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ORIGINAL RESEARCH

Antimicrobial Susceptibility Trends Among Gram-Negative Bacilli Causing Bloodstream Infections: Results from the China Antimicrobial Resistance Surveillance Trial (CARST) Program, 2011–2020

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Purpose: The antimicrobial resistance profiles of gram-negative bacilli causing bloodstream infections have changed over time, while comprehensive and real-time surveillance data are limited in China. This study aimed to review the antimicrobial susceptibility trends among main gram-negative bacilli isolated from blood specimens in China.

Methods: From 2011 to 2020, a total of 4352 non-duplicate isolates were collected from 21 tertiary hospitals in 18 provinces or cities across China. Antimicrobial susceptibility testing was conducted by the agar dilution method recommended by the Clinical and Laboratory Standards Institute (CLSI), and the results were interpreted using CLSI criteria.

Results: During this 10-year surveillance period, meropenem and imipenem were the most effective agents against *Escherichia coli* (resistance remaining <5%). The proportion of ESBL-producing isolates in carbapenem-susceptible *E. coli* displayed a decreasing trend (from 72.9% to 51.2%). The resistance rates of *Klebsiella pneumoniae* to meropenem and imipenem increased from 3.3% and 1.6% in the 2011–12 period to 15.0% and 15.4% in the 2019–20 period, respectively. Carbapenems and amikacin were the most active agents against *Enterobacter cloacae*. The resistance rates of *Pseudomonas aeruginosa* to meropenem and imipenem increased from 13.1% and 17.7% in the 2015–16 period to 24.5% and 21.0% in the 2019–20 period, respectively. Few agents showed activity against *Acinetobacter baumannii*. The frequency of imipenem-non-susceptible *A. baumannii* remained stable (remaining ~70%).

Conclusion: The rapid spread of carbapenem-resistant *K. pneumoniae* has been serious in recent years. Conversely, the prevalence of ESBL-producing isolates was decreased. Carbapenems are still effective against gram-negative bacilli causing BSIs, except for *A. baumannii*. More attention should be given to *A. baumannii*, considering its high resistance against different classes of antimicrobials.

Keywords: *Enterobacterales*, *P. aeruginosa*, *A. baumannii*, ESBL, carbapenem-resistance

Introduction

Bloodstream infection (BSI) is one of the most common infectious diseases in hospital practice. It can progress to sepsis due to patient- or pathogen-related factors,[1,2] which is associated with extended hospitalization, significant health-care costs, and an increase in mortality.[3,4] Although the spectrum of pathogens causing BSIs is everchanging and varies from region to region, the importance of gram-negative bacilli has increased substantially in recent years.[4,5] The initial antimicrobial options to treat BSIs are driven mainly by an understanding of these pathogens.

Globally, the rapid spread of antimicrobial resistance among gram-negative bacilli has become a serious threat to public health. To deal with this challenge, broad-spectrum antimicrobials such as third-generation cephalosporins and carbapenems have been overprescribed repeatedly, leading to a vicious cycle with further accumulation of selective resistance profiles.[6,7] Patients who develop BSIs caused by extended-spectrum β-lactamase [ESBL]-producing *Enterobacteriaceae*, carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, have limited

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therapeutic options.[8,9] Several studies have demonstrated that these pathogens were the main reasons for the high mortality in BSI.[5,10,11] To understand the extent of the resistance problem and thus stem the tide of BSIs, continuously monitoring trends in antimicrobial resistance among BSI pathogens is of great importance.

The national surveillance program of China Antimicrobial Resistance Surveillance Trial (CARST) was established by the Institute of Clinical Pharmacology, Peking University, to monitor the antimicrobial activities of broad-spectrum agents and the antimicrobial resistance trends among clinical isolates in China. Currently, there are 20 tertiary teaching hospitals from 18 major cities throughout China selected as CARST monitoring sites. These hospitals were representative of nationwide circumstances, based on geographical distribution, medical skill, and the development level of microbiological diagnostic techniques.[12] We previously reported the antimicrobial resistance trends in *Enterobacteriaceae* isolated from blood in 2004 to 2014 and bacterial susceptibility in bloodstream infections in 2015–2016.[13,14] In this study, we report on the antimicrobial susceptibility trends among main gram-negative bacilli isolated from blood specimens from the CARST program between 2011 and 2020.

Materials and Methods

Antimicrobial Agents

Meropenem was purchased from Sumitomo Pharmaceuticals Co., Ltd. (Suzhou, China); imipenem and ertapenem were from Merck and Co., Inc. (Elkton, VA, USA); ampicillin was from INALCO Company (Milan, Italy); piperacillin was from TargetMol Company (Boston, MA, USA); cefepime was from Bristol-Myers Squibb (Shanghai, China); aztreonam was from Shanghai SPH New ASIA Pharmaceutical Co., Ltd. (Shanghai, China); ciprofloxacin was purchased from Shangyu Jingxin Pharmaceutical Co., Ltd. (Hangzhou, Beijing); colistin was from Sigma-Aldrich (Saint Louis, MO, USA); sulbactam was from Guangzhou Baiyunshan Pharmaceutical Co., Ltd. (Guangzhou, China); all other antibiotics were from the National Institute for Food and Drug Control (Beijing, China). Tazobactam was tested in combination with piperacillin at a fixed concentration of 4 μg/mL. Ampicillin-sulbactam were tested in a ratio of 2:1. Cefoperazone-sulbactam were in a ratio of 2:1.

Bacterial Isolates

A total of 4352 non-duplicate BSI isolates, including *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, P. aeruginosa* and *A. baumannii*, were collected from 21 tertiary hospitals (18 in 2011–12; 19 in 2013–14; 18 in 2015–16; 20 in 2017–18; and 20 in 2019–20, with one or two hospitals added or removed from surveillance during the study period) in 18 provinces or cities across China in 2011 to 2020 as part of the CARST program. All isolates were collected biennially by the CARST program over five consecutive 2-year periods (2011–12; 2013–14; 2015–16; 2017–18; and 2019–20) and were sent to a central laboratory (Institute of Clinical Pharmacology, Peking University First Hospital). All bacteria were isolated from the blood samples of patients. Species were identified by the Analytical Profile Index system (API 20E, 20NE [bioMérieux]).

Antimicrobial Susceptibility Testing

MICs were determined by the agar dilution method, with the exception of colistin, which was determined by the broth microdilution method.[15] The interpretative breakpoint criteria were in accordance with those recommended by the Clinical and Laboratory Standards Institute (CLSI) guidelines.[16] Bacterial suspensions were obtained by inoculation with 10^4 CFU of each bacterium via a multipoint inoculator. Disc diffusion was performed to identify ESBL-producing isolates among *E. coli* and *K. pneumoniae*, as recommended by CLSI.[16] If the cefotaxime (30 μg) zone was ≤27 mm or the ceftazidime (30 μg) zone ≤22 mm, ESBL production was defined as a ≥5 mm increase in a zone diameter for cefotaxime (30 μg) or ceftazidime (30 μg) tested in combination with clavulanic acid (10 μg) compared to the zone diameter of the agent when tested alone. Isolates of *P. aeruginosa* and *A. baumannii* were classified as imipenem-susceptible (IPM-S, MIC ≤2 μg/mL) and imipenem-non-susceptible (IPM-NS, MIC >2 μg/mL). *E. coli* ATCC (American Type Culture Collection) 25922, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853 were used as quality control reference strains.

