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ORIGINAL RESEARCH

Long-Term Continuous Antimicrobial Resistance Surveillance Among Nosocomial Gram-Negative Bacilli in China from 2010 to 2018 (CMSS)

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Purpose: The Chinese Meropenem Surveillance Study (CMSS) was conducted every 2 years from 2010 to 2018 to monitor the antimicrobial activity of commonly used antimicrobial agents against nosocomial gram-negative bacilli in China.

Methods: From 2010 to 2018, 6,537 gram-negative bacilli were collected from 14 teaching hospitals. The minimum inhibitory concentrations (MICs) of meropenem and other antimicrobial agents were determined using the agar dilution and broth microdilution methods.

Results: Continuous surveillance indicated that, except for *Klebsiella pneumoniae*, the susceptibility of *Enterobacterales* to carbapenems was relatively stable over time. Carbapenems had the highest activity against the tested isolates, with MIC_{90} values (MIC for 90% of organisms) ranging from 0.032 mg/L to 8 mg/L. More than 90% of bacteria were susceptible to either meropenem or imipenem; more than 80% were susceptible to ertapenem. The prevalence of extended-spectrum beta-lactamase (ESBL)-producing *E. coli, K. pneumoniae*, and *P. mirabilis* each year was 50.4–64.3%, 18–41.2%, and 1.9–33.8%, respectively. The prevalence of carbapenem-resistant *K. pneumoniae* (CRKP) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) continued to increase significantly over time, from 7.6% to 21.2% and 64.6% to 69.3%, respectively. The prevalence of CRKP was higher from urinary tract infections (25.4%) than from bloodstream infections (14.2%), intra-abdominal infections (14.5%), and respiratory infections (14.4%). In total, 129 CRKP isolates were evaluated by PCR; of these, 92 (71.3%) carried the bla_{KPC-2} gene. Colistin maintained very high in vitro antimicrobial activity against *P. aeruginosa* and *A. baumannii* (more than 95% of isolates exhibited susceptibility at all timepoints).

Conclusion: The results indicate an increase in *K. pneumoniae* resistance to carbapenems over time, mainly owing to KPC-type carbapenemase production. *A. baumannii* was severely resistant to carbapenems in China. Ongoing MIC-based resistance surveillance, like CMSS, provides additional data for clinical anti-infective treatment.

Keywords: CMSS, gram-negative bacilli, antimicrobial susceptibility surveillance, carbapenem-resistant

Introduction

In recent years, the proliferation of various multidrug-resistant gram-negative bacteria, such as extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa*, and other carbapenem-resistant gram-negative bacteria, have introduced new challenges to clinical anti-infectious disease treatment and hospital infection control.[1–5] In 2019, in the latest list

of antibiotic-resistance threats released by the United States CDC, the number of drug-resistant bacteria identified in the report had increased from the previous version;[6] this reality makes the clinical challenge of combatting multidrug-resistant bacteria even more complex. However, the prevalence of these multidrug-resistant bacteria in different countries and regions is not uniform. Additionally, the prevalence of multidrug-resistant bacteria changes over time. Factors affecting the prevalence of drug-resistant bacteria include region, population, clinical infection type, and local prescription behavior.[7,8] Therefore, timely and effective antimicrobial susceptibility surveillance is essential for epidemiology, infection control, and empirical antimicrobial agent prescriptions.

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) programme[9–12] was initiated in 1997 with the primary purpose of monitoring changes in the susceptibility of specific bacteria to clinically relevant antibacterial agents such as meropenem. At present, most antimicrobial susceptibility surveillance projects in China are based on historical data review, and there are few projects engaged in the prospective collection of isolates. The Chinese Meropenem Susceptibility Surveillance (CMSS) project was initiated in 2003.[13] Under this project, surveillance of bacterial infections has been performed every 2 years, mainly regarding the susceptibility of specific *Enterobacterales* and non-fermentative bacteria to antimicrobial agents commonly used in China. In this article, we report and summarize the CMSS data from 2010 to 2018. We expect that our results will contribute to both empiric therapy and infection control in the anti-infection field.

Materials and Methods

Bacterial Isolates Collection

Nine *Enterobacterales* species and three non-fermentative bacterial species were collected, including *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Klebsiella aerogenes, Citrobacter freundii, Serratia marcescens, Morgan morganii, Proteus mirabilis, Proteus vulgaris, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Burkholderia cepacia*. All isolates were part of the routine hospital laboratory procedure.

From 2010 to 2018, CMSS surveillance was conducted every 2 years, in a total of five collection rounds. The surveillance years were 2010, 2012, 2014, 2016, and 2018. Thirteen teaching hospitals from 11 central cities (Beijing, Tianjin, Shenyang, Shanghai, Hangzhou, Zhengzhou, Wuhan, Nanjing, Guangzhou, Fuzhou, and Urumqi) throughout China participated in the CMSS program. From March to August each year, 100 non-repeat clinical isolates of gram-negative bacilli were collected in the hospitals. Isolates were identified at the local laboratory and confirmed at the central laboratory (Department of Clinical Laboratory, Peking University People's Hospital, Beijing, China) using colonial morphology, routine biochemical tests, and Vitek system identification (bioMérieux, Hazelwood, MO, USA), as required. All isolates were stored at −80 °C until the MICs were measured.

Antimicrobial Susceptibility Testing

The MICs of 15 antimicrobial agents were determined for each isolate using the agar dilution method or the broth microdilution method at the central laboratory according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[14] For colistin and tigecycline, the broth microdilution methods were used to determine MICs for all isolates, while agar dilution methods were used to determine MICs for other antibacterial agents.

Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, MD, USA) was freshly prepared for susceptibility testing. The antimicrobial agents tested were meropenem (Sumitomo Pharmaceuticals Co., Osaka, Japan), imipenem (Sigma Chemical Co., St Louis, MO, USA), ertapenem (Sigma), ceftazidime (Sigma), cefotaxime (Sigma), ceftriaxone (Sigma), cefepime (Sigma), piperacillin/tazobactam (TZP; Wyeth Pharmaceuticals, Collegeville, PA, USA), cefoperazone/sulbactam (CSL, 2:1; Sigma), clavulanic acid (Sigma), cefoxitin (Sigma), amikacin (Sigma), ciprofloxacin (Bayer AG, Leverkusen, Germany), levofloxacin (Bayer AG), tigecycline (MedChem Express, Monmouth Junction, NJ, USA), and colistin (Sigma). The procedures for each set of tests were validated by determining the MICs for quality control isolates (*Escherichia coli* ATCC 25922, *Klebsiella pneumonia* ATCC 700603 and *Pseudomonas aeruginosa* ATCC 27853) as recommended by the CLSI standards.[14] The results were interpreted according to the most recent CLSI M100-S29 breakpoints.[14] The cefoperazone-sulbactam MIC breakpoint used the breakpoint of cefoperazone for *Enterobacterales* in the CLSI M100-S29.[14] Tigecycline MICs interpretation refers to the breakpoint of the US FDA (www.fda.gov/drugs/development-resources/tigecycline-injection-products). Colistin MICs interpretation refers to the breakpoint of the European

Committee on Antimicrobial Susceptibility Testing (EUCAST).[15]

The CLSI extended-spectrum beta-lactamase (ESBL)-screening criterion (MIC ≥2 mg/L for either ceftazidime or cefotaxime) was applied to all the *E. coli, K. pneumoniae, and P. mirabilis* isolates. ESBL production was confirmed using two drug pairs, cefotaxime alone or cefotaxime plus clavulanic acid and ceftazidime alone or ceftazidime plus clavulanic acid. An isolate was considered ESBL-producing if the addition of clavulanic acid reduced the MIC of either of the beta-lactam agents by three-fold or more. *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 were used as controls for the confirmatory ESBL test.

Carbapenemase Gene Detection

The six primary carbapenemase genes (bla_{KPC}, bla_{NDM}, bla_{IMP}, bla_{VIM}, bla_{SIM}, and bla_{OXA-48}) of 233 CRE isolates were amplified using PCR as previously described.[16,17] The PCR products were purified using a Universal DNA Purification Kit (Tiangen Biotech, Beijing, China) and sequenced by Sanger sequencing on an ABI PRISM 3730XL system (Applied Biosystems, Foster City, CA, USA). The sequences were aligned using the NCBI BLAST tool to determine the specific carbapenemase genotype.

Data Analysis and Statistical Analysis

Case reports, including the patient's clinical diagnosis, the date of collection specimen, and the type of infection, were collected along with the strains. All the antimicrobial susceptibility test data were analyzed by WHONET 5.6.

Ethical Statement

This study was approved by the Ethics Review Committee (ERC) of Peking University People's Hospital. Informed consent was not needed due to that the medical records and patient information were anonymously reviewed and collected.

Results

Distribution of Isolates

From 2010 to 2018, in total, 6,537 gram-negative bacilli were collected. The distribution of organisms was: *Escherichia coli* (1022/6537, 15.6%), *Klebsiella pneumoniae* (983/6537, 15%), *Acinetobacter baumannii* (926/6537, 14.2%), *Pseudomonas aeruginosa* (922/6537, 14.1%), *Enterobacter cloacae* (829/6537, 12.7%), *Citrobacter freundii* (398/6537, 6.1%), *Proteus mirabilis* (333/6537, 5.1%), *Serratia marcescens* (315/6537, 4.8%), *Klebsiella aerogenes* (303/6537, 4.6%), *Morgan morganii* (214/6537, 3.3%), *Burkholderia cepacia* (209/6537, 3.2%), and *Proteus vulgaris* (83/6537, 1.3%). The majority of the isolates were recovered from blood culture specimens (2589/6537, 39.6%), followed by urine (836/6537, 12.8%), sputum (803/6537, 12.3%), drainage (353/6537, 5.4%), secretion (305/6537, 4.7%), pus (261/6537, 4%), abdominal fluid (252/6537, 3.9%), bile (213/6537, 3.3%), wound (146/6537, 2.2%), pleural fluid (121/6537, 1.9%), cerebrospinal fluid (109/6537, 1.7%), catheter (92/6537, 1.4%), broncho-alveolar lavage (66/6537, 1%), and other specimens (391/6537, 6%).

Antimicrobial Activity Against Major Organisms from 2010 to 2018

The antimicrobial activity against major organisms from 2010 to 2018 is described in Table 1. During this period, the susceptibility of *E. coli* to carbapenems remained between 91.9% and 100%. The susceptibility of *E. coli* to ceftriaxone and cefotaxime was between 29.8% and 38.9%, but the susceptibility to ceftazidime remained between 63.2% and 65.6%. More than 95% of *E. coli* were susceptible to tigecycline and colistin in each monitoring year. There was no significant change in the MIC_{90} data of the 15 antimicrobials against *E. coli*.

The susceptibility of *K. pneumoniae* to meropenem, imipenem, and ertapenem decreased from 93.5%, 93.5%, and 91.8% in 2010 to 79.7%, 80.2%, and 78.4 in 2018, respectively. In 2010, the MIC_{90} data of *K. pneumoniae* against meropenem, imipenem, and ertapenem were 0.064 mg/L, 0.5 mg/L, and 0.5 mg/L, respectively. In 2018, the MIC_{90} data of *K. pneumoniae* against meropenem, imipenem, and ertapenem increased to 64 mg/L, 16 mg/L, and 256 mg/L, respectively. *K. pneumoniae* susceptibility to several antimicrobial agents was significantly reduced over time, including susceptibility to cefoxitin (from 81.1% in 2010 to 67.6% in 2018), piperacillin-tazobactam (from 87.1% in 2010 to 73.4% in 2018), amikacin (from 90% in 2010 to 85.1% in 2018). *K. pneumoniae* susceptibility to colistin remained between 98.2% and 99.5%. In all of the years except for 2010, the susceptibility of *K. pneumoniae* to tigecycline remained above 90%.

Table 1 Overall in vitro Susceptibility to 15 Antimicrobial Agents of Clinical Gram-Negative Isolates in China, 2010–2018

