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Time series analysis of antibacterial usage and bacterial resistance in China: observations from a tertiary hospital from 2014 to 2018

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Purpose: To describe trends and correlation between antibacterial exposure and bacterial resistance from hospitalized patients in a hospital in southern China.

Patients and methods: This study used hospital-wide data regarding antimicrobial resistance and consumption between January 1, 2014 and December 31, 2018. Antibacterial consumption was expressed as antimicrobial use density (AUD). The changes in trends and associations between antibacterial utilization and resistance were analyzed using linear regression and time series analysis.

Results: The total AUD of all antimicrobials decreased year by year (50.66 in 2014 vs 44.28 in 2018, P=0.03). The annual use of antimicrobials, such as penicillins, monobactams, aminoglycosides, macrolides, and lincosamides, significantly decreased (P<0.05), while the annual use of quinolones and tetracyclines significantly increased (P<0.05). Among the top ten isolated bacteria, antimicrobial resistance trends of *Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Staphylococcus aureus*, and *Staphylococcus epidermidis* significantly decreased (P<0.05). Significant positive correlation was found between AUD of carbapenems and resistance rate of *Acinetobacter baumannii* to imipenem (β=32.87, P<0.01), as well as the correlation between AUD of quinolones and resistance rate of *Enterococcus faecium* to levofloxacin (β=104.40, P<0.01).

Conclusion: The consumption of antibiotics and antibiotic resistance has been significantly improved in this tertiary hospital. Additionally, the efforts of China's antibiotic management may be suggested by the relationship between indicated antibiotic resistance and consumption. However, overall AUD levels and poor control of the use of antibiotics, such as quinolones and tetracyclines, still require strengthened management.

Keywords: antibacterial usage, bacterial resistance, time series analysis, China

Introduction

After more than 70 years of widespread use of antibiotics in treating infectious diseases, antibiotic resistance is now being considered as a worldwide problem.[1] In September 2016, antibiotic resistance became the fourth health issue after HIV, non-communicable diseases, and Ebola to be discussed by the United Nations General Assembly.[2] In most cases, antibiotic-resistant infections lead to longer hospital stays with costlier treatments and a need for more toxic antibiotics, as well as resulting in greater disability and death compared with infections that are easily treatable with antibiotics.[3,4] According to reports, current worldwide deaths attributable to antibiotic resistance, including antimalarial and antiviral resistance,

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have been estimated to be about 700,000 per year, with as high as $20 billion in excess direct health care costs.[5] If the current trend continues, deaths will reach 10 million per year by 2050.[2,6]

Similarly, antibiotic resistance is receiving increasing attention from government and medical institutions in China. The total usage of antibiotics was approximately 162,000 tons, accounting for approximately half of the antibiotic usage worldwide, including human use (48%) and use in animals (52%) in China in 2013. The per-capita usage of antibiotics in China is more than 5 times that in Europe and the United States.[7] Statistical data from antibacterial resistance investigation collected by the China Antimicrobial Surveillance Network (CHINET), which involved 34 hospitals from 25 provinces covering 960 million people, showed that gram-negative bacilli have higher antimicrobial resistance in China.[2] The problem of antibiotic resistance, for example, the carbapenem-resistant *Klebsiella pneumonia* (*K. pneumoniae*), is becoming increasingly prominent globally as well as in China. In accordance with a European Center for Disease Prevention and Control report, significant increasing trends of carbapenem-resistant *K. pneumoniae* were discovered in 5 of the 24 reporting countries between 2009 and 2012.[8] Moreover, carbapenem-resistant *Klebsiella pneumonia* was significantly different in China, increasing from 3.0% in 2005 to 20.9% in 2017. The problem of gram-negative bacilli resistance to carbapenems has attracted great attention in China. However, antibiotic resistance results from nationwide studies were variable at different time periods in China. For instance, in distinct studies from CHINET, *Acinetobacter baumannii*, which showed high resistance rates against 5 commonly used antimicrobials, had different probabilities of resistance in 2005–2014 and 2014–2017.[9,10] The resistance rate of imipenem increased from 31% in 2005 to 62.4% in 2014, while the latest results show that the resistance rate reached 70.7% in 2017. As for amikacin, the resistance levels decreased between 2005 and 2014 and then increased from 2014 to 2017. Therefore, antibiotic resistance surveillance is a long-term repetitive process. It is necessary to understand the trends of antibiotic resistance that continue over time to develop a better management strategy for the use of antibiotics. Moreover, health authorities of China have been taking steps to address the serious problem of antibiotic resistance. In 2016, 14 ministries led by the National Health Commission of China jointly issued the National Action Plan for Containing Antibacterial Resistance (2016–2020).[11] Strengthening the supervision of antibiotic usage is one of the major tasks indicated for dealing with antibacterial resistance in this action plan.

