *K. pneumoniae* was resistant to both polymyxin B and meropenem. However, some strains showed co-resistance to meropenem with other antibiotics, including tigecycline (2%), imipenem (16%), amikacin (27%), colistin (37%), and levofloxacin (41%).

Conclusion: The rates of isolation and drug resistance of *K. pneumoniae* in PICU have significantly increased over 7 years. Careful antibiotic use, infection control strategies, and appropriate antibiotic combinations are crucial in addressing this problem.

Keywords: pediatric intensive care unit, *Klebsiella pneumoniae*, bacterial drug resistance

Introduction

The incidence of *Klebsiella pneumoniae* (*K. pneumoniae*), which is a commonly encountered opportunistic Gram-negative pathogen that causes nosocomial infections, has been increasing progressively across China.[1] Particularly noteworthy are the documented *K. pneumoniae* outbreaks in neonatal wards and pediatric intensive care units (PICUs). The escalating use of invasive therapeutic procedures, immunosuppressive agents, hormonal therapies, and broad-spectrum antibiotics has significantly contributed to the rising prevalence and drug resistance of *K. pneumoniae*. According to available reports, the mortality rate among individuals who are affected by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is approximately 42.1%.[2] Children diagnosed with CRKP bloodstream infection have a mortality rate of 43.2%,[3] whereas adults have a higher mortality rate of 54.3%.[2] To address the issue of antimicrobial resistance surveillance in PICU patients, the China PICU

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Pathogen Surveillance Network (CHIPS) was established in 2021. This network includes 17 tertiary care children's hospitals located in 11 provinces and the autonomous regions of mainland China. To obtain a comprehensive understanding of the clinical manifestations of *K. pneumoniae* infection in pediatric patients who are admitted to the PICU and to assess the susceptibility of isolated strains to various drugs, we conducted a systematic analysis of the in vitro drug sensitivity of *K. pneumoniae* strains that were identified in the PICUs belonging to CHIPS. The results of this investigation provide significant insights into the prevention of nosocomial infections and the appropriate use of antibiotics.

Methods

Data Collection

All the data in this study (basic information of patients, site of infection, drug susceptibility testing) were collected from the CHIPS database between 1 January 2016 and 31 December 2022, which includes 17 hospitals in China, including Children's Hospital of Fudan University, Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Children's Hospital affiliated to Shanghai Jiaotong University, Children's Hospital Affiliated to Zhejiang University Medical School, Children's Hospital of Soochow University, Ningbo Women and Children's Hospital, Children's Hospital of Wuxi City, the First Affiliated Hospital of Xiamen University, Xiamen Children's Hospital, Xi'an Jiaotong University Affiliated Children's Hospital, Shenzhen Children's Hospital, Anhui Children's Hospital, Henan Children's Hospital, Kaifeng Children's Hospital, Hunan Children's Hospital, Jiangxi Provincial Children's Hospital, and Kunming Children's Hospital.

The *K. pneumoniae* strains were consecutively collected from 2016 to 2022 in each hospital. The types of specimens included respiratory tract, blood, cerebrospinal fluid, urine, intestinal tract, pus, exudate, and various types of catheter tip specimens. Isolate inclusion and exclusion criteria of *K. pneumoniae* were performed stringently in each hospital according to unified standards. For the duplicated strains isolated from the same sample, only the first strain was included, and strains collected from different samples were all included for further study. Colonized strains which did not cause any clinical symptoms or diseases were excluded in this study.

Bacteria Identification and Antimicrobial Susceptibility Testing

All *K. pneumoniae* strains were identified by the matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS, Bruker, France). The antimicrobial susceptibility tests were carried out on the Vitek 2 compact system, using AST-GN13 commercial cards (bioMérieux, France). For the antimicrobials that were not covered in GN13 card, we performed Kirby–Bauer test (KB) to get the susceptibility. The antimicrobial susceptibility tests were conducted and interpreted according to the criteria of Clinical and Laboratory Standards Institute (CLSI) 2022.[4] *E. coli* ATCC 25922 was served as the quality control strain for susceptibility testing.

Statistical Analysis

The data were exported and subjected to antimicrobial susceptibility analysis using WHO-NET 5.6 software, a tool provided by the World Health Organization Bacterial Resistance Surveillance Network. Statistical analysis was conducted using GraphPad Prism 9.0 software (GraphPad Software, Boston, USA). Data were analyzed using the *t*-test, one-way ANOVA test, $\chi 2$ test or Fisher's exact test, $\chi 2$ trend test, as appropriate. A p-value of < 0.05 was considered statistically significant.

Results

K. Pneumoniae Strains Detected Over 7 Years

Between the years 2016 and 2022, a total of 26,613 strains were identified within the PICUs of various medical centers. Among these strains, *K. pneumoniae* accounted for 2588 (9.7%). *K. pneumoniae* ranked as the second most prevalent strain of Gram-negative bacteria following *Acinetobacter baumannii* and represented 8–11% of the total pathogens detected annually (Figure 1A). The number of *K. pneumoniae* detections fluctuated considerably in the years 2018–2019 but has been relatively stable over the last 3 years of the study period, with an average of approximately 330 strains

