

# Correlation between Antibiotic Resistance of Main Gram-Negative Pathogens and Antibiotic Consumption in a General Hospital of China

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## Research article

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## Abstract

**Purpose** Our hospital is a newly established hospital in China, which is located in the tropics. Better depicting antibiotic consumption and antibiotic resistance may help better develop and implement an antibiotic stewardship with regional characteristics.

**Methods** Total antibiotic prescriptions, patient days and microbiological data from January 2014 to December 2017 were collected. Antibiotic use density (AUD) was expressed as daily defined dose (DDD) and normalized per 100 patient-days. The resistance rates of Gram-negative pathogens against commonly used antibiotics were calculated. The relationship between antibiotic consumption and bacterial resistance rate was described by Pearson's correlation coefficient.

**Results** Different from mainland China, *A. baumannii* was the leading Gram-negative pathogen, followed by *K. pneumoniae*, *E. coli* and *P. aeruginosa*. The AUD was gradually increased from 2014 to 2016, while it was slowly decreased in 2017. Ceftazidime/tazobactam, levofloxacin and meropenem were the top three consumed antibiotics. The proportion of multidrug resistant (MDR) Gram-negative bacteria was increased (>40%) before 2016, and it was decreased in 2017. The prevalence of MDR *A. baumannii* and MDR *P. aeruginosa* was correlated with the AUD of  $\beta$ -lactam/lactamase inhibitors, fluoroquinolones and carbapenems. The increased AUD of meropenem had positive effects on the incidence of carbapenem-resistant *A. baumannii* and *P. aeruginosa*.

**Conclusions** Our study showed that there was an association between the resistance density of Gram-negative pathogens and the consumption of  $\beta$ -lactam/lactamase inhibitors, carbapenems and fluoroquinolones. Collectively, a multifaceted antimicrobial stewardship is necessary to decrease resistance density of available antibiotics.

## Introduction

The resistance of microorganisms diminishes the efficacy of existing antibiotics, which has aroused the attention of many hospitals worldwide. Increasing use of antibiotics is closely associated with the emergence of resistance due to the enhanced selective pressure on bacteria<sup>[1-3]</sup>. Such ineffectiveness of antibiotics leads to great challenges in infected patients<sup>[4, 5]</sup>. However, the discovery of new antibiotics cannot overcome the current problems caused by antimicrobial resistance<sup>[6]</sup>.

In order to combat the antimicrobial resistance, two great efforts have been made in recent years worldwide and in China. First, an increased effort has been directed towards controlling irrational antibiotic use and raising public awareness of prudent use of antibiotics<sup>[7]</sup>. In the past 10 years, more and more policies and guidelines concerning the antimicrobial stewardship have been established in China to improve the intelligent use of antibiotics. Most hospitals in China have gradually implemented such policies. These policies include restricting the types of antibiotics, setting the targets for antibiotic prescription in hospitalized patients and prophylactic use of antibiotics in operations<sup>[8]</sup>. Previous studies have indicated the possibility of a causal link between antimicrobial resistance and the dosage of antibiotics<sup>[9, 10]</sup>. On the other hand, scholars have paid more attention to other factors, such as geographical environment, bacterial distribution, patients' condition, antimicrobial use behavior, and infection control measures, which may affect the trend of antimicrobial resistance. Reports received from different hospitals across the world have shown varied prevalence of antimicrobial resistance<sup>[11]</sup>. According to China Antimicrobial Resistance Surveillance System (CARSS) data, the resistance rates of bacteria in Hainan Province are generally lower than the national average. For example, the incidence of carbapenem-resistant *K. pneumoniae* is 3.1% vs. 8.7%, and that of carbapenem-resistant *A. baumannii* is 43.0% vs. 60.0%.<sup>12</sup> Hainan Hospital of PLA General Hospital is located in Sanya (Hainan Province, China), which has an environment of high humidity and high temperature all over the year. The bacterial distribution and antimicrobial resistance may be different from those in the mainland.

In the present study, we aimed to give an overview of the changing pattern of antibiotic usage and antimicrobial resistance of Gram-negative pathogens in Hainan Hospital of PLA General Hospital over a period of 4 years (from 2014 to 2017) through retrospective research methods. Simultaneously, we explored the correlation between antimicrobial resistance and antibiotic consumption.