Data Analysis

All data, including patient and microbiological information, were analyzed using Statistical Package for the Social Sciences 26.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Distribution of Isolates

Among the 4352 BSI gram-negative bacilli collected from 2011 to 2020, the most common pathogens overall were *E. coli* (1655), followed by *K. pneumoniae* (1074), *A. baumannii* (723), *P. aeruginosa* (622) and *E. cloacae* (278). The majority of isolates came from non-intensive care patients (*E. coli*, 88.3%; *K. pneumoniae*, 79.9%; *E. cloacae*, 82.7%; *P. aeruginosa*, 77.2%; and *A. baumannii*, 50.1%).

Changes in Antimicrobial Susceptibility of *E. coli*

During the 10-year study period, the susceptibility profiles for *E. coli* remained stable for most antibiotic agents (Table 1). Carbapenems and amikacin were still the most effective agents against *E. coli* (susceptibility remaining >95%). From 2011–12 to 2019–20, the MIC_{50} and MIC_{90} values of carbapenems against *E. coli* all varied within ± one 2-fold dilution step. Although the susceptibilities of meropenem (97.0% susceptible) and imipenem (97.0% susceptible) in the 2019–20 period showed slight declines compared to previous study periods, both agents displayed superior in vitro activities. *β*-Lactam combination agents, including piperacillin-tazobactam and cefoperazone-sulbactam, were also active agents, against which 88.3–92.3% and 75.0–80.6% of *E. coli*, were susceptible, respectively. Although the susceptibility rate has been increasing over time, the sensitivity of *E. coli* to third-generation cephalosporins, aztreonam and gentamicin remained low. The susceptibility rates to ceftazidime were much higher than those to cefotaxime and ceftriaxone. The proportion of ESBL-producing isolates in carbapenem-susceptible *E. coli* displayed a discernible decreasing trend overall and in different regions of China during the surveillance period (overall from 72.9% in 2011–12 to 51.2% in 2019–20) (Figure 1A). As expected, the susceptibility rates of ESBL-producing *E. coli* to meropenem and imipenem were both ~100% during the study period.

Changes in Antimicrobial Susceptibility of *K. pneumoniae*

The susceptibility profiles of *K. pneumoniae* were similar to those of *E. coli* (Table 2). Carbapenems and amikacin were the most active agents against *K. pneumoniae*. However, the susceptibility rates of *K. pneumoniae* to meropenem and imipenem decreased from 96.7% and 98.4% in the 2011–12 period to 84.6% and 84.6% in the2019–20 period, respectively. The sensitivity of *K. pneumoniae* to piperacillin-tazobactam was slightly higher than that to cefoperazone-sulbactam. The susceptibility rates to third-generation cephalosporins, aztreonam, gentamicin and ciprofloxacin fluctuated slightly and were low. An ESBL phenotype was less frequently observed in *K. pneumoniae* than in *E. coli*. The nationwide proportion of ESBL-producing isolates in carbapenem-susceptible *K. pneumoniae* during the study period fluctuated around 24.9% and 44.6%, but overall displayed a decreasing tendency (Figure 1B). The proportion of ESBL-producing isolates in carbapenem-susceptible *K. pneumoniae* decreased in all regions of China from 2011 to 2016, and fluctuated differently thereafter (Figure 1B). The susceptibility rates of ESBL-producing *K. pneumoniae* to meropenem and imipenem were both ~95% from 2011 to 2018; however, the susceptibility rates both decreased to ~85% in the last surveillance period.

Changes in Antimicrobial Susceptibility of *E. cloacae*

Carbapenems and amikacin were the most active agents against *E. cloacae* (Table 3). Susceptibility rates of *E. cloacae* to meropenem and imipenem were higher than those to ertapenem. The sensitivity to piperacillin-tazobactam was similar to that to cefoperazone-sulbactam. The susceptibility rates to piperacillin, third-generation cephalosporins and aztreonam were always low, while sensitivity to cefepime was much higher than that to third-generation cephalosporins. The sensitivity of *E. cloacae* to gentamicin (susceptibility remaining >85% from 2013 to 2020) was higher than those of *E. coli* and *K. pneumoniae*.

Changes in Antimicrobial Susceptibility of *P. aeruginosa*

The susceptibility rates of *P. aeruginosa* to meropenem and imipenem decreased from 80.8% and 72.3% in the 2015–16 period to 69.7% and 62.6% in the 2019–20 period, respectively (Table 4). A similar trend was observed in the sensitivity of *P. aeruginosa* to piperacillin-tazobactam (susceptibility rate from 80.0% in 2015–16 to 73.5% in 2019–20) and cefoperazone-sulbactam (susceptibility rate from 80.8% in 2015–16 to 68.4% in 2019–20). Ceftazidime and cefepime maintained high activities against *P. aeruginosa*, with >70% of isolates being susceptible over the study period.

Table 1 Change in MIC_{50} and MIC_{90} Values of Each Antimicrobial Agent Against *E. coli* (Units: μg/mL)

