Trends and correlation between antibacterial consumption and carbapenem resistance in Gram-negative bacteria in a tertiary hospital in China from 2012 to 2019

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Abstract

Background: To investigate the trends and correlation between antibacterial consumption and carbapenem resistance in Gram-negative bacteria from 2012 to 2019 in a tertiary-care teaching hospital in southern China.

Methods: This retrospective study included data from hospital-wide inpatients collected between January 2012 and December 2019. Data on antibacterial consumption were expressed as defined daily doses (DDDs)/1000 patient-days. Antibacterials were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The trends in antimicrobial usage and resistance were analyzed by linear regression, while Pearson correlation analysis was used for testing the correlation.

Results: An increasing trend in the annual consumption of tetracyclines, β -lactam/ β -lactamase inhibitor (BL/BLI) combinations, and carbapenems was observed ($P < 0.05$). The carbapenem resistance of *Acinetobacter baumannii* (*A. baumannii*) significantly increased ($P < 0.05$) from 18% in 2012 to 60% in 2019. Moreover, a significant positive correlation was found between the resistance to carbapenems in *A. baumannii* ($\beta = 0.745$, $P < 0.05$) and *Escherichia coli* (*E. coli*) ($\beta = 0.736$, $P < 0.05$) and the consumption of carbapenems, while the resistance rate of *A. baumannii* to carbapenems was positively correlated with cephalosporin/ β -lactamase inhibitor (C/BLI) combinations ($\beta = 0.910$, $P < 0.01$) and tetracyclines usage ($\beta = 0.745$, $P < 0.05$). We also found that the use of quinolones was positively correlated with the resistance rate of *Burkholderia cepacia* (*B. cepacia*) to carbapenems ($\beta = 0.717$, $P < 0.05$), and the increasing use of carbapenems ($\beta = -0.869$, $P < 0.01$) and penicillin/ β -Lactamase inhibitor (P/BLI) combinations ($\beta = -0.871$, $P < 0.01$) were significantly correlated with reduced resistance of *Enterobacter cloacae* (*E. cloacae*) to carbapenems.

Conclusion: Our results revealed significant correlations between the consumption of antibiotics and rates of carbapenem resistance in Gram-negative bacteria. Implementing proper management strategies and reducing the unreasonable use of antibacterial drugs may be an effective measure to reduce the spread of carbapenem-resistant Gram-negative bacteria (CRGN), which should be further confirmed by more studies.

Background

Increasing antibacterial resistance and associated infections have become the global health threat [1]. Antibacterial resistance can lead to unresponsiveness to treatment, resulting in persistent illness and increased risk of death [2]. Multidrug-resistant organisms have adverse effects not only on patients who are infected but also on patients not infected with multidrug-resistant bacteria. All patients are affected by the lack of appropriate antibiotic regimens due to the less efficient antimicrobial agents [3].

Among the many antibiotic-resistant bacteria infections, carbapenem-resistant Gram-negative bacteria (CRGN), which mainly include carbapenem-resistant Enterobacteriaceae (CRE), *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* (CRPA), pose a significant threat to humanity with reference to mortality, medical burden, and trends in antimicrobial resistance [4]. The emergence and spread of CRGN are considered to be mainly related to hydrolysis of carbapenemase, changes in membrane permeability [5], overuse of antimicrobials, and healthcare-associated infections [6]. In their report, the EU and European Economic Area estimated that the burden of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) increased the most (by 6.16 times) among the bacterial species studied in terms of a number of infections and deaths during 2007–2015, followed by carbapenem-resistant *Escherichia coli* (CREC) [7]. In the face of rapidly increasing antimicrobial resistance, the World Health Organization (WHO) ranked CRGN as the most urgent bacteria in 2017 [8].

According to the data from China Antibacterial Surveillance Network, the usage rate and DDDs/100 patient-days in inpatients have shown a downward trend from 2011 to 2017 since the rectification of the clinical application of antimicrobials in China in 2011. However, the consumption of carbapenems increased, with a rise of carbapenem resistance rate in Gram-negative bacteria. Therefore, it was proposed to strengthen the management of carbapenems and tigecycline to reduce carbapenem resistance in China in February 2017. Based on the fact that the use of antibiotics can create selective pressure favoring the spread of resistance [9], further explorations of the relationship between consumption of more antimicrobial agents and carbapenem resistance could provide a basis for effective and scientific management of antimicrobials. The aim of this study was to describe the changing trend of antibacterial usage and the prevalence of CRGN from 2012 to 2019 in a tertiary hospital and evaluate the correlation between them.