The widespread use of antibiotics, especially use of broad-spectrum antibiotics which are effective against a variety of bacteria, is the most important factor leading to antibiotic resistance.[12] Additionally, from 2000 to 2010, Brazil, Russia, India, China, and South Africa accounted for three-quarters of the increase in antibiotic consumption.[13] Although increasing antibiotic use makes greater resistance inevitable, it is unclear whether reducing the use of antibiotics will lead to a certain reduction in antibiotic resistance,[14–19] and antibiotic resistance rates will change with time and management policies. Since the implementation of antibacterial management in a tertiary-care teaching hospital in northwest China in 2009, studies have evaluated the trend and correlation of antibacterial resistance and usage from 2009 to 2013 in this hospital.[20] The purpose of this study was to describe the trends and correlation between antibacterial exposure and bacterial resistance from hospitalized patients in a comprehensive hospital from 2014 to 2018 and further to evaluate the effectiveness of the latest antibacterial use management in China.

Materials and methods

Setting and study design

The study protocol was approved by the Research Ethics Committee of Xiangya Hospital (2018121128). This study was conducted at Xiangya Hospital, a tertiary comprehensive academic hospital, located in the southern region of China. The hospital has over 3500 beds with over 3 million emergency department visits and over 130,000 patient discharges annually. This study used hospital-wide data regarding antimicrobial resistance and consumption of both adult and child patients for 5 years between January 1, 2014 and December 31, 2018. The data were obtained from the Intravenous Infusion Safety Evaluation Center of Hunan Province in Changsha, Hunan.

Antibacterial utilization

Antibiotics were classified based on the Anatomical Therapeutic Chemical (ATC) classification system proposed by the WHO.[21] The defined daily dose (DDD), which was developed using the ATC index, is the assumed average maintenance dose per day for a drug used for its main indication in adults. According to the 2019 version of the ATC/DDD classification, antibacterial consumption was defined as the number of defined daily doses/100 patient-days (DDDs/100 PDs) and expressed as antimicrobial use density (AUD), which is positively correlated with antibacterial consumption.[22] Prophylactic usage and therapeutic medication were not distinguished in this study.

Inclusion and exclusion criteria of microbiology data

A total of 49,123 cases with data of bacterial resistance were recruited from hospitalized patients of this tertiary comprehensive hospital, including all positive clinical specimens (blood, sterile fluid, sputum, urine, wound, and anaerobic specimens) between 2014 and 2018. Microbiological isolates from community samples, outpatient clinics, or the emergency room were excluded. Among these patients, susceptibilities of isolates in 48,732 cases to all antibacterials tested were integrally recorded as susceptible, intermediate, or resistant as per the latest Clinical and Laboratory Standards Institute document. Eight thousand six hundred seven cases with the same susceptibility results for duplicate samples from the same patient were excluded, and 40,125 cases with complete, nonrepetitive susceptibility results were included in our clinical study (Figure S1). The resistance rate of those 40,125 cases was defined as the percentage of total isolates that were resistant to the selected antibacterial agents. Isolates with intermediate susceptibility were not included in the analysis.

