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ORIGINAL ARTICLE

Resistance reported from China antimicrobial surveillance network (CHINET) in 2018

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Abstract

The aim of this study is to investigate the antimicrobial susceptibility of strains isolated from the major hospitals in China. A total of 44 teaching hospitals were involved. Antimicrobial susceptibility testing was conducted by Kirby-Bauer automated systems, and results were interpreted using CLSI criteria. Totally 244,843 strains were isolated in 2018, of which gram-negative bacilli and gram-positive cocci were accounting for 71.8% and 28.2%, respectively. 39.7% of isolates were cultured from lower respiratory tract, 18.8% from urine, 14.8% from blood, 1.3% from cerebrospinal fluid, respectively. Of those, the five major species were most often isolated (65.5%, 63%, 52.3%, and 30.3%). The resistance rate of MRSA to most antimicrobial agents was significantly higher than that of MSSA strains, except for to trimethoprim-sulfamethoxazole in urine specimen. *E.coli* was still highly susceptible to carbapenem antibiotics, and the resistance rate was less than 5%. Carbapenem resistance among *Klebsiella pneumoniae*, especially cultured from cerebrospinal fluid, increased significance from 18.6 to 64.1%. The resistance rates of *Pseudomonas aeruginosa* to carbapenems were nearly 30% in the blood, in urine, and in the lower respiratory tract, but about 60% of that in cerebrospinal fluid. About 80% of *Acinetobacter baumannii* strains was resistant to imipenem and meropenem, respectively. Bacterial resistance of five major clinical isolates from cerebrospinal fluid to common antibiotics (in particular Carbapenem-resistant *Klebsiella pneumoniae*) currently shows an increasing trend. It is worth to emphasize the importance of serious control of hospital infection and better management of clinical use of antimicrobial agents.

Keywords Bacterial resistance surveillance · Antimicrobial susceptibility testing · Methicillin-resistant *Staphylococcus* · Carbapenem-resistant gram-negative bacilli

Introduction

In recent years, the prevalence of multidrug-resistant bacteria represented by gram-negative bacilli has rapidly increased, which have posed great challenges for the clinical anti-infective treatment. Bacterial resistance surveillance is one of the most important basic tasks to understand the change of resistant bacteria and to prevent its further spreading. In this analysis, we reported the antimicrobial resistance of clinically important pathogens from China antimicrobial surveillance network (CHINET).

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Materials and methods

Participating hospitals and bacterial strains

A total of 44 hospitals were obtained in the CHINET in 2018. Most of the hospitals included are the largest in each province or city; altogether, they represent 26 provinces or cities (about nine hundred million population). In order to avoid duplicate counts, only one isolate from the same species was included per patient, based on the personal identifying code and hospital, per year. Species identification of the isolates was

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performed by automated systems such as Vitek, Phoenix, or MALDI-TOF.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed followed the guidelines recommended by the Clinical and Laboratory Standards Institute (CLSI) [1], in which the US FDA standard was adopted for tigecycline test, and the criteria for polymyxinB against *Enterobacteriaceae* are referred to the epidemiological cutoff value of colistin in the CLSI file (MIC ≤2 μg/mL for wild strains; MIC ≥4 μg/mL for non-wild strains).

Quality control

Staphylococcus aureus ATCC 25923, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 were used as internal quality control. Carbapenem-resistant *Enterobacteriaceae* (CRE) is defined as being resistant to any of imipenem, meropenem, or ertapenem.

Results

Percentage of major clinical strains

A total of 244,843 clinical isolates were collected, of which 69,057 strains of gram-positive bacteria accounted for 28.2% and 175,786 strains of gram-negative bacteria accounted for 71.8%. Most isolates (39.7% of 244,843) were cultured from lower respiratory tract. Of those, the five major species were most often isolated (65.5%). Urine isolates were mainly from women (66.7% of five major species) and *E. coli* was mostly often isolated (46.6%). From blood, the most frequently organism was also *E. coli* (23.1%). The five major species accounted for 30.3% in cerebrospinal fluid. The percentage of five major species isolated from four specimens is shown in Table 1.