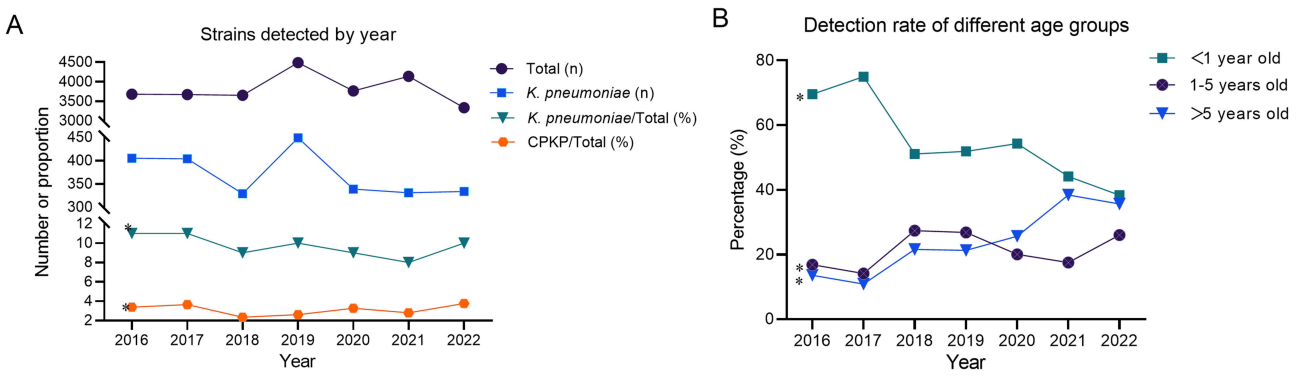

Figure 1 Distribution of *K. pneumoniae* strains detected by year. (**A**) The number of pathogens including *K. pneumoniae* strains detected by year and the percentage of *K. pneumoniae* and CRKP of the total. (**B**) The proportion of *K. pneumoniae* strains detected across age groups in children by year. *K. pneumoniae*, *Klebsiella pneumoniae*. CRKP, carbapenem-resistant *Klebsiella pneumoniae*. *The trend chi-square test result indicates P<0.05.

detected annually. The findings indicate a statistically significant linear increase in the detection rate of *K. pneumoniae* over the years (P < 0.001). Specifically, the overall detection rate of CRKP was 3.1%, with a gradual rise from 2.5% in 2018 to 3.8% in 2022, showing a consistent linear trend (P < 0.05).

Among the 2588 *K. pneumoniae* strains analyzed, 1585 and 1003 were in male and female children, respectively. The distribution of detected strains across age groups was as follows: 1442 strains in the infant group (55.7%), 548 strains in the 1–5-year group (21.2%), and 598 strains in the > 5-year group (23.1%). The seasonal distribution of all the detected strains was represented by 561, 649, 710, and 668 strains in spring, summer, autumn, and winter, respectively, with no statistically significant differences observed among the seasons. The age distribution of *K. pneumoniae* detections across the years is depicted in Figure 1B. From 2016 to 2022, a gradual decline of *K. pneumoniae* detections from 65.6% to 38.3% was observed in infants (P<0.05). Conversely, the proportion of detections in children aged > 5 years rose from 13.6% to 35.6% (P<0.05).

Distribution of *K. Pneumoniae* Bacterial Strains

Most of the identified *K. pneumoniae* strains were sourced from multiple anatomical sites, including the respiratory tract, blood, urinary tract, pus, ascites, skin mucosa, catheters, digestive tract, cerebrospinal fluid, and other locations. The distribution of detections across these sites is illustrated in Figure 2A.

The lower respiratory tract, blood, and urinary tract were the primary sites where 71.1%, 8.6%, and 7.1%, respectively, of the total identified *K. pneumoniae* strains were detected. The percentage of *K. pneumoniae* detections in the respiratory tract decreased from 81.4% to 67.4% over the past 5 years (Figure 2B). In contrast, the detection rate of blood and urinary tract has steadily increased over the years.

The examination of specimen sources of *K. pneumoniae* infections across various age groups (Figure 2C) revealed a consistent distribution of common infection sites. The respiratory tract, blood, and urinary tract were predominant sites and collectively accounted for more than 80% of the cases. Notably, a slightly higher *K. pneumoniae* detection rate was observed in the lower respiratory tract (76.8%) of infants than in children older than 1 year (62.6–65.2%). Conversely, the *K. pneumoniae* detection rate in the blood (7.2%) and urinary tract (5.2%) were slightly less in children > 1 year of age than in children in other age groups.

Resistance Rates of *K. Pneumoniae* to Common Antibiotics

The resistance rates of *K. pneumoniae* to various antibiotics are depicted in Table 1 and Figure 3. While the resistance rates of cefuroxime and cefotaxime exhibit a linear decreasing trend (P<0.05), it is noteworthy that the majority of second- and third-generation cephalosporins displayed resistance rates to *K. pneumoniae* that surpassed 50%. The resistance rate to beta-lactamase inhibitor combination therapies such as cefoperazone/sulbactam declined from 51.7% in 2018 to 12.2% in 2021, followed by an increase to 25.7% in 2022. In contrast, the resistance rate to ceftazidime/avibactam over the past 3 years