Strain and Agent	2011–2012			2013–2014			2015–2016			2017–2018			2019–2020		
	MIC_{50}	MIC_{90}	%S/R[a]	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R
E. coli	n=248			n=320			n=338			n=346			n=403		
Meropenem	0.01	0.03	98.8/0.81	0.03	0.06	98.4/1.25	0.01	0.03	97.9/2.1	0.01	0.03	98.8/0.9	0.03	0.03	97.0/2.7
Imipenem	0.06	0.12	99.2/0.81	0.12	0.12	98.6/1.25	0.12	0.25	97.6/2.4	0.12	0.12	98.8/0.9	0.12	0.25	97.0/3.0
Cefoperazone-sulbactam[b]	8	32	81.0/8.9	8	32	75.0/9.4	8	32	76.3/9.8	4	64	79.2/10.4	4	32	80.6/9.7
Piperacillin-tazobactam[c]	2	16	90.3/5.6	2	16	90.3/5.6	2	16	92.3/4.4	2	16	91.6/5.5	2	32	88.3/7.2
Piperacillin	256	512	12.5/74.6	512	512	15.6/72.8	256	512	16.9/71.3	256	512	13.9/69.1	256	512	13.4/71.5
Cefotaxime	ND	ND	ND	64	512	37.2/62.8	4	64	44.1/52.7	32	512	42.2/57.5	32	512	42.2/57.3
Ceftazidime	4	64	52.4/38.7	1	64	61.3/34.1	2	128	60.9/32.8	1	64	62.7/30.3	1	64	65.8/25.1
Ceftriaxone	64	512	23.0/76.6	128	512	37.2/62.8	128	512	37.6/62.1	64	512	42.8/56.9	64	512	42.7/56.8
Cefoperazone	128	512	26.2/64.1	128	512	38.1/60.3	128	512	40.2/57.7	64	512	44.2/54.9	64	512	44.7/51.6
Cefepime	4	32	38.3/31.5	4	64	45.9/37.8	4	64	47.3/34.6	2	64	55.2/28.0	2	128	53.6/28.3
Aztreonam	16	128	41.5/52.0	8	256	47.8/44.4	8	128	49.1/41.4	4	128	52.0/38.4	4	128	51.9/39.0
Colistin	ND	ND	ND	0.5	0.5	-/1.9	0.5	1	-/1.8	0.5	1	-/4.6	1	1	-/1.7
Gentamicin	16	128	44.8/52.8	4	128	50.0/49.4	2	128	52.4/47.3	2	256	54.3/45.7	2	256	59.8/38.2
Amikacin	2	8	93.5/6.0	2	4	96.6/3.1	2	8	97.7/2.1	4	8	95.1/3.5	4	8	96.8/3.0
Ciprofloxacin	16	64	29.4/68.1	16	128	33.1/64.7	8	128	40.8/56.2	8	128	32.4/61.0	8	128	29.0/62.5
Tigecycline	0.25	0.5	-/-	0.25	0.5	-/-	0.25	0.5	-/-	0.25	0.5	-/-	0.5	0.5	-/-
ESBL-producing *E. coli*	n=180			n=187			n=188			n=182			n=204		
Meropenem	0.01	0.03	100/0	0.03	0.06	99.5/0	0.01	0.03	100/0	0.01	0.03	99.5/0	0.03	0.03	100.0/0
Imipenem	0.06	0.12	100/0	0.12	0.12	100/0	0.12	0.12	100/0	0.12	0.12	99.5/0	0.12	0.25	100.0/0
Cefoperazone-sulbactam	16	64	75.6/10.6	16	64	62.6/11.8	16	64	64.4/12.8	16	64	65.4/16.5	16	64	69.6/13.7
Piperacillin-tazobactam	2	16	91.7/5.6	2	16	91.4/2.1	2	16	93.6/2.1	4	16	91.8/4.9	2	32	89.7/4.9
Piperacillin	256	512	0/94.4	512	512	0.5/97.9	512	512	0/98.4	512	512	0/98.4	512	512	0/98.0
Cefotaxime	128	512	0.6/98.9	256	512	0/100	256	512	0/100	256	512	0.0/100.0	256	512	0/100.0
Ceftazidime	8	64	40.0/47.8	16	128	40.1/51.9	8	128	41.5/49.5	8	128	37.9/50.0	8	128	42.6/40.2
Ceftriaxone	64	512	0/100.0	256	512	0/100	256	512	0/100	256	512	0/98.9	256	512	0.5/99.5
Cefoperazone	256	512	4.4/83.3	512	512	1.6/96.8	256	512	1.1/95.7	256	512	1.6/96.7	256	512	3.4/92.6
Cefepime	8	64	18.9/40.6	16	128	12.8/59.4	16	128	12.2/56.4	8	128	20.3/50.0	8	256	15.2/50.0
Aztreonam	32	128	25.0/67.2	32	256	16.0/71.1	32	256	16.5/67.0	16	256	17.6/66.5	32	256	14.2/69.6
Colistin	ND	ND	ND	0.5	0.5	-/2.1	0.5	1	98.4/1.6	0.5	1	-/4.4	1	1	-/2.0
Gentamicin	32	128	41.1/56.7	32	256	41.2/57.8	32	128	46.3/53.7	4	256	52.2/47.8	2	128	55.9/40.2
Amikacin	2	8	93.3/6.7	2	8	95.2/4.8	2	8	97.9/2.1	4	16	93.4/4.4	4	8	98.0/2.0
Ciprofloxacin	16	128	22.2/76.1	16	128	18.7/79.7	32	128	25.0/73.4	32	128	16.5/78.6	16	128	15.2/77.5
Tigecycline	0.25	0.5	-/-	0.25	0.5	-/-	0.25	0.5	-/-	0.25	0.5	-/-	0.5	1	-/-

Notes: [a]CLSI 2021 breakpoints were applied. [b]Cefoperazone-sulbactam was tested at a ratio of 2:1, and the breakpoint of cefoperazone was used here for cefoperazone-sulbactam. [c]Tazobactam was tested in combination with piperacillin at a fixed concentration of 4 μg/mL. Adapted from Liu XJ, Lyu Y, Li Y, et al. Trends in antimicrobial resistance against *Enterobacteriaceae* strains isolated from blood: a 10-year epidemiological study in mainland China (2004–2014). *Chin Med J*. 2017;130(17):2050–2055[13] and *J Glob Antimicrob Resist*, 17, Zhang F, Li Y, Lv Y, et al. Bacterial susceptibility in bloodstream infections: results from China Antimicrobial Resistance Surveillance Trial (CARST) program, 2015–2016. 276–282, Copyright 2019, with permission from Elsevier.[14]

Abbreviations: ESBL, extended-spectrum *β*-lactamase; MIC, minimum inhibitory concentration; MIC_{50} and MIC_{90}, MIC for 50% and 90% of the organisms, respectively; S, percent susceptible; R, percent resistant; ND, not determined; -, no breakpoint.

The susceptibility rates to amikacin were higher than those to gentamicin. The overall IPM-NS *P. aeruginosa* frequency increased during the study period, and the greatest increase occurred between the 2015–16 period and 2017–18 period, with the frequency increased from 27.7% in the 2015–16 period to 35.8% in the 2017–18 period (Figure 1C). Trends in the prevalence of IPM-NS *P. aeruginosa* varied widely among different regions of China from 2011 to 2020 (Figure 1C). During the surveillance period, a marked increase was observed in the sensitivity of IPM-NS *P. aeruginosa* to amikacin (54.5% susceptible in the 2011–12 period; 91.4% susceptible in the 2019–20 period).

Changes in Antimicrobial Susceptibility of *A. baumannii*

Few agents showed in vitro activity against *A. baumannii*, with colistin and tigecycline being the two agents with low MIC_{90} values during the 10-year study period (Table 5). The susceptibility rates of *A. baumannii* to carbapenems were ≤30%. The susceptibility rates to the *β*-lactam combination agent cefoperazone-sulbactam were also low, with only ~30% of isolates being susceptible in each of the study periods. Although amikacin was the most effective agent apart from colistin and tigecycline, the susceptibility rates to amikacin were <50%, with the highest values of 47.3% in the 2019–20 study period. The MIC_{50} and MIC_{90} values of tigecycline against *A. baumannii* were higher than those against *Enterobacteriaceae*. In general, the frequency of IPM-NS *A. baumannii* remained high and stable over the course of the study, with the proportion remaining ~70% (Figure 1D). Trends in the prevalence of IPM-NS *A. baumannii* varied among different regions in China, but almost all regions showed the high prevalence from 2011 to 2020 (Figure 1D). The susceptibility rates of IPM-NS *A. baumannii* to most agents were <5%, and the resistance was serious.

