

Clinical Distribution Characteristics of 1439 Carbapenem-Resistant *Escherichia coli* Strains in China: Drug Resistance, Geographical Distribution, Antibiotic MIC50/90

Purpose: To explore the clinical distribution characteristics and antimicrobial susceptibilities of carbapenem-resistant *Escherichia coli* (CR-ECO) in Hebei Province, China, from 2017 to 2019, and provide data on the treatment of this bacterial infection and the prevention of its spread.

Materials and Methods: A total of 1439 CR-ECO strains were collected from 2017 to 2019 in Hebei Province, China. Drug sensitivity tests were performed using the minimum inhibitory concentration (MIC) method, and the data were analyzed statistically using WHONET 5.6 software.

Results: A total of 54,377 strains of *Escherichia coli* were isolated in Hebei Province from 2017 to 2019, of which 1439 strains were CR-ECO (2.65%). The highest proportion (33.78%) of strains was isolated from urine, and the detection rate showed a slow downward trend over the past 3 years. CR-

ECO was mainly detected in densely populated and economically developed areas. Of all the patients, 54.2% were from the medical ward; the ratio of male to female patients with CR-ECO infections was 1.35:1; elderly patients and adults accounted for 59.6% and 30.8%, respectively, whereas minors and newborns accounted for 4.9% and 4.7%, respectively. For CR-ECO, the drug resistance rates to β -lactams were all higher than 80% and there was an annual increasing trend, while the drug resistance rates to quinolones remained nearly unchanged. The rate of resistance to amino-glycosides was relatively low, especially to amikacin (approximately 22%). The MIC50 of other antibacterial drugs, except amikacin, was equal to or higher than the breakpoint of drug resistance.

Conclusion: From 2017 to 2019, the isolation rate of CR-ECO in Hebei Province, China, remained stable; however, the drug resistance rates showed an upward trend, primarily in cases of urinary tract infections in older men; the resistance rate to amikacin was the lowest. **Keywords:** Enterobacteriales bacteria, multidrug resistance, MIC50/MIC90, regional distribution

Comment [HK1]: Enterobacteriales

Introduction

Since the advent of penicillin, human beings have discovered and invented various types of antibacterial drugs, which play an extremely important role in the treatment of different infections. However, evidence that reduced susceptibility to antibiotics has been increasing worldwide.¹ In Spain, the resistance rate of *Klebsiella pneumo-*

nia to imipenem increased nearly 13 times from 2010 to 2014.² Data on bacteremia

UNDER PEER REVIEW

tertiary hospitals in Hebei Province, China, from 2017 to 2019. A total

patients from 90 Swiss hospitals showed a linear increase in *Staphylococcus aureus* resistance to oxacillin during hospitalization.³ From 2010 to 2017, the proportion of *Escherichia coli* isolated from 25 tertiary hospitals in Greece insensitive to third-generation cephalosporins, carbapenems, and fluoroquinolones was increasing.⁴ There are even strains that are insensitive to many antibiotics, such as “multi-drug-resistant bacteria, pan-drug-resistant bacteria, and super bacteria”.^{5–8} Carbapenem antibiotics, as broad-spectrum β -lactam drugs, can treat infections caused by *Enterobacteriales* bacteria and are regarded as the “last line of defense” for infection treatment.⁹ Unfortunately, the resistance rate of *Enterobacteriales* bacteria to carbapenems has been increasing year by year.^{12–14} Carbapenem-resistant *Enterobacteriales* (CRE) is a serious public health threat with significant morbidity and mortality, and it has been listed as an urgent threat to bacterial drug resistance by the World Health Organization.^{15–18} In a study of 138 CRE-infected patients treated with ceftazidime/avibactam, the 30-day mortality rate was still as high as 34%.¹⁹ β -lactamase gene transport on mobile components is a key mechanism for the rapid global spread of CRE.^{11,18} With the extensive use of carbapenem antibiotics, carbapenem-resistant *Escherichia coli* (CR-ECO) has evolved, resulting in a dilemma in the selection of antimicrobials for infections with this bacterium. *Escherichia coli* ST131 producing *Klebsiella pneumoniae* carbapenemase (KPC) was isolated in Italy. Sequencing showed that the strain contained the *kpc-2* variant and TEM-1 β -lactamase.²⁰ In 2020, *Escherichia coli* ST131 O16: H5 producing *oxa-244* was isolated from German patients for the first time.²¹ The spread of such variants thus poses a serious threat to public health.^{4,21} Compared with CRKP, CR-ECO has obviously not attracted enough attention, and its resistance rate, geographical distribution, and other data are unknown in Hebei Province, China. Therefore, the aims of this study were to explore the clinical distribution characteristics and antimicrobial susceptibility of CR-ECO in Hebei Province, China, from 2017 to 2019, and to provide data supporting the treatment of this bacterial infection and the prevention of its spread.