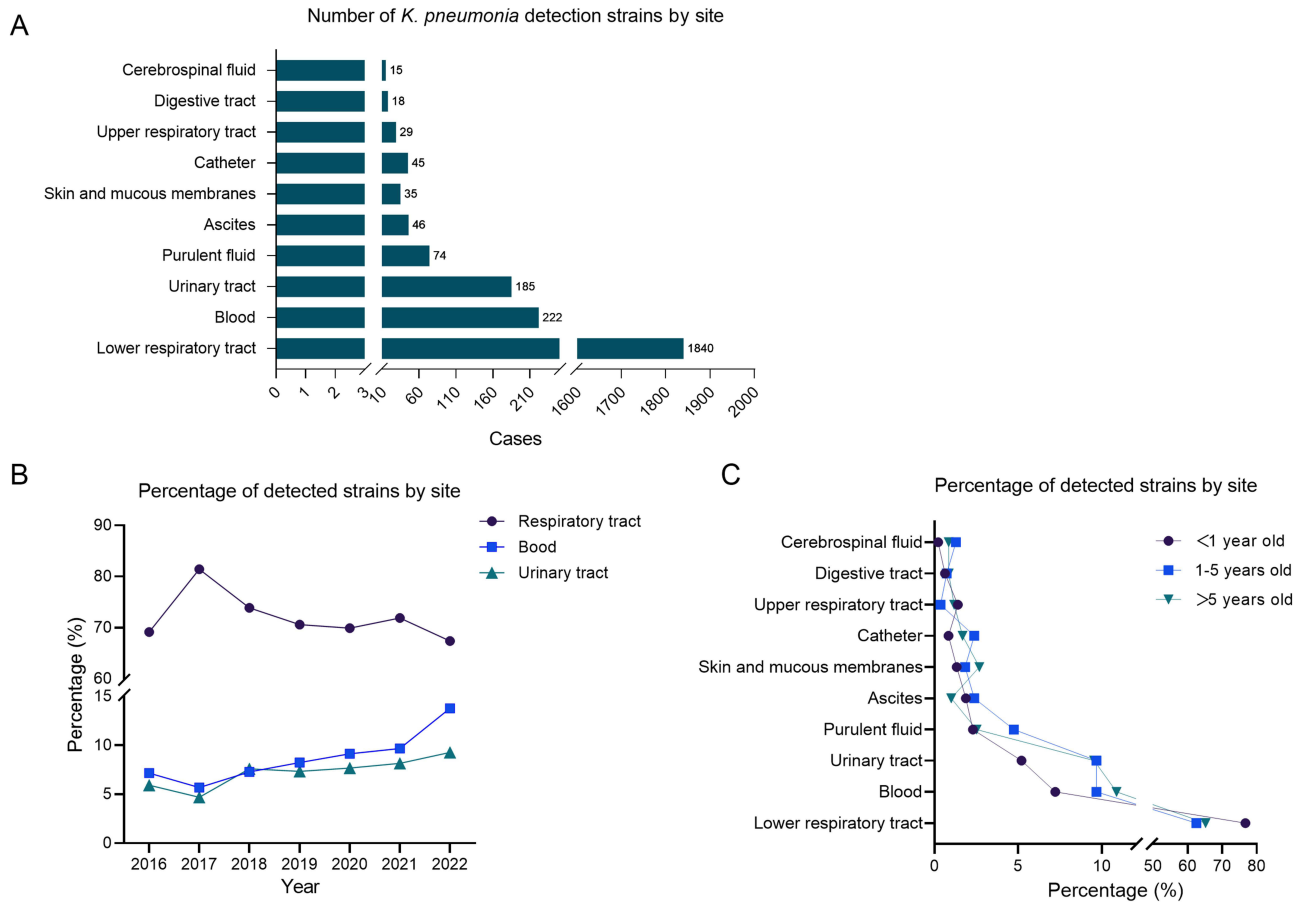

Figure 2 Distribution of *K. pneumoniae* infection sites. (**A**) The main *K. pneumoniae* site distribution was detected across all years. (**B**) The percentage of *K. pneumoniae* detected in the most common sites of infection (respiratory tract, blood, and urinary tract) by year. (**C**) The distribution of infection sites for *K. pneumoniae* strains detected in children across age groups. *K. pneumoniae, Klebsiella pneumoniae.*

ranged from 9.1% to 20.8%, a range significantly lower than that of other cephalosporins. The resistance rate of *K. pneumoniae* to penicillin drugs—specifically ampicillin—was above 92%–95%. The resistance rate of amoxicillin-clavulanate showed a linear downward trend over 7 years (P<0.05), decreasing from 70% to 48%. Over the last 3 years of the study period, the resistance rate to piperacillin/tazobactam was approximately 31%–33%. The resistance rate of *K. pneumoniae* to carbapenem antibiotics exhibited a consistent linear increase (P<0.05), rising steadily from 36.75% in 2016 to 38.6% in 2022. *K. pneumoniae*'s resistance rates to the three commonly used carbapenems were ranked as follows: meropenem > imipenem > ertapenem. In recent years, a gradual increase from 14.8% to 35.2% has been observed in the resistance rate to ertapenem. *K. pneumoniae*'s resistance rates to the three carbapenems were similar and ranged from 33% to 40%. Over the last 5 years of the study period, the resistance rate of *K. pneumoniae* to levofloxacin gradually decreased, declining from 41.6% in 2016 to 25.7% in 2022. Despite the slight decrease in the resistance rates to moxifloxacin and ciprofloxacin in 2022, these rates remained high at 63.8% and 44.6%, respectively. *K. pneumoniae*'s resistance rate to amikacin declined notably, decreasing from 29.1% in 2016 to 9.1% in 2022. *K. pneumoniae* had heightened sensitivity to polymyxin B, polymyxin E, and tigecycline, with resistance rates all below 10%. However, in more recent years, the resistance rates to polymyxins and tigecycline fluctuated significantly. Specifically, in 2022, the resistance rate to polymyxin B reached 3.8%, surpassing the 1.2% resistance rate for tigecycline. The resistance rate of *K. pneumoniae* to colistin fluctuated between 18% and 27%, showing a gradual upward trend in recent years.

Table 1 Resistance of *K. Pneumoniae* to the Commonly-Used Antimicrobials (%)

