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ORIGINAL RESEARCH

Antibiotic Use Thresholds for Carbapenem-Resistant Gram-Negative Bacteria: A Nonlinear Time-Series Study

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Background: To study the association between antimicrobial use density (AUD) and carbapenem-resistant gram-negative bacteria (CRGN) detection rate in a Hospital from 2015 to 2023 and to determine the critical threshold for antimicrobial drug use.

Methods: The consumption of antibiotics and the detection rates of four CRGN from inpatients were obtained on quarterly. Regression discontinuity design was used to determine the effect of antibiotics on the detection rates of CRGN. Nonlinear time-series analysis with generalized additivity models (GAMs) was applied. A P value of <0.05 and the adjusted R^2 value of >0.3 were considered statistically significant.

Results: The consumption of antibiotics remained stable from 2015 to 2019, then showed a decreasing trend from the first quarter of 2020 to the first quarter of 2021, subsequently showed a gradual increasing trend from the second quarter of 2021 to the fourth quarter of 2023. The detection rate of carbapenem-resistant *Acinetobacter baumannii* (CRAB) exceeded 50% from the first quarter of 2015 to the second quarter of 2019, even above 90% from the fourth quarter of 2018 to the second quarter of 2019, then the rate gradually decreased. The detection rates of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) both showed increasing trend from the first quarter of 2015 to the second quarter of 2019, while showed gradual decreasing trend from the fourth quarter of 2019 to the third quarter of 2023. We found that the detection rates of CRGN were significantly associated with the consumption of carbapenems, aminoglycosides, fluoroquinolones, and glycopeptides (lag coefficient [1-3], $P < 0.05$, adjusted R^2 [0.347–0.808]).

Conclusion: AUD is associated with the detection rates of CRGN. To reduce the detection rates of CRGN, we determined thresholds for carbapenems, aminoglycosides, fluoroquinolones, and glycopeptides at 5.82, 0.06, 7.09, and 0.77 Defined Daily Doses (DDDs)/(100 patient-days), respectively.

Keywords: gram-negative bacteria, carbapenems, antimicrobial use density, nonlinear time series analysis

Introduction

Bacterial resistance represents a major threat to global public health.[1] Approximately 1.27 million deaths world wide can be directly attributed to antibiotic-resistant bacteria infection in 2019.[2] Gram-negative bacteria (GNB) are becoming an increasingly common pathogens inpatients, among which carbapenem-resistant Gram-negative bacteria (CRGN) pose a huge obstacle to antibiotic application.[3] The results of China Antimicrobial Surveillance Network (CHINET) in 2022 indicated that the isolation rates of clinical GNB were 2.51 times higher than those of Gram-positive bacteria. The most dominant GNB isolated were *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Acinetobacter baumannii* (*A. baumannii*), consistent with previous years.[4,5] This results also showed the resistance to carbapenems (CBM) in the four bacterial species mentioned above increased from 2005 to 2018, while had a decreasing trend from 2019 to 2021.

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Carbapenem antimicrobials are widely used in treating serious infections with GNB. CRGN mainly include carbapenem-resistant *Escherichia coli* (CREC), carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem- resistant *Klebsiella pneumoniae* (CRKP), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), were also the common bacterium acquired in hospitals. CRGN pose the major threat to humans in terms of mortality, healthcare burden and antimicrobial resistance.[6] Antibiotical resistance of GNB was usually induced by plasmids mediating multiple resistance genes, which leaded to more toxic or higher-level antibiotics in clinical practice, thereby increasing the clinical safety risks and healthcare burden on patients.[7,8] In the European Union and the European Economic Area, CRKP and CREC were considered to be the pathogens with the highest mortality rates among infected patients.[9] The resistance of GNB make great difficult in developing antimicrobial regimens. There is still controversy over whether controlling CBM consumption alone can control the detection rates of CRGN. Previous studies have indicated the correlation between the consumption of CBM and the detection rate of CRGN.[10] Several studies even showed a potential association between the overuse of CBM and the detection rates of CRGN.[11–13] However, some other studies did not reach the consistent conclusion.[14,15] Although antimicrobial stewardship can delay antimicrobial resistance,[16] excessive restriction may be counterproductive. Previous studies have proposed the definition of a threshold, which represents the maximum consumption of a type of antibiotic, also proposed the relationship between the consumption of antibiotics and resistance at the same time.[17] Subsequently, theoretical and mathematical models showed that nonlinear time series analysis is more conducive to determining these relationships and thresholds than linear time series analysis, such as spline regression, vector autoregressive model (VAR), and generalized additive model (GAM).[18,19]

Therefore, in this study, we explored the correlation between detection rates of CRGN and antimicrobial use density (AUD) of six classes in a tertiary hospital of China from 2015 to 2023. The critical thresholds of carbapenems, fluoroquinolones, third-generation cephalosporins, aminoglycosides, penicillins, and glycopeptides were determined based on a nonlinear time-series analysis method, thus provide new ideas for optimizing anti-infective therapeutic schemes in clinical practice.