Materials and Methods

General Information

The strains were isolated from the urine, sputum, blood, secretions, and other clinical specimens of patients in 43

4718

Comment [HK2]: *Staphylococcus aureus*

Comment [HK3]: *Enterobacteriales* to *Enterobacteriales*. In entire chapter

Comment [HK4]: Type of study - Retrospective?

Comment [HK5]: Secretions – not usually a good microbiological specimen. Specify

of 1439 *CR-ECO* strains were obtained. To avoid duplication of statistics in the same patient, the first *CR-ECO* isolated from this patient was screened with WHONET 5.6 software for the study. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were obtained from the Clinical Inspection Center of the National Health and Wellness Committee of the People's Republic of China. The bacterial drug sensitivity test recommended by the American Institute of Clinical and Laboratory Standardization (CLSI) was used, and drug sensitivity was determined using the CLSI drug sensitivity breakpoint of the 2019 edition.²²

Methods

Instruments and Reagents

We used the BacT/ALERT 3D120 automatic blood culture instrument (BIO PARTICIPATIONS Co., LTD, Marcy-l'Étoile, France). The blood culture bottles were obtained from the original factory. The bacterial identification instrument, Phoenix 100, FX-200 automatic blood culture instrument (Becton, Dickinson and Company, New Jersey, USA) was used and the biochemical reaction tubes and drug sensitive reaction tubes were all obtained from the original factory. The bacterial solid culture medium used was the MacConkey Agar Medium (Dijing Microbiology Technology Co., LTD, Guangzhou, China).

Research Methods

The strains were inoculated into the MacConkey Agar Medium at 35 °C for 24 h. The bacterial solution was prepared to 0.5 McFarland Standards, and 20 µL was added to the drug sensitive broth. This was mixed well, and the mixture was poured onto the drug sensitive reaction plate. The remaining bacterial solution was poured onto the biochemical reaction plate. These plates were then placed in the bacterial identification instrument, the Phoenix 100, for the identification and drug sensitivity tests, and the results were read after 24 hours.

The bacterial drug sensitivity test recommended by the American Institute of Clinical and Laboratory Standardization (CLSI) was used, and drug sensitivity was determined using the CLSI drug sensitivity breakpoint of the 2019 edition. *CR-ECO* was defined as an

isolate with imipenem and/or meropenem (MICs ≥ 4 µg/mL).

Statistical Processing

WHONET 5.6 software was used for data analysis (World Health Organization, Geneva, Switzerland). Images were

Comment [HK6]: Clinical & Laboratory Standards Institute (CLSI)

Comment [HK7]: All 43 centers followed same protocol?

Comment [HK8]: bioMérieux?

Comment [HK9]: BD BACTEC FX 200

formed with GraphPad prism software (Version 8.4.0, Insightful Science Co., LTD, San Diego, CA, USA) and Adobe Illustrator 2019 software (Adobe Systems Incorporated Co., LTD, SAN Jose, California, USA).

Results

A total of 54,377 strains of *Escherichia coli* were isolated in Hebei Province, China, from 2017 to 2019, including the 1439 strains of *CR-ECO* (2.65%). Among the 1439 strains of *CR-ECO*, 439 strains (2.81%, 439/15,599) were isolated in 2017, 461 strains (2.40%, 461/19,241) in 2018, and 539 strains (2.76%, 539/19,999) in 2019. Among these, 486 urine samples (33.77%) ranked first, 419 sputum samples (29.12%) second, and 131 (9.10%) blood sample third. Furthermore, 73 catheters and 72 secretions ranked fourth (5.10%) and fifth places (5.00%), respectively (Table 1).