Antimicrobials	2016 (n=405)		2017 (n=404)		2018 (n=329)		2019 (n=429)		2020 (n=339)		2021 (n=331)		2022 (n=334)		Total (n=2591)	
	RR* (%)	SR* (%)	RR (%)	SR (%)	RR (%)	SR (%)	RR (%)	SR (%)	RR (%)	SR (%)	RR (%)	SR (%)	RR (%)	SR (%)	RR (%)	SR (%)
Ampicillin	92.4	1.6	93.2	1.2	95.6	1.7	95.6	1	92.3	1	93	1.4	95.7	0	93.8	1.2
Piperacillin	90.7	6.2	77	16.3	94.4	5.6	80.9	15.6	71.4	27.3	76.1	21.6	64.9	33.8	80.5	16.5
Cefazolin	79.8	4.8	78.1	8	81.3	9.4	83.8	8.2	73.7	13.7	75.1	16.9	77	18	79.1	10
Cefuroxime	82.8	16.1	74.7	23.6	82.6	17.4	77	20.3	64.6	34.2	70.5	28.1	71.7	28.3	74.8	24
Ceftazidime	53.7	43.6	47.6	46.8	55.8	39.9	56.3	41.9	54.9	42.5	52	43.5	54.7	42.8	53.5	43.1
Ceftriaxone	59.3	40.7	63.8	35.6	68.7	31.3	70.2	29.5	66.6	33.1	68.4	31.6	72.5	27.5	67	32.8
Cefotaxime	92	5.3	81.2	13.4	82.8	15.6	77.1	22	66.7	31.4	70.9	27.6	61.8	36	76.7	21.1
Cefepime	52.3	43.7	45.7	48.5	55.2	41.5	51.5	45.2	49.6	47.2	48.6	48.3	52.2	45	50.7	45.6
Amoxicillin/clavulanic acid	69.9	16.5	65.5	20.7	64	21.3	60.7	26.5	40.3	38.3	50.4	33.1	48	39.8	53.8	31
Ampicillin/Sulbactam	70.4	26.2	66	28.5	75.1	20.8	76.7	20.6	68	28.8	67.1	27.3	69.6	26.9	70.6	25.4
Ticarcillin/clavulanic acid	60	33.3	61.5	15.4	100	0	62.1	31	75.9	17.2	75.9	10.3	44.7	52.6	63	28.6
Piperacillin/Tazobactam	32.4	63.1	29.3	66.3	44.8	53.4	37.7	56.4	32.2	59.8	31.4	61.3	33.9	59.1	34.4	60.2
Cefoperazone/Sulbactam	43.9	33.3	41.1	43.8	51.7	34.9	30.3	22.9	19.5	21	12.2	18.5	25.7	18.5	30.8	26.5
Ceftazidime/Avibactam	/	/	/	/	/	/	/	/	13.9	86.1	20.8	79.2	9.1	90.9	15.6	84.4
Aztreonam	53.2	43.7	51.6	47.6	57.6	41.1	57.6	41.7	58.5	41.5	54.8	45.2	55.8	43	55.4	43.6
Ertapenem	14.8	82.5	17	80.8	33.3	64.7	20.8	76.3	18.9	80.8	20.3	79.7	35.2	64.8	22.3	76.2
Imipenem	26.9	72.1	25.5	73	40.4	59	39.4	59.7	27.7	71.1	27.7	71.4	33.8	65	31.6	67.3
Meropenem	44.1	55	38.4	61.2	47.8	51.5	48.5	50.6	35.2	63.7	33.1	66.5	40.2	59.8	41.8	57.6
Amikacin	15.9	84.1	14.7	85.1	29.1	70.6	21.8	78.2	14.4	85.6	13.4	86.3	9.1	90.6	16.9	82.9
Gentamicin	40.7	59.3	30.6	68.6	41.8	56	40.8	57.9	27	71.6	22.6	74.7	24.7	74.4	34.1	64.7
Tobramycin	13.9	66.4	15.2	66.9	15.7	74.4	22.7	65.5	18.5	73	23.3	59.4	20.5	64	18	67.1
Ciprofloxacin	36.1	43.9	42.4	44.2	56.8	30.1	50.6	37.3	50.8	39.7	59.6	28.3	46.2	40.2	47.8	38.4
Levofloxacin	24.4	41.1	21.5	41.2	41.6	26.3	32.8	32.5	30.1	39.2	35.3	32.4	29	34.6	30.4	35.6
Moxifloxacin	77.8	0	78.6	0	76	0	78.9	5.6	75	18.2	90.3	8.3	63.8	29.3	77.8	8.5
Cotrimoxazole	47.2	41.2	37.9	42.2	45.7	37.2	46.4	43.5	34.2	53.1	43.8	51.1	52.7	44.1	43.9	44.5
Phosphomycin	18	75.3	19.3	71.9	27.3	62.2	15.5	79.9	17.1	78	18.1	81	25	69.6	19.9	74.1
Polymyxin B	0	100	0	100	1.3	98.7	2.2	97.8	0	100	0	100	3.8	96.2	1	99
Chloramphenicol	58.5	41.5	45.6	45.6	41.7	54.2	21.1	71.9	12.5	70.8	26.7	73.3	30.8	69.2	37.2	58.1
Doxycycline	/	/	/	/	100	0	57.1	42.9	50	50	62.3	37.7	61.1	38.9	60.3	39.7
Minocycline	/	/	/	/	100	0	27.6	37.9	29.3	46.3	43.7	33.8	24.5	54.7	33.7	42.3
Tetracycline	42.5	57.5	41.4	58.6	50.9	49.1	48.4	48.4	49.4	50.6	56.3	39.1	49.3	50.7	48.4	50.2
Tigecycline	5.8	73.1	4.7	90.6	0	98	2.2	91.8	2.7	92.6	1	95.6	1.2	97	2	93.3

Abbreviations: *RR, resistance rate. SR, susceptibility rate. "/", no relevant data available.