Methods

Data Source

In this study, the data of antimicrobial consumption and carbapenem resistance rate in each quarter are from the Second Qilu Hospital of Shandong University. This hospital is a university affiliated hospital in northern China with 2431 beds, it is a tertiary comprehensive hospital with teaching functions. Inclusion criteria: 1. Patients with hospital acquired infections, 2. The pathogen specimen was qualified, 3. The clinical data was complete. Exclusion criteria: 1. Infection or suspected infection occurred pre-admission, 2. Hospitalization time <48 hours, 3. The pathogen specimen was polluted or not qualified, 4. Repeated bacterial strained in the same part of the same patient.

Bacterial Isolates and Susceptibility Testing

E. Susceptibility testing followed the guidelines for the testing of specimens in the clinical microbiology laboratory of National Health Commission of the People's Republic of China. For quality control, standard ATCC strains of *E. coli* ATCC®25922, *K. pneumoniae* ATCC®700603 and *P. aeruginosa* ATCC®27853 were utilized. Meropenem represents carbapenem drugs for susceptibility testing. Antimicrobial susceptibility testing using MicroScan WalkAway plus,[20] and follow the Clinical and Laboratory Standards Institute (CLSI) guidelines. Results were interpreted based on CLSI guidelines.

Frequency and Intensity of Antimicrobial Drug Use

Antimicrobials were classified using the Anatomical Therapeutic Chemical (ATC) system.[21] We focused on six antimicrobial classes commonly prescribed in our hospital: penicillins (penicillin G, amoxicillin, ampicillin, piperacillin/tazobactam), aminoglycosides (amikacin, etilmicin), fluoroquinolones (moxifloxacin, levofloxacin), carbapenems (imipenems, meropenems), glycopeptides (vancomycin, telicoplanin), and third-generation cephalosporins (ceftriaxone, Cefotaxime, cefixime, cefoperazone/sulbactam, ceftazidime). The frequency of antimicrobial use was calculated as drug consumption (g) quarterly divided by relevant defined daily dose (DDD), based on World Health Organization (WHO). AUD was

measured as DDDs × 100 per number of patient-days in the same period, expressed as DDDs per 100 patient-days.[22] Patient-days were the total number of days that the patient spent in a single hospitalization when CRBN was detected.

Statistical Analysis

Data were analyzed by R version 4.3.2. Regression discontinuity designs (RDDs) are a promising tool to evaluate the causal effects of quality improvement interventions outside of a randomized clinical trial.[23] In this study, we adopted this analysis method to determine the effect of AUD on the resistance rate of CRGN. A cubic regression model of the intervention variable and the outcome variable was constructed based on global parameter estimation regression discontinuity (RD), with the following model equation:

$$Y_i = \alpha + \beta \times treatment + \beta 1 \times (time - cutpoint)^k + \beta 2 \times treatment \times (time - cutpoint)^k + \varepsilon_i$$

where Y_i denotes the total detection rates of CRGN, treatment denotes the total AUD of six classes of antibiotics, β is the treatment effect of the total AUD on Y_i at the cutoff point, cutpoint denotes the time-cutpoint, β1 is the coefficient of the kth term of the difference in time between a given time and the time of the cutoff point, β2 is the coefficient of the interaction term between treatment and the kth term of the difference, and Ɛi denotes the residual term.

