



Antibiotic consumption versus the prevalence of carbapenem-resistant Gram-negative bacteria at a tertiary hospital in China from 2011 to 2017

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ARTICLE INFO

Article history:

Received 18 July 2018

Received in revised form

18 September 2018

Accepted 8 October 2018

Keywords:

Antibiotic consumption
carbapenem-resistant Gram-negative
bacteria

Klebsiella pneumoniae

Acinetobacter baumannii

Pseudomonas aeruginosa

ABSTRACT

Purpose: China launched a 3-year rectification scheme on the clinical use of antibiotics in 2011, and a specific scheme on carbapenem use in February 2017. This study investigated the trends in and correlations between antibiotic consumption and the prevalence of carbapenem-resistant Gram-negative bacteria (CRGN) at a tertiary hospital during these years, particularly in carbapenem consumption.

Methods: The data were collected per quarter from 2011 to 2017. The trends in antibiotic consumption and resistance were analyzed by regression analysis, while Spearman correlation analysis was used to assess the correlations.

Result: The total consumption of antibiotics halved during the 7-year study period, from 770.15 DDDs/1000 PDs in quarter 1 of 2011 to 395.07 DDDs/1000 PDs in quarter 4 of 2017. Meantime, carbapenem consumption showed the significant increase, from 28.71 DDDs/1000 PDs to 49.2 DDDs/1000 PDs. The detection rates of CRGN (carbapenem-resistant *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*) remained stable ($P > 0.05$). The positive correlation was only discovered between the resistance rate of carbapenem-resistant *K. pneumoniae* and the usage of carbapenems, which included meropenem and imipenem, with coefficients of 0.543, 0.537, and 0.497 ($P < 0.05$), respectively. There was no more significant correlation in this study.

Conclusion: The total consumption of antibiotics reduced significantly in the analysed hospital, which could be related to the antimicrobial stewardship programme. However, the carbapenem consumption was increased. The specific index should be established to limit the application of carbapenems. This study identified the positive correlation between the detection rate of carbapenem-resistant *K. pneumoniae* and carbapenem consumption. More research is needed to confirm the impact of restricting and appropriated use of carbapenems on the prevalence of CRGN.

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Introduction

World health leaders have described antibiotic resistant microorganisms as “nightmare bacteria” that “pose a catastrophic threat” to people in every country in the world [1]. Infections caused by resistant bacteria, particularly carbapenem-resistant Gram-negative bacteria (CRGN), which are difficult to treat, leading to high mortality and morbidity, prolonged length of hospital stay, and excessive costs [2,3]. However, CRGN is increasing world-

wide. A European survey revealed the prevalence of carbapenemase producing Enterobacteriaceae in 13 of 38 European countries in 2015, compared with 6 of 38 in 2013, and a similar or higher spread of *Acinetobacter baumannii* (AB) [4]. In February 2017, WHO recognises carbapenem-resistant *A. baumannii* (CRAB), *Pseudomonas aeruginosa* (PA), and Enterobacteriaceae pathogens of crucial importance for the development of novel antibiotics [5].

The overuse and misuse of antibiotics are crucial contributing factors to the emergence and spread of bacterial resistance. The WHO is aware of the harm, and a programme was launched in April 2011, which entitled “Against drug resistance: no action today, no drugs available tomorrow”. Meanwhile, the Chinese government launched the special 3-year rectification scheme on the

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Table 1
Trends in the consumption of antibiotic classes during 2011–2017.

