

Impact of COVID-19 Pandemic on carbapenem-resistant Enterobacteriaceae bloodstream infection: a single-center study in China

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Abstract

Introduction: The problem of carbapenem resistance in *Enterobacteriaceae* is becoming increasingly serious, and Carbapenem-Resistant *Enterobacteriaceae* (CRE) has become a major problem in clinical infection, especially in intensive care units (ICU). The purpose of the study is to explore the impact of the occurrence of COVID-19 on the bloodstream infection of CRE (CRE-BSI) and carbapenem resistance.

Methodology: In this study, adult patients with CRE-BSI from January 2019 to January 2023 were collected to perform a single-center cross-sectional study, who were divided into pre-COVID-19, COVID-19 until "New Ten" (only accept non-COVID-19 patients), and post-"New Ten" group (accept COVID-19 and non-COVID-19 patients), according to the epidemic prevention and control policy.

Results: Among 184 CRE-BSI cases confirmed during pre-COVID-19, COVID-19 until "New Ten" and post-"New Ten" periods, the CRE-BSI rates were 7.81, 8.13, and 9.63 cases per 100,000 hospitalization days. Correspondingly, the carbapenem resistance rates in *Enterobacteriaceae* were 18.6%, 16.4%, and 19.0%, respectively, although no significant statistical differences were noted between the examined periods. The intensity of antimicrobial use increased significantly ($p < 0.001$) after the outbreak of the epidemic, and even increased to 1.5 times after the implementation of the "New Ten" compared to the pre-COVID-19 period. Notably, the utilization of third- and fourth-generation cephalosporins experienced a significant increase in CRE-BSI patients during the COVID-19 epidemic ($p = 0.013$).

Conclusions: During the epidemic, an increased broad-spectrum antimicrobial use happened in CRE-BSI patients.

Key words: Drug resistant; multiple resistant bacteria; carbapenem-resistant *Enterobacteriaceae*; COVID-19.

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Introduction

CRE infections have emerged as a significant global public health crisis due to their high mortality and morbidity rates, placing a substantial burden on society. In China, the prevalence of CRE varies considerably, with reported rates ranging from 0.34 to 14.97 cases per 10,000 discharge days across different provinces [1]. Among these, CRE-BSIs are particularly concerning, as they are associated with prolonged hospital stays and increased mortality. These infections can also lead to a cascade of complications, cross-infections, and secondary infections in healthcare settings, further straining healthcare systems [2,3].

Various studies have highlighted the severe consequences of antimicrobial resistance (AMR) during pandemics, such as those caused by Influenza, SARS, MERS, and COVID-19 [4]. In fact, the pandemic extends the impact of drug resistance beyond patients with COVID-19 themselves to document an ecological impact of the pandemic on AMR. Data from

the Centers for Disease Control and Prevention show an increase in the incidence of AMR, including carbapenem-resistant *Acinetobacter* and extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-E) during COVID-19 pandemic [5]. A study in Iran even found that *Klebsiella pneumoniae* developed increased resistance to ceftriaxone by approximately 30% [6]. It is widely believed that the surge in drug resistance is mainly due to the widespread use of antibiotics. The COVID-19 pandemic has raised significant concerns about antibiotic resistance and the use of antibiotics, especially in low to middle-income countries (LMICs) [7]. Early investigations into COVID-19 revealed that patients with severe infections were particularly vulnerable to co-infections or secondary infections, often involving drug-resistant pathogens. Alarming, the use of antibiotics for prophylactic purposes exceeded the actual incidence of bacterial co-infections and secondary infections, with approximately 74% of these antibiotics being

quinolones and third-generation cephalosporins. Furthermore, research indicates a correlation between the increased use of meropenem and the rising prevalence of carbapenem-resistant Gram-negative infections among ICU patients with COVID-19 in 2020 [8]. However, the impact of the epidemic on patients not infected with COVID-19 currently remains largely unexplored.

Since late 2019, China has implemented various epidemic prevention and control measures to curb the spread of COVID-19. Notably, the introduction of the “New Ten” [9], a set of ten preventive and control measures, has profoundly impacted Chinese society and, particularly, the healthcare system. Before the introduction of the “New Ten”, China conducted large-scale COVID-19 screening, ensuring that COVID-19-infected and non-infected individuals were treated in separate healthcare facilities. After the introduction of the “New Ten”, all COVID-19 patients were admitted to hospitals, and the focus shifted from prevention to treatment.