A nonlinear time series analysis approach based on GAMs was used to assess the association between the consumption of antibiotics and the detection rates of CRGN, and to determine the critical threshold for antimicrobial use, model equations are as follows:[20]

$$g(\mu_Y) = \alpha + f_1(X_1) + f_2(X_2) + \cdots + f_n(X_n)$$

GAM, which is very general and can be used for the identification of the most likely predictors, because it makes a nonparametric estimation of the functional relationships between explanatory (x) and outcome (y) time series, on the basis of iterative data fitting, rather than previous assumptions.[24] Here, adjusted R^2 indicating the association between AUD and the detection rates of CRGN, with closer to 1 indicating a stronger correlation. Lag coefficient (lag) was used to capture dynamic dependencies in time series data and based on the akaike information criterion (AIC). The AIC was calculated based on the likelihood function and the parameters of the model, with smaller value indicating a better model fit degree. Time smoothing term was used to eliminate spurious corr and control quarter variations. X_1 to X_n denote the AUD for different types of antibiotics, $f_i(X_i)$ is an unspecified function that needs to be estimated nonparametrically, and $g(\mu_s)$ represents a function of the conditional mean that response to variable Y. The GAMs model considers the nonlinear relationship between AUD and the resistance rate, time and the resistance rate simultaneously. 95% confidence interval (CI) was used to reflect the reliability of sample estimates. The Models with $P < 0.05$ and adjusted $R^2 > 0.3$ were considered statistically significant. Although the GAMs showed an outstanding fit to the data, it did not provide the intrinsic relationship of the coefficients or variables, so we screened each regression model for potential thresholds by maximizing the gradient rate of change estimates.

Results

Trends in AUD and Detection Rates of CRGN

In total, the inpatients infected with CREC, CRAB, CRKP and CRKP were 142, 5299, 1534 and 1921, respectively. The inpatients infected with CRAB and CRKP stimulataneously were 3. The inpatients infected with both CRAB and CRPA were 2. The inpatients infected with both CRKP and CRPA were 5. The trend of AUD for all classes of antimicrobial drugs from 2015 to 2023 is shown in Figure 1. The consumption of all drugs stabilized basically from the first quarter of 2015 to the fourth quarter of 2019, showed a decreasing trend from the fourth quarter of 2019 to the first quarter of 2021, and then showed a gradual increasing trend from the first quarter of 2021 to the third quarter of 2023. The trend of the detection rates of CRGN is shown in Figure 2. The detection rate of CREC also maintained a stable trend from the first quarter of 2015 to the third quarter of 2023. The detection rate of CRAB has been consistently above 50%, and even above 90% from the fourth quarter of 2018 to the second quarter of 2019, and then gradually decreased. The detection rates of CRKP and CRPA generally on the rise from the first quarter of 2015 to the second quarter of 2019, and showed a gradual decreasing trend from the fourth quarter of 2019 to the third quarter of 2023, as detailed in Figure 2.

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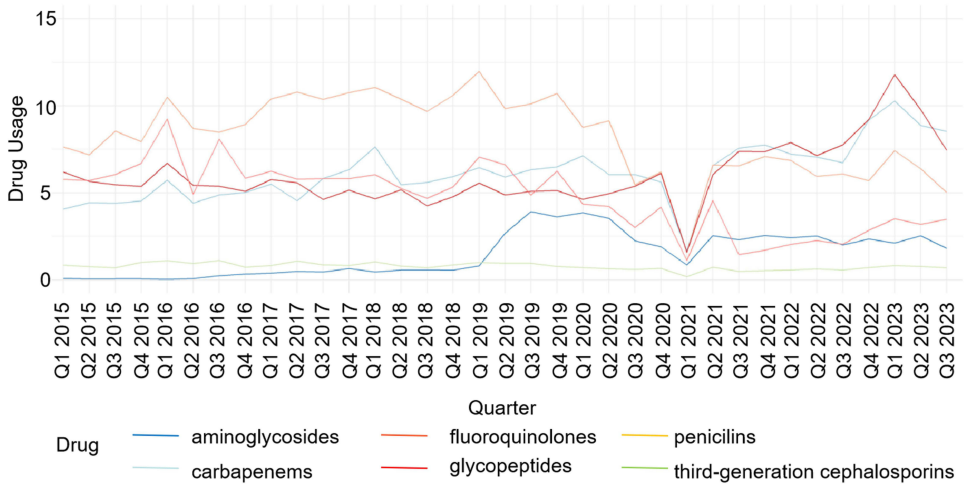

Figure 1 Consumption of 6 types of antibiotics from 2015 to 2023. Consumption of antibiotics was expressed in defined daily doses (DDDs)/100 patient-days for various antibiotic classes.
Abbreviations: DDD, defined daily dose.