Organism	Antimicrobial Agent	2010			2012			2014			2016			2018		
		S%	R%	MIC_{90}	S%	R%	MIC_{90}	S%	R%	MIC_{90}	S%	R%	MIC_{90}	S%	R%	MIC_{90}
E. coli		n=172			n=182			n=198			n=218			n=252		
	Meropenem	98.8	1.2	0.064	100	0	0.064	97.5	2.5	0.032	98.6	0.9	0.032	98	1.2	0.032
	Imipenem	98.8	1.2	0.25	100	0	0.25	97	3	0.25	97.7	0.9	0.25	98	1.6	0.25
	Ertapenem	91.9	2.3	0.5	97.3	0.5	0.25	96.5	3	0.25	97.2	1.8	0.25	95.6	2.4	0.25
	Cefoxitin	67.4	15.7	32	76.4	11	32	70.2	18.7	128	64.2	22.9	64	82.1	11.9	32
	Cefepime	43.6	32.6	32	39	46.2	64	51.5	22.7	64	51.8	21.1	32	55.6	16.7	16
	Ceftazidime	64.5	31.4	32	63.2	32.4	64	63.6	27.8	128	65.6	25.7	64	64.3	29.8	64
	Cefotaxime	34.3	65.1	256	34.1	65.9	256	33.8	65.7	256	29.8	69.3	256	38.9	60.7	128
	Ceftriaxone	34.3	65.7	256	34.1	65.9	256	33.8	66.2	256	29.8	70.2	256	37.3	61.5	256
	CSL	68	14	64	82.4	7.1	32	83.3	6.1	32	81.7	6	32	86.5	5.6	32
	TZP	93.6	4.1	8	96.7	1.6	8	87.9	8.6	64	92.7	4.1	8	91.7	4	8
	Amikacin	94.2	5.8	8	94.5	5.5	8	94.4	5.6	4	96.3	3.2	4	94.4	4.8	8
	Ciprofloxacin	26.2	69.8	32	26.9	69.8	128	30.3	65.2	128	23.4	70.6	128	28.9	63.9	128
	Levofloxacin	–	–	–	31.9	65.4	32	35.4	61.6	32	29.8	65.1	32	31.7	60.2	32
	Colistin	100	0	0.25	96.2	2.7	0.125	95.5	2.5	0.25	97.2	2.3	0.25	96.8	3.2	2
	Tigecycline	98.3	0	1	100	0	0.5	98	0.5	0.5	100	0	0.5	100	0	1
K. pneumoniae		n=170			n=187			n=199			n=205			n=222		
	Meropenem	93.5	5.9	0.064	90.9	8.6	0.5	86.4	13.1	64	84.4	14.6	32	79.7	19.4	64
	Imipenem	93.5	5.3	0.5	91.4	7.5	1	86.4	13.1	16	82	15.6	16	80.2	17.1	16
	Ertapenem	91.8	7.6	0.5	88.8	9.6	1	80.9	17.1	64	81	17.1	32	78.4	20.7	256
	Cefoxitin	81.1	16	128	76.5	17.6	64	67.8	27.6	256	66.3	28.3	>256	67.6	29.3	256
	Cefepime	66.5	22.9	32	61.5	26.2	64	68.8	21.6	64	65.4	19.5	64	64	29.3	128
	Ceftazidime	70.6	24.1	128	71.7	24.1	64	71.9	25.6	256	67.8	28.8	256	63.1	35.1	>256
	Cefotaxime	51.8	44.7	128	59.4	40.1	256	59.8	38.7	256	56.1	43.4	256	57.7	41	256
	Ceftriaxone	51.2	45.3	256	58.8	39.6	256	60.8	38.2	>256	55.6	43.9	256	56.3	42.3	>256
	CSL	74.1	14.7	64	72.7	15.5	128	76.9	19.1	256	74.6	21	256	72.1	25.2	256
	TZP	87.1	11.2	256	85	12.8	256	81.9	16.1	>256	78	20	>256	73.4	23.4	>256
	Amikacin	90	10	16	91.4	8.6	4	89.9	10.1	>256	84.9	15.1	>256	85.1	14.9	>256
	Ciprofloxacin	50.3	37.3	32	58.8	33.7	128	57.3	33.7	64	51.2	38	128	56.3	37.4	64
	Levofloxacin	–	–	–	63.6	28.9	64	63.8	29.6	64	65.9	30.2	32	60.4	32	64
	Colistin	98.2	1.8	0.5	98.4	1.6	0.25	99.5	0.5	0.25	99	0.5	0.25	98.2	1.8	2
	Tigecycline	86.4	3.6	4	90.9	7	2	92	2.5	2	90.7	2.4	2	97.3	0.9	2

E. cloacae		n=173			n=167			n=191			n=163			n=135		
	Meropenem	99.4	0	0.125	99.4	0.6	0.25	97.4	2.6	0.125	96.9	3.1	0.064	95.6	4.4	0.064
	Imipenem	98.8	0.6	0.5	98.2	0.6	0.5	96.9	2.6	0.5	95.1	3.1	0.5	94.1	3.7	0.5
	Ertapenem	77.8	12.3	2	85.6	9.6	1	90.6	4.7	0.5	88.3	6.7	1	86.7	8.1	1
	Cefepime	73.7	14.6	32	71.3	22.2	64	78	7.3	8	75.5	14.1	16	78.5	11.1	16
	Ceftazidime	59.1	36.3	128	61.7	35.9	128	64.4	31.9	128	62.6	35	64	64.4	34.1	256
	Cefotaxime	52	46.2	256	53.9	45.5	128	51.8	46.1	128	54	46	256	56.3	42.2	256
	Ceftriaxone	52.6	45.6	256	53.3	46.1	256	52.9	45	128	54	45.4	256	57	42.2	256
	CSL	76	17	64	78.4	15	64	88	5.8	32	77.3	9.2	32	85.2	8.9	32
	TZP	73.1	17.5	256	89.8	5.4	32	84.8	9.4	64	82.2	11	128	82.2	8.9	64
	Amikacin	95.9	4.1	8	92.2	7.8	8	98.4	1.6	4	95.7	4.3	8	97.8	2.2	4
	Ciprofloxacin	62	29.8	16	68.3	26.9	32	69.1	25.1	16	66.9	23.3	32	65.9	26.7	16
	Levofloxacin	–	–	–	73.7	22.2	16	78.5	18.8	8	77.3	17.2	16	70.4	21.5	8
	Colistin	90.1	9.9	2	95.8	4.2	0.125	93.7	6.3	0.25	97.5	2.5	0.25	74.6	25.4	16
	Tigecycline	88.3	4.7	4	95.2	3.6	1	95.3	1	1	93.9	3.1	1	96.3	0	2
C. freundii		n=81			n=75			n=102			n=81			n=59		
	Meropenem	98.8	0	0.125	96	4	0.125	96.1	3.9	0.064	97.5	2.5	0.064	89.8	10.2	8
	Imipenem	93.8	1.2	1	96	4	0.5	95.1	3.9	0.5	97.5	2.5	0.5	89.8	10.2	4
	Ertapenem	79	12.3	2	93.3	5.3	0.5	94.1	4.9	0.25	95.1	2.5	0.25	89.8	10.2	8
	Cefepime	69.1	13.6	16	78.7	12	32	80.4	6.9	8	80.2	7.4	8	78	11.9	32
	Ceftazidime	51.9	38.3	128	56	34.7	64	64.7	29.4	64	67.9	28.4	64	57.6	37.3	>256
	Cefotaxime	35.8	54.3	128	52	41.3	64	50	42.2	64	60.5	39.5	64	49.2	47.5	256
	Ceftriaxone	42	56.8	256	53.3	41.3	128	50	47.1	64	59.3	39.5	64	52.5	45.8	256
	CSL	87.7	11.1	64	81.3	12	64	87.3	6.9	32	76.5	8.6	32	76.3	13.6	>256
	TZP	90.1	6.2	16	82.7	10.7	128	87.3	5.9	32	87.7	8.6	32	79.7	16.9	>256
	Amikacin	93.8	4.9	8	96	4	4	98	2	2	97.5	2.5	4	94.9	5.1	8
	Ciprofloxacin	38.3	58	32	46.7	48	16	57.8	36.3	16	46.9	34.6	16	50.8	45.8	64
	Levofloxacin	–	–	–	50.7	38.7	8	63.7	31.4	8	59.3	35.8	16	50.8	44.1	16
	Colistin	97.5	2.5	0.25	100	0	0.125	99	1	0.25	100	0	0.25	98.3	1.7	2
	Tigecycline	98.8	0	2	97.3	0	1	99	0	1	91.4	1.2	2	100	0	2
S. marcescens		n=65			n=65			n=70			n=66			n=49		
	Meropenem	100	0	0.064	98.5	1.5	0.064	90	10	0.125	95.5	4.5	0.064	91.8	8.2	0.25
	Imipenem	98.5	0	1	98.5	1.5	0.5	88.6	10	2	95.5	4.5	1	89.8	8.2	2
	Ertapenem	98.5	1.5	0.125	96.9	1.5	0.125	89.9	10.1	8	96.9	3.1	0.064	87.8	12.2	8