Susceptibility of gram-positive cocci to antimicrobial agents

For MRSA, the resistance rate to most antimicrobial agents was significantly higher than that of MSSA strains. However, the resistance rate of MRSA to trimethoprim-sulfamethoxazole was lower than that of MSSA except for in urine specimens (20.5% and 15.5%). 79.6% of MRSA is sensitive to trimethoprim-sulfamethoxazole, and 98.3% of MSSA is sensitive to rifampicin. The resistance rate of MRSA isolated from cerebrospinal fluid to gentamicin, rifampin, and levofloxacin is higher than other three specimens. Four strains of *S. aureus* isolated from blood are resistant to linezolid. No vancomycin-resistant strain was found in *Staphylococcus* (Table 2).

Susceptibility and resistance rate of gram-negative bacilli to antimicrobial agents

From four specimens, the resistance rate of *E. coli* to ceftazidime, cefepime were close to or higher than 30%. The resistance rate of *E. coli* to ciprofloxacin and trimethoprim-sulfamethoxazole were nearly 70%. The resistance rates of *E. coli* to β-lactam/β-lactamase inhibitor combinations and carbapenems were still low, but the resistance rate of *Klebsiella pneumoniae* to imipenem and meropenem was fluctuated around 18.6% and 64.1%, especially the cerebrospinal fluid isolates. The resistance rate of *Klebsiella pneumoniae* to other agents was higher than that of *E. coli* besides ciprofloxacin and trimethoprim-sulfamethoxazole, to polymyxin B and tigecycline were lower (0 and 5.6%) (Table 3). The resistance rates of *Klebsiella pneumoniae* to imipenem and meropenem was increased to 25% and 26.3% in 2018 respectively from 3.0% and 2.9% in 2005, and the resistance rate increased was more than 8 times (Fig. 1).

The resistance rate of 18,534 strains of *Pseudomonas aeruginosa* to imipenem and meropenem was fluctuated around 17.1% and 57.4% respectively. especially for cerebrospinal fluid isolates, the resistance rate of *P. aeruginosa* to amikacin was less than 10% respectively, meantime the resistance rate of *P. aeruginosa* to other agents was < 30%. The

Table 1 Percentage of five major species isolated from four specimens

	Blood		Urine		Lower respiratory tract		Cerebrospinal fluid	
	n	%	*n*	%	*n*	%	*n*	%
Number of isolates	36,359	100.0	46,081	100.0	97,297	100.0	3157	100.0
Escherichia coli	8381	23.1	21,489	46.6	4553	4.7	122	3.9
Klebsiella pneumoniae	5616	15.4	4592	10.0	18,891	19.4	264	8.4
Pseudomonas aeruginosa	1054	2.9	1710	3.7	15,705	16.1	65	2.1
Acinetobacter baumannii	1164	3.2	728	1.6	16,566	17.0	394	12.5
Staphylococcus aureus	2801	7.7	514	1.1	8000	8.2	110	3.5

Table 2 Resistance rates of *Staphylococcus* spp. to antimicrobial agents (%)

Antibiotics	Blood		Urine		Lower respiratory tract		Cerebrospinal fluid	
	MRSA (*n* = 871)	MSSA (*n* = 1880)	MRSA (*n* = 132)	MSSA (*n* = 372)	MRSA (*n* = 3221)	MSSA (*n* = 4462)	MRSA (*n* = 53)	MSSA (*n* = 58)
Penicillin G	100	89.4	100	83.4	100	88	100	87.9
Oxacillin	100	0	100	0	100	0	100	0
Gentamicin	26.8	11.2	27.5	11.6	34	11.9	37.7	15.5
Rifampin	11.8	1.4	9.9	0.8	12.9	0.5	17.3	0
Levofloxacin	34	11.9	49.2	16.5	51.1	10	52.1	13.5
Trimethoprim/sulfamethoxazole	9.9	20.2	20.5	15.5	5.2	18.2	7.5	21.8
Clindamycin	61.7	26	60.2	23.6	61.7	25.9	64.6	26
Erythromycin	84.6	52.2	83	48.9	82.1	53.2	83.7	50
Linezolid	0.2	0.1	0	0	0	0	0	0
Vancomycin	0	0	0	0	0	0	0	0