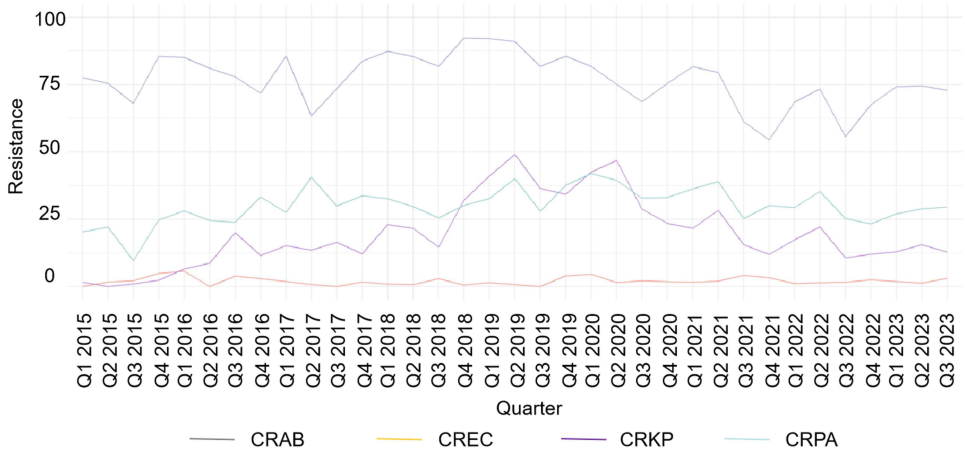

Figure 2 The trends of detection rates of CRGN from 2015 to 2023.
Abbreviations: CRGN, carbapenem-resistant Gram-negative bacteria; CREC, carbapenem-resistant *Escherichia coli*; CRKP carbapenem-resistant *Klebsiella pneumoniae*; CRAB carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa.*

Regression Discontinuity Designs

Since the time of the COVID-19 outbreak, the first quarter of 2020 was used as the exact time breakpoint. In order to better demonstrate the relationship between AUD and the detection rates of CRGN, we plotted locally weighted smoothed fitted graphs, and we found that the two were discontinuous at the breakpoints, as detailed in Figure 3. The smoothed fitted graphs for the relationship between time and AUD are shown in Figure 3a, and the smoothed fitted graphs of time and the detection rates of CRGN are shown in Figure 3b.

A linear regression model was constructed between AUD and the detection rates of CRGN based on the global parameter estimation RD, with a smaller AIC value and a better model fit degree. The results showed an association between the detection rates of CRGN and the AUD of six classes of antibiotics, which is significantly different (β = 0.499, P = 0.039), as shown in Table 1.

Multifactor Time Series Analysis Based on GAM Models

Among the six antibiotics, the detection rate of CRAB was significantly synchronized with the consumption of carbapenems (lag coefficient = 1, P = 0.016, adjusted R^2 = 0.521), fluoroquinolones (lag coefficient = 1, P = 0.001,