Between 2017 and 2019, the characteristics of the 1439 patients with *CR-ECO* infection were as follows: 828 (57.5%) males, 611 (42.5%) females, and the ratio of male to female was 1.35:1. There were 858 (59.6%) older people (>60 years old), 443 (30.8%) adults (18–60 years old), 71 (4.9%) minors (1–18 years old) and 68 (4.7%) newborns (<1 year old), respectively. The 1439 strains of *CR-ECO* were isolated from internal medicine 780 (54.20%), surgery 384 (26.69%), ICU 139 (9.66%), pediatrics 80 (5.56%), emergency 43 (2.99%), and out-patient 11 (0.76%) (Figure 1).

Table 1 Distribution Characteristics of *CR-ECO* Specimens from 2017 to 2019

Specimen Type	2017		2018		2019	
	N	P(%)	N	P(%)	N	P(%)
Urine	152	34.6	156	33.8	178	33.0
Sputum	132	30.0	126	27.3	161	29.8
Blood	44	10.0	48	10.4	39	7.2
Catheter	11	2.5	26	5.6	36	6.6
Secretion	15	3.4	28	6.0	29	5.3
Ascites	6	1.3	18	3.9	21	3.8
Pus	26	5.8	27	5.7	16	2.9
Bile	14	3.1	9	1.9	8	1.4
Drainage	1	0.2	4	0.8	12	2.2
Fecal	9	2.0	2	0.4	3	0.5
Vagina	7	1.5	0	0.0	1	0.1
Other	23	5.2	21	4.5	35	6.4
Total	439	100	461	100	539	100

Abbreviations: N, number; P, proportion.

From 2017 to 2019, 1439 strains of *CR-ECO* were isolated from Hebei Province, China, according to administrative regions, with Shijiazhuang ranking first with 445 strains (30.92%); Tangshan second with 341 strains (23.70%); Cangzhou third with 172 strains (11.95%), and Handan fourth with 103 strains (7.16%), as shown in Table 2.

Analysis of trend results of drug resistance rates from 2017 to 2019 yielded the following: all β -lactamides showed an increasing trend, exceptertapenem, which first decreased and then increased. Among the three aminoglycosides, amikacin first increased and then decreased; gentamicin and tobramycin first decreased and then increased; and the two quinolones, levofloxacin and ciprofloxacin, showed an upward trend first and then a downward trend (Table 3).

Analysis of mean drug resistance rates from 2017 to 2019 yielded the following: piperacillin/tazobactam relative to piperacillin (69.5% vs 92.5%) and ampicillin/sulbactam relative to ampicillin (89.9% vs 96.6%) were significantly reduced; the first to fourth generation cephalosporins represented by cefazolin, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, and cefepime showed a downward trend (91.3% vs 91.2% vs 91.6% vs 88.2% vs 85.7% vs 85.6%). Among carbapenems, ertapenem, imipenem, and meropenem were different (91.3% vs 77.3% vs 72.2%). Among the three aminoglycosides, gentamicin, tobramycin, and amikacin were significantly different (65.0% vs 56.8% vs 22.2%). Levofloxacin was slightly lower than ciprofloxacin (81.0% vs 84.6%); compounds sulfas were relatively low (76.9%) (Table 3).

Discussion

In recent years, due to the irregular use of antibacterial drugs, the resistance rate of *Escherichia coli* to antibacterial drugs has increased. Further, there has been an increase in the appearance of multi-drug resistant *Escherichia coli*.⁸ While carbapenem antibiotics have become the last line of defense against multi-drug resistant *Escherichia coli*, *CR-ECO* has appeared all over the world, resulting in difficulties in the treatment of this bacterial infection.^{13,17,23}

Carbapenase production is the main mechanism of drug resistance of *Enterobacteriales* to carbapenems.²⁴ Carbapenems can be destroyed by direct hydrolysis. Because most carbapenase genes are located on mobile gene elements, they are easily transferred between *Enterobacteriales* and other gram-negative bacilli, leading to widespread epidemics in a short period of time.²⁵