resistance rate of *P. aeruginosa* to imipenem and meropenem showed a steady downward trend from 2005 to 2018 (Fig. 2). The resistance rate of *A. baumannii* to the agents was higher than that of *P. aeruginosa*. From urine, the resistance rate of *A. baumannii* to the agents was fluctuated around 21.8% and 46.7% respectively (Table 4). The resistance rate of cerebrospinal fluid isolates was higher than other three specimens. The resistance rate of *A. baumannii* to imipenem and meropenem showed a rapid rising trend from 2005 to 2018 (Fig. 3).

Discussion

Results of 2018 CHINET antimicrobial surveillance network: (1) The total number of strains collected in 2018 was 244,843, an increase of 28.5% compared with 190,610 in 2017 [2]. Except for *E. coli*, the prevalence of most bacteria out of *Enterobacteriaceae* was slightly higher than that in 2017, among of which, *Klebsiella* spp. was the most. The prevalence of *Acinetobacter spp*. in non-fermented gram-negative bacilli was increased slightly, but *P. aeruginosa* remained unchanged. (2) Routine susceptibility testing results show that either *Enterobacteriaceae* or *A. baumannii*, tigecycline susceptibility testing is of false mediation or false drug resistance, the laboratory should promptly use other methods for review and confirmation.

The bacterial resistance of gram-negative bacteria is becoming more and more serious, and the treatment of certain drug-resistant infections is extremely limited in clinical practice [3–5]. Carbapenems have been considered as the last line

Table 3 Resistance rates of *Enterobacteriaceae* to antimicrobial agents(%)

Antibiotics	Blood		Urine		Lower respiratory tract		Cerebrospinal fluid	
	E. coli (*n* = 8381)	*K. pneumoniae* (*n* = 5616)	*E. coli* (*n* = 21,489)	*K. pneumoniae* (*n* = 4592)	*E. coli* (*n* = 4553)	*K. pneumoniae* (n = 18,891)	*E. coli* (*n* = 122)	*K. pneumoniae* (*n* = 264)
Cefoperazone/Sulbactam	8.3	40.1	4.8	27.9	9.7	32.5	11.5	69
Piperacillin/tazobactam	6.9	37.7	3.8	24.9	8	28.7	10.3	62
Ceftazidime	28.9	45.7	25.9	39.6	34.4	37.5	25.6	70.1
Cefepime	30.3	42.9	25.2	35.3	35.4	35.1	21.7	67.6
Imipenem	3.2	34	1.2	18.6	3.3	25.8	1.7	61.2
Meropenem	3.5	34	1.3	19.8	3.4	27.6	1.7	64.1
Amikacin	2.7	23.1	2.7	16.2	3.4	18.3	2.5	43.7
Ciprofloxacin	65.7	55.6	68.6	59	66.4	47	71	75.4
Trimethoprim/ Sulfamethoxazole	60.3	42.6	53.2	47.6	59	34.7	63.6	41.9
Polymycin B	0	1.4	0.6	0	0	0.4	0	0
Tigecycline	0	2.8	0	5.6	0.1	3.3	0	3.2