(*Continued*)

Table 1 (Continued).

Organism	Antimicrobial Agent	2010			2012			2014			2016			2018		
		S%	R%	MIC_{90}	S%	R%	MIC_{90}	S%	R%	MIC_{90}	S%	R%	MIC_{90}	S%	R%	MIC_{90}
	Cefepime	87.7	9.2	8	83.1	9.2	8	87.1	10	8	92.4	6.1	0.25	85.7	12.2	16
	Ceftazidime	95.4	4.6	2	92.3	4.6	4	88.6	10	8	93.9	1.5	0.5	87.8	10.2	16
	Cefotaxime	78.5	20	32	81.5	18.5	64	81.2	17.4	128	92.2	6.2	0.5	77.6	14.3	128
	Ceftriaxone	80	20	32	81.5	18.5	128	81.2	14.5	64	90.6	6.2	1	81.6	16.3	128
	CSL	93.8	0	16	93.8	4.6	16	90	7.1	16	92.4	6.1	4	85.7	8.2	32
	TZP	98.5	1.5	4	96.9	1.5	4	91.4	8.6	16	95.5	4.5	4	89.8	10.2	128
	Amikacin	90.8	9.2	4	95.4	4.6	4	98.6	0	4	100	0	4	100	0	2
	Ciprofloxacin	76.9	18.5	1	86.2	10.8	1	85.7	14.3	1	90.9	9.1	0.25	85.7	14.3	4
	Levofloxacin	-	-	-	87.7	9.2	1	84.3	10	1	90.9	7.6	0.5	87.8	12.2	8
	Tigecycline	96.9	3.1	2	92.3	0	2	89.9	1.4	4	97	1.5	2	97.9	2.1	1
K. aerogenes		n=56			n=60			n=68			n=60			n=59		
	Meropenem	100	0	0.064	100	0	0.064	97.1	2.9	0.125	98.3	0	0.064	96.6	3.4	0.064
	Imipenem	100	0	0.5	100	0	0.25	97.1	2.9	0.5	96.7	1.7	1	94.9	3.4	0.5
	Ertapenem	91.1	0	0.5	93.3	3.3	0.5	91.2	4.4	0.5	91.7	3.3	0.5	89.8	5.1	1
	Cefepime	78.6	7.1	8	90	6.7	2	86.8	8.8	8	86.7	5	4	88.1	8.5	8
	Ceftazidime	64.3	28.6	64	51.7	41.7	64	63.2	27.9	64	68.3	28.3	32	52.5	40.7	>256
	Cefotaxime	57.1	41.1	64	40	55	32	58.8	38.2	32	55	45	32	50.8	49.2	128
	Ceftriaxone	57.1	39.3	128	45	53.3	64	58.8	39.7	128	53.3	45	64	50.8	45.8	128
	CSL	80.4	16.1	64	90	3.3	16	92.6	4.4	16	90	5	16	84.7	8.5	32
	TZP	69.6	12.5	128	65	6.7	64	79.4	4.4	32	88.3	0	32	71.2	13.6	256
	Amikacin	92.9	7.1	4	100	0	2	98.5	1.5	2	98.3	1.7	2	96.6	3.4	4
	Ciprofloxacin	66.1	33.9	4	73.3	23.3	2	76.5	17.6	1	73.3	25	8	70.7	17.2	2
	Levofloxacin	–	–	–	75	16.7	4	79.4	8.8	1	73.3	18.3	8	72.4	10.3	2
	Colistin	96.4	3.6	0.5	100	0	0.25	92.6	5.9	0.25	100	0	0.25	98.3	1.7	2
	Tigecycline	67.9	14.3	16	93.3	3.3	1	94.1	1.5	1	90	0	2	98.3	0	2
P. mirabilis		n=65			n=66			n=70			n=78			n=54		
	Meropenem	100	0	0.064	100	0	0.064	98.6	1.4	0.064	100	0	0.064	100	0	0.25
	Imipenem	70.8	20	4	100	0	0.5	81.4	2.9	2	89.6	2.6	2	85.2	7.4	2
	Ertapenem	100	0	0.016	100	0	0.125	98.6	1.4	0.125	100	0	0.125	100	0	0.125
	Cefoxitin	96.9	0	4	95.5	4.5	4	97.1	2.9	4	100	0	4	92.6	1.9	8
	Cefepime	72.3	3.1	8	78.8	1.5	8	90	2.9	2	82.1	2.6	4	100	0	1
	Ceftazidime	96.9	1.5	0.5	95.5	4.5	0.25	98.6	1.4	0.25	98.7	1.3	0.5	96.3	1.9	0.5