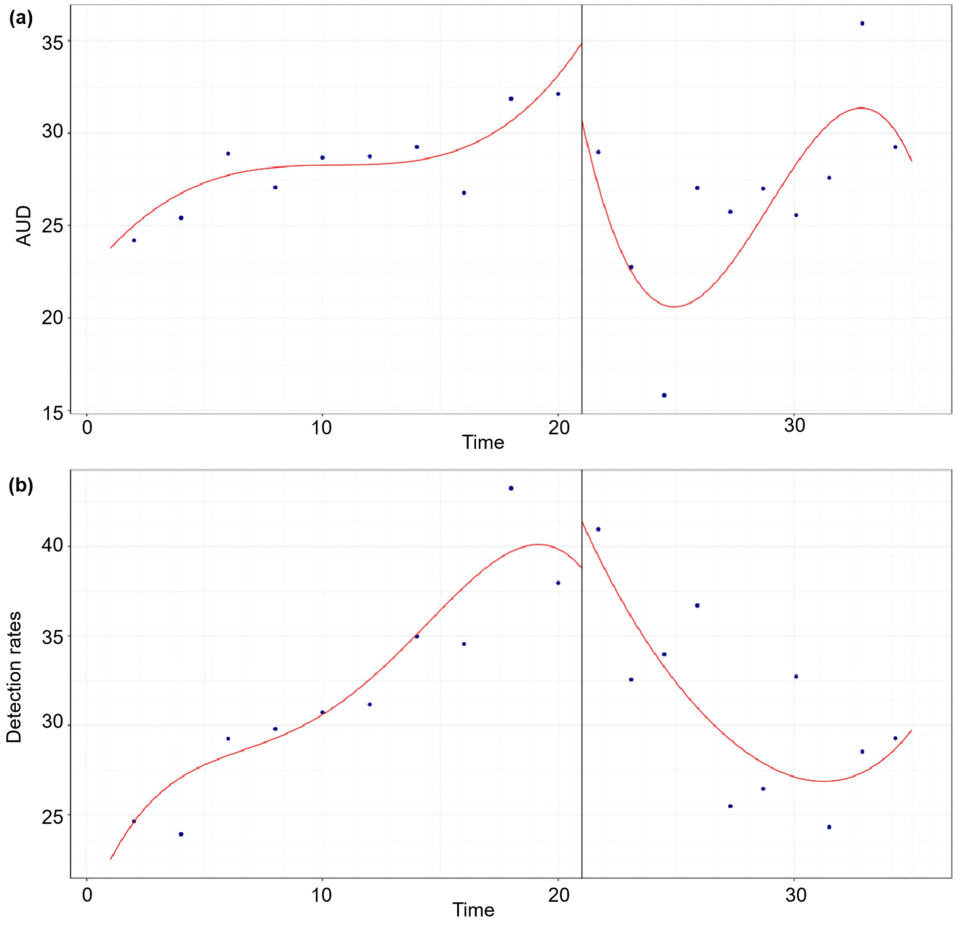

Figure 3 Smooth-fit plots of the relationship between total AUD and the detection rates of CRGN versus time. (**a**) Smooth-fit plot of the relationship between time and dosage density; (**b**) Smooth-fit plot of time and the detection rates of CRGN.
Abbreviations: AUD, antimicrobial use density. CRGN, carbapenem-resistant Gram-negative bacteria.

adjusted R^2 = 0.347), and glycopeptides (lag coefficient = 1, P = 0.001, adjusted R^2 = 0.643) (Table 2). By further analysis, we found the detection rate of CRAB decreased, where the use of carbapenems, aminoglycosides, and glycopeptides were 5.82, 0.06, and 0.77 DDD/(100 patient-days), respectively, which below the thresholds (Figure 4).

The detection rate of CRKP was significantly synchronized with the consumption of carbapenems (lag coefficient = 1, P = 0.001, adjusted R^2 = 0.808), aminoglycosides (lag coefficient = 3, P = 0.006, adjusted R^2 = 0.787) and glycopeptides (lag coefficient = 1, P = 0.005, adjusted R^2 = 0.797) (Table 2). By further analysis, results showed that the resistance rate of *Klebsiella pneumoniae* to carbapenems decreased, where the consumption of carbapenems, aminoglycosides, and glycopeptides was below the thresholds of 5.82, 7.36, and 0.96 DDD/(100 patient-days), respectively (Figure 4).

Table 1 Results of RD of Changes in the Total Detection Rates of CRGN

Variables	*β*	*Se*	*t*	*P*	*95% CI (Lower,Upper)*
Consumption	0.499	0.229	2.174	0.039	(0.050,0.948)
Margin_del	3.465	1.681	2.061	0.049	(0.170,6.760)
I(margin_del^2)	−0.088	0.073	−1.207	0.238	(−0.231,0.055)
I(margin_del^3)	−0.018	0.008	−2.187	0.038	(−0.034,-0.002)
Margin_del:consumption	−0.136	0.062	−2.209	0.036	(−0.258,-0.014)
I(margin_del^2):consumption	0.001	0.002	0.666	0.511	(−0.003,0.005)
I(margin_del^3):consumption	0.001	0.000	2.199	0.037	(0.000,0.002)

Note: Consumption, the AUD of six classes of antibiotics; margin_del, the difference between a given time and the time of cutoff point.