Statistical analysis

The changes in trends of antimicrobial usage and resistance during the study period were evaluated by the linear regression. The linear trend by year is defined as the slope of the response over time, each expressed by a coefficient (β). The trends and associations between antibacterial utilization and acquisition of resistance were analyzed using time series analysis. The relationship between the monthly use of specific antibacterial classes and antibacterial resistance over time was evaluated by the autoregressive integrated moving average (ARIMA) models. The β-value indicates the change of the dependent variable when the independent variable changes by one unit within a uniform time interval, for instance, 1 month. All statistical analyses were conducted with SPSS software, version 18.0 (SPSS, Inc.). P-values of two-tailed tests less than 0.05 were the threshold for statistical significance.

Results

Antibacterial use

The total AUD of all antimicrobials decreased year by year, from 50.66 daily doses/100 patient-days (DDDs/100 PDs) in 2014 to 44.28 DDDs/100 PDs in 2018 (β=−1.61, P=0.03). The varieties of antibiotics increased from 73 in 2014 to 75 in 2018. The top three departments of the highest antibiotic consumption were hematology (AUD: 26.66), neurosurgery (AUD: 23.88), and geriatrics (AUD: 15.53) from 2014 to 2018 (Table S1). Figure 1A and B show the AUD and annual usage trends of antibiotics classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Among them, cephalosporins are one of the most consumed varieties, especially the third and fourth generation cephalosporins. The most frequently used is levofloxacin, followed by ceftriaxone. The annual use of penicillins (J01C), monobactams (J01DF), macrolides and lincosamides (J01F), and aminoglycosides (J01G) significantly decreased (P<0.05), while the annual use of quinolones (J01M) and tetracyclines (J01AA) increased significantly (P<0.05), and the annual usage of other types of antibacterials fluctuated or remained stable, but the trend was not statistically significant (P>0.05).

To explore specific antibiotics during clinical application, further linear regression analysis was performed on detailed categories of antibiotics according to ATC. The trends of antibiotic annual usage, including aminoglycosides, macrolides, lincosamides, and monobactams, were significantly decreased, while tetracyclines, second-generation cephalosporins, and others (A07AA + J01XX) were significantly increased (Table 1).

Bacterial resistance

Bacterial isolates

A total of 40,125 strains were separated from clinical samples in this study. The top ten frequently isolated species were *Escherichia coli* (*E. coli*), *Acinetobacter baumannii* (*A. baumannii*), *Klebsiella pneumonia* (*K. pneumonia*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Candida albicans* (*C. albicans*), *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S. epidermidis*), *Enterococcus faecium* (*E. faecium*), *Enterococcus faecalis* (*E. faecalis*), *and Candida glabrata* (*C. glabrata*). The total rates of top ten bacteria accounted for approximately 70% of all detected bacteria, and 42% were concentrated in gram-