Classes	Levels ^a	Average	Trend	Slope (β)	P
Penicillins and enzyme inhibitor	A; B	29.40 (23.82–35.05)	Increasing	0.816	0.000
Cephalosporins	A; B; C	156.18 (147.62–185.46)	Decreasing	–4.112	0.000
First-generation	A	3.80 (2.42–18.21)	Decreasing	–1.652	0.000
Second-generation	A; B	68.30 (59.14–74.85)	Stable	0.392	0.071
Third-generation	A; B	79.28 (71.39–102.58)	Decreasing	–2.825	0.001
Fourth-generation	C	0.00 (0.00–0.00)	Decreasing	–0.026	0.031
Carbapenems	C	27.54 (20.17–43.14)	Increasing	1.409	0.000
meropenem	C	23.01 (16.52–30.20)	Increasing	0.872	0.000
imipenem	C	5.80 (3.65–12.51)	Increasing	0.536	0.000
Monobactams	C	0.38 (0.22–2.36)	Decreasing	–0.199	0.000
Glycopeptides	C	6.74 (5.17–8.30)	Increasing	0.186	0.000
Oxazolidinone	C	2.56 (1.54–3.64)	Increasing	0.090	0.010
Macrolides, Lincosamides, and streptogramins	A; B	11.60 (9.69–18.40)	Decreasing	–1.146	0.000
Quinolones	A; B	46.42 (39.44–50.88)	Stable	0.40	0.051
Aminoglycosides	A; B	24.68 (14.88–30.18)	Decreasing	–0.053	0.000
Imidazole derivatives	A	21.72 (19.97–25.58)	Decreasing	–0.793	0.001
Steroid antibacterials	A	0.00 (0.00–0.00)	Decreasing	–0.010	0.014
Sulphonamides	A	5.80 (4.68–7.95)	Increasing	0.171	0.000
Total	/	346.44 (329.15–363.12)	Decreasing	–4.744	0.027

Antibacterial consumption is shown as defined daily dose/1000 inpatient-days per quarter, and the average values are presented as median (interquartile range).

^a A: non-restricted; B: restricted; C: specialist antibiotic.

clinical use of antibiotics, and the targets were set for restricting the kinds of antibiotics and antibiotic prescriptions (the detail in Section “Antibacterial stewardship”) [6]. From then, the usage of antibiotics had a significant reduction. However, the consumption of carbapenems was in a worrying increase [7]. Some scholars found that exposure of carbapenems may be concerned with the prevalence of CRGN [8–10]. However, other studies had inconsistent findings [11,12], which may be due to differences in the resistance profiles and antibiotic prescribing practices in different countries. In 2017, National Health and Family Planning Commission of the People’s Republic of China (NHFPC) has been launched the special programme on the clinic application of carbapenems [13]. This study attempted to determine the trends in and correlations between CRGN and antibiotic consumption from 2011 to 2017 at a tertiary hospital, especial in carbapenem consumption. The most frequently Gram-negative bacteria were *Escherichia coli*, *Klebsiella pneumonia* (KB), AB, and PA. Because the carbapenem resistance to *E. coli* was rare, therefore carbapenem-resistant *K. pneumonia* (CRKB), CRAB, and carbapenem-resistant *P. aeruginosa* (CRPA) were involved in this study.

Methods

Design and setting

This study was based on the quarterly data from local monitoring of antibiotic consumption and the carbapenem resistance to Gram-negative bacteria at the First Affiliated Hospital of Xi’an Jiaotong University (FAHXJU). The hospital is a general 2560-bed tertiary-care teaching hospital located in the northwest region of China.

Antibacterial stewardship

From April 2011, a 3-years rectification scheme on the clinical use of antibiotics was launched in China. This is the first time the specific targets for antibiotic prescriptions was set in the tertiary hospitals. For consumption of antibiotic, it was expressed as antibiotic use density and defined as the number of defined daily doses/1000 patient-days (DDDs/1000 PDs) [14], which should be limited to 400 DDDs/1000 PDs or less. Antibiotic procurement was restricted to 50 agents, and the types of carbapenems should be

limited to three or less. During the study time, only meropenem and imipenem were procured in the FAHXJU. Moreover, antibiotics were divided into 3 levels: non-restricted, restricted, and specialist antibiotic. Resident physicians can only prescribe non-restricted antibiotics. Attending physicians can prescribe non-restricted and restricted antibiotics. The specialist antibiotic, such as carbapenems, glycopeptides, and linezolid, which is strictest and only physicians with senior specialized technical qualifications can prescribe them. According to the requirements, a series of antibacterial regulations were established and executed at the FAHXJU in July 2011. Since September 2017, the following information at the FAHXJU should be reported to the provincial health department every month: which one of carbapenems was used, and how many the carbapenems was used. It is the demand of the carbapenem programme.