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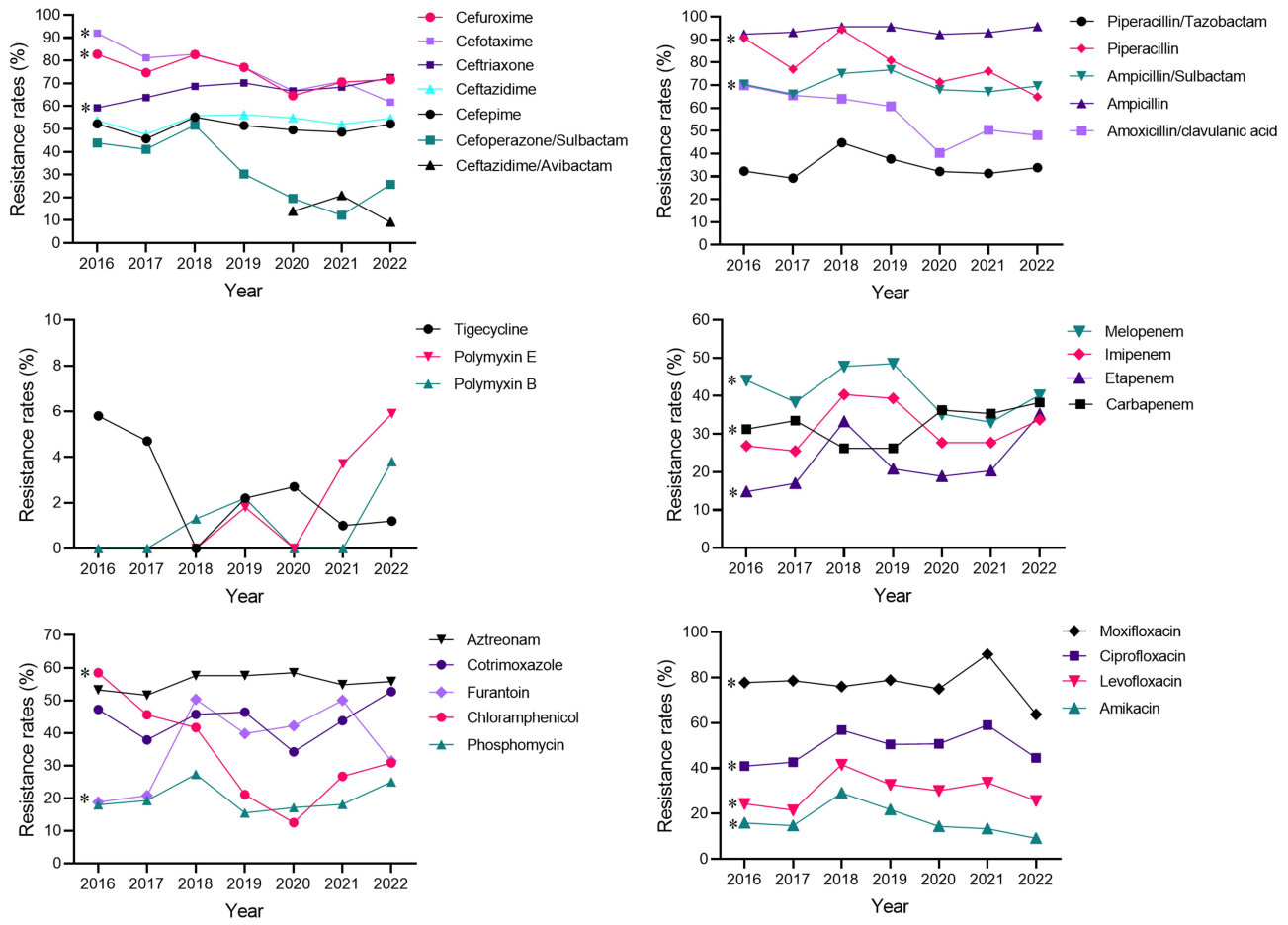

Figure 3 Antimicrobial resistance trends of *Klebsiella pneumoniae* to commonly used antibiotics from 2016 to 2022. *The trend chi-square test result indicates P<0.05.

Analysis of Cross-Resistance in *K. Pneumoniae*

The resistance rates of *K. pneumoniae* strains between 2016 to 2022 were categorized in ascending order; 15 antibiotics exhibited the lowest resistance rates (Figure 4A). The resistance rates of *K. pneumoniae* to all the antibiotics except for polymyxin and tigecycline exceeded 10%. To guide clinical medication, a comprehensive analysis of cross-resistance in *K. pneumoniae* among several antibiotics was conducted. We examined the resistance of strains that were categorized as either sensitive or resistant to meropenem or other frequently employed antibiotics using sensitivity and resistance to meropenem as the independent variable (Figure 4B). Strains with intermediate susceptibility were not included in the analysis. In total, 41% of the strains demonstrated sensitivity to both polymyxin B and meropenem, whereas 56% of the strains were resistant to meropenem but sensitive to polymyxin B. A mere 1% of strains were resistant to polymyxin B but sensitive to meropenem. In contrast to polymyxin B, meropenem exhibited a specific degree of co-resistance with tigecycline (2%), amikacin (27%), levofloxacin (41%), and fosfomycin (37%). Additionally, 16% of strains were resistant to both imipenem and meropenem, whereas 3–7% of strains were resistant to one of imipenem and meropenem.

Discussion

This study presents novel findings regarding the prevalence and dynamics of *K. pneumoniae* resistance across multiple PICUs in China. With a detection rate of 8%–11%, *K. pneumoniae* consistently maintained its position within the top three isolated Gram-negative strains from 2016 to 2020. This finding is comparable to the 14.7% detection rate[5] that was observed in large-scale studies of adults but falls below the prevalence reported for children and neonates in China between 2014 and 2017 (16.8–19.8%).[1] These results suggest that *K. pneumoniae* has emerged as a significant pathogen in pediatric infections. Among the children affected by *K. pneumoniae* infections, infants accounted for 55.7%. The