Methods

Study design and setting

The data for this study were collected from local monitoring of carbapenem resistance in Gram-negative bacteria and antibacterial consumption at Sixth Affiliated Hospital of Guangxi Medical University, which is a comprehensive, tertiary care, university-affiliated, and teaching hospital in the south of China. It is also the largest hospital in Southeast Guangxi, with the actual 2400 open beds.

Bacterial isolates and susceptibility testing

Antibiotic resistance data, which were provided by the hospital's clinical microbiology laboratory, were extracted from the hospital information system. A total of 37710 cases with data on Gram-negative bacterial resistance were recorded and included in the study, including all positive clinical specimens, and 34489 cases with data on six isolated species, including *A. baumannii*, *Pseudomonas aeruginosa* (*P. aeruginosa*), *Klebsiella pneumoniae* (*K. pneumoniae*), *E. coli*, *E. cloacae*, and *B. cepacia*, which were target bacteria to be monitored in the hospital. The resistance rate was

reported as the percentage of resistant isolates among all tested isolates. Antimicrobial susceptibility was tested based on the latest performance standards set by the Clinical and Laboratory Standards Institute (CLSI). Tested isolates that resulted in intermediately resistant were eliminated from this analysis. We retained the first isolate of duplicate test results from the same patient during the same in-patient stay. The isolation rate was calculated as the percentage of total gram-negative bacterial isolates.

Antibacterial consumption

Antibacterial consumption data from 2012 to 2019 were obtained from the hospital information system. According to the Guidelines for ATC classification and DDD assignment 23rd edition (2020) [10], data on antibacterial consumption were expressed as defined daily doses (DDDs)/1000 patient-days. Antibacterials were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

Statistical analysis

The changing trends of antimicrobial use and resistance were analyzed by linear regression. Pearson correlation analysis was used for evaluating the relationship between antibiotic consumption and bacterial resistance rates. A p-value < 0.05 was considered statistically significant.

Results

Antibacterial consumption

Table 1 and Fig. 1 showed the DDDs/1000 patient-days and annual usage trends of antibiotics. During the entire study period, the six top-ranked consumed classes of antimicrobial agents were cephalosporins (except for cephalosporin/β-lactamase inhibitor (C/BLI) combinations), β-lactam/β-lactamase inhibitor (BL/BLI) combinations, quinolones, macrolides, penicillins (except for penicillin/β-Lactamase inhibitor (P/BLI) combinations) and carbapenems. The carbapenem class of antibiotics contained three members in this hospital, including meropenem, imipenem, and biapenem, all of which showed an increasing trend. Among them, the most frequently used was piperacillin-tazobactam, followed by cefuroxime and levofloxacin. The annual consumption of several antibiotics significantly decreased during this period, including amphenicols, cephalosporins (except for C/BLI combinations), and lincosamides ($P < 0.05$). Additionally, there was an increasing trend in the annual consumption of tetracyclines, BL/BLI combinations, and carbapenems ($P < 0.05$). No statistically significant variation was observed in the consumption of macrolides, aminoglycosides, and quinolones ($P > 0.05$).

Table 1
Trends of annual antibacterial consumption during the entire study period