Microbiology data

The hospital’s clinical microbiology laboratory provided data of bacterial identification and antibacterial susceptibility testing. All positive clinical specimens (positive *K. pneumonia*, *A. baumannii*, and *P. aeruginosa* admission) between 2011 and 2017 were included. Both of colonization and infection were involved in the database. Both of colonization and infection were involved. Duplicate isolates from the same person during one hospital stay were excluded, and microbiological isolates from outpatient clinics or the emergency room were also excluded. Identification and susceptibility testing were performed using the automated VITEK 2 automated system (bioMérieux). Susceptibilities of isolates to all antibiotics tested were based on the latest Clinical and Laboratory Standards Institute document (CLSI document M100-S22. Wayne, PA: CLSI, 2012).

Data collection and analysis

During the study period, utilization of antibiotic was obtained from the computerized database of the Department of Pharmacy. The data were collected calculated per quarter from 2011 to 2017 in the FAHXJU. The trend was analyzed by regression analysis, and Spearman correlation analysis was used for testing the correlation. All of the data were analyzed using SPSS software. Probability values of $P < 0.05$ were considered statistically significant.

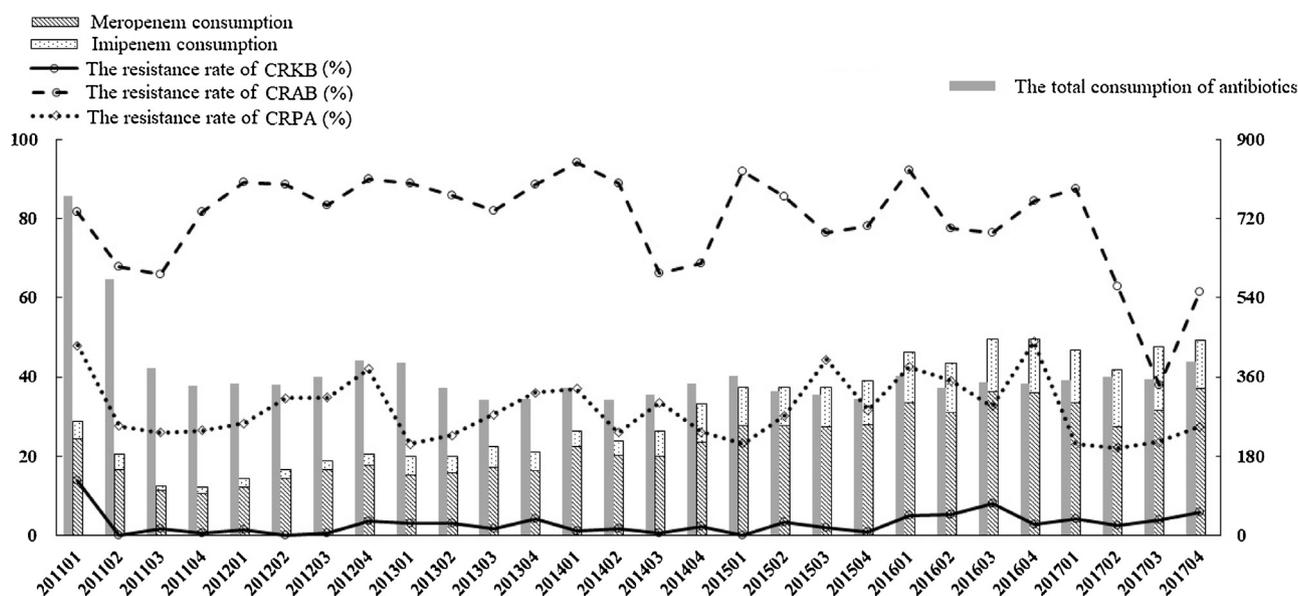


Fig. 1. The trends and correlations between the resistance rates of carbapenem-resistant Gram-negative bacteria and the carbapenem consumption (or the consumption of total antibiotics) during 2011–2017. CRKB carbapenem-resistant *Klebsiella pneumoniae*; CRAB carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*. The consumption of antibiotic was expressed as defined daily doses per 1000 patients per day (DDDs/1000 PDs).