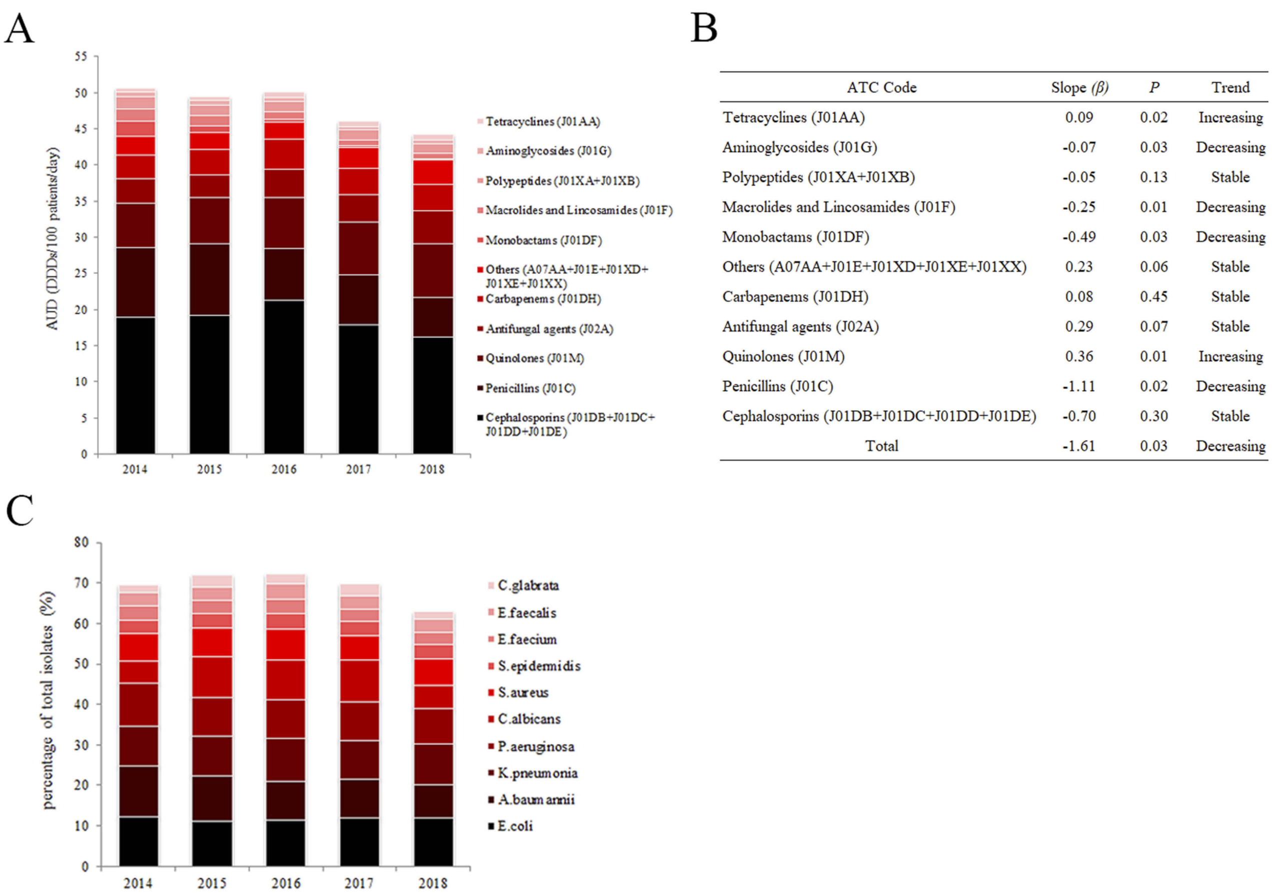

Figure 1 Inpatient antibiotic use and frequency of isolated species in this tertiary comprehensive hospital during 2014–2018. (**A**) Histogram shows the AUD of antibiotics according to the ATC classification. (**B**) Annual usage trends of antibiotics. (**C**) Frequency of top ten isolated species.

Table 1 Annual usage of antibiotic classified by ATC index in this tertiary comprehensive hospital during 2014–2018

ATC Code	Antimicrobial usage (AUD) by year					Linear regression		
	2014	**2015**	**2016**	**2017**	**2018**	**Slope (*β*)**	***P***	**Trend**
Tetracyclines (J01AA)	0.52	0.56	0.81	0.78	0.88	0.09	0.02	Increasing
Aminoglycosides (J01G)	0.69	0.63	0.58	0.40	0.46	−0.07	0.03	Decreasing
Macrolides (J01FA)	1.37	1.21	0.83	0.73	0.65	−0.19	0.01	Decreasing
Lincosamides (J01FF)	0.37	0.26	0.14	0.15	0.14	−0.06	0.05	Decreasing
Monobactams (J01DF)	2.15	0.96	0.36	0.20	0.08	−0.49	0.03	Decreasing
Others (A07AA + J01XX)	1.23	1.15	1.39	1.51	1.74	0.14	0.02	Increasing
Quinolones (J01M)	6.06	6.29	7.08	7.25	7.40	0.36	0.01	Increasing
Second-generation cephalosporins (J01DC)	1.30	1.75	2.94	4.14	4.52	0.88	0.00	Increasing