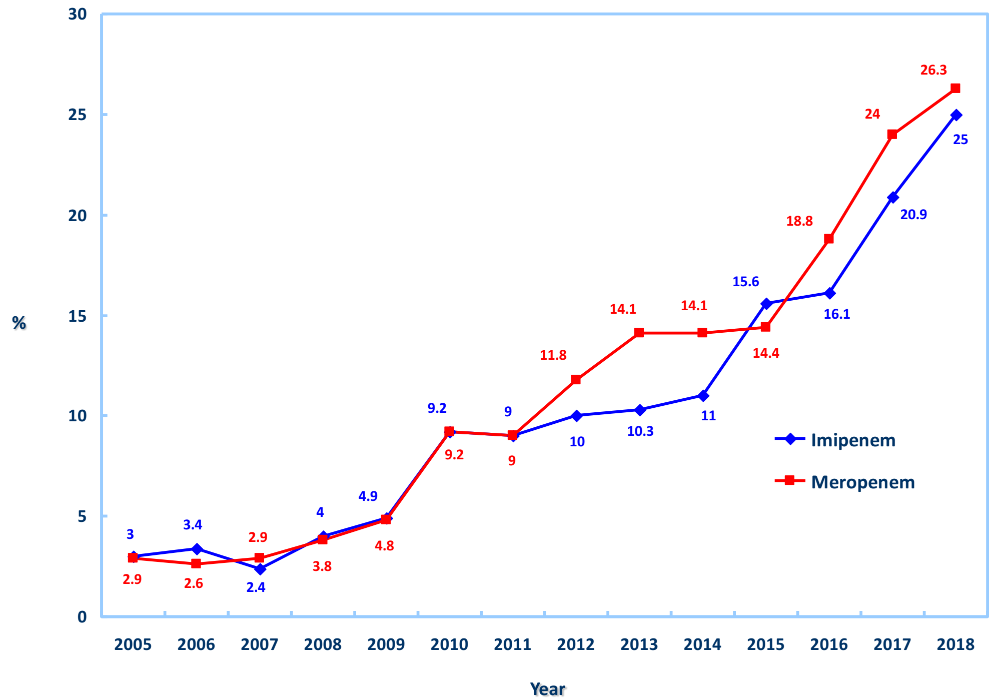

Fig. 1 Resistance Change of *Klebsiella pneumoniae* to Imipenem and Meropenem between 2005 and 2018

of defense against gram-negative infections in the past 10 years. With the rapid increase in the prevalence of carbapenem-resistant strains, especially *K. pneumoniae*, *P. aeruginosa*, *and A. baumannii*, clinical anti-infective treatment has become a difficult problem. CHINET surveillance data [2, 3, 6] over the years showed that the resistance rate of *K. pneumoniae* to imipenem and meropenem was respectively increased from 3.0% and 2.9% in 2005 to 25% and 26.3% in 2018, with more than 8-fold increase. Besides, the annual isolation rate of *K. pneumoniae* was also steadily increasing. The surveillance results showed that the resistance rate of *K. pneumoniae* to carbapenems was > 20%; the resistance rate of *Klebsiella pneumoniae* isolated from only 1 hospital out of 5 children's hospitals to imipenem was 2.5%, while the resistance rate of *Klebsiella pneumoniae* isolated from the remaining hospitals was ranged from 32.1 to 45.5%. Nevertheless, the resistance rates of *P. aeruginosa* and *A. baumannii* to imipenem were close to 30.7% and 73.2% respectively.