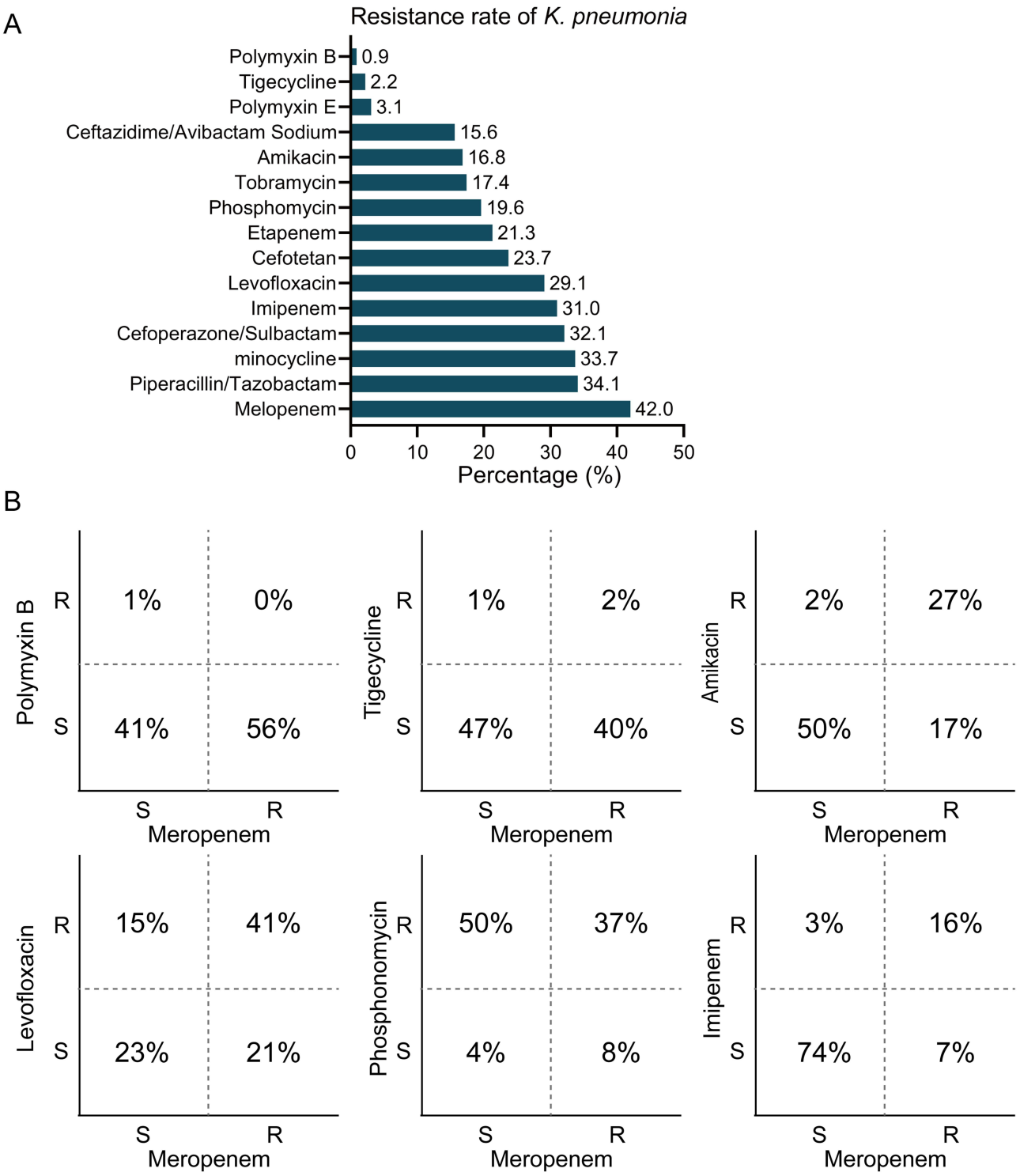

Figure 4 Cross-resistance of *K. pneumoniae* to meropenem and other antibiotics. (**A**) Summary of the 15 antibiotics with the lowest resistance rates in *K. pneumoniae*. (**B**) Summary of the cross-resistance of the same strain to different antibiotics using sensitivity tests. The proportion of intervals in which the strain was resistant to one antibiotic and sensitive to another was calculated. *K. pneumoniae, Klebsiella pneumoniae*. S, sensitive; R, resistant.

primary origins of *K. pneumoniae* strains that were obtained from adult were blood (28.4%), lower respiratory tract (21.8%), wounds (21.3%), and urine (14.7%),[5] however the primary sites for detecting *K. pneumoniae* in the PICUs were the lower respiratory tract (71.1%), blood (8.6%), and urinary tract (7.1%), indicating significant differences compared with adults.

K. pneumoniae demonstrated varying levels of resistance to commonly used antimicrobial agents. The three agents with the lowest antibiotic resistance rates were polymyxin B, tigecycline, and polymyxin E, all of which exhibited resistance rates below 10%. Currently, polymyxin B and tigecycline are considered last-resort therapeutic options for the management of CRKP infections.[6] However, clinicians must consider various factors, including nephrotoxicity, attainable in vivo plasma concentrations, and the emergence of resistance during treatment. Notably, a study in adults indicated that treatment failure may still occur despite the susceptibility of isolates to tigecycline. Within this study, resistance to polymyxin E and polymyxin B gradually increased from 2016 to 2022, evolving from complete sensitivity to resistance rates of 5.9% and 3.8%, respectively. These figures closely align with the reported 5.02% resistance rate for polymyxins in adults.[7] Colistin remains the second-line option for CRKP.[8] Recent reports have indicated that initiating polymyxin B combination therapy within 48 hours of a CRKP bacteremia diagnosis significantly enhances bacterial clearance rates (65.22% vs 29.41%, p = 0.02) and reduces 30-day mortality (39.13% vs 70.59%, p = 0.02) compared with delaying administration over 48 hours.[9] The resistance rate to tigecycline gradually declined from 5.8% in 2016 to 1.2% in 2022. Analysis of CRKP resistance to other antibiotics over 7 years demonstrated that CRKP remained fully susceptible to polymyxin B, whereas the cross-resistance rate to tigecycline was 2%, close to the reported resistance rates of 4%[10]–4.24%[11] of CRKP to tigecycline in adults.