## Materials And Methods

### Study design

This retrospective study was conducted during a 4-year period from January 2014 to December 2017 in Hainan Hospital of PLA General Hospital.

# Bacterial isolates

During the follow-up period, culture-positive pathogenic samples were enrolled in the study. The non-pathogenic bacteria isolated from respiratory tract samples were excluded, such as *Viridans streptococcus*, *Neisseria* spp. and so on<sup>[13]</sup>. Moreover, if samples from the same location were microbiologically tested repeatedly during the same hospitalization, only the first isolate was taken into account for this analysis. Defined multidrug-resistant (MDR) pathogens are insensitive to more than three types of antimicrobial agents (including resistance and intermediate resistance)<sup>[14]</sup>.

## Antibiotic consumption

Yearly data on total antibiotic prescriptions and patient days were collected from the computerized pharmacy databases. Consumption, the antibiotic use density (AUD), was expressed as daily defined dose (DDD) and normalized per 100 patient-days. The DDD is the standard adult daily dose of an antimicrobial agent for a 1-day treatment defined by the World Health Organisation (WHO ATC/DDD Index 2019)<sup>[15]</sup>.

## Antimicrobial susceptibility testing

The antimicrobial sensitivity data were obtained from the microbiology laboratory for the pathogens regardless of whether they were associated with hospital-acquired or community-acquired infection or colonization. Pathogens were specified as resistant by the clinical laboratory using interpretive criteria recommended by Clinical and Laboratory Standards Institute (CLSI). Bacteria were identified by VITEK2 Compact Automatic Microbial Analysis System. Blood and aseptic body fluid samples were cultured by BcaT/AletT 3D 240 automatic blood culture apparatus and matching culture flasks of Meriere Company of France, and transferred to Shaw medium. Non-aseptic parts were cultured on Shaw medium. The sensitivity tests of *Enterobacteriaceae* spp. were conducted by GN13 susceptibility cards, the sensitivity tests of non-fermentative Gram-negative bacteria were conducted by G09 susceptibility cards, and the susceptibility tests of *S. maltophilia* were conducted by manual method. The quality control strains were *E. coli* ATCC25922 and *P. aeruginosa* ATCC227853.

## Correlation analysis

Pearson's correlation coefficient ( $r$ ) was used to describe the relationship between antibiotic consumption and bacterial resistance rate.  $P < 0.05$  was considered as statistically significant. All analyses were performed using SPSS 19.0 (IBM Corporation, Armonk, NY). The correlation coefficient  $r > 0$  indicated a positive correlation; whereas  $r < 0$  suggested a negative correlation. Unrelated or low correlation was defined as  $|r| \leq 0.4$ , moderate correlation was set at  $0.4 < |r| \leq 0.7$ , and  $|r| > 0.7$  showed a high correlation.

# Results

## Distribution characteristics of main Gram-negative bacteria

During the study period, a total of 7,798 bacterial pathogens were analyzed, and 75.96% of them were Gram-negative bacteria. The most frequently isolated pathogen among them was *A. baumannii* (11.68%), followed by *K. pneumoniae* (10.28%), *E. coli* (10.18%) and *P. aeruginosa* (8.69%). The detection rate of *A. baumannii* was significantly increased from 8.51% in 2014 to 14.52% in 2017. However, the detection rate of *E. coli* was dramatically decreased from 13.43% in 2014 to 8.07% in 2017. Moreover, the detection rates of *K. pneumoniae* and *P. aeruginosa* remained stable throughout the study period (Table 1).

## Prevalence of MDR Gram-negative bacteria

Fig 1 presents the trend of antimicrobial resistance of main Gram-negative bacterial pathogens. The prevalence of MDR *A. baumannii* (from 64.79% in 2014 to 70.62% in 2016) and MDR *K. pneumoniae* (from 33.33% in 2014 to 57.08% in 2016) showed a significant increasing trend in 2016, while both of them exhibited a sharp decrease in 2017. The resistance rate of *P. aeruginosa* showed a significant increasing trend in 2015 (from 40.91% in 2014 to 52.65% in 2015), and such rate was decreased from 2016 (from 52.65% in 2015 to 28.31% in 2017).