Comment [HK10]: lactams

Comment [HK11]: Carbapenemase

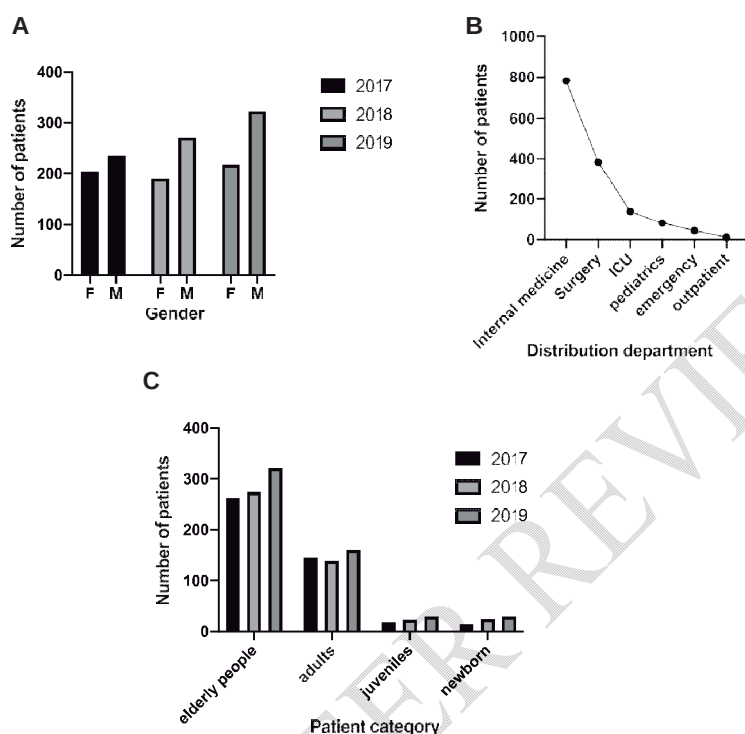


Figure 1 Clinical distribution characteristics of CR-ECO. (A) Gender distribution characteristics of CR-ECO. (B) Distribution characteristics of CR-ECO departments. (C) Age distribution characteristics of CR-ECO.

Modified carbapenem inactivation method in conjunction with EDTA-modified carbapenem inactivation method and simplified carbapenem inactivation method can be used to

detect carbapenems^{24,26} KPC, NDM, IPM, VIM and OXA-48 are common carbapenem resistance genotypes.^{24,27} In 2018, *Escherichia coli* ST131 producing KPC and TEM carbapenemase was isolated from the urine of patients with urinary tract infection for the first time in Italy.²⁰

Comment [HK12]: carbapenemases

Table 2 Regional Distribution Characteristics of CR-ECO Specimens from 2017 to 2019

Territory Name	Year			Total (N)	Proportion (%)
	2017 (N)	2018 (N)	2019 (N)		
Shijiazhuang	145	142	158	445	30.92
Tangshan	107	113	121	341	23.70
Cangzhou	29	60	83	172	11.95
Handan	20	36	47	103	7.16
Xingtai	22	21	18	61	4.24
Chengde	28	18	14	60	4.17
Qinhuangdao	19	17	11	47	3.27
Zhangjiakou	7	7	32	46	3.20
Langfang	11	11	18	40	2.78
Total	439	461	539	1439	100

Abbreviation: N, number.

This study showed that CR-ECO accounted for 2.65% of all *Escherichia coli* that caused clinical infections in Hebei Province, China, from 2017 to 2019. From 2009 to 2014, 593 strains of *Escherichia coli* were isolated from pig feces and rivers in Heilongjiang Province, China, of which CR-ECO accounted for 6.74%.²⁸ Moreover, the CR-ECO isolated in 10 public pig farms in India accounted for 20.5% of all the strains of *Escherichia coli* between 2014 and 2016.²⁹ This indicates that CR-ECO spreads in the environment, and that the separation rate is higher than that of human patients. In Hebei Province, China, the highest separation rate of CR-ECO was from murine, accounting for about 33% of the total. Studies have

Table 3 Drug Sensitivity Data of CR-ECO to Various Antibacterial Drugs from 2017 to 2019