Antimicrobial class	Annual consumption of antibiotics (DDDs/1000 patient-days)								Linear regression		
	2012	2013	2014	2015	2016	2017	2018	2019	Slope(β)	P	Trend
Tetracyclines	0.71	0.06	2.87	4.07	2.49	5.28	5.08	6.78	0.871	0.001	Increasing
Amphenicols	1.06	0.91	0.76	0.44	0.49	0.57	0.53	0.45	-0.079	0.009	Decreasing
Penicillins (except for P/BLI combinations)	26.98	16.46	14.85	10.06	11.85	10.79	12.24	13.84	-1.470	0.072	Stable
BL/BLI combinations	73.09	63.88	90.08	122.26	149.85	176.25	179.49	197.33	20.642	0.000	Increasing
P/BLI combinations	57.47	42.74	63.39	89.29	111.45	143.94	145.26	165.17	18.217	0.000	Increasing
C/BLI combinations	15.62	21.14	26.69	32.97	38.40	32.31	34.24	32.17	2.425	0.020	Increasing
Cephalosporins (except for C/BLI combinations)	200.71	208.67	169.56	170.48	182.50	157.53	126.69	121.53	-11.765	0.001	Decreasing
First-generation	31.01	23.33	18.97	14.49	13.58	10.72	9.05	8.86	-3.001	0.000	Decreasing
Second-generation	84.40	99.06	98.36	97.53	105.56	80.33	71.46	74.49	-3.017	0.135	Stable
Third-generation	85.30	86.27	52.23	58.46	63.35	66.47	46.17	38.18	-5.747	0.013	Decreasing
Carbapenems	3.09	3.97	7.20	11.55	16.34	22.93	19.23	23.84	3.257	0.000	Increasing
imipenem	1.72	1.58	2.91	3.76	4.16	4.64	3.47	4.46	0.407	0.008	Increasing
meropenem	1.37	2.39	4.29	7.79	12.15	16.71	13.58	16.13	2.391	0.000	Increasing
biapenem	0	0	0	0	0.02	1.59	2.19	3.25	1.030	0.015	Increasing
Macrolides	26.84	38.66	45.00	45.19	40.44	38.58	26.82	30.11	-0.718	0.580	Stable
Lincosamides	16.09	9.00	0.58	0.63	0.68	0.43	0.22	0.24	-1.848	0.027	Decreasing
Aminoglycosides	10.52	9.63	11.98	9.08	9.11	8.56	6.94	9.15	-0.396	0.072	Stable
Quinolones	100.35	81.53	90.38	91.47	112.51	108.03	63.12	54.02	-4.076	0.225	Stable

Bacterial resistance

Bacterial isolates

Consecutive, non-duplicate bacterial isolates were collected from patients treated at the hospital. Altogether 11813 E. coli isolates, 7412 K. pneumonia isolates, 7583 P. aeruginosa isolates, 4936 A. baumannii isolates, 2007 E. cloacae isolates, and 738 B. cepacia isolates detected between 2012 and 2019 were included in the analysis. Figure 2A shows the trend of the isolation rate of these species. Isolation rates of K. pneumonia, P. aeruginosa, and A. baumannii maintained stable ($P > 0.05$), while E. coli, E. cloacae, and B. cepacia showed a downward trend over recent years ($P < 0.05$).

Carbapenem resistance

Figure 2B shows the results of the study for analyzing carbapenem resistance trends in Gram-negative bacteria. The carbapenem resistance of A. baumannii significantly increased ($P < 0.05$) from 18% in 2012 to 60% in 2019. In contrast, a significant decrease in carbapenem resistance of E. cloacae was observed ($P < 0.01$). However, the remaining four Gram-negative isolates revealed no significant difference in carbapenem resistance ($P > 0.05$).

Correlation between antibacterial consumption and carbapenem resistance

Table 2 and Fig. 3 show the association between resistance to carbapenem and antibacterial usage of different classes from 2012 to 2019. A significant positive correlation was found between the consumption of tetracyclines ($\beta = 0.745$, $P < 0.05$), BL/BLI combinations ($\beta = 0.714$, $P < 0.05$), C/BLI combinations (only including cefoperazone-sulbactam) ($\beta = 0.910$, $P < 0.01$), meropenem ($\beta = 0.755$, $P < 0.05$), imipenem ($\beta = 0.923$, $P < 0.01$) and carbapenems ($\beta = 0.745$, $P < 0.05$) and the rate of CRAB. Conversely, there was a significant negative correlation between the consumption of penicillins (except for P/BLI combinations) ($\beta = -0.904$, $P < 0.01$), amphenicols ($\beta = -0.927$, $P < 0.01$), first-generation cephalosporins ($\beta = -0.864$, $P < 0.01$) and lincosamides ($\beta = -0.938$, $P < 0.01$) and the rate of CRAB. Moreover, the usage of meropenem ($\beta = 0.713$, $P < 0.05$) and carbapenems ($\beta = 0.736$, $P < 0.05$)

was positively correlated with the rate of CREC. Carbapenem-resistant *E. cloacae* showed a significant negative correlation with the usage of P/BLI combinations ($\beta=-0.871$, $P<0.01$), BL/BLI combinations ($\beta=-0.872$, $P<0.01$), meropenem ($\beta=-0.865$, $P<0.01$) and carbapenems ($\beta=-0.869$, $P<0.01$), but a significant positive correlation with total cephalosporins (except for C/BLI combinations) use ($\beta=0.727$, $P<0.05$). Moreover, carbapenems resistance in *B. cepacia* was positively correlated with quinolones use ($\beta=0.717$, $P<0.05$). Unexpectedly, there was no significant correlation between antibacterial consumption and carbapenem resistance in *P. aeruginosa* and *K. pneumonia* ($P>0.05$). Moreover, we found that the rise of carbapenems usage is consistent with an increase in the number of Gram-negative isolates resistant to carbapenems ($\beta=0.796$, $P<0.05$)(Fig. 4).