Discussion

BSIs are caused by a wide variety of pathogens, mainly *Staphylococcus aureus* and *E. coli*.[5,8,14] However, many surveillance programs show an ongoing increase in the detection of gram-negative bacilli, many of which are multidrug-resistant (MDR), in BSI, worldwide.[17,18] Majority of the gram-negative bacteria in these studies have been *E. coli, K. pneumoniae* and *P. aeruginosa*.[19,20] Early empirical and adequate agents against these pathogens are essential to reduce the occurrence of bacterial resistance and thus improve patient outcomes. In recent years, the rising resistance rate of gram-negative bacilli has been a serious problem globally. The antimicrobial resistance profiles of gram-negative bacilli causing bloodstream infections have changed over time, while comprehensive and real-time surveillance data are limited in China. In the present study, we evaluated the susceptibility profiles of the most common gram-negative bacteria isolated from blood specimens to antimicrobial agents that are regularly used clinically.

E. coli was the most common BSI-associated bacteria. Data from the SENTRY Antimicrobial Surveillance Program showed that *E. coli* was more prominent than *S. aureus* and contributed to 24.0% of BSIs worldwide from 2013 to 2016.[5] A study in Southwest China also indicated that *E. coli* (accounting for 32.03% of BSIs) was the most frequently isolated bacteria causing BSIs.[9] Similar to previous reports, rates of resistance in *E. coli* remained relatively stable for many antibiotic agents in China from 2011 to 2020.[21,22] During the study period, cefotaxime resistance rates in *E. coli* were always higher than those of ceftazidime. In China, $bla_{CTX\text{-}M}$ was the most common ESBL genotype and was widespread throughout the country.[23,24] The CTX-M *β*-lactamases with the ability to hydrolyze cefotaxime and ceftriaxone were responsible for the high cefotaxime resistance rates.[25] A decreasing trend in the resistance rates of *E. coli* to third-generation cephalosporins was observed during the 10-year period. The possible explanation underlying this was that the use of third-generation cephalosporins was decreased and carbapenems became the important choice in the empirical treatment of BSIs due to the widespread of ESBL in nosocomial infections. Although the detection rates of carbapenem-non-susceptible *E. coli* remained low in the 10-year period, the treatments for infections caused by this pathogen are a challenging problem in clinics. Carbapenemases, particularly metallo-*β*-lactamase (MBL), are the primary causes of carbapenem resistance in *E. coli* in China.[26] *β*-Lactam-*β*-lactamase inhibitor combinations (BL-BLIs) are some of the efficacious antibiotic agents against carbapenem-resistant bacteria. However, the currently approved combinations possess activity against serine-*β*-lactamases, and clinical BL-BLIs approved for metallo-*β*-lactamases are not available.[27]

K. pneumoniae was the second most frequent cause of BSI among gram-negative bacteria and contributed to ~10% of BSIs worldwide.[5] Data from China showed that *K. pneumoniae* accounted for 11.1% of BSIs in China.[9] In the past decade, the utilization of carbapenems in clinical treatments has become necessary due to the proliferation of MDR pathogens in clinical

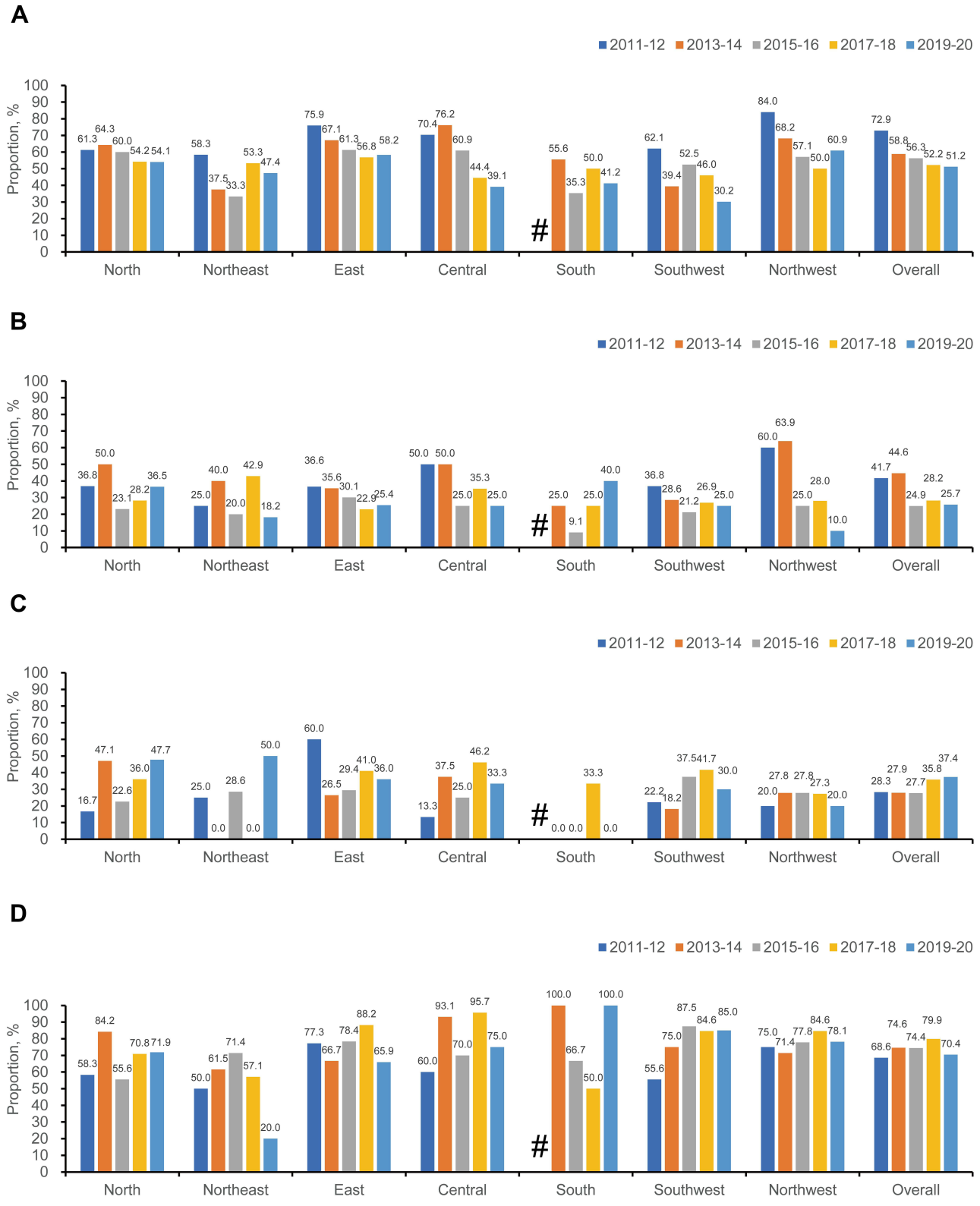

Figure 1 Changes over time in the prevalence of ESBL-producing EC in CSEC (**A**), ESBL-producing KP in CSKP (**B**), Imipenem-NS PA (**C**) and Imipenem-NS AB (**D**) overall and in different regions of China (2011–2020).

Notes: #Means that data in South China in the 2011–12 period were not available.