	Cefotaxime	63.1	33.8	8	62.1	34.8	16	75.7	20	8	61.5	34.6	16	61.1	38.9	32
	Ceftriaxone	64.6	26.2	8	65.2	33.3	16	78.6	15.7	8	65.4	29.5	8	63	35.2	32
	CSL	100	0	4	100	0	4	98.6	0	4	100	0	4	100	0	4
	TZP	100	0	1	100	0	1	100	0	1	98.7	0	1	100	0	0.5
	Amikacin	96.9	3.1	4	95.5	4.5	4	92.9	2.9	2	98.7	0	4	92.6	5.6	8
	Ciprofloxacin	32.3	67.7	32	37.9	62.1	32	52.9	44.3	16	44.9	55.1	64	38.9	57.4	32
	Levofloxacin	–	–	–	40.9	45.5	8	55.7	30	8	47.4	48.7	8	44.4	51.9	8
P. aeruginosa		n=185			n=178			n=201			n=205			n=153		
	Meropenem	70.8	25.9	32	71.3	21.9	16	69.2	21.4	16	66.3	25.4	16	73.2	22.9	16
	Imipenem	49.2	28.1	32	59.6	30.3	32	67.7	28.9	16	56.6	34.1	32	66	29.4	32
	Cefepime	73.5	13	32	79.2	10.7	32	80.6	10	16	80	8.3	16	80.4	11.8	32
	Ceftazidime	79.5	16.8	64	83.7	13.5	32	76.1	16.9	64	78.5	17.1	64	80.4	17.6	64
	CSL	70.8	22.2	128	77.5	13.5	64	76.6	15.4	64	73.7	18.5	64	75.8	14.4	128
	TZP	68.1	20	256	77.5	16.3	256	74.6	13.9	128	76.1	12.2	128	75.8	10.5	128
	Amikacin	85.9	13.5	>256	89.3	9.6	32	92	6	8	89.3	9.8	32	98	1.3	8
	Ciprofloxacin	65.9	25.9	32	78.7	16.9	4	77.1	17.9	8	78.5	17.6	8	74.5	20.3	16
	Levofloxacin	–	–	–	74.2	18	8	70.1	20.4	8	70.7	19.5	16	69.3	24.8	32
	Colistin	98.4	0.5	1	97.2	2.2	1	99.5	0	1	100	0	1	97.2	2.8	2
A. baumannii		n=180			n=172			n=209			n=202			n=163		
	Meropenem	32.8	64.4	64	34.9	64	64	28.2	70.8	64	20.3	79.2	64	34.4	65	64
	Imipenem	33.3	62.8	64	36.6	62.2	64	29.2	70.3	64	19.3	80.2	64	30.1	69.3	64
	Cefepime	25	66.1	64	31.4	65.7	256	26.8	71.3	256	19.3	76.7	128	33.1	63.8	128
	Ceftazidime	25.6	72.2	256	33.7	65.1	>256	26.8	71.8	>256	21.3	78.2	>256	35	63.8	>256
	CSL	28.9	39.4	64	33.1	44.8	128	29.7	57.4	64	24.8	51	64	35	32.5	64
	TZP	24.4	71.1	256	29.1	67.4	>256	25.4	71.3	>256	17.8	80.2	>256	31.9	66.9	>256
	Amikacin	35.6	64.4	>256	43	55.8	>256	32.1	67.9	>256	34.2	65.8	>256	46.6	52.8	>256
	Ciprofloxacin	23.3	76.7	32	32	67.4	128	25.4	73.7	128	20.8	79.2	128	31.9	66.9	128
	Levofloxacin	–	–	–	33.1	58.1	16	28.7	56	16	22.3	58.9	16	32.5	61.3	16
	Colistin	97.8	2.2	1	100	0	0.5	99	1	0.5	100	0	0.5	100	0	1
	Tigecycline	44.4	13.9	8	80.2	1.2	4	76.6	3.3	4	78.7	4.5	4	87.3	3.8	4

Abbreviations: MIC, minimum inhibitory concentration; MIC_{90}, MIC for 90% of the organisms, respectively; %S, percent susceptible; %R, percent resistant; CSL, cefoperazone/sulbactam; TZP, piperacillin/tazobactam.

The susceptibility of *E. cloacae* to meropenem and imipenem decreased each year, from 98.8–99.4% in 2010 to 94.1–95.6% in 2018. In each year, the monitoring results showed that the proportion of *E. cloacae* resistant to colistin was between 2.5–25.4%.

The susceptibility of *C. freundii* to meropenem and imipenem decreased from 98.8% and 93.8% in 2010, respectively, to 89.8% to both drugs in 2018. Simultaneously, the MIC_{90} increased to 8 mg/L and 4 mg/L for meropenem and imipenem, respectively. The susceptibility rate of *C. freundii* to cefoperazone-sulbactam and piperacillin-tazobactam was more than 75% in all the years tested; the susceptibility to amikacin, colistin, and tigecycline was over 90%.

From 2010 to 2018, the susceptibility of *P. aeruginosa* to meropenem increased from 70.8% to 73.2%, and the susceptibility to imipenem increased from 49.2% to 66%. Simultaneously, the *P. aeruginosa* isolates exhibited increased susceptibility to cefepime, ceftazidime, cefoperazone-sulbactam, piperacillin-tazobactam, and amikacin. The susceptibility of *P. aeruginosa* to ciprofloxacin and levofloxacin was reduced over time.

A. baumannii susceptibility to meropenem and imipenem was less than 40% in all of the study years. The MIC_{90} of *A. baumannii* for piperacillin-tazobactam, amikacin, and ceftazidime was higher than 128 mg/L, and the MIC_{90} for cefoperazone-sulbactam was between 64–128 mg/L. *A. baumannii* resistance to colistin was less than 3%.