We hypothesize that during the COVID-19 pandemic, the standards for antibiotic use may have declined, while delays in specimen processing due to heavy workloads and staffing shortages may have occurred. These factors, along with other unmentioned variables, could have potentially impacted the emergence and development of drug-resistant bacteria in medical institutions. We believe there is a need for a broader consideration of environmental and social factors influencing CRE infection within the framework of One Health. This study aims to evaluate the impact of the COVID-19 pandemic on the incidence of CRE-BSI, to prepare for the challenges posed by emerging antimicrobial resistance in the current and future pandemics.

Methodology

Study Subjects

A single-center, cross-sectional study was conducted from January 2019 to January 2023 at a tertiary hospital in Hangzhou, China. This hospital has a total of 1,651 beds and has recorded 490,940 hospitalization days in 2022. During our study period, we meticulously documented cases of hospitalized *Enterobacteriaceae* BSIs and collected pertinent clinical data from CRE-BSI patients. CRE are defined by meeting either of the following criteria: 1. Resistance to any carbapenem antibiotic (imipenem, meropenem, ertapenem, or doripenem). Note: For organisms with intrinsic reduced susceptibility to imipenem, interpretation should be based on

susceptibility results for other carbapenems besides imipenem. 2. Production of a carbapenemase. The study was approved by the Ethics Committee of the hospital (ZN-20230830-0194-01).

From January 2020 to November 2022, the hospital functioned as a non-designated COVID-19 facility, requiring nucleic acid or antigen tests for all incoming patients, with negative results necessary for admission. Following the introduction of the “New Ten” in December 2022, the hospital started admitting patients who tested positive for COVID-19.

For the purposes of this study, patients with CRE-BSI were categorized into three groups:

1. Pre-COVID-19 group: January to December 2019;
2. COVID-19 until “New Ten” group: January 2020 to November 2022;
3. Post- “New Ten” group: December 2022 to January 2023.

Inclusion criteria

1. Age ≥ 18 years;
2. Positive blood culture for *Enterobacteriaceae*;
3. Meeting the diagnostic criteria for BSI as outlined by the Ministry of Health of China [10];
4. Availability of complete clinical data.

Exclusion criteria

1. Incomplete clinical data;
2. For patients with multiple positive blood cultures for the same species within three months, only the first isolate was included in the analysis.

Date Collection

The following data were collected for this study:

1. Patient demographic characteristics: Age and gender.
2. Timing of CRE infection: Time of blood specimen delivery.
3. Risk factors for CRE infection: Factors present before hospitalization and at the time of blood culture testing, as identified in previous studies [11,12]. These included: Underlying conditions (diabetes, chronic obstructive pulmonary disease [COPD]); Central venous catheter (CVC) placement; Surgical procedures (including ERCP); Mechanical ventilation; Admission to ICU; Immunosuppression (malignant tumors, chemotherapy, immunosuppressive therapy, long-term glucocorticoid therapy); Antimicrobial drug treatments (Carbapenems, Aminoglycosides, Quinolones, and third/fourth generation cephalosporin) [13-15].
4. Time interval between blood specimen

Table 1. Characteristics of Clinical Information and Bacterial Distribution Among CRE-BSI Patients (2019.01-2023.01).

	2019.01-12, n = 50, M (IQR) Or n (%)	2020.01-12, n = 42, M (IQR) Or n (%)	2021.01-12, n = 33, M (IQR) Or n (%)	2022.01-12, n = 55, M (IQR) Or n (%)	2023.01, n = 4, M (IQR) Or n (%)	Total n = 184, M (IQR) Or n (%)
Bacterial species						
<i>K. pneumoniae</i>	44 (88.0)	31 (73.8)	25 (75.8)	46 (83.6)	4 (100.0)	150 (81.5)
<i>E. coli</i>	5 (10.0)	4 (9.5)	2 (6.1)	4 (7.3)	0 (0)	15 (8.2)
<i>Other strains</i>	1 (2.0)	7 (16.7)	6 (18.2)	5 (9.1)	0 (0)	19 (10.3)
Age	74.5 (21.3)	74.5 (22.0)	73.0 (18.0)	72.0 (24.0)	79.0 (8.5)	73.5 (20.0)
Sex (male)	37 (74.0)	29 (69.0)	20 (60.6)	35 (63.6)	3 (75.0)	124 (67.4)
Department (ICU)	18 (46.0)	25 (59.5)	20 (62.5)	28 (50.9)	3 (75.0)	94 (51.0)

submission and result reporting (in days).