Abbreviations: ESBL, extended-spectrum *β*-lactamase; EC, *Escherichia coli*; CSEC, carbapenem-susceptible *Escherichia coli*; KP, *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; Imipenem-NS, imipenem-non-susceptible; PA, *Pseudomonas aeruginosa*; AB, *Acinetobacter baumannii*.

Table 2 Change in MIC_{50} and MIC_{90} Values of Each Antimicrobial Agent Against *K. pneumoniae* (Units: μg/mL)

Strain and Agent	2011–2012			2013–2014			2015–2016			2017–2018			2019–2020		
	MIC_{50}	MIC_{90}	%S/R[a]	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R
K. pneumoniae	n=122			n=179			n=241			n=259			n=273		
Meropenem	0.01	0.03	96.7/3.3	0.03	1	89.9/10.1	0.03	128	83.4/16.2	0.03	128	79.5/20.5	0.03	128	84.6/15.0
Imipenem	0.12	0.25	98.4/1.6	0.12	2	89.4/8.9	0.12	64	82.6/17.4	0.12	64	79.5/19.7	0.12	32	84.6/15.4
Cefoperazone-sulbactam[b]	2	32	80.3/9.0	4	256	70.4/21.2	0.5	512	71.8/23.2	1	512	67.2/29.0	1	512	67.8/27.1
Piperacillin-tazobactam[c]	2	64	83.6/9.8	4	512	83.8/13.4	4	512	76.8/21.6	4	512	70.7/25.1	4	512	78.4/17.6
Piperacillin	64	512	46.0/48.4	256	512	44.1/53.1	16	512	53.1/41.5	16	512	50.2/46.3	16	512	52.4/44.0
Cefotaxime	ND	ND	ND	16	512	47.5/52.0	0.06	512	60.2/39.4	0.12	512	55.2/44.8	0.12	512	58.2/41.4
Ceftazidime	0.5	64	73.0/22.1	1	128	63.1/35.2	0.25	256	65.1/32.0	0.5	512	61.8/35.1	0.5	256	64.5/30.0
Ceftriaxone	0.25	256	52.5/46.7	16	512	48.0/52.0	0.12	512	60.6/39.4	0.12	512	55.2/44.8	0.12	512	59.3/40.7
Cefoperazone	4	512	54.1/39.3	32	512	49.7/49.2	0.5	512	60.6/38.2	2	512	55.6/43.6	1	512	60.4/38.8
Cefepime	0.25	32	66.4/17.2	1	64	56.4/31.3	0.06	128	66.0/25.3	0.06	256	59.5/34.7	0.06	256	64.1/31.9
Aztreonam	0.25	128	66.4/31.1	1	256	56.4/39.1	0.12	512	65.1/34.9	0.12	512	61.0/37.8	0.12	512	62.3/35.9
Colistin	ND	ND	ND	0.5	1	-/1.1	1	2	-/2.5	1	4	-/13.5	1	2	-/5.1
Gentamicin	0.5	128	67.2/31.1	1	128	66.5/33.0	1	512	71.0/28.2	0.5	512	71.8/27.0	1	512	73.6/25.3
Amikacin	1	2	93.4/6.6	2	4	92.2/7.8	1	512	86.3/12.4	2	512	86.9/12.7	2	512	88.6/11.4
Ciprofloxacin	0.12	32	59.8/29.5	0.12	32	60.3/34.1	0.06	64	58.1/35.3	0.5	256	48.6/46.3	0.12	128	54.9/40.3
Tigecycline	0.5	2	-/-	1	2	-/-	0.5	2	-/-	1	4	-/-	1	4	-/-
ESBL-producing *K. pneumoniae*	n=49			n=77			n=54			n=63			n=71		
Meropenem	0.01	0.06	100.0/0.0	0.03	0.06	93.5/6.5	0.03	0.06	94.4/3.7	0.03	0.12	96.8/3.2	0.03	32	85.9/12.7
Imipenem	0.12	0.25	100.0/0.0	0.12	1	96.1/3.9	0.12	0.5	92.6/7.4	0.12	0.25	96.8/3.2	0.25	16	87.3/12.7
Cefoperazone-sulbactam	16	64	65.3/14.3	16	128	51.9/28.6	32	128	46.3/35.2	32	128	46.0/38.1	64	256	28.2/53.5
Piperacillin-tazobactam	4	32	79.6/6.1	4	256	83.1/11.7	8	512	74.1/22.2	8	512	63.5/22.2	8	512	69.0/19.7
Piperacillin	512	512	0.0/98.0	512	512	0.0/97.4	512	512	1.9/96.3	512	512	0.0/100.0	512	512	2.8/97.2
Cefotaxime	64	256	2.0/95.9	128	512	0.0/98.7	128	512	0.0/98.1	256	512	0.0/100.0	256	512	0.0/98.6
Ceftazidime	8	128	49.0/38.8	16	128	37.7/59.7	16	128	24.1/66.7	32	256	28.6/60.3	16	128	22.5/60.6
Ceftriaxone	64	512	2.0/95.9	256	512	3.9/98.7	256	512	0.0/100.0	256	512	0.0/100.0	512	512	1.4/98.6
Cefoperazone	128	512	4.1/79.6	512	512	6.5/90.9	512	512	1.9/94.4	512	512	0.0/96.8	512	512	2.8/94.4
Cefepime	8	32	30.6/34.7	16	64	18.2/54.5	8	128	18.5/46.3	16	512	17.5/60.3	32	256	12.7/73.2
Aztreonam	16	256	32.7/61.2	64	256	20.8/68.8	64	256	16.7/83.3	64	512	22.2/74.6	64	512	11.3/85.9
Colistin	ND	ND	ND	0.5	1	-/2.6	1	2	-/5.6	1	4	-/17.5	1	2	-/2.8
Gentamicin	32	512	34.7/65.3	64	256	33.8/64.9	32	256	42.6/55.6	8	256	47.6/49.2	32	512	39.4/56.3
Amikacin	1	512	85.7/14.3	2	64	90.9/9.1	2	32	90.7/9.3	2	8	90.5/9.5	2	512	88.7/11.3
Ciprofloxacin	1	128	28.6/53.1	2	64	27.3/61.0		256	13.0/68.5	16	512	12.7/74.6	8	256	15.5/77.5
Tigecycline	1	2	-/-	1	4	-/-	1	2	-/-	1	4	-/-	1	4	-/-

Notes: [a]CLSI 2021 breakpoints were applied. [b]Cefoperazone-sulbactam was tested at a ratio of 2:1, and the breakpoint of cefoperazone was used here for cefoperazone-sulbactam. [c]Tazobactam was tested in combination with piperacillin at a fixed concentration of 4 μg/mL. Adapted from Liu XJ, Lyu Y, Li Y, et al. Trends in antimicrobial resistance against *Enterobacteriaceae* strains isolated from blood: a 10-year epidemiological study in mainland China (2004–2014). *Chin Med J*. 2017;130(17):2050–2055[13] and *J Glob Antimicrob Resist*, 17, Zhang F, Li Y, Lv Y, et al. Bacterial susceptibility in bloodstream infections: results from China Antimicrobial Resistance Surveillance Trial (CARST) program, 2015–2016. 276–282, Copyright 2019, with permission from Elsevier.[14]

Abbreviations: ESBL, extended-spectrum *β*-lactamase; MIC, minimum inhibitory concentration; MIC_{50} and MIC_{90}, MIC for 50% and 90% of the organisms, respectively; S, percent susceptible; R, percent resistant; ND, not determined; -, no breakpoint.

