European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:2275–2281
https://doi.org/10.1007/s10096-019-03673-1

ORIGINAL ARTICLE

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

Fupin Hu[1,2] · Yan Guo[1,2] · Yang Yang[1,2] · Yonggui Zheng[1,2] · Shi Wu[1,2] · Xiaofei Jiang[3] · Demei Zhu[1,2] · Fu Wang[1,2] · on behalf of the China Antimicrobial Surveillance Network (CHINET) Study Group

Received: 27 May 2019 / Accepted: 6 August 2019 / Published online: 2 September 2019

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).

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

Fupin Hu and Yan Guo contributed equally to this work.

✉ Demei Zhu
zhu_demei@163.com

[1] Institute of Antibiotics, Huashan Hospital, Fudan University, Shanghai, China

[2] Key Laboratory of Clinical Pharmacology of Antibiotics, Ministry of Health, Shanghai, China

[3] Laboratory Medicine, Huashan Hospital, Fudan University, Shanghai, China

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

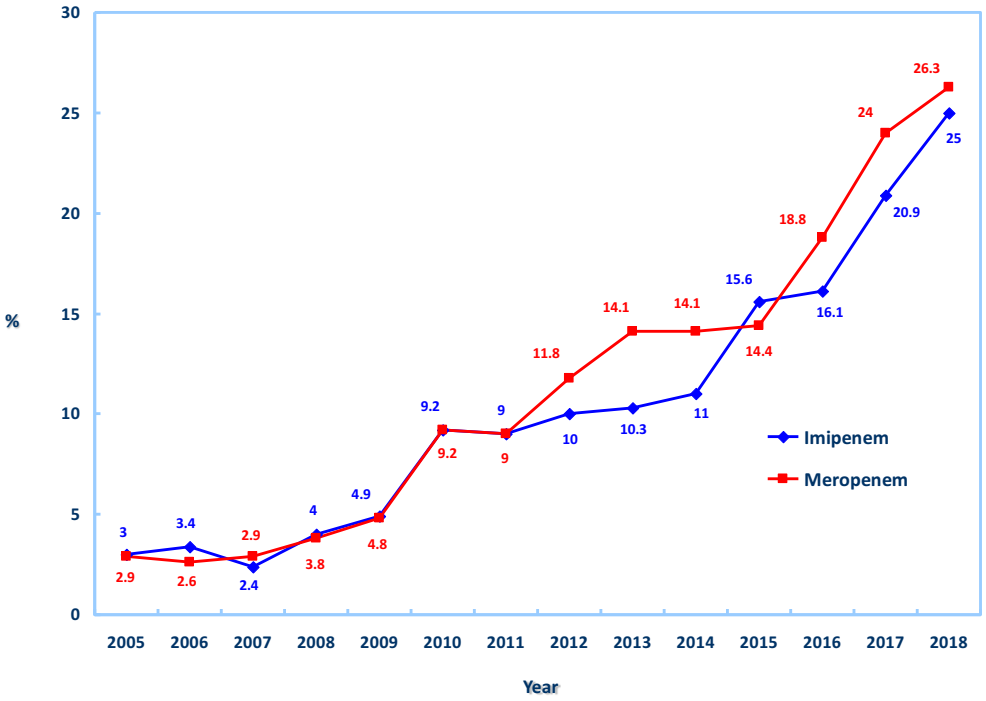

Fig. 1 Resistance Change of *Klebsiella pneumoniae* to Imipenem and Meropenem between 2005 and 2018

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.