5. The intensity of antibiotic use, expressed as defined daily doses per 100 patients per day (DDDs/100PD).

Strain identification and antibiotic susceptibility testing were performed using the Merieux VITEK 2 Compact system. Carbapenem resistance was defined as a minimum inhibitory concentration (MIC) of ≥ 2 mg/L for ertapenem or a MIC of ≥ 4 mg/L for imipenem or meropenem, following the criteria established by the Clinical and Laboratory Standards Institute (CLSI).

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 25.0. Continuous variables that followed a normal distribution were presented as mean $\pm$ standard deviation (SD), while non-normally distributed variables were presented as median [interquartile range (IQR)]. For normally distributed data, analysis of variance (ANOVA) was used, while the Wilcoxon rank-sum test was utilized for non-normally distributed data. Group comparisons were conducted using Fisher's exact test or the chi-square test, as appropriate.

Our analysis focused on assessing differences in carbapenem resistance among *Enterobacteriaceae* before and after the implementation of COVID-19 prevention and control measures. We also examined potential influencing factors. A $p < 0.05$ was considered statistically significant.

Results

CRE-BSI Strain Distribution and Clinical Data

In this retrospective observational study, a total of 2,299 positive *Enterobacteriaceae* blood culture cases were initially identified. After applying the specified inclusion and exclusion criteria, 1,056 cases of *Enterobacteriaceae* BSIs were included, of which 184 were CRE. The median age of patients with CRE-BSI was 73.5 years, and the male-to-female ratio was higher among the affected individuals. *Klebsiella pneumoniae* was the most frequently detected pathogen ($n = 150$, 81.5%), followed by *Escherichia coli* ($n = 15$, 8.2%). Other pathogens ($n = 19$, 10.3%) identified included *Serratia marcescens*, *Klebsiella oxytoca*, *Enterobacter cloacae*, and *Klebsiella aerogenes*. Notably, the proportion of ICU admissions for CRE-BSI increased from 46.0% in 2019 to 75.0% in 2023, indicating a rising trend (Table 1).

Table 2. Comparison of Clinical Information and Bacterial Distribution Among Three Groups.

Item	pre-COVID-19, n = 50	COVID-19 until "New Ten", n = 126	post- "New Ten", n = 8	Statistical value	p
Age	74.5 (21.25)	73.0 (20.25)	76.5 (25.0)	Z = -0.06	0.973
Sex (male)	37 (74.0)	80 (63.5)	5 (62.5)	$\chi^2 = 1.82$	0.402
Department (ICU)	18 (36.0)	60 (47.6)	6 (75.0)	$\chi^2 = 4.85$	0.086
Strain distribution					
<i>Klebsiella pneumoniae</i>	44 (88.0)	98 (77.8)	8 (100.0)		
<i>E. coli</i>	5 (10.0)	10 (7.9)	0	$\chi^2 = 6.93$	0.104
<i>Other strains</i>	1 (2.0)	18 (14.3)	0		
Susceptibility factors					
Central vein catheterization	32 (64.0)	82 (65.1)	4 (50.0)	$\chi^2 = 0.74$	0.723
Mechanical Ventilation	22 (44.0)	63 (50.0)	6 (75.0)	$\chi^2 = 2.59$	0.257
ICU admission	23 (46.0)	72 (57.1)	6 (75.0)	$\chi^2 = 3.05$	0.234
Surgery	25 (50.0)	60 (47.6)	2 (25.0)	$\chi^2 = 1.66$	0.437
Suffering from diabetes, COPD	18 (36.0)	42 (33.3)	3 (37.5)	$\chi^2 = 0.15$	0.960
immunosuppression	26 (52.0)	48 (38.1)	1 (12.5)	$\chi^2 = 5.43$	0.064
Antimicrobial exposure					
Carbapenems	30 (60.0)	73 (57.9)	2 (25.0)	$\chi^2 = 3.42$	0.199
Quinolones	3 (6.0)	17 (13.5)	2 (25.0)	$\chi^2 = 3.26$	0.166
Aminoglycosides	3 (6.0)	15 (11.9)	1 (12.5)	$\chi^2 = 1.39$	0.551
Cephalosporins (third and fourth)	19 (38.0)	78 (61.9)	5 (62.5)	$\chi^2 = 8.38^*$	0.013
Specimen submission - Reporting time	3.52 $\pm$ 0.12	3.32 $\pm$ 0.15	3.25 $\pm$ 0.16	F = 0.35	0.704