Table 3 Change in MIC_{50} and MIC_{90} Values of Each Antimicrobial Agent Against *E. cloacae* (Units: μg/mL)

Agent	2011–2012 (n=29)			2013–2014 (n=62)			2015–2016 (n=71)			2017–2018 (n=59)			2019–2020 (n=57)		
	MIC_{50}	MIC_{90}	%S/R[a]	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R
Meropenem	0.03	1	93.1/6.9	0.03	1	91.9/4.8	0.03	0.5	94.4/5.6	0.03	4	86.4/10.2	0.06	2	89.5/7.0
Imipenem	0.25	1	93.1/6.9	0.5	2	88.7/4.8	0.25	1	93.0/7.0	0.25	2	89.8/8.5	0.25	2	87.7/8.8
Cefoperazone-sulbactam[b]	8	64	65.5/24.1	1	128	75.8/17.7	1	64	76.1/14.1	1	128	79.7/15.3	1	64	64.9/21.1
Piperacillin-tazobactam[c]	4	256	72.4/13.8	4	128	75.8/12.9	4	128	77.5/15.5	4	256	79.7/15.3	4	128	66.7/19.3
Piperacillin	128	512	24.1/55.2	4	512	58.1/30.6	8	512	60.6/26.8	4	512	62.7/30.5	8	512	57.9/38.6
Cefotaxime	ND	ND	ND	0.5	512	56.5/43.5	1	512	52.1/42.3	1	512	54.2/45.8	2	256	49.1/45.6
Ceftazidime	32	256	34.5/62.1	0.5	256	62.9/33.9	1	256	66.2/32.4	0.5	512	62.7/33.9	1	256	52.6/43.9
Ceftriaxone	64	256	27.6/72.4	0.5	512	54.8/45.2	1	512	53.5/40.8	0.5	512	57.6/40.7	1	512	50.9/49.1
Cefoperazone	64	512	41.4/55.2	2	512	66.1/27.4	2	512	67.6/29.6	1	512	69.5/28.8	1	512	57.9/36.8
Cefepime	4	32	48.3/34.5	0.06	16	83.9/12.9	0.25	32	76.1/12.7	0.06	32	76.3/15.3	0.12	16	77.2/14.0
Aztreonam	32	256	41.2/58.6	0.12	128	67.7/29.0	0.25	256	62.0/36.6	0.25	256	62.7/33.9	0.25	64	56.1/38.6
Gentamicin	0.5	128	65.5/34.5	0.5	64	87.1/12.9	0.5	16	87.3/11.3	1	128	88.1/11.9	0.5	4	91.2/8.8
Amikacin	1	8	93.1/6.9	2	4	98.4/1.5	1	4	97.2/1.4	2	8	96.6/1.7	2	8	94.7/5.3
Ciprofloxacin	0.25	16	51.7/41.4	0.06	1	72.6/17.7	0.03	4	69.0/15.5	0.03	1	66.1/15.3	0.03	8	73.7/24.6
Levofloxacin	0.5	32	58.6/27.6	0.12	2	74.2/14.5	0.12	2	77.5/14.1	0.12	2	71.2/11.9	0.06	16	77.2/19.3
Tigecycline	ND	ND	ND	1	2	-/-	1	4	-/-	1	4	-/-	0.5	1	-/-

Notes: [a]CLSI 2021 breakpoints were applied. [b]Cefoperazone-sulbactam was tested at a ratio of 2:1, and the breakpoint of cefoperazone was used here for cefoperazone-sulbactam. [c]Tazobactam was tested in combination with piperacillin at a fixed concentration of 4 μg/mL. Adapted from Liu XJ, Lyu Y, Li Y, et al. Trends in antimicrobial resistance against *Enterobacteriaceae* strains isolated from blood: a 10-year epidemiological study in mainland China (2004–2014). *Chin Med J*. 2017;130(17):2050–2055[13] and *J Glob Antimicrob Resist*, 17, Zhang F, Li Y, Lv Y, et al. Bacterial susceptibility in bloodstream infections: results from China Antimicrobial Resistance Surveillance Trial (CARST) program, 2015–2016. 276–282, Copyright 2019, with permission from Elsevier.[14]

Abbreviations: MIC, minimum inhibitory concentration; MIC_{50} and MIC_{90}, MIC for 50% and 90% of the organisms, respectively; S, percent susceptible; R, percent resistant; ND, not determined; -, no breakpoint.

Table 4 Change in MIC_{50} and MIC_{90} Values of Each Antimicrobial Agent Against *P. aeruginosa* (Units: μg/mL)

Strain and Agent	2011–2012			2013–2014			2015–2016			2017–2018			2019–2020		
	MIC_{50}	MIC_{90}	%S/R[a]	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R
P. aeruginosa	n=78			n=122			n=130			n=137			n=155		
Meropenem	0.5	16	70.5/25.6	0.5	16	73.8/18.9	0.5	16	80.8/13.1	0.5	64	66.4/26.3	1	32	69.7/24.5
Imipenem	2	16	71.8/23.1	2	32	72.1/22.1	2	16	72.3/17.7	2	32	64.2/32.1	2	32	62.6/31.0
Cefoperazone-sulbactam[b]	8	64	71.8/16.7	8	64	75.4/15.6	8	64	80.8/12.3	4	128	75.2/19.0	8	128	68.4/20.0
Piperacillin-tazobactam[c]	4	128	74.4/12.8	4	128	74.6/13.1	4	64	80.0/10.0	8	256	74.5/20.4	8	256	73.5/19.4
Piperacillin	8	256	65.4/19.2	8	128	73.0/13.1	8	128	75.4/11.5	4	256	73.0/19.0	16	256	62.6/20.6
Ceftazidime	2	64	73.1/24.4	2	32	82.0/12.3	2	32	84.6/11.5	2	64	80.3/17.5	2	64	73.5/21.9
Cefepime	2	32	73.1/14.1	2	32	83.6/10.7	2	16	86.9/7.7	2	128	78.1/16.8	2	32	74.8/12.3
Aztreonam	8	512	65.4/24.4	8	64	69.7/20.5	8	32	69.2/19.2	8	64	65.7/19.7	8	64	58.7/27.7
Gentamicin	2	512	71.8/25.6	2	512	82.0/14.8	2	8	86.2/8.5	2	128	87.6/11.7	4	8	78.7/9.7
Amikacin	4	512	82.1/17.9	4	16	90.2/8.2	2	8	94.6/5.4	4	8	97.1/2.2	4	16	94.8/3.2
Ciprofloxacin	0.25	32	60.2/33.3	0.12	8	73.8/16.4	0.25	2	83.1/13.1	0.25	32	72.3/21.9	0.5	8	69.7/18.1
Colistin	2	2	-/3.8	2	2	-/7.4	2	2	-/9.2	1	2	-/2.9	2	2	-/7.7
Imipenem-NS *P. aeruginosa*	n=22			n=34			n=36			n=49			n=58		
Meropenem	16	64	13.6/86.4	8	64	20.6/64.7	4	64	38.9/41.7	16	512	12.2/73.5	16	512	31.0/62.1
Imipenem	16	256	0.0/81.8	16	64	0.0/79.4	8	32	0.0/63.9	16	512	0.0/89.8	16	512	0.0/82.8
Cefoperazone-sulbactam	32	256	40.9/45.5	32	256	41.2/38.2	16	128	55.6/30.6	32	512	46.9/46.9	32	512	41.4/37.9
Piperacillin-tazobactam	64	256	45.5/31.8	32	512	44.1/29.4	16	512	61.1/25.0	32	512	46.9/44.9	16	512	50.0/37.9
Piperacillin	64	512	31.8/36.4	32	512	38.2/29.4	16	512	61.1/25.0	32	512	49.0/42.9	32	512	39.7/39.7
Ceftazidime	32	512	31.8/63.6	32	512	61.8/26.5	4	128	69.4/25.0	4	128	57.1/40.8	8	128	53.4/39.7
Cefepime	16	64	22.7/45.5	8	512	58.8/26.5	4	128	63.9/22.2	8	512	51.0/38.8	8	512	53.4/27.6
Aztreonam	64	512	13.6/63.6	8	512	38.2/55.9	8	256	50.0/38.9	16	512	28.6/44.9	32	512	34.5/55.2
Gentamicin	32	512	31.8/59.1	32	512	64.7/26.5	2	512	63.9/22.2	2	512	77.6/12.2	4	32	63.8/19.0
Amikacin	8	512	54.5/45.5	4	512	76.5/20.6	4	256	86.1/13.9	4	16	91.8/6.1	4	16	91.4/6.9
Ciprofloxacin	4	32	22.7/68.2	1	64	41.2/38.2	0.5	64	55.6/36.1	1	64	40.8/46.9	1	32	48.3/39.7
Colistin	2	2	-/4.5	2	2	-/2.9	2	4	-/11.1	1	2	-/2.0	2	2	-/8.6