Fig 1 Changing pattern in prevalence of MDR Gram-negative bacteria from 2014 to 2017. MDR-AB: Multidrug-resistant *A. baumannii*; MDR-PA: Multidrug-resistant *P. aeruginosa*; MDR-KP: Multidrug-resistant *K. pneumoniae*.

## Resistance rate of main Gram-negative bacteria to main antibiotics

*A. baumannii* showed a higher resistance density to all antibiotics during the study period. The resistance rates of *A. baumannii* to ceftazidime and piperacillin/tazobactam were roughly above 70%. In addition, its resistance rates to amikacin and levofloxacin were

basically between 60% and 70%. Moreover, the resistance rates of *A. baumannii* to meropenem and imipenem was significantly increased from 67.61% and 60.94% in 2014 to 75.19% and 73.81% in 2017, respectively (Table 2).

*K. pneumoniae* showed a high susceptibility to carbapenems and amikacin (95%–100%). However, its susceptibility to cephalosporin and fluoroquinolone antibiotics was only 60%–80% (Table 2).

*P. aeruginosa* was sensitive to amikacin (>85%). However, it showed a lower sensitivity to piperacillin/tazobactam, ceftazidime, fluoroquinolones and carbapenems. In contrast, the resistance rates of *P. aeruginosa* to meropenem and imipenem were significantly increased throughout the study period from 7.32% and 13.11% in 2014 to 39.13% and 35.79% in 2017, respectively (Table 2).

#### Consumption of antibiotics

From 2014 to 2016, the total AUD was gradually increased, while only a small reduction was observed in 2017. During the 4-year period, the most commonly prescribed antibiotic subgroup was  $\beta$ -lactam/lactamase inhibitors with 13.27 DDD per 100 patients (23.56%), fluoroquinolones with 10.51 DDD per 100 patients (18.65%), nitroimidazoles with 5.52 DDD per 100 patients (9.80%) and carbapenems with 4.16 DDD per 100 patients (7.37%) (Fig 2).

*Fig 2 Changing pattern in AUD of various antimicrobial agents from 2014 to 2017.* AUD: antibiotic use density; DDD: defined daily dose. pd: patient-day.

The AUD of ceftazidime/tazobactam was the highest among commonly prescribed antibiotic subgroups, while it showed a significant decreasing trend during the study period. The AUD of ceftazidime/tazobactam was decreased from 9.62 to 5.78 from 2014 to 2016. Levofloxacin showed a second highest AUD with a downward trend throughout the 4 years. The AUD of levofloxacin was decreased from 8.58 in 2014 to 5.85 in 2016. A significant increase was noted in consumption of carbapenems. Among them, the AUD of meropenem was the highest with a significant increasing trend, and the AUD of imipenem-cilastatin remained relatively stable (Fig 3).

*Fig 3 Changing pattern in AUD of mainly used antibiotics from 2014 to 2017.*

AUD: antibiotic use density; DDD: defined daily dose. pd: patient-day.

#### Correlations between MDR rate of Gram-negative bacteria and consumption of antimicrobials

Table 3 summarizes the correlations between antimicrobial resistance and antibiotic consumption. The consumption of total antimicrobials, ceftazidime/tazobactam, cefoperazone/sulbactam and levofloxacin demonstrated a high positive correlation with the MDR rate of *A. baumannii*, while there was a moderate negative correlation between the MDR rate of *A. baumannii* and the consumption of meropenem. However, the detection rate of MDR *K. pneumoniae* showed a high negative correlation with the consumption of  $\beta$ -lactam/enzyme inhibitors and levofloxacin. For *P. aeruginosa*, the increasing consumption of total antibiotic had a significant positive correlation with the increasing resistance rate. In contrast, the consumption of imipenem/cilastatin demonstrated a negative correlation with the resistance rate of *P. aeruginosa*, and it was positively correlated with the consumption of ceftazidime/tazobactam, cefoperazone/sulbactam and levofloxacin (Table 3).