Table 2
The association between resistance to carbapenem and antibacterial usage for the entire study period

Antibiotic consumption	Carbapenem resistance for isolated species											
Antibiotic class	E. coli		K. pneumonia		P. aeruginosa		A. baumannii		E. cloacae		B. cepacia	
	Correlations											
	Slope(β)	P	Slope(β)	P	Slope(β)	P	Slope(β)	P	Slope(β)	P	Slope(β)	P
Tetracyclines	0.695	0.056	0.115	0.787	0.588	0.125	0.745	0.034	-0.694	0.056	-0.083	0.844
Amphenicols	-0.372	0.364	-0.563	0.146	-0.585	0.128	-0.927	0.001	0.666	0.072	-0.376	0.358
Penicillins (except for P/BLI combinations)	-0.264	0.528	-0.682	0.062	-0.678	0.064	-0.904	0.002	0.505	0.202	-0.371	0.366
BL/BLI combinations	0.659	0.076	0.134	0.751	0.382	0.351	0.714	0.046	-0.872	0.005	-0.001	0.998
P/BLI combinations	0.700	0.053	0.057	0.894	0.350	0.396	0.654	0.079	-0.871	0.005	-0.081	0.849
C/BLI combinations	0.249	0.552	0.576	0.135	0.482	0.227	0.910	0.002	-0.662	0.074	0.488	0.219
Cephalosporins (except for C/BLI combinations)	-0.544	0.164	0.111	0.794	-0.394	0.333	-0.588	0.125	0.727	0.041	0.244	0.561
First-generation	-0.513	0.193	-0.346	0.402	-0.542	0.165	-0.864	0.006	0.800	0.017	-0.107	0.801
Second-generation	-0.553	0.155	0.49	0.217	-0.100	0.813	0.014	0.973	0.493	0.214	0.627	0.096
Third-generation	-0.348	0.398	-0.007	0.987	-0.400	0.326	-0.693	0.057	0.598	0.117	0.026	0.951
Carbapenems	0.736	0.037	0.176	0.677	0.424	0.295	0.745	0.034	-0.869	0.005	-0.002	0.996
imipenem	0.635	0.091	0.450	0.263	0.603	0.113	0.923	0.001	-0.673	0.068	0.340	0.410
meropenem	0.713	0.047	0.220	0.601	0.425	0.293	0.755	0.030	-0.865	0.006	0.046	0.914
biapenem	0.561	0.439	-0.915	0.085	0.169	0.831	-0.442	0.558	-0.751	0.249	-0.994	0.006
Macrolides	-0.172	0.684	0.703	0.052	0.492	0.216	0.468	0.242	0.359	0.382	0.607	0.110
Lincosamides	-0.329	0.426	-0.469	0.241	-0.640	0.087	-0.938	0.001	0.558	0.151	-0.304	0.464
Aminoglycosides	-0.219	0.602	-0.248	0.554	-0.205	0.626	-0.328	0.428	0.669	0.070	0.037	0.930
Quinolones	-0.199	0.637	0.484	0.224	0.113	0.791	0.040	0.924	0.482	0.226	0.717	0.045

Discussion

In the present study, we observed that cephalosporins (except for C/BLI combinations) had the largest consumption variety during the entire study period, despite showing a downward trend. In addition, the consumption of BL/BLI combinations showed an increasing trend, and piperacillin-tazobactam was the most frequently used antibiotic, which was consistent with a previous study conducted at a tertiary hospital in China [11]. Previous studies have shown that the history of using 3rd generation cephalosporins is an independent risk factor for extended-spectrum β -lactamase (ESBL)-producing *K. pneumoniae* or *E. coli* bacteremia [12]. Due to the high prevalence of ESBLs, the rational application of cephalosporins, especially 3rd generation of cephalosporins is extremely important. The replacement of 3rd generation cephalosporins by BL/BLI combinations was considered as a suitable strategy for reducing the incidence of ESBL-producing Enterobacteriaceae [13–15]. Additionally, our results revealed a significant increase in the consumption of carbapenems. Global antibiotic consumption of carbapenems has increased between 2000 and 2010 [16], which is consistent with the growth trend monitored from 2000 to 2015 [17]. Our results confirmed that the rise of carbapenems usage was consistent with an increase in the number of infections resistant to carbapenems during the entire study period. Yet, it is undeniable that the overuse of carbapenems presents an important problem and carbapenems should be used more rationally.