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Table 2 Multifactorial Time Series Analysis of the Detection Rates of CRGN and the Consumption of Antibiotics, 2015–2023

Antimicrobics \ CRGN	CREC			CRAB			CRKP			CRPA		
	R^2	Lag[a]	*P*	R^2	Lag[a]	*P*	R^2	Lag[a]	*P*	R^2	Lag[a]	*P*
Carbapenems	0.222	1	0.023	0.521	1	0.016	0.808	1	0.001	0.457	1	0.154
Fluoroquinolones	0.049	1	0.526	0.347	1	0.011	0.744	4	0.208	0.421	3	0.745
Aminoglycosides	0.054	1	0.613	0.452	2	0.489	0.787	3	0.006	0.449	4	0.180
Third-generation cephalosporins	0.037	1	0.383	0.502	1	0.314	0.735	1	0.591	0.430	1	0.417
Penicillins	0.053	1	0.599	0.452	1	0.637	0.734	1	0.780	0.436	1	0.123
Glycopeptides	0.205	1	0.044	0.643	1	0.001	0.797	1	0.005	0.445	1	0.284

Notes: Lag[a] and R^2 were derived from GAM models. Time delays (in quarters) between in the consumption of antibiotics and the rates of resistance. Models with adjusted R^2 > 0.3 were considered statistically significant.

Discussion

This study analyzed potential non-linear associations between the detection rates of CRGN and the consumption of six classes of antibiotics from 2015 to 2023. Fluoroquinolones and third-generation cephalosporin were the most widely used anti-infective drugs in clinical practice, which is similar to the results of some previous studies. However, the consumption in this study was higher than that in Europe.[18] The total consumption of antibiotics in our hospital showed a plummeting trend in the first quarter of 2021, which was in line with the time of the managing of COVID-19 in Jinan, China. Subsequently, the total consumption of antibiotics gradually increased with the termination of COVID-19 in the fourth quarter of 2022. Here, we found that the detection rates of CRGN for four classes of antibiotics showed a decreasing trend from 2019 to 2022. The main reason of such situation is that, first, the managing of COVID-19 changed the management and prescribing pattern in hospital, resulting in a decreasing consumption of antibiotics.

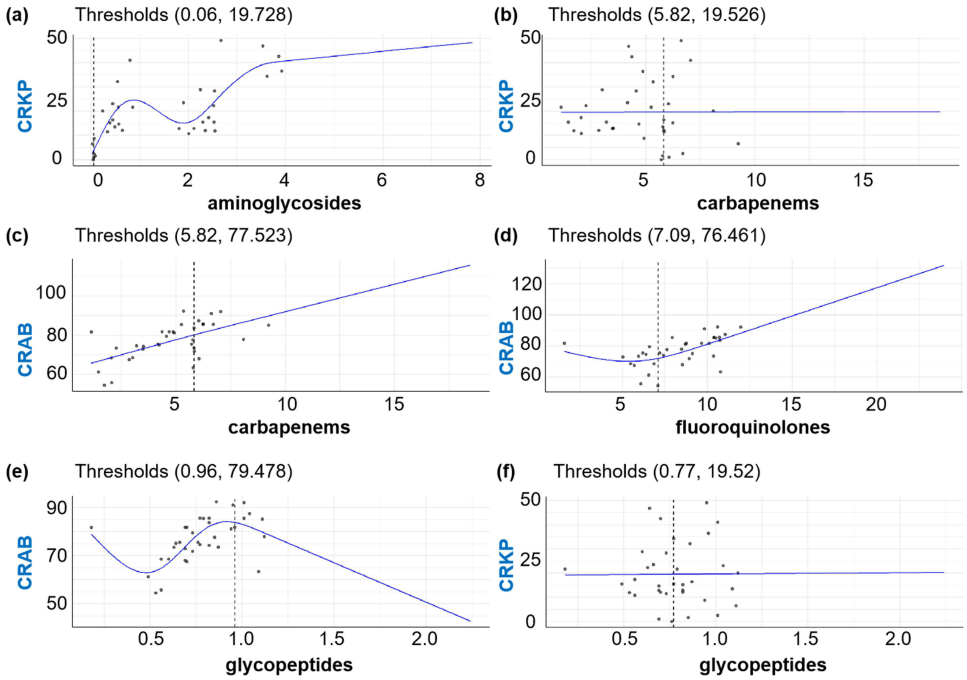

Figure 4 The threshold of the relationship between the detection rates of CRGN and the consumption of antibiotics was estimated through maximizing the rate of gradient change. (**a**) GAM Model of aminoglycosides to CRKP with Gradient-Based Threshold; (**b**) GAM Model of carbapenems to CRKP with Gradient-Based Threshold; (**c**) GAM Model of carbapenems to CRAB with Gradient-Based Threshold; (**d**) GAM Model of fluoroquinolones to CRAB with Gradient-Based Threshold; (**e**) GAM Model of glycopeptides to CRAB with Gradient-Based Threshold; (**f**) GAM Model of glycopeptides to CRKP with Gradient-Based Threshold.