Table 2

The trends and correlations between the resistance rates of CRGN and the carbapenem consumption (or the consumption of total antibiotics) during 2011–2017.

CRGN	Trend	Slope (β)	P	Correlation							
				Meropenem ^a		Imipenem ^a		Carbapenem ^a		Total antibiotics ^a	
				Coefficient	P	Coefficient	P	Coefficient	P	Coefficient	P
The resistance rate of CRKB	Stable	0.048	0.486	0.537	0.003	0.497	0.007	0.543	0.003	0.184	0.349
The resistance rate of CRAB	Stable	-0.507	0.083	-0.206	0.293	-0.303	0.117	-0.268	0.168	-0.093	0.638
The resistance rate of CRPA	Stable	-0.059	0.754	0.131	0.506	-0.053	0.791	0.090	0.651	-0.123	0.533

Note. All of the data were calculated per quarter. CRGN carbapenem-resistant Gram-negative bacteria; CRKB carbapenem-resistant *Klebsiella pneumoniae*; CRAB carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*.

^a The consumption of antibiotic was expressed as defined daily doses per 1000 patients per day (DDDs/1000 PDs).

Results

Antibiotic consumption

The total consumption of antibiotics decreased from 770.15 DDDs/1000 PDs in quarter 1 of 2011 to 395.07 DDDs/1000 PDs in quarter 4 of 2017 ($\beta = -4.744$, $P = 0.027$, Table 1 and Fig. 1), and the antibiotic consumption decreased by 48.70%. Cephalosporin was the largest varieties of consumption, and it also decreased significantly ($\beta = -4.112$, $P < 0.05$). In Table 1, the consumption of many antibiotic classes revealed the significant decreases, including monobactams, aminoglycosides, imidazole derivatives, steroid antibacterials, macrolides, lincosamides and streptogramins ($P < 0.05$). However, the five of antibiotic classes showed the significant increases in consumption, which included carbapenems, glycopeptides, oxazolidinone, sulphonamides, and penicillins and enzyme inhibitor ($P < 0.05$). The consumption of these antibiotic classes increased from 28.71, 5.16, 2.13, 4.00, 34.72 DDDs/1000 PDs in quarter 1 of 2011 to 49.20, 8.95, 5.80, 9.55, 60.52 DDDs/1000 PDs in quarter 4 of 2017, respectively. Quinolone consumption remained stable during this period ($P > 0.05$).

The prevalence of CRGN

In this study, a total of 15173 Gram-negative bacteria were collected: 2265 isolates (KB 834; AB 810; PA 621) in 2011, 2646 (KB 884; AB1008; PA 754) isolates in 2012, 2279 isolates (KB 733; AB

881; PA 665) in 2013, 1498 isolates (KB 570; AB 445; PA 483) in 2014, 2050 isolates (KB 583; AB 758; PA 709) in 2015, 2526 isolates (KB 970; AB 771; PA 785) in 2016, and 1909 isolates (KB 787; AB 496; PA 626) in 2017. Trends for these rates of CRGN remained stable ($P > 0.05$), and it was listed in Table 2.

Relationship between the detection rates of CRGN and antibiotic consumption (2011–2017)

Table 2 provided the comparisons between the antibiotic consumption and the resistance rates for CRGN by quarter during the 7-year period. The positive correlations were discovered between the detection rate of CRKB and the usage of carbapenems, which included meropenem and imipenem, with coefficients of 0.543, 0.537, and 0.497 ($P < 0.05$), respectively. Meanwhile, no significant association was presented for other CRGN (CRAB or CRPA) and carbapenem consumption (or the total consumption of antibiotics).