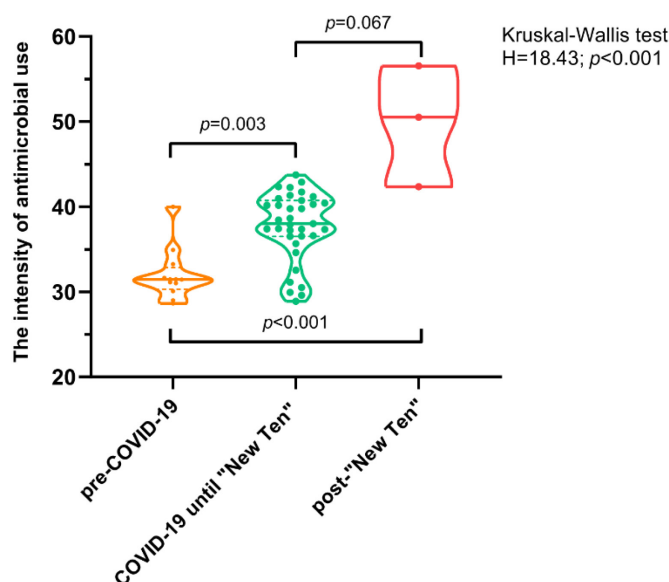
The Impact of COVID-19 on CRE-BSI

Table 2 presents the distribution of bacterial strains in three groups: pre-COVID-19, COVID-19 until “New Ten”, and post- “New Ten”. The number of CRE-BSI cases was 50, 126, and 8, respectively, across the three groups. There was no significant difference in bacterial species distribution between the groups ($p = 0.104$), with *Klebsiella pneumoniae* being the dominant pathogen. Statistical analysis of CRE susceptibility factors revealed no significant differences in mechanical ventilation, central venous catheterization, ICU admission, surgical status, underlying diabetes or COPD, immunosuppression status, or the time difference between pathogen specimen collection and reporting. However, there were statistically significant differences in the empirical use of third- and fourth-generation cephalosporins among the three groups of CRE-BSI patients ($p < 0.05$). The use of carbapenems, quinolones, and aminoglycosides did not show significant differences (Table 2). Furthermore, there was a significant difference in the intensity of antimicrobial drug use among the three groups ($p < 0.001$), as determined by the Kruskal-Wallis test. Further pairwise comparisons revealed significant differences between the pre-COVID-19 and COVID-19 until “New Ten” groups ($p = 0.003$), as well as between the pre-COVID-19 and post- “New Ten” groups ($p < 0.001$), as shown in Figure 1.

Carbapenem Resistance and CRE-BSI Rates Comparisons

This study documented the incidence of nosocomial CRE-BSI and carbapenem resistance, illustrating their trends using curves and bars (Figure 2). The number of CRE-BSI cases fluctuated significantly each year, but

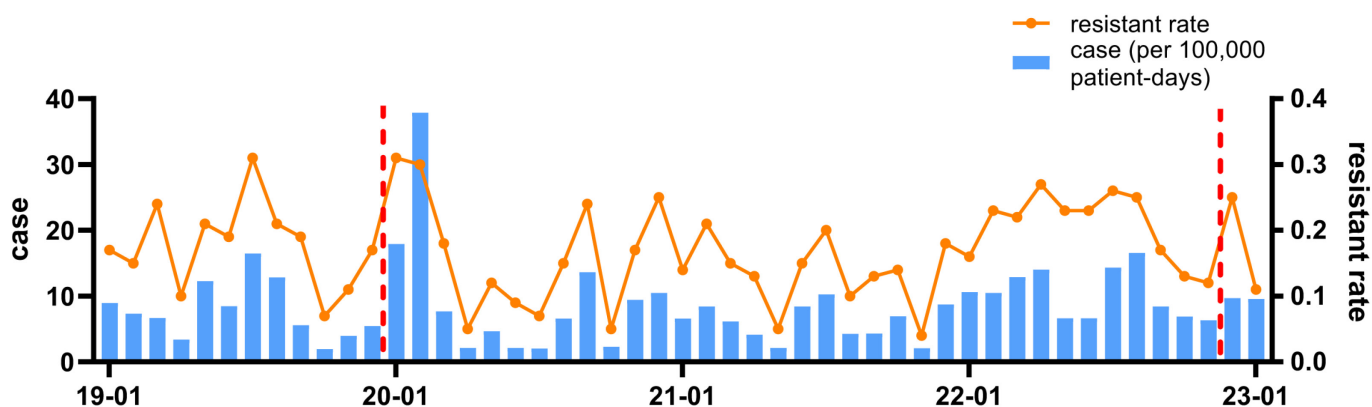
Figure 1. Violin Plot: Comparison of Antimicrobial Use Intensity Across Three Groups.