Carbapenems have been identified as the most potent β-lactam antibiotics for the treatment of *Enterobacteriaceae* infections. However, in recent years, invasive iatrogenic procedures and the increased prevalence of irrational antimicrobial drug usage in clinical settings have led to a significant rise in the resistance of *K. pneumoniae* to carbapenem antibiotics. A Chinese monitoring study that spanned 16 years revealed a continuous increase in the resistance rate of *K. pneumoniae* to imipenem and meropenem. Specifically, the resistance rates for imipenem and meropenem rose from 3.0% and 2.9%, respectively, in 2005 to 23.2% and 24.2%, respectively, in 2020.[12] Over 3 years, a consistent annual increase was observed in the resistance rates of *K. pneumoniae* to three antibiotics. Specifically, the resistance rate of ertapenem rose from 14.8% to 35.2%, and the resistance trends of meropenem, ertapenem, and imipenem showed similar increasing resistance rates (from 33.1%, 18.9%, and 27.7% in 2020 to 40.2%, 35.2%, and 33.8% in 2022, respectively). These resistance rates surpassed those reported in previous studies in adult populations.[12] CRKP has two primary resistance mechanisms: the synthesis of carbapenemases such as KPC, NDM, VIM, IMP, and OXA-48 for carbapenem hydrolysis and the synthesis of extended-spectrum β-lactamases or AmpC enzymes combined with structural mutations. The first mechanism predominantly contributes to CRKP's resistance to carbapenems. Resistance genes can disseminate across diverse bacterial strains via conjugation, transformation, and transduction and drive a gradual escalation in resistance rates.[13,14] According to China's national monitoring, the prevalence of CRKP rose from 3.2% in 2011 to 7.6% in 2015.[15] CRKP has been documented as the cause in 55.0% of carbapenem-resistant *Enterobacteriaceae* (CRE) cases in children;[16] NDM was the predominant carbapenemase (67.6%), followed by KPC (26.4%). Multicenter studies in adults have indicated that CRKP is responsible for 66.7%[17]–77.0%[18] of CRE cases, whereas 77%[17]–90.8%[7] of CRKP cases were found to be KPC producers. The study findings indicate that the detection rate of CRKP in PICUs ranged from 2.4% to 3.8%, with a progressive increase in the proportion of *K. pneumoniae* detected annually (ie, from 26.2% in 2019 to 38.3% in 2022). Reports have indicated that adult patients in the intensive care unit who carry *K. pneumoniae* strains have a proportion of CRKP as high as 54%.[19]

This study revealed a gradual decline in the resistance rates to amoxicillin/clavulanic acid over the years (ie, from 69.9% in 2016 to 48.0% in 2021). In contrast, the resistance rates to piperacillin/tazobactam remained relatively stable at approximately 33.0% over 7 years, lower than the rates reported in adults (71.4% and 84.9%,[5] respectively). Furthermore, the resistance rates of *K. pneumoniae* to cefotaxime, cefuroxime, and ceftriaxone all exceeded 60%. The resistance rate to ceftriaxone grew consistently over the years, reaching a level comparable to that of cefotaxime and cefuroxime by 2022. The relatively stable resistance rates of ceftazidime and cefepime of approximately 50% over 7 years may be attributable to their frequent empirical usage in clinical settings. Notably, the resistance rate of cefoperazone-sulbactam, among the enzyme inhibitor combination formulations, experienced an overall decline from 43.9% in 2016 to 12.2% in 2021, before experiencing a subsequent increase to 25.7% in 2022, which may be associated with the usage rate of cefoperazone-sulbactam in clinical practice.

Ceftazidime-avibactam (CAZ-AVI) is a novel combination of a beta-lactam antibiotic and a beta-lactamase inhibitor that has gained significant usage in clinical settings for the targeted treatment of challenging Gram-negative infections caused by carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp), OXA-48-producing *Enterobacterales*, and

difficult-to-treat *Pseudomonas aeruginosa*.[20] Since its development, CAZ-AVI has been used extensively in clinical practice, and initial clinical studies have demonstrated its favorable clinical and antimicrobial effectiveness.[21,22] A review by Burcu Isler suggested that CAZ-AVI is the most effective treatment option for OXA-48-producing CRKP.[8] In adults, studies that have examined the treatment of infections caused by KPC-Kp strains indicate no significant difference in mortality rates between patients who were treated solely with CAZ-AVI and those who received combination regimens (26.1% vs 25.0%).[23] Additionally, extending the infusion time of CAZ-AVI to a minimum of 3 hours can improve survival outcomes.[23] CAZ-AVI is well tolerated in newborns and children under 5 years of age,[24] however, real-world studies on pediatric *K. pneumoniae* infections are scarce, and many studies have reported the emergence of resistance.[25–27] A multicenter study in adults revealed a 3.7% resistance rate of CRKP to CAZ/AVI.[28] However, on the basis of data collected between 2019 and 2022, this study indicated that the resistance rate of *K. pneumoniae* to CAZ-AVI ranged from 9.1% to 20.8%. Although this rate is significantly more favorable than that observed with other enzyme inhibitor combination formulations, it remains considerably higher than the resistance rate reported in adults. This phenomenon may be attributed to the composition of the PICU participants in this study, who tended to require longer antibiotic use and more frequent invasive procedures.

K. pneumoniae had a relatively elevated sensitivity toward aminoglycosides and fluoroquinolones, although a declining trend has been observed in recent years. Specifically, the resistance rates for amikacin and levofloxacin in 2022 were 9.1% and 25.7% respectively, deviating significantly from the rates reported among adult populations.[5] However, the clinical use of these two drug classes is highly restricted in young children. Fosfomycin is a bactericidal antibiotic that is commonly used for simple urinary tract infections caused by sensitive bacteria.[29] The efficacy of fosfomycin against multidrug-resistant bacteria has been established in recent years, making it a recommended alternative for the treatment of CRKP infections.[30] This study revealed a gradual rise in fosfomycin resistance (ie, within the 18–27% range) among *K. pneumoniae*s. Moreover, the cross-resistance rate between meropenem and fosfomycin reached 37%, thus discouraging the use of these agents for CRKP infections in the PICUs.

Given the limited medication choices available for children, this population faces significant constraints. Carbapenem antibiotics are the ultimate therapeutic option for managing infections induced by Gram-negative multidrug-resistant bacteria. The escalating prevalence of CRKP infections imposes a substantial financial strain on patients and amplifies mortality rates among afflicted individuals. This predicament represents a formidable obstacle to pediatric anti-infection therapies and constitutes a significant global public health concern. This study aimed to assess the potential cross-resistance of the widely used carbapenem antibiotic meropenem with other antibiotics. The objective was to predict the resistance patterns of alternative antibiotics in cases in which initial treatment with meropenem was ineffective. The findings indicated the differing likelihood for *K. pneumoniae* strains that are resistant to meropenem to exhibit resistance to other antibiotics. Specifically, the cross-resistance rates were as follows: polymyxin B (0%), tigecycline (2%), imipenem (16%), amikacin (27%), fosfomycin (37%), and levofloxacin (41%). Hence, using carbapenems in conjunction with other antimicrobial agents is advised for the management of infections caused by multidrug-resistant strains, as substantiated by combined drug susceptibility findings. Prior research has demonstrated the efficacy of treating CRKP infections with combination therapy that involves tigecycline and polymyxin or carbapenems in conjunction with aminoglycosides.[31] Hence, using carbapenems in conjunction with other antimicrobial agents for the management of infections caused by multidrug-resistant strains is recommended, as substantiated by combined drug susceptibility findings.