Discussion

In this study, we tracked antibiotic consumption since 2011 with the aim of providing insight to explore the trends in and correlations with the carbapenem resistance of Gram-negative bacteria. The first noteworthy finding of this study is that the total consumption of antibiotics had from 770.15 DDDs/1000 PDs in quarter 1 of 2011 to 395.07 DDDs/1000 PDs in quarter 4 of 2017. The trend was similar to previous study in 151 hospitals

in China [7]. These findings reflect the impact of the national 3-year action conducted by the Chinese government. The Chinese government plays a substantial role in controlling antibiotic usage in public hospitals, which may be related to the public hospital management system that is governed by bureaucratic rules in China [15]. The consumption of many antibiotics decreased, however, the usage of carbapenems and glycopeptides increased significantly during the study period ($P < 0.05$). The significantly increasing trends were observed for these two antibiotic classes in a nationwide descriptive epidemiological study in China from 2011–2014 [7]. Furthermore, the increased consumption of them has been observed in the Republic of Korea from 2008 to 2012 [16]. These two classes were classed as the specialist antibiotic, which were used only in hospitals in China. It could be partly explained by the rise in the global burden of multi-drug resistant bacteria, especial in the ESBL-producing bacteria and MRSA [17,18]. Another possible reason was that the FAHXJU is a general tertiary hospitals that absorbed a large number of critically ill patients with serious diseases. However, the overuse of carbapenems is a serious problem in China. Qu et al. found that the consumption of meropenem in 2014 was more than 10 DDDs/1000 PDs in the Chinese hospitals [7], and it was approximated 40 DDDs/1000 PDs in quarter 4 of 2017 at the FAHXJU. However, the consumption of carbapenems in 2016 was 0.05 DDDs/1000 PDs in the European hospitals [19]. Chinese government launched carbapenem programme in February 2017. The effect of carbapenem programme was weakened, because it lacked the specific index to limit the application of carbapenems.

A second noteworthy finding of this study is that the resistance rates of CRGN (CRKB, CRAB, and CRPA) remained stable during the 7-years. According to antimicrobial resistance surveillance reports in China [18,20,21], the resistance rates of these three CRGN presented the slight decrease in the national level. The prevalence of CRKB exhibited a tiny decrease from 9.4% in 2011 to 8.7% in 2016, with the detection rate of CRAB from 61.4% to 60%, and the resistance rate of CRPA from 29.1% to 27.4% in the same time. In quarter 4 of 2017, the resistance rate of CRKB at the FAHXJU was slightly lower than the national level in 2016, and the detection rates of other two CRGN (CRAB and CRPA) were similar to the national level. The prevalence of CRGN demonstrated the obviously regional differences. According the ECDC surveillance report in 2014, the percentage of CRKB ranged from zero (7 countries) to 60.5% (Greece), and CRPA was above 10% in 19 of 29 reporting countries. Meantime, the percentage of CRAB was high [4].

How to control the spread of CRGN is a public health concern of growing importance in worldwide. Carbapenems are the last-line group of antibiotics and are mainly used in hospitals to treat patients with confirmed or suspected infections involving multidrug-resistant Gram-negative bacteria [9]. Some researches released that the usage of carbapenems is a risk factor for subsequent infection with CRGN. In this study, we found the positive correlation between the resistance rate of CRKB and the consumption of carbapenems (both of meropenem and imipenem). Hu et al. also found that exposure to carbapenems is an independent risk factor for CRKP infection [9]. A meta-analysis also demonstrated that the prevalence of CRKB was shown to be associated with the consumption of carbapenems [10]. Peleg and Hooper suggested that longer treatment with carbapenems in large doses have increased the antibiotic selection pressure, allowing carbapenem-resistant bacteria to develop a plethora of carbapenem resistance mechanisms [22]. However, these conclusions were controversial. Jiao et al. found exposure to glycopeptides was an independent risk factor for CRKP infection/colonization, rather than carbapenems [12]. It might be many factors involved in the development of CRGN, such as length of hospital stay [23], medical devices [24], and the hospital environment [25]. Furthermore, the increased use of carbapenems was not significant association with the detection rate