generally exhibited cyclical trends. However, in early 2020, particularly in February, there was a notable increase in the number of CRE infections, accompanied by a significant rise in the carbapenem resistance rate compared to the same period in previous years. In 2021, the carbapenem resistance rate decreased, but by 2022, it began to rise again. This upward trend was particularly evident in early 2023, when the carbapenem resistance rate increased significantly.

Over this period, the average CRE-BSI incidence was 8.07 cases per 100,000 hospitalization days, and the average carbapenem resistance rate was 17.66%. Yearly data revealed the following CRE-BSI incidence rates: 7.81 in 2019, 8.28 in 2020, 5.97 in 2021, and 10.33 in 2022 per 100,000 hospitalization days. Although there was an overall upward trend, a notable

Figure 2. Time Trends in CRE-BSI Rate and Carbapenem Resistance Rate of Enterobacteriaceae.



Red line: Group dividing line (2019.01-2019.12: pre-COVID-19 group; 2020.01-2022.11: COVID-19 until “New Ten” group; 2022.12-2023.01: post- “New Ten” group).

decrease in 2021 was observed, though statistically insignificant. No significant seasonal correlation with CRE-BSI incidence was found.

Regarding carbapenem resistance, the rates were as follows: 18.59% in 2019, 17.72% in 2020, 13.41% in 2021, and 20.60% in 2022. A declining trend was observed from 2019 to 2021, followed by a rebound in 2022, although this trend did not reach statistical significance.

The data were further categorized based on the epidemic prevention and control periods, and the results are summarized in Table 3. The carbapenem resistance rates of *Enterobacteriaceae* BSI in the pre-COVID-19, COVID-19 until “New Ten”, and post- “New Ten” groups were 18.6%, 16.4%, and 19.0%, respectively. The CRE-BSI rates were 7.81, 8.13, and 9.63 cases per 100,000 hospitalization days. Chi-square analysis of carbapenem resistance rates and CRE-BSI incidences revealed no statistically significant differences among the three groups.

Discussion

The Impact of COVID-19 on the Antibiotic use

Since the emergence of COVID-19 as a global pandemic in late 2019, the disease has caused significant morbidity and mortality worldwide. Beyond its profound effects on public health and society, COVID-19 has also contributed to the escalation of bacterial resistance. In the early stages of the outbreak, China implemented robust measures to control the source and monitor the epidemic. From January 2020 to November 2022, significant attention was paid to infection prevention and control within medical institutions, maintaining a semblance of normalcy in epidemic control [16]. Local medical facilities were carefully chosen for the isolation, diagnosis, and treatment of COVID-19 patients, differentiating between designated and non-designated institutions. Infection prevention and control measures were integrated into the entire spectrum of hospital management. Stringent isolation and protection protocols were enforced for patients from medium and high-risk areas, while regular nucleic acid testing was conducted for other patients during their hospitalization. Enhanced measures, such as improved ventilation, disinfection, and stricter hand hygiene

protocols for healthcare workers were implemented to mitigate the transmission of the novel coronavirus within healthcare settings. Following the introduction of the 'New Ten' guidelines for epidemic prevention and control on December 7, 2022, which strengthened epidemic risk zoning and population stratification management, and all hospitals no longer distinguish between designated and non-determined hospitals. China shifted its focus from epidemic control to the medical treatment of COVID-19 [9].

In our study, we analyzed the antibiotic usage among hospitalized CRE-BSI patients during three distinct periods. The results revealed an increased usage of quinolones, aminoglycosides, and third-generation cephalosporins, with the latter almost doubling in empirical treatment. Compared to data from other countries [17], these antibiotic consumption results are concerning. It is essential to acknowledge that antibiotic usage in China saw a significant increase during the COVID-19 pandemic.