The isolation rate of the six bacterial isolates did not show an increasing trend in recent years. Instead, *E. coli*, *E. cloacae*, and *B. cepacia* showed a downward trend. As expected, *E. coli* was always shown as the most common isolate from 2012 to 2019 but was still highly sensitive to carbapenem antibiotics. Carbapenem resistance rates in *K. pneumoniae* at the hospital were significantly lower than the national level and relatively stable, ranging from 2% in 2012 to 3% in 2019. According to the reports from the bacterial resistance surveillance system in China [18, 19], the Incidence of CRKP showed a significant increase from 8.9% in 2005 to 26.3% in 2018. Surprisingly, the detection rate of CRKP declined for the first time in 2019 [18]. The rate of CRAB was the highest in all isolated species that were studied thus far, showing a rapidly rising trend between 2012 and 2019, which was valid for the whole country [18–20]. In China, the rate of CRAB was nearly 80% in 2019. Based on the fact that *A. baumannii* has a resistance rate of more than 50% to most antibacterial drugs, it is very important to select antibacterial agents based on the results of susceptibility testing [21].

Because of the urgent need to improve the rational use of antibiotics, a multidisciplinary antibiotic team (made up of infectious disease specialists, microbiologists, clinical pharmacists, and clinicians) was established in 2017 at the hospital. This team focused on appropriate administration of antibiotic therapy for inpatients, pointing out medication errors, and offering corrected suggestions. Coincidentally, carbapenem resistance rates in *K. pneumoniae*, *P. aeruginosa*, *E. cloacae*, and *B. cepacia* showed a downward trend from 2017 to 2019. Consequently, reducing the unreasonable use of antibacterial drugs may be an effective measure to reduce the spread of CRGN; however, further studies are needed to confirm these observations.

Our results showed a significant positive correlation between the resistance to carbapenems in *A. baumannii* and *E. coli* and the consumption of carbapenems, which was consistent with the study conducted across 153 tertiary hospitals in China [22]. Previous studies have indicated that the increasing rate of CRAB was related to carbapenem exposure [23, 24]. Carbapenems are the most powerful antibiotics for ESBL-producing Enterobacteriaceae. However, for CRGN infections, carbapenems need to be used with other antimicrobial agents for forming antimicrobial combinations and are recommended to be used in a high-dose with minimum inhibitory concentration (MIC) within a certain range [25], which can increase the use of carbapenem and other antibacterial drugs, further aggravate carbapenem resistance and produce new issues of drug resistance. Different from the results of Tan et al [26], which showed no significant association between the usage of BL/BLI combinations and the prevalence rates of CRAB, the resistance rate of *A. baumannii* to carbapenems was positively correlated with cefoperazone-sulbactam usage in the present study. We also observed a positive correlation between the consumption of tetracyclines and the resistance rate of *A. baumannii* to carbapenems.

Among the complicated mechanisms of CRAB, the most important one is the production of carbapenemases, which can be either inherent or obtained [27]. Similarly, combination treatments of two or more antibiotics were recommended for the treatment of severe infections with CRAB, aiming to achieve bactericidal effects through synergies at concentrations below the respective MIC of the relevant substances [28]. Among the many combination therapies, cefoperazone/sulbactam-based combination regimen, which is usually combined with tigecycline, minocycline, carbapenems or aminoglycosides, is most commonly used for the treatment of carbapenem-resistant and extensively drug-resistant *A. baumannii* infections [25]. Therefore, it is understandable that increased consumption of cefoperazone-sulbactam and tetracyclines is associated with carbapenem resistance of *A. baumannii*.