of CRAB (or CRPA) in this study. However, Abdallah et al. found that restricting carbapenems, even for a short duration, may be an effective strategy for managing the problem of CRPA [26]. The appropriated use of carbapenems might be a substantial factor. The total consumption of antibiotics was fallen by a half during the study period, however, the resistance rates of CRGN was stable. An interesting phenomenon was showed in Fig. 1. At the beginning of the antimicrobial stewardship programme, the total consumption of antibiotics was descending, and carbapenem consumption was also decreased. Meanwhile, the detection rates of CRGN also were reduced. The continued research is needed to investigate the impact of restricting and appropriated use of carbapenems on the prevalence of CRGN

There also was the several limitations in this study. First, this study was retrospective, and it was only conducted in one tertiary-care teaching hospital. This design has the risk of ecological bias, since the use of data from individual patients might give different results. Second, there was not an established criterion for differentiating infection from colonization of these bacteria in the study. Third, the density of antibiotic use might not accurately reflect the real antibiotic use in adults with renal impairment; however, it is the most commonly applied metric for measuring antibiotic use. Furthermore, there might be many reasons for the prevalence of CRGN. However, the change in the usage of antibiotics, especial in carbapenem consumption, which was the main focus in this study.

Conclusion

During the study period, the total consumption of antibiotics reduced significantly in FAHXJU, which could be related to the antimicrobial stewardship programme. However, carbapenem consumption was increased. The carbapenem programme did not work well, and the specific index should be established to limit the application of carbapenems. Meanwhile, the resistance rates of CRGN was stale. A positive correlation was found between the resistance rate of CRKB and the consumption of carbapenems (both of meropenem and imipenem). There was no significant correlation between other CRGN (CRAB or CRPA) and carbapenem consumption. More research is needed to confirm the impact of restricting and appropriated use of carbapenems on the prevalence of CRGN.

Funding

This study was funded by the Programs for Science and Technology Development of Shaanxi Province, China (No. 2016SF-167 and No. 2017SF-186).

Competing interests

None declared.

Ethical approval

This study was approved by the Institutional Review Board of First Affiliated Hospital of Xi'an Jiaotong University (2017-LSKZ-73).

Acknowledgement

We would like to thank Prof. Jiangbin Ye (Stanford University) for assistance with language editing.

References

- [1] Laxminarayan R, Matsoso P, Pant S, Brower C, Rottingen JA, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016;387:168–75.