#### Correlation between antimicrobial resistance and dosage of commonly used antibiotics

Table 4 shows correlation between AUD and antimicrobial resistance. The consumption of ceftazidime and meropenem demonstrated a significant positive correlation with the resistance rate of *A. baumannii* against piperacillin/tazobactam ( $r = 0.971, 0.977, P < 0.05$ ). However, the consumption of imipenem/cilastatin demonstrated a significant negative correlation. Antimicrobial resistance to cefoperazone/sulbactam was positively correlated with the consumption of ceftazidime, ceftazidime/tazobactam, cefoperazone/sulbactam and meropenem, while it was negatively correlated with the consumption of imipenem/cilastatin. The resistance rate to meropenem and imipenem had a high positive correlation with the consumption of ceftazidime ( $r = 0.938, 0.995, P < 0.05$ ) and meropenem ( $r = 0.986, 0.99, P < 0.05$ ).

The resistance rate of *K. pneumoniae* to piperacillin/tazobactam was positively correlated with the consumption of ceftazidime/tazobactam and cefoperazone/sulbactam, while it was negatively correlated with the consumption of meropenem and imipenem.

The resistance of *P. aeruginosa* to piperacillin/tazobactam had a high positive correlation with the consumption of ceftazidime and meropenem ( $r = 0.919, 0.845$ ), while it was negatively correlated with the consumption of imipenem/cilastatin ( $r = -0.903$ ). The resistance to cefoperazone/sulbactam showed a high positive correlation with the consumption of cefoperazone/sulbactam ( $r = 0.95, P < 0.05$ ).

## Discussion

In the past 4 years, the prevalence of Gram-negative bacteria in our hospital showed an upward trend year by year. The detection rate of *A. baumannii* was the highest and increased during the study period, which was higher than that reported by CHINET<sup>[16]</sup>. The environment of tropical region might be conducive to the growth of *A. baumannii*. It has been reported that the number of community-acquired pneumonia caused by *A. baumannii* is increased in tropical regions, such as tropical Northern Australia and tropical middle-income countries<sup>[17, 18]</sup>. Moreover, our data indicated that the detection rate of carbapenem-resistant *A. baumannii* was about 70%, exhibiting an upward trend, which was significantly higher than that of most provinces in China<sup>[12]</sup>. The possible reason could be that most pathogens of *A. baumannii* in this study were isolated from ICU patients with poor immune function and critical illness. Severe illness, more invasive operations and extensive exposure to antibiotics might increase the antimicrobial resistance.

Optimistically, the resistance rate of *K. pneumoniae* to carbapenems in our hospital was less than 10%, which was lower than that of mainland China<sup>[12]</sup>. In 2017, the resistance rate of *K. pneumoniae* to meropenem in China has been increased to above 20%<sup>[16]</sup>. It was speculated that the resistance rate of *K. pneumoniae* to carbapenems in some tropical areas might be lower compared with the non-tropical areas. For example, the resistance rate of *K. pneumoniae* to carbapenems in Hainan Provincial People's Hospital in 2010 is much lower than that of CHINET in the same period<sup>[19, 20]</sup>. A recent study in a children's hospital in South Africa has shown that *K. pneumoniae* is sensitive to meropenem and imipenem<sup>[21]</sup>.

Widespread use of antibiotics has accelerated the incidence of antibiotic resistance. The antimicrobial stewardship is one important measure to impel and enhance the reasonable usage of antibiotics, and to ensure the continuous effectiveness of antimicrobials. The implementation of antimicrobial stewardship has received more concerns worldwide<sup>[22, 23]</sup>. Studies in hospitals have shown that the stewardship may decrease the incidence of nosocomial infections caused by carbapenem-resistant *A. baumannii*<sup>[24]</sup>. At the same time, improved monitoring of hospital-acquired infections and effective infection control measures may be the best way to solve the present problem<sup>[25]</sup>. The emergence of MDR Gram-negative pathogens is becoming a major health concern in our hospital. To control the resistance of Gram-negative pathogens, infection control programs and antimicrobial stewardship were implemented from the end of 2016 to 2017. We classified the management on antibiotics, implemented the Guiding Principles of Clinical Use of Antibiotics, and strengthened the intervention for prophylactic use of antibacterial in perioperative period about clean surgery and comments on antimicrobial prescription in our hospital.