This article is a comprehensive examination and evaluation of the resistance patterns exhibited by *K. pneumoniae* strains in multi-center PICUs in China over 6 years. The study findings are pivotal for elucidating the distribution characteristics of *K. pneumoniae* strains and the alterations in antibiotic-resistant bacteria within PICUs. Moreover, the outcomes of this research offer valuable guidance for the appropriate clinical use of antibiotics.

Conclusions

In summary, *K. pneumoniae*'s clinical isolation rate in Chinese PICUs has been growing consistently over the years, and the similarly growing annual *K. pneumoniae* resistance rates require close attention. The main site of *K. pneumoniae* infection is the respiratory tract, and the resistance rates to meropenem and imipenem have risen over the years. Given the high antibiotic resistance identified in the study, using antibiotics rationally and strictly implementing clinical

management strategies for antimicrobial drugs are essential for curbing the emergence of bacterial resistance in PICUs and reducing nosocomial infections.

Abbreviations

CHIPS, China paediatric Intensive care Unit Pathogen Surveillance Network; *K. pneumoniae*, Klebsiella pneumoniae; PICU, Pediatric intensive care unit; CRKP, Carbapenem-resistant Klebsiella pneumoniae strains; CRE, Carbapenem-resistant Enterobacteriaceae; CAZ-AVI, Ceftazidime-avibactam; KPC-Kp, Carbapenemase-producing Klebsiella pneumoniae.

Data Sharing Statement

Data and materials used in this work are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

This was a retrospective analysis and all data were obtained anonymously through an electronic medical record information system. The study was approved by the Ethics Committee of the Children's Hospital of Fudan University, and the requirement for informed consent was waived (approval number [2021] 431). This study was in compliance with the Declaration of Helsinki.

Consent for Publication

All authors gave consent for publication.

Collaborators

Members and affiliations of China Paediatric Intensive care Unit Pathogen Surveillance Network (CHIPS)

Panpan Fan[1], Pan Fu[2], Jing Liu[1], Xiaolei Zhang[1], Yixue Wang[1], Yingying Zhang[1], Ting Zhu[1], Caiyan Zhang[1], Chuanqing Wang[2], Guoping Lu[1], Gangfeng Yan[1], Hong Ren[3], Juanzhen Li[3], Yucai Zhang[4], Yiping Zhou[4], Chengmei Zhang[5], Zhenjie Chen[5], Mingming Zhou[5], Zhengjiang Bai[6], Saihu Hang[6], Lili Hang[6], Hehe Chen[7], Yao Zheng[7], Qunying Chen[7], Pengwei Zhu[8], Yong Li[8], Yan Xu[8], BiZhen Zhu[9], Huixuan Shi[9], Shaoxian Hong[10], Yukun Huang[10], Meilian Huang[10], Danqun Jing[11], Wenjia Tong[11], ChengYu Zhang[11], Weiguo Yang[12], Weike Mang[12], Qing meng[12], Yibing Cheng[13], Qunqun Zhang[13], Kaijie Gao[13], Huiming Xu[14], Yuxia Li[14], Hanghai Ding[14], Xiulan Lu[15], Jiaotian Huang[15], Jianlong Liu[15], Yourong Zhu[16], Yuanyuan Chen[16], Shufang Xiao[17], Juan He[17], Li Jiang[17], Jianli Chen[18], Yi Lin[18], Jia Lei[18]

Affiliations

1 Department of Pediatric Intensive Care Unit, Children's Hospital of Fudan University, National Center for Children's Health, Shanghai, People's Republic of China
2 Clinical Microbiology Laboratory, Department of Nosocomial Infection Control, Children's Hospital of Fudan University, National Center for Children's Health, Shanghai, People's Republic of China
3 Department of Pediatric Intensive Care Unit, Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
4 Department of Pediatric Intensive Care Unit, Shanghai Children's Hospital affiliated to Shanghai Jiaotong University, Shanghai, People's Republic of China
5 Department of Pediatric Intensive Care Unit, Children's Hospital Affiliated to Zhejiang University Medical School, Hangzhou, People's Republic of China
6 Department of Pediatric Intensive Care Unit, Children's Hospital of Soochow University, Suzhou, People's Republic of China
7 Department of Pediatric Intensive Care Unit, Ningbo Women and Children's Hospital, Ningbo, People's Republic of China
8 Department of Pediatric Intensive Care Unit, Wuxi Children's Hospital, Wuxi, People's Republic of China
9 Department of Pediatric Intensive Care Unit, The First Affiliated Hospital of Xiamen University, Xiamen, People's Republic of China

10 Department of Pediatric Intensive Care Unit, Xiamen Children's Hospital, Xiamen, People's Republic of China
11 Department of Pediatric Intensive Care Unit, Anhui Children's Hospital, Hefei, People's Republic of China
12 Department of Pediatric Intensive Care Unit, Shenzhen Children's Hospital, Shenzhen, People's Republic of China
13 Department of Pediatric Intensive Care Unit, Henan Children's Hospital, Zhengzhou, People's Republic of China
14 Department of Pediatric Intensive Care Unit, Kaifeng Children's Hospital, Kaifeng, People's Republic of China
15 Department of Pediatric Intensive Care Unit, Hunan Children's Hospital, Changsha, People's Republic of China
16 Department of Pediatric Intensive Care Unit, Jiangxi Provincial Children's Hospital, Nanchang, People's Republic of China
17 Department of Pediatric Intensive Care Unit, Kunming Children's Hospital, Kunming, People's Republic of China
18 Department of Pediatric Intensive Care Unit, Guiyang Children's Hospital, Guiyang, People's Republic of China

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Disclosure

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