The use of broad-spectrum antibiotics became more prevalent during the pandemic, with clinicians frequently choosing these drugs to treat elderly patients with multiple comorbidities and severe pneumonia [18]. However, study has revealed that the use of antimicrobials did not effectively prevent disease progression, ICU admissions, or mortality [19]. Additionally, overuse of antibiotics can lead to the emergence of multidrug-resistant bacteria and increased mortality [20]. This trend may be due not only to clinicians' less stringent control of antimicrobial use indications but also to the healthcare system's shift in prioritizing COVID-19 prevention efforts over the monitoring of antimicrobial resistance, thus reallocating resources.

The Impact of COVID-19 on CRE-BSI

Many studies have reported an increase in CRE infections and carbapenem resistance rates among severe COVID-19 patients during the pandemic [21-24], often linked to factors such as mechanical ventilation, ICU admission, extended hospital stays, and multiple comorbidities within this patient population. In the context of current epidemic prevention and control measures, we believe that the surge in CRE infections during this period can also be

Table 3. Chi-Square Test Results for Carbapenem-Resistant Rate and CRE Bloodstream Infection Rate Among Three Groups.

Group	Resistant rate (%)	Chi-square		CRE bloodstream infection rate (cases per 100,000 hospitalization days)	Chi-square	
		χ^2	<i>p</i>		χ^2	<i>p</i>
pre-COVID-19	18.6 (50/269)			7.81		
COVID-19 until "New Ten"	16.4 (126/734)	0.49	0.78	8.13	0.30	0.859
post-"New Ten"	19.0 (8/53)			9.63		

attributed to several factors [25]: increased hospitalizations, which facilitated the spread of multidrug-resistant bacteria; a reduced focus on antimicrobial drug management; and heightened use of broad-spectrum antimicrobial drugs. Furthermore, the shift in hospital infection control focus from preventing drug-resistant bacteria to managing the diagnosis, treatment, and transportation of COVID-19 patients, alongside the protection of medical personnel has led to a decrease in drug resistance monitoring. Additionally, the reduced capacity of microbiology laboratories for bacterial culture and drug resistance testing has exacerbated this issue. These factors may have negatively impacted non-designated hospitals and significantly contributed to the rise in bacterial resistance.

In our study, we compared carbapenem resistance rates and CRE bloodstream infection rates across three different periods: pre-COVID-19, COVID-19 until "New Ten" and post-"New Ten". Our findings did not reveal significant differences among the three groups, consistent with the results of recent studies [26,27]. Furthermore, we assessed risk factors associated with CRE infection as indicated by current researches [13-15]. Indeed, for carbapenem-resistant *Enterobacteriaceae* (CRE), the use of carbapenem is the most powerful driver for selecting resistant strains. In this study, the exposure rate to carbapenem across the three CRE bloodstream infection (BSI) groups ranged from 25% to 60%. In the post-"New Ten Guidelines" group, this figure was significantly lower than the average. We believe this outcome is influenced by the following factors: 1) small sample size and short study duration; 2) patients in this group were primarily concentrated in the ICU, where prolonged hospitalization and increased invasive medical procedures (such as mechanical ventilation) further elevate the incidence of healthcare-associated CRE infections. And we found no statistically significant differences in the distribution of these risk factors, except for an increased use of third- and fourth-generation cephalosporins. This may suggest that despite the increased use of antimicrobials during epidemic prevention and control, their impact on carbapenem resistance in *Enterobacteriaceae* in non-designated hospitals, managed under standardized antibiotic protocols, remains limited. However, it is important to note that the effects of antimicrobial use can be long-term, potentially contributing to a sustained rise in resistant infections long after the acute phase of the pandemic has subsided.

However, there were some limitations in our study.

The results of our single-center study may have been influenced by factors such as a small sample size and reduced patient intake and hospital stays during the epidemic period. Therefore, we urge other medical institutions to continue collaborative efforts in researching and monitoring antimicrobial resistance trends.

Conclusions

The incidence of CRE and the carbapenem resistance rates in *Enterobacteriaceae* have remained unchanged before and after the outbreak of the COVID-19 pandemic in China. However, it is clear that the use of certain broad-spectrum antibiotics in medical institutions has been increasing, regardless of the presence of concurrent COVID-19 infections. It is essential to recognize the potential impact of excessive use of broad-spectrum antibiotics on the development of drug-resistant bacteria.

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Conflict of interest

No conflict of interest is declared.

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