In our present study, a reduction of the AUD in the entire hospital was observed in 2017 after the implementation of antimicrobial stewardship. We found that the total AUD and that of amceftazidime/tazobactam and levofloxacin were significantly decreased. As the antibiotic consumption was decreased after clinical application management of antibacterial drugs, the prevalence of MDR Gram-negative pathogens was correspondingly decreased. This result was similar to the previous studies<sup>[4, 7]</sup>. Moreover, antimicrobial stewardship could help ensure the continuous effectiveness of antimicrobials. For example, the sensitivity of *A. baumannii* to  $\beta$ -lactam/enzyme inhibitors and *K. pneumoniae* to carbapenems remained steady during the study period in our hospital.

Antimicrobial resistance and antibiotic consumption affect each other. Antimicrobial resistance may impact the antibiotic prescription of physicians, and similarly antibiotic consumption may in turn increase the selective pressure on certain classes of antibiotics in pathogens<sup>[26, 27]</sup>. In order to reduce the antimicrobial resistance, it is necessary to continuously strengthen the hospital infection control and antimicrobial stewardship. Some measures are being taken into consideration, such as to rich public knowledge about antibiotic use, to apply information technology to pre-review prescription, to intervene irrational antimicrobial prescriptions (no-indication prescription, incorrect doses and over-treatment, and so on), and to monitor and control the use of antibiotics with high resistance and over prescription ( $\beta$ -lactam/enzyme inhibitors, fluoroquinolones, and carbapenems). Furthermore, the communication between laboratorians and clinicians should be further improved in addition to surveillance of bacterial resistance.

Our study has some limitations. First, this study was performed in a single center. Because antimicrobial resistance rates vary among hospitals and units, the results may not be representative and reproducible in other institutions. Therefore, the antimicrobial resistance rate and antibiotic consumption could be overestimated. Second, this surveillance was only performed from 2014 to 2017, because our hospital was established in 2014. The correlations in this study might not be sufficient basis for the hospital management and medical decision making. A long-term study should be conducted to provide more valuable information. Finally, we analyzed the correlation between antibiotic consumption and antimicrobial resistance regardless of other factors, such as age, sex, underlying diseases and education of patients. Even if statistically significant, the consumption of certain antibiotic drugs might not be the only factor affecting antimicrobial resistance.

## Conclusions

Collectively, our current data demonstrated that the characteristics of bacterial distribution and antimicrobial resistance in our hospital were different from those in mainland China. Increasing use of carbapenems was significantly associated with the incidence of meropenem-resistant *A. baumannii*, and the AUD of mainly used antibiotics, such as  $\beta$ -lactamase/enzyme inhibitors as well as fluoroquinolones and carbapenems, had positive effects on the prevalence of MDR Gram-negative bacteria. Although there was a decreasing trend in AUD of main antibiotics and MDR Gram-negative bacteria after the implementation of antimicrobial stewardship since the end of 2016, it is still necessary to continue the antimicrobial stewardship that meet the regional characteristics of our hospital.

## Declarations

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### *Conflict of interest*

There is no conflict of interest to be declared. The authors alone are responsible for the content and writing of the paper.

### *Ethical approval*

The protocol was approved by Medical Ethics Committee of PLA General Hospital (approval number: S2018–192–01).

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## Tables

**Table 1. Distribution of bacterial species from 2014 to 2017**

bacteria	2014		2015		2016		2017		total	
	n.	(%)	n.	(%)	n.	(%)	n.	(%)	n.	(%)
<b>Gram-negative bacteria</b>	596	71.46	1308	73.28	1575	75.21	2444	79.22	5923	75.96
<i>A. baumannii</i>	71	8.51	181	10.14	211	10.08	448	14.52	911	11.68
<i>Acinetobacter</i> spp.	27	3.24	24	1.34	50	2.39	55	1.78	156	2.00
(without <i>A. baumannii</i> )										
<i>E. cloacae</i>	30	3.60	35	1.96	45	2.15	48	1.56	158	2.03
<i>Enterobacter</i> spp.	45	5.40	144	8.07	246	11.75	371	12.03	806	10.34
(without <i>E. cloacae</i> )										
<i>K. pneumoniae</i>	75	8.99	206	11.54	239	11.41	282	9.14	802	10.28
<i>Klebsiella</i> spp.	31	3.72	46	2.58	67	3.20	142	4.60	286	3.67
(without <i>K. pneumoniae</i> )										
<i>E. coli</i>	112	13.43	207	11.60	226	10.79	249	8.07	794	10.18
<i>P. aeruginosa</i>	66	7.91	136	7.62	151	7.21	325	10.53	678	8.69
Other Gram-negative bacteria	139	16.67	329	18.43	340	16.24	524	16.99	1332	17.08
<b>Gram-positive bacteria</b>	238	28.54	477	26.72	519	24.79	641	20.78	1875	24.04
<b>Total</b>	834	100	1785	100	2094	100	3085	100	7798	100