Notes: [a]CLSI 2021 breakpoints were applied. [b]Cefoperazone-sulbactam was tested at a ratio of 2:1, and the breakpoint of cefoperazone for *Enterobacteriaceae* was used here for cefoperazone/sulbactam. [c]Tazobactam was tested in combination with piperacillin at a fixed concentration of 4 μg/mL. Adapted from *J Glob Antimicrob Resist*, 17, Zhang F, Li Y, Lv Y, et al. Bacterial susceptibility in bloodstream infections: results from China Antimicrobial Resistance Surveillance Trial (CARST) program, 2015–2016. 276–282, Copyright 2019, with permission from Elsevier.[14]

Abbreviations: MIC, minimum inhibitory concentration; MIC_{50} and MIC_{90}, MIC for 50% and 90% of the organisms, respectively; S, percent susceptible; R, percent resistant; -, no breakpoint; imipenem-NS *P. aeruginosa*, imipenem-non-susceptible *P. aeruginosa*.

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Table 5 Change in MIC_{50} and MIC_{90} Values of Each Antimicrobial Agent Against *A. baumannii* (Units: μg/mL)

Strain and Agent	2011–2012			2013–2014			2015–2016			2017–2018			2019–2020		
	MIC_{50}	MIC_{90}	%S/R[a]	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R	MIC_{50}	MIC_{90}	%S/R
A. baumannii	n=70			n=138			n=160			n=169			n=186		
Meropenem	32	64	30.0/68.6	64	128	24.6/74.6	32	64	26.3/73.8	32	64	20.1/79.3	32	128	29.6/70.4
Imipenem	16	64	30.0/68.6	32	128	25.4/73.9	32	64	25.6/73.1	32	64	20.1/79.9	32	64	29.6/70.4
Ampicillin-sulbactam[b]	ND	ND	ND	64	128	23.2/73.2	64	128	23.8/71.9	64	128	20.7/75.7	64	128	29.6/68.3
Cefoperazone-sulbactam[c]	32	128	30.0/47.1	64	128	26.1/65.2	64	128	26.3/58.1	64	128	23.1/67.5	64	128	33.3/61.3
Piperacillin-tazobactam[d]	256	512	28.6/70.0	512	512	23.2/75.4	512	512	23.1/76.3	512	512	18.9/81.7	512	512	29.0/69.9
Piperacillin	256	512	18.6/72.9	512	512	10.1/77.5	512	512	11.3/76.9	512	512	14.8/96.4	512	512	18.8/71.0
Ceftazidime	64	512	28.6/70.0	128	512	24.6/74.6	128	512	24.4/75.0	128	512	21.3/76.9	128	512	31.2/68.8
Ceftriaxone	512	512	7.1/70.0	512	512	5.8/76.8	512	512	5.6/76.9	512	512	7.7/75.7	512	512	6.5/68.8
Cefotaxime	256	512	8.6/71.4	512	512	10.9/76.1	512	512	12.5/76.3	512	512	12.4/75.1	512	512	13.4/68.8
Cefepime	32	256	28.6/60.0	128	256	20.3/74.6	64	256	22.5/75.0	64	256	19.5/76.3	64	256	29.0/68.8
Gentamicin	512	512	30.0/70.0	512	512	26.1/73.2	512	512	25.6/71.9	512	512	24.3/71.6	512	512	36.0/59.1
Amikacin	512	512	35.7/62.9	512	512	34.1/65.9	512	512	33.8/66.3	512	512	38.5/61.5	512	512	47.3/52.7
Ciprofloxacin	32	64	30.0/70.0	64	128	23.2/76.8	64	128	23.8/76.3	64	256	24.3/75.7	64	256	31.2/68.8
Colistin	1	2	-/4.3	0.5	1	-/4.3	1	2	-/1.9	1	2	-/5.3	1	2	-/5.4
Tigecycline	ND	ND	ND	4	4	-/-	2	2	-/-	2	4	-/-	4	8	-/-
Imipenem-NS *A. baumannii*	n=48			n=103			n=119			n=135			n=131		
Meropenem	32	128	0.0/100.0	64	128	0.0/100.0	32	64	0.8/99.2	32	64	1.5/98.5	64	128	0.0/100.0
Imipenem	32	128	0.0/100.0	64	128	0.0/99.0	32	64	0.0/98.3	32	64	0.0/100.0	64	128	0.0/100.0
Ampicillin-sulbactam	ND	ND	ND	64	128	1.9/93.2	64	128	0.8/94.1	64	128	2.2/93.3	64	256	0.0/96.9
Cefoperazone-sulbactam	64	128	4.2/64.6	64	128	3.9/85.4	64	128	4.2/76.5	64	128	4.4/84.4	64	128	5.3/87.0
Piperacillin-tazobactam	256	512	2.1/97.9	512	512	0.0/99.0	512	512	0.8/99.2	512	512	0.7/99.3	512	512	0.0/98.5
Piperacillin	512	512	2.1/97.9	512	512	0.0/100.0	512	512	0.0/99.2	512	512	0.7/99.3	512	512	0.0/99.2
Ceftazidime	128	512	4.2/95.8	256	512	1.9/98.1	256	512	2.5/96.6	256	512	3.7/95.6	256	512	3.1/96.9
Ceftriaxone	512	512	0.0/95.8	512	512	0.0/98.1	512	512	0.0/99.2	512	512	0.0/94.1	512	512	0.0/96.9
Cefotaxime	512	512	0.0/97.9	512	512	1.0/98.1	512	512	0.0/98.3	512	512	0.7/93.3	512	512	0.0/96.9
Cefepime	32	256	2.1/83.3	128	256	0.0/97.1	128	256	0.0/98.3	128	256	0.7/94.8	128	256	0.0/96.9
Gentamicin	512	512	4.2/95.8	512	512	6.8/92.2	512	512	5.0/92.4	512	512	5.9/88.9	512	512	11.5/81.7
Amikacin	512	512	12.5/85.4	512	512	13.6/86.4	512	512	15.1/84.9	512	512	23.0/77.0	512	512	25.2/74.8
Ciprofloxacin	32	64	4.2/95.8	64	128	1.9/98.1	64	256	1.7/98.3	128	256	5.9/94.1	128	256	3.1/93.1
Colistin	1	2	-/6.3	0.5	1	-/3.9	1	2	-/1.7	1	2	-/3.0	1	2	-/4.6
Tigecycline	2	4	-/-	4	4	-/-	2	4	-/-	4	8	-/-	4	8	-/-