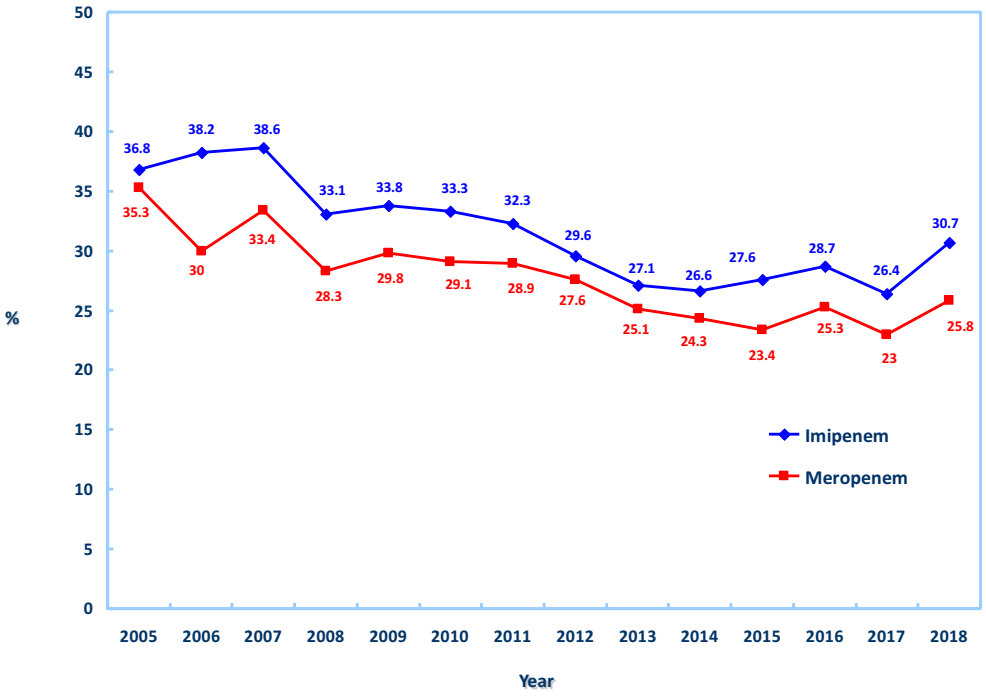

Fig. 2 Resistance Change of *Pseudomonas aeruginosa* to Imipenem and Meropenem between 2005 and 2018

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

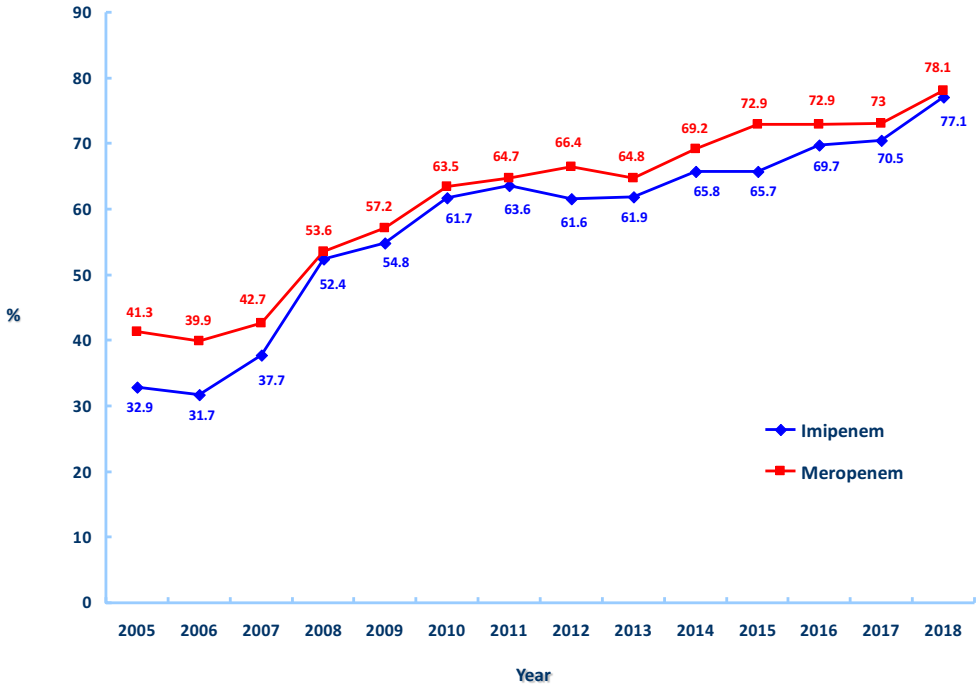

Fig. 3 Resistance Change of *Acinetobacter baumannii* to Imipenem and Meropenem between 2005 and 2018

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.

Acknowledgments We gratefully acknowledge the contributions of the members of CHINET for collection of the isolates tested in this study.