Note: Listing antibiotic only with significant difference.

negative bacteria (including *E. coli, A. baumannii, K. pneumonia, P. aeruginosa*), 17% were concentrated in gram-positive bacteria (including *S. aureus, S. epidermidis, E. faecium, E. faecalis*), and 11% were concentrated in fungus (including *C. albicans, C. glabrata*). *E. coli* was the most common strain in the past 3 years. Figure 1C shows the percentage of ten species in all isolated strains per year, and Table S2 displays the numbers and rank order of these species by year.

Antibacterial resistance

Then, we focused on antibacterial resistance problems among the top ten isolated species. Using linear regression, we found that eight isolated species had significantly different rates of resistance to antibiotics (P<0.05), including *E. coli, A. baumannii, K. pneumonia, P. aeruginosa, C. albicans, S. aureus, S. epidermidis,* and *E. faecium* (Table S3).

The isolated species which have significant decreasing trends of antimicrobial resistance are as follows (Figure 2A). 1) For *E. coli*, the resistance rates to amikacin (β=−0.37), aztreonam (β=−3.72), trimethoprim/sulfamethoxazole (β=−2.56), ciprofloxacin (β=−2.72), cefepime (β=−5.19), ceftriaxone (β=−3.57), tobramycin (β=−1.42), and levofloxacin (β=−2.57) were significantly decreased in 5 years. 2) For *P. aeruginosa*, the resistance rates to gentamicin, ceftazidime, and tobramycin were significantly decreased. The coefficients (β) of *P. aeruginosa* to gentamicin, ceftazidime, and tobramycin were −4.30, −3.03, and −4.93, respectively. 3) For *C. albicans*, the resistance rate to fluconazole was significantly decreased (β=−2.74), with a relatively lower resistance rate compared to other isolated species. 4) For *S. aureus*, the resistance rates of rifampicin (β=−2.96), gentamicin (β=−3.36), and tetracycline (β=−2.97) were significantly decreased. 5) For *S. epidermidis*, the resistance rate of tetracycline was significantly decreased (β=−2.88).

The isolated species which have significant increasing trends of antimicrobial resistance are as follows (Figure 2B). 1) For *A. baumannii*, the resistance rates to aztreonam (β=2.70), ciprofloxacin (β=2.79), gentamycin (β=2.76), cefepime (β=2.27), ceftriaxone (β=2.04), and imipenem (β=2.43) were significantly increased in 5 years. 2) For *K. pneumonia*, the resistance rate to cefoxitin was significantly increased year by year, from 25.34% in 2014 to 100.00% in 2018 (β=18.96). 3) For *P. aeruginosa*, the resistance rates to ampicillin/sulbactam were significantly increased (β=0.07). 4) For *E. faecium*, the resistance rates of ampicillin (β=5.25), ciprofloxacin (β=2.99), ceftriaxone (β=0.26), and levofloxacin (β=4.00) were significantly decreased.

However, the trend of isolated species including *E. faecalis* and *C. glabrata* found no statistical difference in various antibacterial resistance.

Correlation

The association between antibacterial resistance and antibiotic usage from 2014 to 2018 is shown in Table S4. The analysis by the ARIMA model showed that the resistance rates of *A. baumannii* and *E. faecium* were significantly positively correlated with the AUD of antibiotics. The usage of carbapenems was positively correlated with the resistance rates of *A. baumannii* to imipenem (β=32.87, P<0.01) (Figure 3A). The β-value indicated that the resistance rate of *A. baumannii* to imipenem increased (or decreased) by 32.87% when carbapenem usage increased (or decreased) per AUD each month. The usage of quinolones was positively correlated with the resistance rates of *E. faecium* to levofloxacin (β=104.40, P<0.01) (Figure 3B). Nonetheless, we did not find any significant relationship between the usage of other antibacterial agents and resistance rates.