Notes: [a]CLSI 2021 breakpoints were applied. [b]Ampicillin-sulbactam were tested in a ratio of 2:1. [c]Cefoperazone-sulbactam was tested at a ratio of 2:1, and the breakpoint of cefoperazone for *Enterobacteriaceae* was used here for cefoperazone/sulbactam. [d]Tazobactam was tested in combination with piperacillin at a fixed concentration of 4 μg/mL. Adapted from *J Glob Antimicrob Resist*, 17, Zhang F, Li Y, Lv Y, et al. Bacterial susceptibility in bloodstream infections: results from China Antimicrobial Resistance Surveillance Trial (CARST) program, 2015–2016. 276–282, Copyright 2019, with permission from Elsevier.[14]

Abbreviations: MIC, minimum inhibitory concentration; MIC_{50} and MIC_{90}, MIC for 50% and 90% of the organisms, respectively; S, percent susceptible; R, percent resistant; -, no breakpoint; imipenem-NS *A. baumannii*, imipenem-non-susceptible *A. baumannii*.

settings. Such an increase in carbapenem consumption has been accompanied by the emergence of carbapenem-resistant gram-negative pathogens. A significant increase in the detection rate of carbapenem-resistant *K. pneumoniae* (CRKP) was observed during the 10-year period. Other studies also demonstrated that CRKP increased seriously in China and few agents were effective against these pathogens. In China, *Klebsiella pneumoniae* carbapenemase-2 (KPC-2) is responsible for phenotypic resistance in most CRKP strains.[26,28] Novel β-lactamase inhibitor combinations display activities against CRKP, including ceftazidime-avibactam, meropenem-vaborbactam and imipenem-relebactam, which are currently approved or in late stages of development.[29] In addition, the resistance rates of *K. pneumoniae* to ciprofloxacin have been increasing and ciprofloxacin is not an appropriate choice in the treatment of *K. pneumoniae* BSIs.

Among all *Enterobacteriaceae, E. cloacae* ranks third in its ability to cause bloodstream infections.[5,20] In China, MBL genes and KPC genes were both detected in *E. cloacae* in previous studies.[30,31] Carbapenem resistance genes might be shared between bacterial species via horizontal transfer. In general, the ciprofloxacin activities against *E. cloacae* showed a trend to increase, and the agent continued to be an effective choice.

The previous studies revealed that *P. aeruginosa* was the most common non-fermentative gram-negative bacteria causing BSIs and contributed to ~5% of BSIs worldwide.[5] The prevalence of *P. aeruginosa* in BSIs was ~3% in China.[9] In general, the resistance profiles for *P. aeruginosa* displayed a first decrease and then increase for most agents during the study period. The increased use of carbapenems in recent years was related to the increased rates of IPM-NS *P. aeruginosa* in the last two surveillance periods. Imipenem resistance cannot cause resistance against other antibiotics but may be indicative of rising MDRs based on previous data.[32] MDR in *P. aeruginosa* is a growing public health problem and is challenging to treat. Institutions and researchers have been paying increased attention to new treatments for carbapenem-resistant and MDR *P. aeruginosa*, and several studies reported that combination therapy might be an effective strategy, exemplified by colistin-based combination therapy.[33] In addition, aminoglycosides could be considered as a therapeutic option since they retained activity against MDR *P. aeruginosa*.

A. baumannii was another most common non-fermentative gram-negative bacteria causing BSIs and accounted for 2% of BSIs worldwide in the past 20 years.[5] A similar prevalence was observed in a Chinese surveillance program.[9] Infections caused by *A. baumannii* are problematic for patients due to this pathogen's resistance against different classes of antibiotics. The level of MDR for *A. baumannii* is higher than that observed in *K. pneumoniae* and *P. aeruginosa* globally.[34] Carbapenems are considered to be a front-line option for infections caused by MDR, but carbapenem resistance is serious in *A. baumannii*. Tigecycline and colistin could be potentially used for MDR *A. baumannii* infections.[35] However, resistance to colistin is also emerging.[36] The high trend of resistance in *A. baumannii* is a crisis to the public health considering its ability to survive in harsh environments, predilection for the seriously ill within intensive care units, and a wide variety of resistance mechanisms. Strict antimicrobial management and effective infection control policy should be enforced to reduce the production and spread of resistance.

Conclusion

In summary, our study generated a complete picture of variation in pathogen frequency and antibiotic resistance trends among gram-negative bacilli causing BSI. The susceptibility profiles for *E. coli*, the major cause of BSIs, remained constant during the 10 years. The prevalence of ESBL-producing isolates in *E. coli* and *K. pneumoniae* were both decreased. However, a significant increase in the carbapenem resistance rates in *K. pneumoniae* has been observed. The resistance profiles for *P. aeruginosa* have displayed a trend to increase for most agents in recent years. Carbapenems are still the effective options against gram-negative bacilli, except for *A. baumannii*. The resistance trend in *A. baumannii* was serious and few agents were effective against these pathogens. The last-resort antibiotics such as tigecycline and colistin could be potentially used for MDR *A. baumannii* BSIs. The spread control of *A. baumannii* within the hospital environment is of great urgency.

Ethics Approval and Consent to Participate

Since the project falls under the category observational study and all bacterial strains were from residual samples used in clinical diagnosis or were strains from their subcultures, it has been determined they meet the criteria for exemption. This project does not involve any patient information nor does it affect the normal diagnosis and treatment of patients, and

after consultation with the human research ethics committee of the Institutional Review Board of Peking University First Hospital, ethical approval was waived and written patient consent was not required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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