Their names and affiliations are as follows: Yingchun Xu and Xiaojiang Zhang from the Peking Union Medical College Hospital; Zhaoxia Zhang and Ping Ji from the First Affiliated Hospital of Xinjiang Medical University; Mei Kang and Chao He from West China Hospital, Sichuan University; Chuanqing Wang and Leiyan He from the Children's Hospital of Fudan University; Yuanhong Xu and Ying Huang from the First Affiliated Hospital of Anhui Medical University; Zhongju Chen and Ziyong Sun from Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology; Yuxing Ni and Jingyong Sunfrom Ruijin Hospital, Shanghai Jiaotong University School of Medcine; Yunzhuo Chu and Sufei Tian from the First Affiliated Hospital of China Medical University; Zhidong Hu and Jin Li from Tianjin Medical University General Hospital; Yunsong Yu and Jie Lin from Sir Run Run Shaw Hospital, Zhejiang University School of Medicine; Bin Shan and Yan Du from the First Affiliated Hospital of Kunming Medical University; Sufang Guo and Yanyan Wang from the First Affiliated Hospital of Inner Mongolia Medical University; Lianhua Wei and Xin Wang from the Gansu Provincial Hospital; Hong Zhang and Chun Wang from the Children's Hospital of Shanghai; Yunjian Hu and Xiaoman Ai from Beijing Hospital; Chao Zhuo and Danhong Su from the First Affiliated Hospital of Guangzhou Medical University; Ruizhong Wang and Hua Fang from the Pudong New Area People's Hospital; Bixia Yu from the Zhejiang Ningbo Zhenhai Longsai Hospital; Ping Gong and Miao Song from the People's Hospital of Zigui, Hubei Province; Dawen Guo and Jinying Zhao from the First Affiliated Hospital of Harbin Medical University; Wen'en Liu and Yanming Li from Xiangya Hospital, Central South University; Yan Jin and Yueling Wang from Shandong Provincial Hospital; Kaizhen Weng and Yirong Zhang from the Jinjiang Municipal Hospital; Xuesong Xu and Chao Yan from the China-Japan Union Hospital, Jilin University; Xiangning Huang and Hua Yu from the Sichuan Provincial People's Hospital; Yi Li and Shanmei Wang from the Henan Provincial People's Hospital; Lixia Zhang and Juan Ma from the Shaanxi Provincial People's Hospital; Shuping Zhou and Jiangwei Ke from the Jiangxi Provincial Children's Hospital; Lei Zhu and Jinhua Meng from the Children's Hospital of Shanxi; Wenqi Song and Fang Dong from the Beijing Children's Hospital, Capital Medical University; Han Shen and Wanqing Zhou from the Nanjing Drum Tower Hospital, Affiliated Hospital of Nanjing; Gang Li and Wei Jia from the General Hospital of Ningxia Medical University; Jinsong Wu and Yuemei Lu from the Shenzhen People's Hospital; Jihong Li from the Second Hospital of Hebei Medical University; Jiangshan Liu from Jinchang Hospital of integrated traditional Chinese and Western Medicine; Longfeng Liao from The People's Hospital of Ganxian; Hongqin Gu from Guangrao County People's Hospital; Lin Jiang from The People's Hospital of Huixian, Henan Province; Wen He from Central Hospital of Yingkou Development Zone, Liaoning Province; Shunhong Xue from Huzhu County People's Hospital, Qinghai Province; Jiao Feng from The People's Hospital of Linshui, Sichuan Province; Rui Dou from Lixin County People's Hospital; and Chunlei Yue from Jiutai People's Hospital.

Funding information This work was supported in part by the Pfizer Investigator Initiated Research (grant WI207259) and the National Natural Science Foundation of China (grant 81871690).

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.

Disclaimer The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Clinical and Laboratory Standards Institute (CLSI) (2018) Performance standards for antimicrobial susceptibility testing. M100 28th edition. Wayne, PA
2. Hu FP, Guo Y, Zhu DM, Wang F, Jiang XF, Xu YC et al (2018) 2017 surveillance of bacterial resistance in China. Chin J Infect Chemother 18(3):241–251
3. Hu FP, Guo Y, Zhu DM, Wang F, Jiang XF, Xu YC et al (2016) Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005-2014. Clin Microbiol Infect 22(Suppl 1):S9–S14
4. Qin X, Yang Y, Hu F, Zhu D (2014) Hospital clonal dissemination of Enterobacter aerogenes producing carbapenemase KPC-2 in a Chinese teaching hospital. J Med Microbiol 63(Pt 2):222–228
5. Zhu DM, Wang F, Hu FP, Jiang XF, Ni YX, Sun JY et al (2011) 2010 surveillance of bacterial resistance in China. Chin J Infect Chemother 11(5):321–329
6. Hu FP, Guo Y, Zhu DM, Wang F, Jiang XF, Xu YC et al (2017) CHINET 2016 surveillance of bacterial resistance in China. Chin J Infect Chemother 17(5):481–491
7. Wang H, Yu YS, Wang MG, Ni YX, Ma Y, Ren JK et al (2013) Expert consensus on the procedure of tigecycline in vitro susceptibility test. Chin J Lab Med 26(7):584–587
8. Zhang R, Liu L, Zhou H, Chan EW, Li J, Fang Y et al (2017) Nationwide surveillance of clinical Carbapenem-resistant Enterobacteriaceae (CRE) strains in China. EBioMedicine. 19:98–106
9. Yin D, Dong D, Li K, Zhang L, Liang J, Yang Y et al (2017) Clonal dissemination of OXA-232 Carbapenemase-producing Klebsiella pneumoniae in neonates. Antimicrob Agents Chemother 61(8)