- [2] Guidelines for the Prevention and Control of Carbapenem-Resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Health Care Facilities; 2017. Geneva.
- [3] Perez F, Bonomo RA. Evidence to improve the treatment of infections caused by carbapenem-resistant Gram-negative bacteria. *Lancet Infect Dis* 2018;18:358–60.
- [4] European Centre for Disease Prevention and Control (ECDC). Carbapenem-resistant *Acinetobacter baumannii* in healthcare settings. <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/8-Dec-2016-RRA-Acinetobacter%20baumanni-Europe.pdf>. [Accessed 31 October 2017].
- [5] World Health Organization Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics <http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/>. [Accessed 27 February 2017].
- [6] National Health and Family Planning Commission of the people's Republic of China. Notice regarding national special measure scheme on clinical use of antibiotics in 2011 <http://www.nhfpc.gov.cn/zwgkzt/wsbysj/201104/51376.shtml>. [Accessed April 2011, in Chinese].
- [7] Qu X, Yin C, Sun X, Huang S, Li C, Dong P, et al. Consumption of antibiotics in Chinese public general tertiary hospitals (2011–2014): trends, pattern changes and regional differences. *PLoS One* 2018;13:e0196668.
- [8] Tam VH, Hirsch EB, Lasco TM, Gentry LO, Palmer HR. Correlation of hospital carbapenem consumption and resistance trends in selected gram-negative bacteria. *Ann Pharmacother* 2012;46:1120–2.
- [9] Hu Y, Ping Y, Li L, Xu H, Yan X, Dai H. A retrospective study of risk factors for carbapenem-resistant *Klebsiella pneumoniae* acquisition among ICU patients. *J Infect Dev Ctries* 2016;10:208–13.
- [10] Liu P, Li X, Luo M, Xu X, Su K, Chen S, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection: a meta-analysis. *Microb Drug Resist* 2018;24:190–8.
- [11] Ho CM, Ho MW, Liu YC, Toh HS, Lee YL, Liu YM, et al. Correlation between carbapenem consumption and resistance to carbapenems among Enterobacteriaceae isolates collected from patients with intra-abdominal infections at five medical centers in Taiwan, 2006–2010. *Int J Antimicrob Agents* 2012;(Suppl):S24–8.
- [12] Jiao Y, Qin Y, Liu J, Li Q, Dong Y, Shang Y, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection/colonization and predictors of mortality: a retrospective study. *Pathog Global Health* 2015;109:68–74.
- [13] National Health and Family Planning Commission of the people's Republic of China. Notice regarding to further strengthen the use of antibiotics and reduce antibiotic resistance <http://www.nhfpc.gov.cn/zyygj/s7659/201703/d2f580480cef4ab1b976542b550f36cf.shtml>. [Accessed March 2017, in Chinese].
- [14] WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. <https://www.whocc.no/filearchive/publications/guidelines.pdf>. [Accessed 30 January 2018].
- [15] Sun X, Jackson S, Carmichael GA, Sleigh AC. Prescribing behaviour of village doctors under China's New Cooperative Medical Scheme. *Soc Sci Med* 2009;68:1775–9.
- [16] Yoon YK, Park GC, An H, Chun BC, Sohn JW, Kim MJ. Trends of antibiotic consumption in Korea according to national reimbursement data (2008–2012): a population-based Epidemiologic study. *Medicine* 2015;94:e2100.
- [17] Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014;14:742–50.
- [18] Hu FP, Guo Y, Zhu DM, Wang F, Jiang XF, Xu YC, et al. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005–2014. *Clin Microbiol Infect* 2016;22(Suppl 1):S9–14.
- [19] European Centre for Disease Prevention and Control (ECDC). Antimicrobial consumption – Annual Epidemiological Report for 2016. https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2016-AMC.pdf. [Accessed 19 February 2018].
- [20] China Antimicrobial Resistance Surveillance System A report of China antimicrobial resistance in 2015. <http://www.carss.cn/Sys/res/file/201512/20151220130134.7741.482f3b7ae95841998a37898e2ab2fa87.2015年监测报告.pdf>. [Accessed 15 June 2017, in Chinese].
- [21] China Antimicrobial Resistance Surveillance System. A report of China antimicrobial resistance in 2016. <http://www.carss.cn/Report/Details?ald=403>. [Accessed 20 December 2017, in Chinese].
- [22] Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. *N Engl J Med* 2010;362:1804–13.
- [23] Zhang JF, Chen BL, Xin XY, Zhao HB, Wang HY, Song H, et al. Carbapenem resistance mechanism and risk factors of *Pseudomonas aeruginosa* clinical isolates from a University Hospital in Xi'an, China. *Microb Drug Resist* 2009;15:41–5.
- [24] Voor In 't Holt AF, Severin JA, Lesaffre EM, Vos MC. A systematic review and meta-analyses show that carbapenem use and medical devices are the leading risk factors for carbapenem-resistant *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2014;58:2626–37.
- [25] Kateete DP, Nakanjako R, Namugenyi J, Erume J, Joloba ML, Najjuka CF. Carbapenem resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* at Mulago Hospital in Kampala, Uganda (2007–2009). *SpringerPlus* 2016;5:1308.
- [26] Abdallah M, Badawi M, Amirah MF, Rasheed A, Mady AF, Alodat M, et al. Impact of carbapenem restriction on the antimicrobial susceptibility pattern of *Pseudomonas aeruginosa* isolates in the ICU. *J Antimicrob Chemotherapy* 2017;72:3187–90.