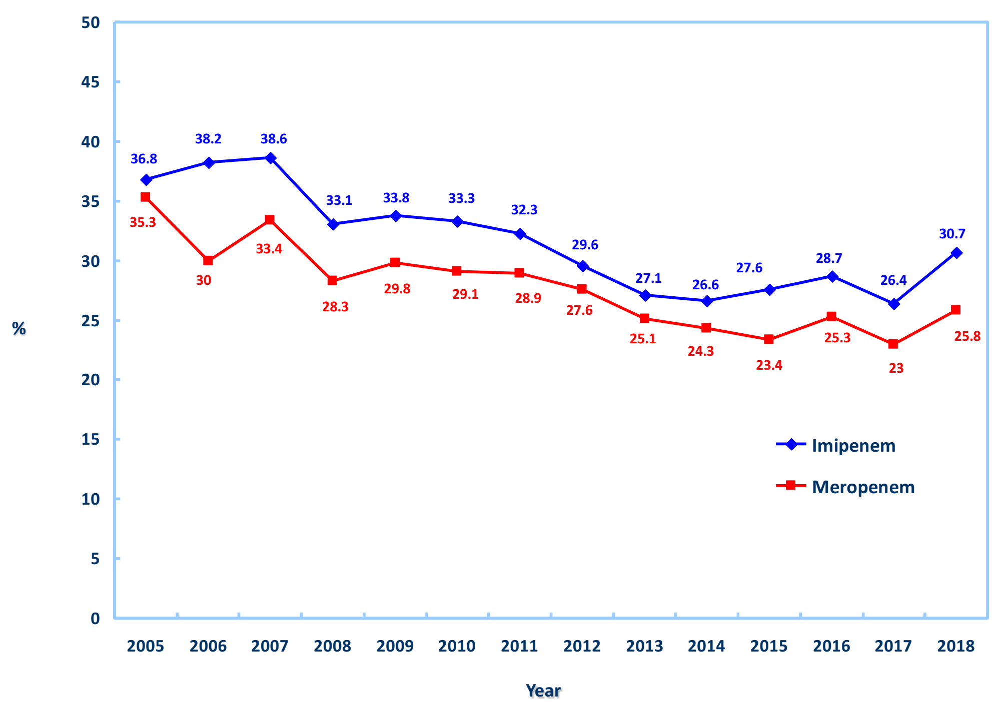

Fig. 2 Resistance Change of *Pseudomonas aeruginosa* to Imipenem and Meropenem between 2005 and 2018

Table 4 Resistance rates of non-fermentative gram-negative bacilli to antimicrobial agents (%)

Antibiotics	Blood		Urine		Lower respiratory tract		Cerebrospinal fluid	
	P. aeruginosa (*n* = 1054)	*A. baumannii* (*n* = 1164)	*P. aeruginosa* (*n* = 1710)	*A. baumannii* (*n* = 728)	*P. aeruginosa* (*n* = 15,705)	*A. baumannii* (*n* = 16,566)	*P. aeruginosa* (*n* = 65)	*A. baumannii* (*n* = 394)
Cefoperazone/sulbactam	14.3	59.2	14.5	26.1	17.9	52.7	32.1	60.9
Piperacillin/tazobactam	15.4	76.9	12.7	41.3	17.3	79.5	30.8	84.1
Ceftazidime	18.4	78.6	14.3	43.5	20.2	79.2	31.2	85
Cefepime	14.3	79.4	13.6	42.8	16.6	77.8	30.2	86.4
Imipenem	29.2	79.2	19.7	41.6	33.8	79.8	55.4	85.4
Meropenem	24.9	78.2	17.1	40.1	28.8	80.7	57.4	85.6
Amikacin	4.4	58.3	5	27.3	7.1	59.1	23.4	61.1
Ciprofloxacin	16.7	78.8	26.1	46.7	25.8	80.6	37.3	84
Trimethoprim/sulfamethoxazole	NA	58.8	NA	31.3	NA	58.5	NA	61.6
Aztreonam	23.9	NA	21.5	NA	31.1	NA	52.7	NA
Minocycline	NA	26.4	NA	21.8	NA	28.3	NA	35.7
Polymycin B	0	1	3	2.9	1.8	0.7	0	0
Tigecycline	NA	6.2	NA	2.9	NA	4.9	NA	2.1