Multi-Drug-Resistant Bacteria from 2010 to 2018

Information on the major resistant gram-negative bacilli in each surveillance year is listed in Table 2. Among carbapenem-resistant *Enterobacterales*, the incidence of carbapenem-resistant *K. pneumoniae* was increased each year, from 7.6% in 2010 to 21.2% in 2018. Among the other *Enterobacterales* isolates, higher carbapenem resistance rates were observed in *C. freundii* (2.5–12.3%), *S. marcescens* (1.5–12.2%), and *E. cloacae* (4.7–12.1%). The incidence of carbapenem-resistant *E. coli* varied between 0.5% and 3.5%. From 2010 to 2016, the incidence of carbapenem-resistant *A. baumannii* increased significantly from 64.4% to 80.2% (with an incidence of 69.3% in 2018). The incidence of ESBL-producing *E. coli* fluctuated between 50.4% and 64.3%. Using the CLSI phenotypic confirmation method, we found that the proportion of ESBL produced by *K. pneumoniae* decreased from 41.2% in 2010 to 18% in 2018. The prevalence of multidrug-resistant bacteria in the different infection types is shown in Table 3. We analyzed specimens of the four major infection sources separately, including bloodstream infections (BSIs), intra-abdominal infections (IAIs), respiratory infections (RIs), and urinary tract infections (UTIs). The prevalence of CRKP (25.4%, 18/71) in UTIs was higher than that of CRKP in BSIs (27.7%, 156/564), IAIs (26.7%, 35/131), and RIs (29.8%, 31/104). The prevalence of CRAB (56.4%, 22/39) in UTIs was lower than that of CRAB in BSIs (73.2%, 298/407), IAIs (72.4%, 84/116), and RIs (72.9%, 145/199). ESBL-producing *E. coli, K. pneumoniae*, and *P. mirabilis* from the urinary tract were also more prevalent than the other three types of infection. The proportion of carbapenem-resistant *Serratia marcescens* (12.3%, 10/81) in BSIs was higher than that in IAIs (6.9%, 2/29), RIs (5.7%, 7/122), and UTI (0%, 0/38).

Table 2 Prevalence by Year of Multidrug-Resistant Gram-Negative Isolates Isolates

Organism	% (No. of Isolates)				
	2010	2012	2014	2016	2018
CR-*C. freundii*	12.3 (10/81)	5.3 (4/75)	4.9 (5/102)	2.5 (2/81)	10.2 (6/59)
CR-*K. aerogenes*	0 (0/56)	3.3 (2/60)	4.4 (3/68)	3.3 (2/60)	5.1 (3/59)
CR-*E. cloacae*	12.1 (21/173)	9.6 (16/167)	4.7 (9/191)	6.7 (11/163)	8.1 (11/135)
CR-*E. coli*	2.3 (4/172)	0.5 (1/182)	3.5 (7/198)	1.8 (4/218)	2.4 (6/252)
CR-*K. pneumoniae*	7.6 (13/170)	9.6 (18/187)	17.6 (35/199)	17.6 (36/205)	21.2 (47/222)
CR-*S. marcescens*	1.5 (1/65)	1.5 (1/65)	11.4 (8/70)	4.5 (3/66)	12.2 (6/49)
ESBL-*E. coli*	61.6 (106/172)	64.3 (117/182)	57.6 (114/198)	62.8 (137/218)	50.4 (127/252)
ESBL-*K. pneumoniae*	41.2 (70/170)	32.1 (60/187)	24.6 (49/199)	28.3 (58/205)	18 (40/222)
ESBL-*P. mirabilis*	33.8 (22/65)	31.8 (21/66)	21.4 (15/70)	20.5 (16/78)	1.9 (1/54)
CR-*A. baumannii*	64.4 (116/180)	64 (110/172)	70.8 (148/209)	80.2 (162/202)	69.3 (113/163)
CR-*P. aeruginosa*	29.2 (54/185)	31.5 (56/178)	30.8 (62/201)	34.1 (70/205)	29.4 (45/153)

Notes: Carbapenem-resistant isolates are defined as *Enterobacterales*, which were resistant to any of the resistant to meropenem, imipenem, and ertapenem; *A. baumannii* and *P. aeruginosa* which as any of the resistant to meropenem and imipenem.

Abbreviations: CR, carbapenem resistant; ESBL, extended-spectrum β-lactamases.

Table 3 Prevalence of Multidrug-Resistant Gram-Negative Isolates in Different Infection Types

Organism	% (No. of Isolates)			
	BSIs	IAIs	RIs	UTIs
CR-*A. baumannii*	73.2 (298/407)	72.4 (84/116)	72.9 (145/199)	56.4 (22/39)
CR-*C. freundii*	7 (3/43)	4.9 (4/82)	6.9 (7/101)	8.9 (11/124)
CR-*K. aerogenes*	1.8 (1/56)	8 (4/50)	3.5 (4/115)	2.3 (1/44)
CR-*E. cloacae*	7.4 (18/244)	8.4 (10/119)	7.4 (20/270)	14.4 (13/90)
CR-*E. coli*	2.4 (17/710)	1.5 (2/134)	9.1 (2/22)	1 (1/100)
CR-*K. pneumoniae*	14.2 (80/564)	14.5 (19/131)	14.4 (15/104)	25.4 (18/71)
CR-*P. aeruginosa*	47 (156/332)	44 (66/150)	46.8 (102/218)	44.3 (35/79)
CR-*S. marcescens*	12.3 (10/81)	6.9 (2/29)	5.7 (7/122)	0 (0/38)
ESBL-*E. coli*	57.9 (411/710)	54.5 (73/134)	59.1 (13/22)	63 (63/100)
ESBL-*K. pneumoniae*	27.7 (156/564)	26.7 (35/131)	29.8 (31/104)	38 (27/71)
ESBL-*P. mirabilis*	10.9 (5/46)	16.7 (6/36)	16.1 (10/62)	28.9 (39/135)

Notes: Carbapenem-resistant isolates are defined as *Enterobacterales*, which were resistant to any of the resistant to meropenem, imipenem, and ertapenem; *A. baumannii* and *P. aeruginosa* which as any of the resistant to meropenem and imipenem.

Abbreviations: BSIs, bloodstream infections; IAIs, intra-abdominal infections; RIs, respiratory infections; UTIs, urinary tract infections; CR, carbapenem resistant; ESBL, extended-spectrum beta-lactamases.

Cumulative MIC Analysis of E. coli, K. pneumoniae, P. aeruginosa, and A. baumannii Against Antimicrobial Agents