Table 2. Resistance rate of main Gram-negative bacteria against antimicrobials from 2014 to 2017

Antimicrobial agents	2014			2015			2016			2017		
	A.	K.	P.	A.	K.	P.	A.	K.	P.	<i>A.baumannii</i>	K.	P.
	<i>baumannii</i>	<i>pneumoniae</i>	<i>aeruginosa</i>	<i>baumannii</i>	<i>pneumoniae</i>	<i>aeruginosa</i>	<i>baumannii</i>	<i>pneumoniae</i>	<i>aeruginosa</i>	<i>pneumoniae</i>	<i>aeruginosa</i>	
Carbapenem	71.43	25.68	19.35	78.74	21.05	37.76	75.00	44.00	27.27	74.60	15.56	28.09
Meropenem/tazobactam	69.44	0	9.09	73.41	9.14	13.97	69.79	10.46	16.56	68.02	3.40	14.21
Meropenem/sulbactam	42.42	17.81	35.94	48.55	11.65	40.74	45.55	28.81	40.00	42.62	14.98	30.43
Colistin	67.61	1.39	7.32	73.89	0	27.78	72.25	8.90	26.09	75.19	0	39.13
Polymyxin B	60.94	1.35	13.11	71.26	5.34	25.00	71.56	11.30	26.97	73.81	2.42	35.79
Polymyxin E	65.38	5.48	3.28	64.39	2.43	14.71	66.67	5.93	14.57	63.01	6.80	6.84
Colistin	61.54	12.33	11.11	68.39	16.50	25.74	55.45	30.93	25.00	67.73	19.81	20.00

Table 3. Correlation between AUD of mainly used antibiotics and prevalence of MDR Gram-negative bacteria

AUD	Correlation ( <i>r</i> )		
	MDR-AB	MDR-KP	MDR-PA
Total	0.778	-0.178	<b>0.964*</b>
Ceftazidime/tazobactam	0.905	-0.772	0.66
Cefoperazone/sulbactam	0.94	-0.648	0.789
Levofloxacin	0.82	-0.869	0.503
Meropenem	-0.437	0.456	0.341
Imipenem/cilastatin	0.182	-0.463	-0.535

MDR-AB: Multidrug-resistant; MDR-AB: Multidrug-resistant *A. baumannii*; MDR-PA: Multidrug-resistant *P. aeruginosa*; MDR-KP: Multidrug-resistant *K. pneumoniae*  $r$ : Pearson's correlation coefficient; \*:  $P < 0.05$ .