NA not available

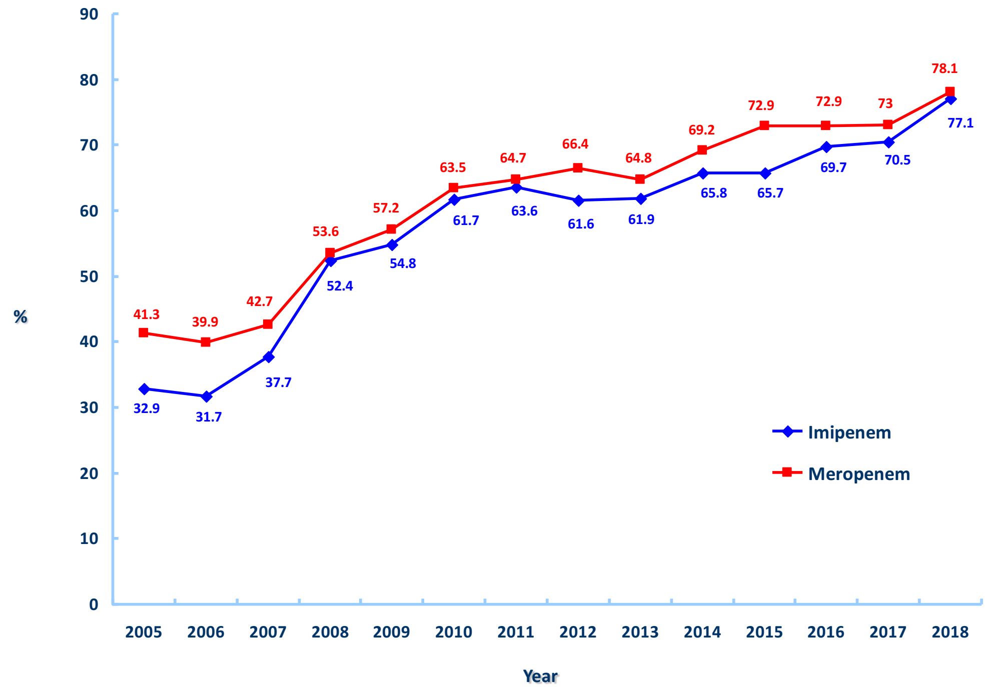

Fig. 3 Resistance Change of *Acinetobacter baumannii* to Imipenem and Meropenem between 2005 and 2018

Among 13,102 strains of CRE, the top three isolates were *K. pneumoniae* (73.5%, 9625/13102), *E. coli* (8.6%, 1123/13102) and *Enterobacter cloacae* (5.4%, 701/13102). The resistance rate of *Klebsiella spp.* isolated from 44 hospitals to imipenem was in range of 0% to 53.1%, and the resistance rate of *P. aeruginosa* to imipenem was in range of 1.7 to 45.2% to imipenem; the resistance rate of *Acinetobacter* spp. to imipenem was from 3.8 to 91.4%. Studies have shown that carbapenem-resistant strains are highly resistant to most commonly used antimicrobial agents; the majority of resistant strains are only sensitive to tigecycline and polymyxin B. In order to cope with infections caused by such super-resistant bacteria, the laboratory person shall actively communicate with clinical to add some potentially effective drug tests, such as polymyxinB, tigecycline, and ceftazidime-avibactam. However, microbiological laboratory personnel should pay special attention to problems in running susceptibility testing for polymyxin and tigecycline. Currently, CLSI does not recommend to use disk diffusion method, agar dilution method, or other drug susceptibility methods for polymyxinB antimicrobial susceptibility testing, which must use the microbroth dilution method. In vitro activity of tigecycline are affected by many factors, including the media type, preparation time, detection method of medium, type of strain, selection of breakpoint, etc. [7]. Therefore, when tigecycline susceptibility was measured by laboratory paper dispersion method and automated systems method, the susceptibility should be further confirmed using microbroth dilution method if moderately sensitive or resistant results were shown.

Producing KPC-type carbapenemase or NDM-1 metalloenzyme is the most important resistance mechanism of *Enterobacteriaceae* to carbapenems, and the resistance mechanisms of different populations and strains from different regions showed some difference. The results have showed that the CRE strains isolated from child patients mainly produced NDM-1 type metalloenzyme, while the strains isolated from adult patients mainly produced KPC-type carbapenemase. From the perspective of the geographical distribution, the clinically isolated CRE strains in northern China hospitals produced more NDM-1 metalloenzyme strains and less KPC-type carbapenemase strains than that in the Southern China hospital [8]. In addition, clinical laboratories shall strengthen the detection of class D carbapenemases in CRE strains, in particular, the OXA-48 carbapenemase family including OXA-181 and OXA-232 carbapenemases. Since the current methods recommended by CLSI and related literature are unable to effectively detect OXA-type carbapenemase, it may appear as a false-negative result. Studies have shown that in China, there are reports about the prevalence of clonal strains induced by the infection of *K. pneumonia* producing OXA-type carbapenemase. These drug-resistant strains were mainly measured in the strains isolated from children patients [9]. In the future, the implementation of a multicenter epidemiological investigation on CRE strains is required in our country, so as to clarify the prevalence of CRE strains among the inpatients, in particular in those with critical illness. It could provide an important reference for effective infection prevention and control subsequently.

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Compliance with ethical standards

The study is conducted on already available data. Ethical approval was approved by the Institutional Review Board of Huashan Hospital, Fudan University (Number:2018-408).

Conflict of interest The authors declare that they have no conflict of interest.

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