Discussion

China is one of the countries with serious problems in terms of antibiotic misuse and antibiotic resistance.[23–25] The government has closely followed the issue of antibiotic resistance in China and has developed a series of strategies at the national level. This study used the standardized ATC/DDD index to study the utilization and changing patterns of antimicrobials. In this study, the use of penicillins, monobactams, aminoglycosides, macrolides and lincosamides was significantly reduced, while the use of second-generation cephalosporins, quinolones, and tetracyclines was significantly increased in China's tertiary comprehensive hospitals from 2014 to 2018. The AUD of antibiotics was reduced from 50.66 in 2014 to 44.28 in 2018. Compared to previous reports, the antibiotic consumption of other studies done in China was similar to our study. In the study of tertiary comprehensive hospital, the use of monobactams, aminoglycosides, macrolides and lincosamides was decreased from 2011 to 2017.[26] The studies of 65 public general hospitals and 89 tertiary general hospitals showed AUD of antibiotics was decreased in China from 2010 to 2014 and from 2011 to 2015.[22,27] However, a previous study showed stable consumptions of several antibiotics, such as second-generation cephalosporins and quinolones, whose consumptions were increased in our study.[26] In addition, according to the requirements for Chinese Antimicrobials Special Rectification Activity issued by the National Health Commission, the AUD of antibiotic should be limited to less than 40,[28] suggesting that Chinese hospitals still need strong management standards for antibiotic use, especially for the AUD increased types, to promote the selection, dosage, and course of antibiotics.[29]

In the analysis of antibiotic consumption and resistance, the detection ratios of gram-negative bacteria and gram-positive bacteria in our study were basically consistent with the overall situation in China.[10] Additionally, in accordance with previous studies, the imipenem-resistant *A. baumannii* was associated with usage of carbapenem in