Table 4. Correlation between AUD and antimicrobial resistance

AUD	Antimicrobial resistance	Correlation ( <i>r</i> )					
		Piperacillin/tazobactam	Cefoperazone/sulbactam	Meropenem	Imipenem	Amikacin	Levofloxacin
Ceftazidime	<i>A. baumannii</i>	<b>0.971*</b>	0.35	0.938	<b>0.995*</b>	-	-
	<i>K. pneumoniae</i>	0.025	0.666	-0.973	0.503	-	-
	<i>P. aeruginosa</i>	0.919	-0.857	0.747	0.943	-	-
Ceftazidime/tazobactam	<i>A. baumannii</i>	<b>-0.327</b>	<b>0.574</b>	<b>-0.539</b>	<b>-0.524</b>	-	-
	<i>K. pneumoniae</i>	0.351	0.018	0.137	0.209	-	-
	<i>P. aeruginosa</i>	-0.277	0.863	-0.769	-0.769	-	-
Cefoperazone/sulbactam	<i>A. baumannii</i>	<b>-0.149</b>	<b>0.685</b>	<b>-0.414</b>	<b>-0.362</b>	-	-
	<i>K. pneumoniae</i>	0.475	0.139	0.258	0.406	-	-
	<i>P. aeruginosa</i>	-0.068	<b>0.95*</b>	-0.643	-0.643	-	-
Meropenem	<i>A. baumannii</i>	<b>0.977*</b>	0.463	<b>0.986*</b>	<b>0.99*</b>	-	-
	<i>K. pneumoniae</i>	-0.146	-0.18	-0.042	0.384	-	-
	<i>P. aeruginosa</i>	0.845	-0.23	0.877	0.919	-	-
Imipenem/cilastatin	<i>A. baumannii</i>	<b>-0.997*</b>	<b>-0.592</b>	<b>-0.896</b>	<b>-0.96*</b>	-	-
	<i>K. pneumoniae</i>	-0.125	-0.101	-0.251	-0.627	-	-
	<i>P. aeruginosa</i>	-0.903	-0.2	-0.822	-0.863	-	-
Amikacin	<i>A. baumannii</i>	-	-	-	-	-	-
	<i>K. pneumoniae</i>	-	-	-	-	<b>-0.581</b>	-
	<i>P. aeruginosa</i>	-	-	-	-	-0.165	-
Levofloxacin	<i>A. baumannii</i>	-	-	-	-	-	<b>-0.12</b>
	<i>K. pneumoniae</i>	-	-	-	-	-	<b>-0.42</b>
	<i>P. aeruginosa</i>	-	-	-	-	-	-0.162

AUD: antibiotic use density; - No correlation analysis was performed; \*:  $P < 0.05$ .

## Figures

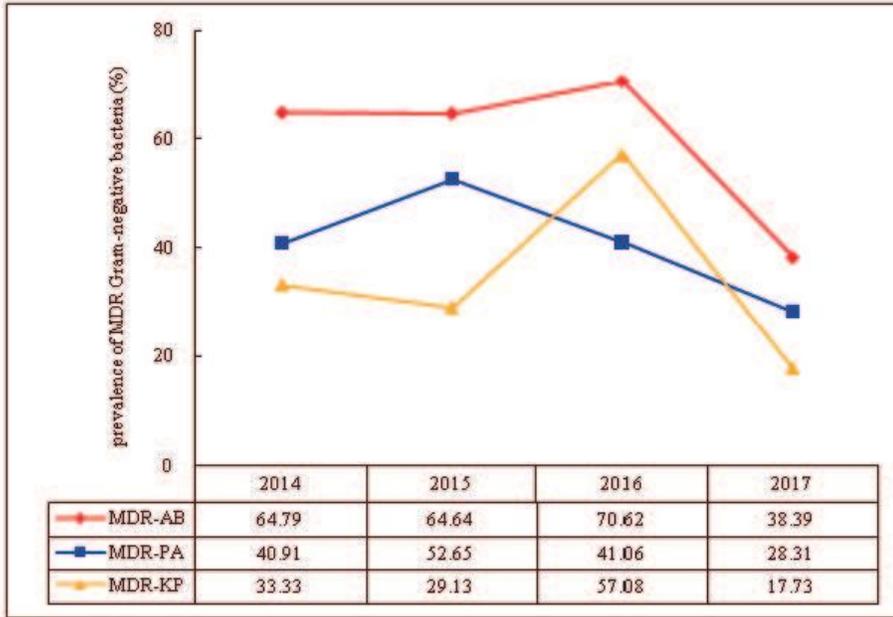


Figure 1

Changing pattern in prevalence of MDR Gram-negative bacteria from 2014 to 2017. MDR-AB: Multidrug-resistant *A. baumannii*; MDR-PA: Multidrug-resistant *P. aeruginosa*; MDR-KP: Multidrug-resistant *K. pneumonia*.