Antibiotic Name	2017			2018			2019			Average Value		
	N	R(%)	S(%)	N	R(%)	S(%)	N	R(%)	S(%)	N	R(%)	S(%)
Ampicillin	346	95.1	3.5	339	97.1	1.2	471	97.2	1.7	1148	96.6	2.1
Piperacillin	278	91	5.8	220	91.8	3.2	226	94.7	4.4	719	92.5	4.6
Cefazolin	343	84.6	15.5	383	93.5	6.5	374	95.2	4.8	1092	91.3	8.7
Cefuroxime	315	88.9	9.8	343	92.1	6.4	353	92.6	6.8	1004	91.2	7.7
Ceftriaxone	322	87.6	12.1	305	93.1	6.2	375	93.9	5.6	996	91.6	7.9
Cefotaxime	167	81.4	18	153	92.8	7.2	140	91.4	8.6	458	88.2	11.6
Compound sulfamethoxazole	336	81	19	382	72.8	27.2	439	77.9	22.1	1149	76.9	23.1
Ciprofloxacin	349	80.8	16.3	408	87	11.5	477	85.3	10.9	1226	84.6	12.7
Levofloxacin	349	77.7	18.1	417	82.5	13.7	513	82.3	14	1271	81.0	15.1
Ampicillin/sulbactam	267	92.5	4.1	368	87.5	7.1	466	90.1	4.9	1093	89.8	5.5
Gentamicin	348	67	30.5	414	62.1	34.3	473	66.2	28.3	1227	65.0	30.9
Tobramycin	245	55.9	31.8	255	53.3	29.4	248	61.7	19.4	743	56.8	27.1
Aztreonam	283	82.3	15.2	236	77.5	19.9	286	82.5	16.4	801	81.0	17
Cefepime	352	84.9	13.4	426	84.5	10.6	514	87.2	8	1284	85.6	10.4
Ceftazidime	351	79.5	18.5	344	89	9.6	510	88	10	1197	85.7	12.4
Amoxicillin/clavulanic acid	137	39.4	49.6	97	89.7	8.2	120	86.7	9.2	353	69.1	24.6
Piperacillin/tazobactam	355	62.5	31.3	422	69	18.5	507	75.1	16.2	1276	69.5	21.2
Meropenem	361	62.3	32.7	402	74.9	17.9	472	78	18.2	1227	72.2	22.4
Imipenem	357	66.1	30.5	424	79.7	13	511	82.8	12.7	1284	77.3	17.8
Ertapenem	91	91.2	8.8	88	90.9	9.1	84	91.7	7.1	263	91.3	8.3
Amikacin	351	22.8	72.9	425	35.5	58.6	513	19.3	78.6	1281	22.2	70.6

Abbreviations: N, number of strains; R, drug resistance rate; S, sensitivity rate.

shown that the most common pathogen found in urine is *Escherichia coli*, of which 70.3% are multi-drug resistant bacteria, 1.65% CR-ECO, while 0.8% produce the bla_{OXA-48} gene.³⁰ In Hebei Province, China, there are more male than female patients with CR-ECO infection (1.35 vs 1), while in the United States, 59% were women.³¹ In addition, the majority (90.4%) of the CR-ECO infected people in Hebei Province, China, are older persons and adults, with only 9.6% being newborns and minors. According to the statistics of two teaching hospitals in London, 51.2% of the CR-ECO patients are between 16 and 64 years old, while 48.8% patients were over 64 years old.¹² The median age of the CR-ECO infected people in the United States was 66 years old.³¹ According to the above data, CR-ECO causes infections mainly in older patients. In this study, the CR-ECO inpatients accounted for 99.2%, with the highest proportion being in internal medicine, exceeding 50%, while the ICU accounted for approximately 10%. Johnson et al.³² showed that patients with CR-ECO infection mainly were admitted to the ICU. In Table 2, the CR-ECO isolated clinically from Shijiazhuang and Tangshan in 2017–2019 showed

first and second places in all the cities in Hebei Province, China, respectively, while the total proportions of the two cities exceeded half of the province; Langfang and Zhangjiakou were the last and penultimate places, respectively. The total proportion was about 6%. In 2019, the China Antimicrobial Resistance Surveillance Network (CARSS) showed that the top five provinces and cities in China with respect to the CR-ECO separation rates were Beijing, Liaoning, Henan, Jiangsu, and Shanghai, and the five provinces and cities with the lowest separation rates were Tibet, Gansu, Ningxia, Inner Mongolia, and Shanxi. In America, the CR-ECO separation rates in Georgia, Maryland, and New York were significantly higher than those in Colorado, New Mexico, and Oregon.³¹ This indicates that CR-ECO is distributed mainly in densely populated and economically developed areas.