Abbreviations: CRGN, carbapenem-resistant Gram-negative bacteria; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; GAM, generalized additivity model.

Second, there was a decreasing number of inpatients, following with a decreasing number of patients admitted with GNB infections. Third, it may be related to the results achieved by actively implementing the national policy of rational application of antibiotics. All above led to the decline in the detection rates of CRGN at last. Although the COVID-19 breakpointis used, the infected patients were not treated at our hospital, so there was no impact on data quality. With the standardized management and rational application of antibiotics in hospitals, the strengthening of cooperation between laboratories and clinical practice, as well as the increasing awareness of doctors on the prevention and control of drug-resistant bacterial infections, the prevalence of drug-resistant bacteria was curbed.

In this study, we found that the detection rates of CRGN were significantly associated with the consumption of carbapenems, fluoroquinolones, aminoglycosides, and glycopeptides ($P < 0.05$). We determined thresholds for the use of carbapenems, aminoglycosides, fluoroquinolones, and glycopeptides at 5.82, 0.06, 7.09, and 0.77 DDD/(100 patient-days), respectively. A relevant study identified the threshold for carbapenem AUD in Chinese tertiary hospitals as 3.1 DDD/(100 patient-days).[25] The reason for the variation may be that healthcare systems, antibiotic usage, molecular epidemiology and antibiotic resistance patterns vary from region to region, and therefore antibiotic stewardship thresholds tailored to local data may be more valuable in preventing infections.[26] In view of high AUD increasing the chances of bacteria coming into contact with antibiotics, and continuous exposure to β-lactam antibiotics could select for mutant strains that producing AmpC enzymes.[20] Previous studies have shown that the resistance of *Klebsiella pneumoniae* to ceftazidime was time-dependent with the prescription of β-lactamase inhibitors, third-generation cephalosporins and fluoroquinolones.[27,28] These thresholds may provide quantitative goals for management, ie, delaying the progression of resistance while avoiding excessive antibiotic restriction. When we found the AUD of carbapenem exceeded 5.82 DDD, and the detection rate of CRKP rose simultaneously, we initiated mandatory multidisciplinary consultations to optimize medication plans or develop alternative strategies. Finally, the AUD of carbapenem significantly decreased, accompanied by a significant decrease in the detection rate of CRKP. The detection rate of CRAB is the highest among the CRGN and has been increasing during 2012–2022 in China.[29–31] We analyzed the correlation between threshold and resistance rates quarterly, and suspended the use of antibiotic for one quarter that have exceeded the threshold, which also reduces the use of carbapenems to a certain extent. This study offers insights into factors influencing carbapenem resistance in Gram-negative bacteria beyond mere consumption. Here, we emphasize the need for precise usage criteria to ensure the appropriate use of carbapenem. Further studies are required to confirm the impact of quinolones and third-generation cephalosporins on the detection rates of CRGN.

There are limitations to this study. This study just collected and analyzed the data of a single tertiary comprehensive hospital, it did not account for confounding factors such as duration of hospitalization and severity of illness. Therefore, broader studies encompassing multiple centers and community settings are necessary. Additionally, as a retrospective study, it does not represent at the individual-level. The complexity of resistance mechanisms at the individual level and other factors like patient population variances and infection control measures may also affected our findings.

Conclusions

In summary, this study found that AUD is associated with the detection rates of CRGN. We found that the thresholds for carbapenems, aminoglycosides, fluoroquinolones, and glycopeptides were 5.82, 0.06, 7.09, and 0.77 DDD/(100 patient-days), respectively. The hospital should monitor the thresholds regularly, which provide quantitative reference to avoid empirical drug overuse in clinical. When the usage of a certain antibiotic approaches the threshold, priority should be given to optimize medication plans or develop alternative strategies. Besides, antibiotic management based on threshold can reduce unnecessary use of high-level antibiotics, which is consistent with the concept of WHO. The clinical application of antibiotics needs to be diversified, and the screening stress of bacterial resistance genes could diminish through reducing AUD reasonably. This study provided a potential strategy for adopting a more appropriate therapeutic plan and effectively controlling resistance rate of antibiotics in clinical practice.

Data Sharing Statement

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

Ethics Approval and Patient Consent Statement

This study was approved by the Institutional Review Board of The Second Qilu Hospital of Shandong University.

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Disclosure

The authors report no conflicts of interest in this work.

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