Figure 1 shows the cumulative distribution of the MICs of different types of antimicrobial agents against the four majors gram-negative bacteria (*E. coli, K. pneumoniae, P. aeruginosa*, and *A. baumannii*). All three carbapenems had an MIC of less than 1 mg/L for more than 95% of the *E. coli* isolates (Figure 1A). When the MIC value was between 0.25 mg/L and 8 mg/L, the difference between the curve of *K. pneumoniae* and the curve of *E. coli* was clear. For the *P. aeruginosa* curve (Figure 1B), the MIC of meropenem was lower than 2 mg/L for 70% of the isolates, and the MIC of imipenem was lower than 2 mg/L for 60% of the isolates. The MIC of meropenem and imipenem was greater than 8 mg/L in more than 75% of the isolates of *A. baumannii*. Figure 1C and D show the cumulative MIC percentage curves of the three generation cephalosporins against the four majors gram-negative bacteria. For *K. pneumoniae*, when the MIC was below 0.5 mg/L, the proportion of ceftriaxone- and cefotaxime-susceptible isolates was higher than the proportion of ceftazidime-susceptible isolates. When the MIC was above 0.5 mg/L, the proportion of ceftriaxone- and cefotaxime-susceptible isolates was lower than that of ceftazidime-sensitive isolates. This phenomenon also appeared in the curve of *E. coli*, but the demarcated MIC value became 0.25 mg/L. Ceftazidime has significantly higher antibacterial activity against *P. aeruginosa* than against *A. baumannii*. For ciprofloxacin and levofloxacin, an MIC value lower than 4 mg/L was effective for more than 70% of the isolates of *K. pneumoniae*, and an MIC value lower than 1 mg/L was noted for 60–70% of the isolates. For ciprofloxacin and levofloxacin (Figure 1E), an MIC value below 2 mg/L was feasible for more than 40% of the isolates of *E. coli*, and an MIC value below 0.5 mg/L was effective for 35–40% of the isolates. For *A. baumannii* (Figure 1F), when the treatment concentrations of ciprofloxacin and levofloxacin were below 2 mg/L, the MIC distribution of the two drugs was not appreciably different. When the concentration was above 2 mg/L, more than 70% of the isolates were responsive to less than 8 mg/L of levofloxacin, and only about 30% of the isolates responded to less than 8 mg/L of ciprofloxacin. The differences in the distribution of the MIC values of levofloxacin and ciprofloxacin against *P. aeruginosa* were mainly concentrated between the MIC values of 0.125 m/L and 1 mg/L. The MIC distribution of cefoperazone-sulbactam and piperacillin-tazobactam on *E. coli* is shown in Figure 1G. When the MIC value was above 16 mg/L, the MIC distributions of the two agents to *E. coli* was not much different. The cumulative MIC curves of cefoperazone-sulbactam and piperacillin-tazobactam on *P. aeruginosa* almost coincided (Figure 1H). For *A. baumannii*, when the MIC value was above 16 mg/L, cefoperazone-sulbactam had better antibacterial activity in vitro.

Prevalence of Major Carbapenemase Genes in All CRE Isolates

Of the 295 CRE isolates, 233 were tested by PCR for the major carbapenemase genes. As shown in Table 4, in total,

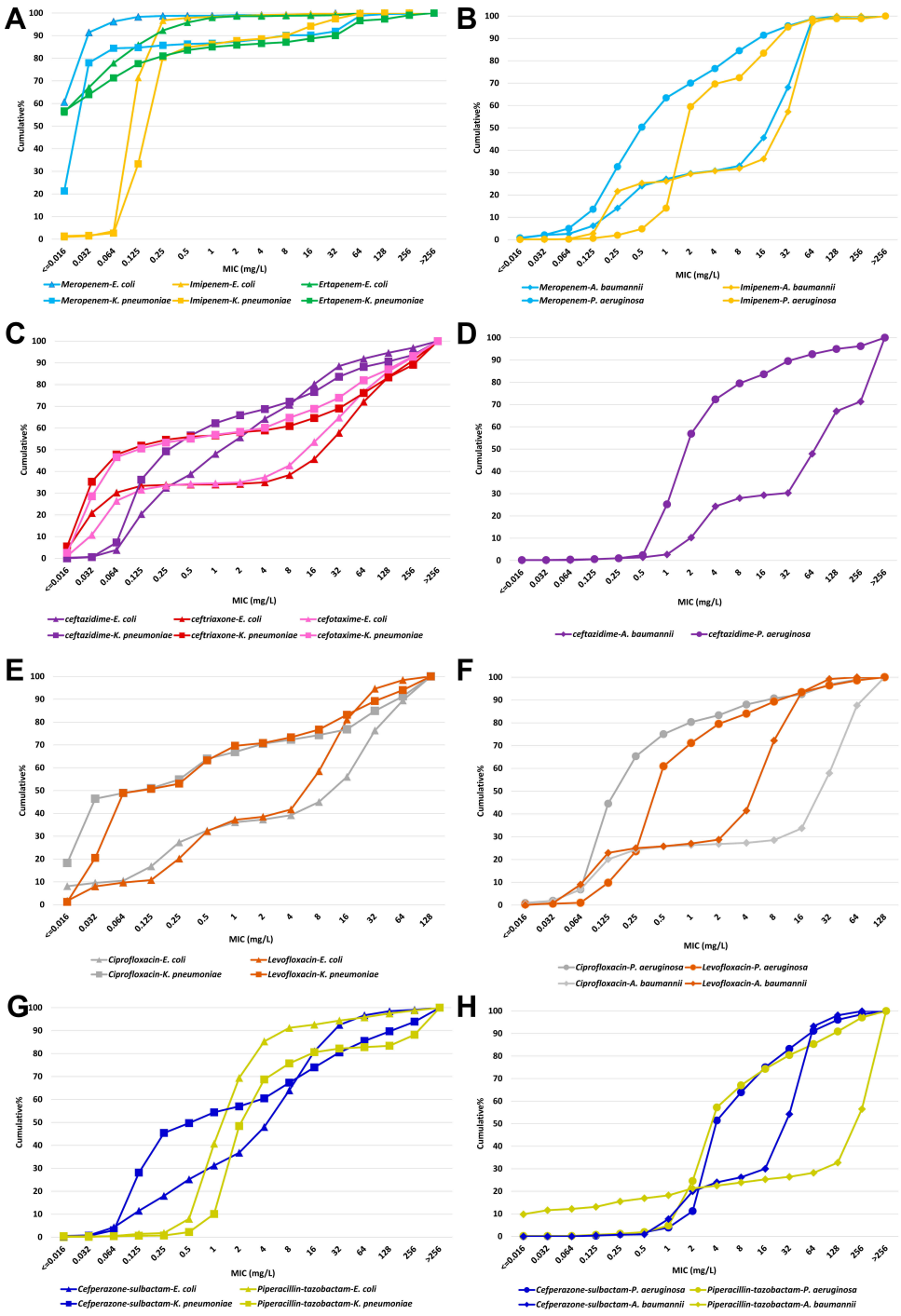

Figure 1 Cumulative MIC of *E. coli, (K) pneumoniae, (P) aeruginosa*, and *A. baumannii* against antimicrobial agents. (**A** and **B**) Cumulative MIC of *E. coli, K. pneumoniae, P. aeruginosa*, and *A. baumannii* against carbapenems. (**C** and **D**) Cumulative MIC of *E. coli, K. pneumoniae, P. aeruginosa*, and *A. baumannii* against major cephalosporins including ceftazidime, ceftriaxone, and cefotaxime. (**E** and **F**) Cumulative MIC of *E. coli, K. pneumoniae, P. aeruginosa*, and *A. baumannii* against quinolones. (**G** and **H**) Cumulative MIC of *E. coli, K. pneumoniae, P. aeruginosa*, and *A. baumannii* against cefoperazone-sulbactam and piperacillin-tazobactam.