Contrary to what was expected, the increasing use of carbapenems and P/BLI combinations during the study period was significantly correlated with reduced resistance of *E. cloacae* to carbapenems. Nevertheless, the biochemical and molecular studies on *E. cloacae* have shown genomic heterogeneity, and the consumption of carbapenems has been indicated as an independent risk factor for the infection of imipenem-heteroresistant *E. cloacae* [29], which may be selected for highly resistant and pathogenic strains. Accordingly, this finding did not provide a strong basis for the selection of antimicrobials to *E. cloacae* infections. Given the lack of related research on the correlation between antibacterial consumption and carbapenem resistance of *E. cloacae*, further research is needed to verify this association. It is difficult to treat infections caused by *B. cepacia*, because of the high level of intrinsic and acquired resistance to many antimicrobial agents. Therefore, treatment is usually based on susceptibility testing. Carbapenems have proven to be one of the most reliable antibacterial drugs [30]. Yet, we found that the use of quinolones was positively correlated with the resistance rate of *B. cepacia* to carbapenems, which prompts us to pay more attention to the use of quinolones to slow down the resistance of *B. cepacia* to carbapenems.

There are some limitations in this study. Firstly, this study was conducted only at one tertiary hospital, while carbapenem resistance rates and antibacterial consumption may vary widely across hospitals; therefore, a multicentered study with more relevant data is needed to explore the correlation between antibacterial consumption and CRGN. Secondly, the development of carbapenem resistance in Gram-negative infection is associated with various factors, and the selective pressure of antibacterial drugs is only one of them. Multi-factor analysis needs to be further studied.

Conclusion

The present study demonstrated significant correlations between the consumption of antibiotics and the rates of CRGN. Implementing proper management strategies and reducing the unreasonable use of antibacterial drugs may be an effective measure to reduce the spread of CRGN, which needs to be further verified by more studies.

Abbreviations

A. baumannii: *Acinetobacter baumannii*; *E. coli*: *Escherichia coli*; *B. cepacia*: *Burkholderia cepacia*; *E. cloacae*: *Enterobacter cloacae*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *K. pneumonia*: *Klebsiella pneumonia*; CRGN: carbapenem-resistant Gram-negative bacteria; CRE: carbapenem-resistant Enterobacteriaceae; CRAB: carbapenem-resistant *Acinetobacter baumannii*; CRPA: carbapenem-resistant *Pseudomonas aeruginosa*; CRKP:

carbapenem-resistant *Klebsiella pneumoniae*; CREC: carbapenem-resistant *Escherichia coli*; ESBL: extended-spectrum β -lactamase; BL/BLI: β -lactam/ β -lactamase inhibitor; C/BLI: cephalosporin/ β -lactamase inhibitor; P/BLI: penicillin/ β -Lactamase inhibitor; DDDs: defined daily doses; ATC: Anatomical Therapeutic Chemical; CLSI: Clinical and Laboratory Standards Institute; MIC: minimum inhibitory concentration; WHO: World Health Organization.

Declarations

Ethical approval

This study was reviewed and approved by the Ethical Committee of Sixth Affiliated Hospital of Guangxi Medical University (Approval No.2019052).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CL and XZ carried out the studies, participated in collecting data, and drafted the manuscript. CL, PP and XZ performed the statistical analysis and critically for important intellectual content. LZ, GM, and LZ participated in acquisition, analysis, or interpretation of data. All authors read and approved the final manuscript.

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Figures

Figure 1

Inpatient antibiotic use for the entire study period.

Figure 2

Trends of isolation rate of Gram-negative bacteria and resistance rates of carbapenem-resistant Gram-negative bacteria for the entire study period. (A) Trends of isolation rate of Gram-negative bacteria. (B) Trends of resistance rates of carbapenem-resistant Gram-negative bacteria.

Figure 3

Correlation between antibiotics usage and carbapenem resistance rates in *E. coli*, *A. baumannii*, *E. cloacae*, and *B. cepacia* for the entire study period. (A) Correlation between usage of carbapenems and carbapenem resistance in *E. coli*. (B) Correlation between usage of tetracyclines, carbapenems, and C/BLI combinations and carbapenem resistance in *A. baumannii*. (C) Correlation between usage of carbapenems and P/BLI combinations and carbapenem resistance in *E. cloacae*. (D) Correlation between the consumption of quinolones and carbapenem resistance in *B. cepacia*.

Figure 4

Correlation between carbapenems usage and number of Gram-negative isolates resistant to carbapenems for the entire study period.