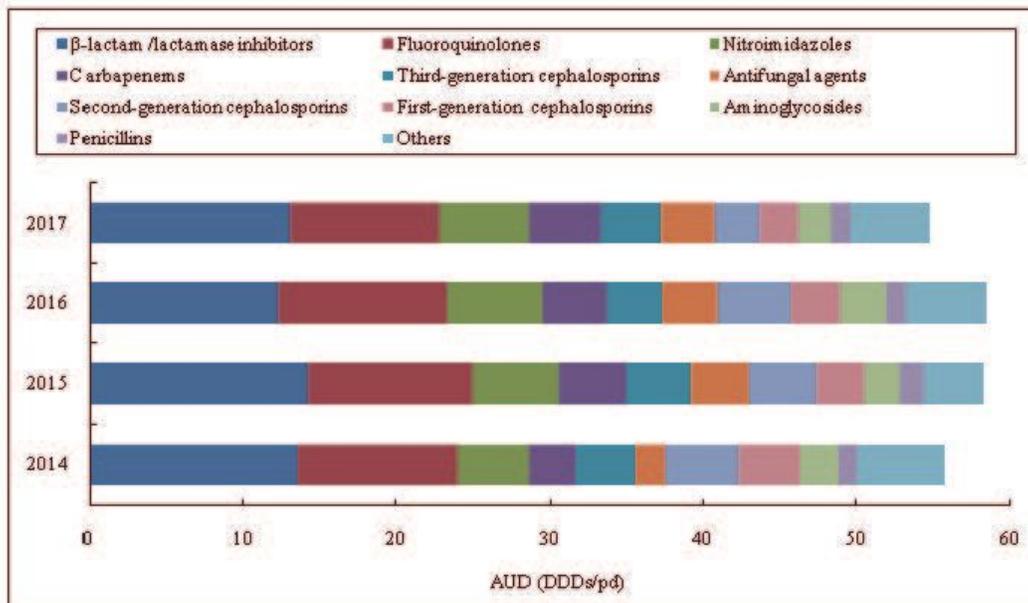
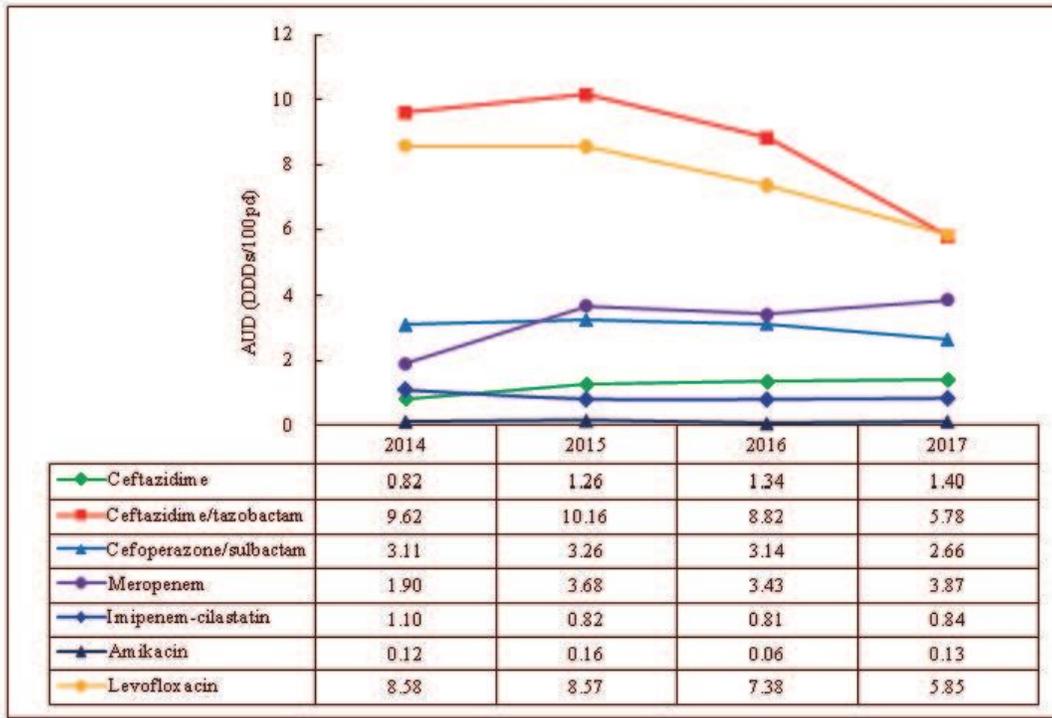


Figure 2

Changing pattern in AUD of various antimicrobial agents from 2014 to 2017. AUD: antibiotic use density; DDD: defined daily dose. pd: patient-day.



**Figure 3**

Changing pattern in AUD of mainly used antibiotics from 2014 to 2017. AUD: antibiotic use density; DDD: defined daily dose. pd: patient-day.