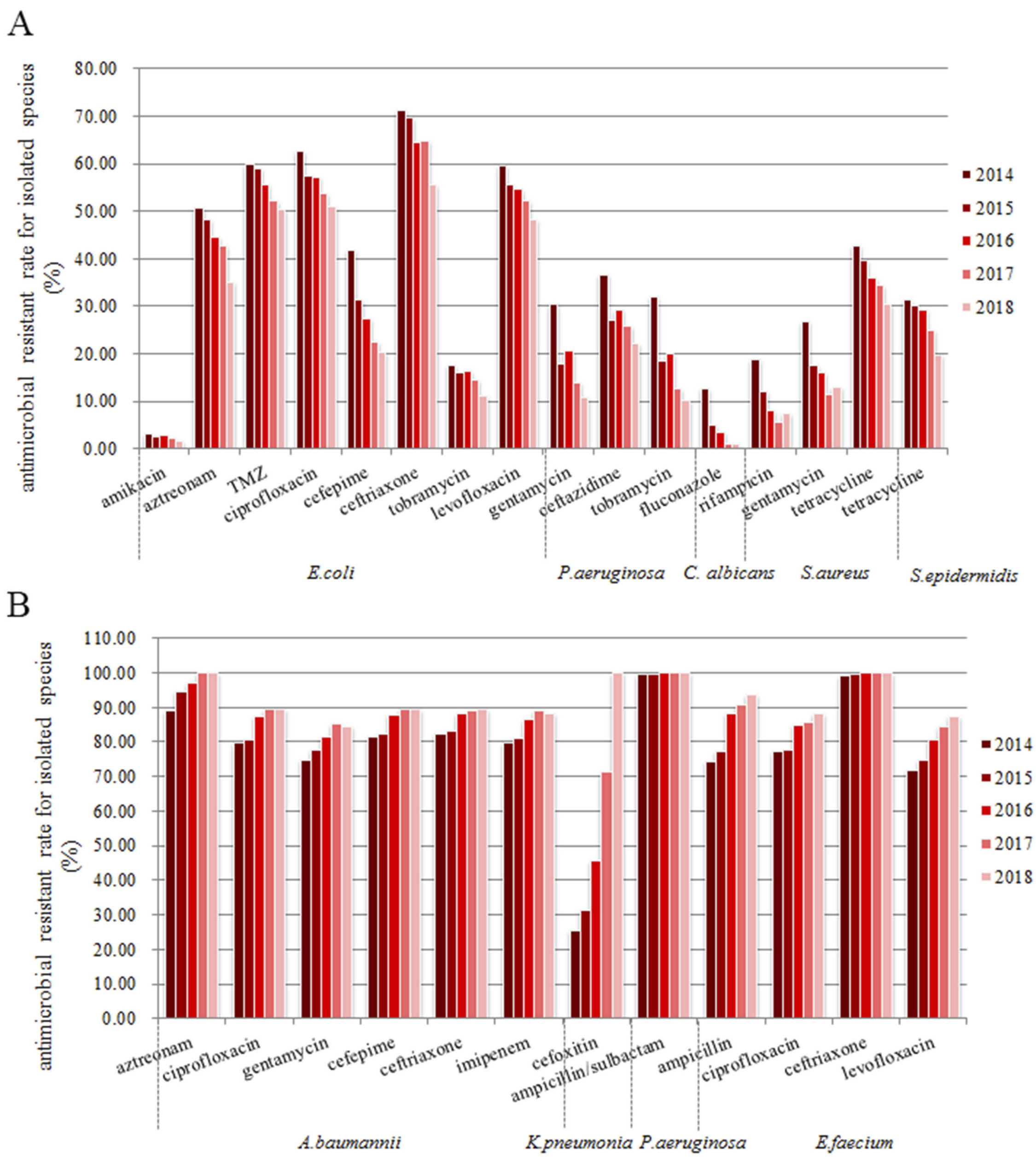

Figure 2 Antimicrobial resistance of top ten isolated species from inpatients in this tertiary comprehensive hospital during 2014–2018. (**A**) Significant decreasing trends of antimicrobial resistance. (**B**) Significant increasing trends of antimicrobial resistance.

our study. Carbapenem-resistant *A. baumannii* (CRAB) is known worldwide as an extremely important hospital pathogen. It mainly affects weak patients, causes pneumonia and blood infections, and has a high mortality rate.[30,31] CRAB infection has become a serious clinical challenge due to its very limited therapeutic options.[32] The mechanisms of resistance mainly include overexpression of intrinsic and/or acquired β-lactamases and overexpression of the efflux pump which expels antibiotics and from alterations in outer membrane porins.[33,34] Some clinical studies and literature reviews have indicated that exposure to carbapenems significantly increases the risk of acquiring CRAB.[35,36] Similar to the results of Wickman et al, the resistance rate of *E. faecium* to levofloxacin was strongly correlated with quinolones usage in our study.[37] Infections caused by *E. faecium* have been increasing and currently account for around 40% of all enterococcal infections.[38] Moreover, outbreaks of hospital-acquired vancomycin-resistant enterococci infections are increasingly reported worldwide, causing nosocomial bacteremia, infective