129 *K. pneumoniae* were tested by PCR: 92 isolates were detected to carry the $bla_{\text{KPC-2}}$ gene, 14 isolates carried the bla_{NDM} gene, and one isolate carried the bla_{IMP} gene. Forty-four *E. cloacae* were tested for carbapenemase genes by PCR; of these, 2 carried the bla_{KPC} gene, 7carried the bla_{NDM} gene, and 2 carried the bla_{IMP} gene; 33 isolates did not carry these three carbapenemase genes. Twenty-five isolates of *C. freundii* were tested by PCR; of these, 9 isolates carried bla_{NDM}, 2 isolates carried bla_{KPC}, and 2 isolates carried both the bla_{KPC} and bla_{IMP} genes.

Table 4 Prevalence of Major Carbapenemase Genes in All Carbapenem-Resistant *Enterobacterales* Isolates

Organisms	Carbapenemase Gene							PCR Negative	Not Tested	Total
	bla_{KPC-2}	$bla_{KPC-2+IMP-1}$	bla_{NDM-1}	bla_{NDM-5}	bla_{NDM-7}	bla_{IMP-1}	bla_{IMP-4}			
K. pneumoniae	92		10	2	2		1	22	20	149
E. cloacae	2		5	2		1	1	33	24	68
C. freundii	2	2	9				1	11	2	27
E. coli	1		2	4				9	6	22
S. marcescens	3							11	5	19
K. aerogenes	1							4	5	10
Total	101	2	26	8	2	1	3	90	62	295

Twenty-five isolates of *E. coli* were tested by PCR; of these, six isolates carried $bla_{NDM,}$ and one isolate carried bla_{KPC}.

Discussion

In comparison with the last CMSS surveillance report, the resistance rates of *K. pneumoniae* and *A. baumannii* to carbapenem drugs are gradually increasing. Thus, the current status of antimicrobial resistance is grim. We found that the incidence of major multidrug-resistant bacteria is different in different types of infection. The prevalence of ESBL-*E. coli*, ESBL-*K. pneumoniae*, ESBL-*P. mirabilis*, and CRKP from UTIs were significantly higher than those from the other three infection types (BSIs, IAIs, and RIs).

Our data is based on the standard agar dilution method and micro-broth dilution method, which can provide accurate MIC data for clinical use. For anti-infective treatment, MIC data is essential in the treatment of severe infections. When providing individualized treatment, it is necessary to combine pharmacokinetic/pharmacodynamic (PK/PD) data and MIC determinations to calculate the dosage of the antimicrobial agent(s) to be administered to the patient.[18] The clinical application of PK/PD theory is one of the many reliable strategies that are effective in realizing the therapeutic potential of existing antimicrobial agents.[19] The CLSI had lowered the susceptible breakpoint of quinolone for the treatment of *Enterobacterales* and *P. aeruginosa* in the 2019 update.[14] Especially in the treatment of severely infected patients, new breakpoints are used to determine the dosage of antimicrobial agents, and a corresponding area under the curve (AUC)/MIC target can be achieved by evaluating the corresponding drug dosage.[20–22] From the cumulative MIC of *E. coli, K. pneumoniae*, and *P. aeruginosa* against levofloxacin and ciprofloxacin, we can see that the new breakpoint has a lower effect on the susceptibility rate of the two drugs in vitro.

Our multi-center research shows that the prevalence of CRKP in China has been increasing over the past ten years. The prevalence of CRKP increased from 7.6% in 2010 to 21.2% in 2018. This result is consistent with the surveillance conducted by China's most significant drug surveillance network: China antimicrobial resistance surveillance system (CARSS).[23] The mortality after CRKP infection is very high. In some studies, the mortality rate of CRKP bacteremia was as high as 50–70%.[24,25] In this study, the primary resistance mechanism of CRKP was caused by carbapenemase encoded by plasmid-mediated bla_{KPC}, which is consistent with our previous CRE-related studies.[26–28] Several studies have shown that CRKP carrying bla_{KPC}-type plasmids can occur in large-scale outbreaks or spread in hospitals. These reports have highlighted the considerable obstacles clinicians face in the prevention and control of nosocomial infections.[29,30] At present, in the clinical treatment of CRKP infection, it is recommended to provide a combination of drugs that are sensitive to in vitro antimicrobial susceptibility tests within the allowable range, extend the infusion time, and increase the dose to achieve the goal of T%> MIC.[19,31] Our data show that tigecycline, colistin, and amikacin also maintain high in vitro activity against *K. pneumoniae*. Meropenem has shown in vitro activity against other *Enterobacterales*, including *E. coli, E. cloacae*, and *C. freundii*.

The susceptibility of *A. baumannii* to carbapenems declined significantly from 2010 to 2018. In the treatment of CRAB, there are fewer options for antimicrobial agents as indicated by the in vitro susceptibility tests; thus, the treatment of a CRAB infection often requires combined treatment. Attention should be paid to the MIC of antimicrobial agents as well.[32] The susceptibility of *P. aeruginosa* to carbapenem is increasing, and the

susceptibility to other anti-pseudomonas drugs is also increasing. Simultaneously, domestic CHINET research shows that the incidence of carbapenem-resisitant *P. aeruginosa* was also decreasing, in accordance with the results of this study.[33]

Conclusion

The data of the CMSS from 2010 to 2018 show that the current situation of antimicrobial resistance in China is severe. The results indicate an increase in *K. pneumoniae* resistance to carbapenems over time, mainly owing to KPC-type carbapenemase production. *A. baumannii* was severely resistant to carbapenems in China. Ongoing MIC-based resistance surveillance, like CMSS, provides additional data for clinical anti-infective treatment.

Abbreviations

CARSS, China antimicrobial resistance surveillance system; CLSI, Clinical and Laboratory Standards Institute; CMSS, Chinese Meropenem Surveillance Study; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacterales*; ESBL, extended-spectrum beta-lactamase; MICs, minimum inhibitory concentrations; MYSTIC, Meropenem Yearly Susceptibility Test Information Collection; BSIs, bloodstream infections; IAIs, intra-abdominal infections; RIs, respiratory infections; UTIs, urinary tract infections.

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Disclosure

The authors report no conflicts of interest in this work.

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