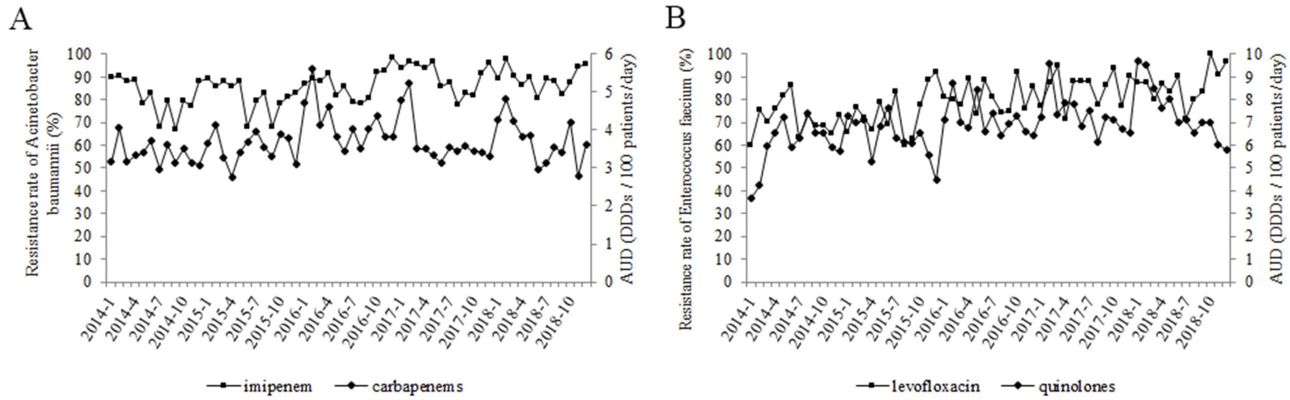

Figure 3 Correlation between antibiotics usage and resistance rates of *A. baumannii* and *E. faecium* in this tertiary comprehensive hospital during 2014–2018. (**A**) Correlation between usage of carbapenems and resistance rates of *A. baumannii* to imipenem. The resistance rate of *A. baumannii* to imipenem is represented as the AUD on the left y-axis and the consumption of carbapenems is shown on the right y-axis. (**B**) Correlation between usage of quinolones and resistance rates of *E. faecium* to levofloxacin. The resistance rate of *E. faecium* to levofloxacin is represented as the AUD on the left y-axis and the consumption of quinolones is shown on the right y-axis.

endocarditis, and intra-abdominal and urinary tract infections that have limited treatment options.[39,40] If quinolones must be used to treat serious *E. faecium* infections, it is recommended to select drugs such as DX-619 that have the activity and propensity to select susceptible mutants.

There are some limitations to this study. First, the scope of research is only one tertiary hospital. Although comprehensive monitoring networks for bacterial resistance have been established in China, the data of antibiotic use for participating hospitals were not fully included; therefore, the next step is to collect data exploring the relationship between antibiotic resistance and consumption in a future multicenter study. Second, the relationship between antibiotic resistance and consumption may be nonlinear, and further optimization of statistical methods can be attempted.[41] Finally, the use of AUD for antibiotic consumption may not be well correlated with subsequent antibiotic resistance development.[20]

In conclusion, the consumption of antibiotics and antibiotic resistance has been significantly improved in China. After clarifying the relationship between antibiotics and drug resistance, the next step may be to explore the critical threshold of antibiotic selection pressures, beyond which resistant genes and pathogens gain a survival advantage.[41] These findings may help clinicians take appropriate precautions to reduce mortality in such patients.[42]

Abbreviations

E. coli, Escherichia coli; A. baumannii, Acinetobacter baumannii; K. pneumonia, Klebsiella pneumonia; P. aeruginosa, Pseudomonas aeruginosa; C. albicans, Candida albicans; S. aureus, Staphylococcus aureus; S. epidermidis, Staphylococcus epidermidis; E. faecium, Enterococcus faecium; E. faecalis, Enterococcus faecalis; C. glabrata, Candida glabrata; TMZ, trimethoprim/sulfamethoxazole; ATC, Anatomical Therapeutic Chemical; AUD, antimicrobial use density; CRAB, carbapenem-resistant *A. baumannii*.

Ethical approval

This study was reviewed and approved by the Ethical Committee of Xiangya Hospital of Central South University (Approval No. 2018121128).

Informed consent

According to the "Human Biomedical Research Ethical Review Procedures" approved by the National Health and Family Planning Committee of China (No. 11, Section 39), informed consent was waived because of the retrospective nature of the study. After the following circumstances have been reviewed and approved by the ethics committee, the informed consent form can be waived if research is conducted using human body materials or data that can identify information, and the subjects cannot be found, and the research project does not involve personal privacy and commercial interests.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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