At present, the antibiotics used to treat CRE are limited. Polymyxin, tigecycline, fosfomycin and aminoglycosides are the drugs of choice for the treatment of CRE infections; however their clinical use is limited by their pharmacokinetics and side effects.^{13,17,33} The drug resistance rate of piperacillin/tazobactam was 23% lower

Comment [HK13]: bla_{OXA-48}

than that of piperacillin, and the drug resistance rate of ampicillin/sulbactam was 6.8% lower than that of ampicillin, which proved that the antibacterial activity of penicillin plus enzyme inhibitor was higher than that of a single drug preparation. For carbapenem-sensitive *Escherichia coli*, the resistance rate of piperacillin/tazobactam is less than one-tenth of that of piperacillin.³⁴ In this study, the resistance rate of the first to the fourth generation cephalosporins to *CR-ECO* showed a downward trend, indicating that the level of cephalosporins increased with the increase in antibacterial activity. However, it is worth noting that the overall drug resistance rate of *CR-ECO* to cephalosporins is still very high, over 85%. Among the third generation cephalosporins, the antibacterial activity of ceftazidime against *CR-ECO* was superior to that of cefotaxime and ceftriaxone. In North America, the sensitivity of ceftazidime/avibactam to *CR-ECO* was much higher than that of ceftazidime (92% vs 19%).³⁵ In this study, the drug resistance rates of *CR-ECO* toertapenem, imipenem, and meropenem were 91.3%, 77.3%, and 72.2%, respectively. Johnston et al.³⁵ showed that the sensitivity rates of meropenem, imipenem, and ertapenem were 59%, 29%, and 4%, respectively. It can be seen that the antibacterial activity of the above three carbapenems against *CR-ECO* descending order is meropenem, imipenem, and ertapenem. When treating infections caused by multidrug-resistant gram-negative bacteria, aminoglycosides are recommended, especially for urinary tract infection caused by renal accumulation. Considering the ototoxicity and nephrotoxicity of such drugs, drug MIC should be monitored for individualized treatment.¹³ In this study, the antibacterial activity of amikacin against *CR-ECO* was 41.1 and 42.4 percentage points higher than that of tobramycin and gentamicin, respectively. Amikacin showed higher antimicrobial activity against *CR-ECO* than gentamicin in Asia-Pacific (68% vs 31%) and Europe (78% vs 50%).³⁵ The resistance rates of *CR-ECO* to gentamicin and amikacin in China were 59.3% and 13.2%, respectively.³³ Amikacin has shown high activity against *CR-ECO* and can be used as an empirical drug candidate for the treatment of *CR-ECO* infections. However, we should pay close attention to its adverse reactions such as ototoxicity and nephrotoxicity.

The MIC₅₀/MIC₉₀ refers to the minimum inhibitory concentration of antibacterial drugs that can inhibit the growth of pathogens by 50%/90%.³⁶ In this study

(Table 4), the *CR-ECO* MIC₅₀ in Hebei Province, China, was equal to or slightly higher than the resistance breakpoints of most antibiotics. The MIC₅₀ of cefotaxime and ceftriaxone was 16 times that of the resistance breakpoint, but the MIC₅₀ of amikacin was far lower than that of the resistance breakpoint, which was 6.25% of the resistance breakpoint and 25% of the sensitivity breakpoint. In this study, amikacin had a higher activity against *CR-ECO* than other antibacterial drugs (Table 3). Unfortunately, *C*

R-ECO still showed a high drug resistance rate to new antibacterial drugs, with sensitivity rates of 45% (MIC₅₀ ≥ 256 µg/mL) and only 10% (MIC₅₀ ≥ 256 µg/mL) to ceftazidime/tazobactam.³⁷

Conclusion

In conclusion, the detection rate of *CR-ECO* in Hebei Province, China, remained relatively stable from 2017 to 2019, while the drug resistance to commonly used antibiotics in the clinic was high, especially the drug resistance rate to penicillins and cephalosporins, which was as high as 90.0%. To treat this bacterial infection, sensitive antibacterial agents should be selected according to the results of drug sensitivity tests. *CR-ECO* mainly causes urinary tract infections in older male inpatients. In addition, *CR-ECO* is distributed mainly in densely populated and economically developed areas in Hebei Province, China. To understand the epidemiological characteristics of the *CR-ECO* area, it is necessary to monitor drug resistance data. A limitation of this study is that the isolates were not sequenced for drug-resistant genotypes, so the transmission trajectories could not be accurately tracked. The administration of carbapenems should be strengthened to delay the generation of *CR-ECO*. To prevent the spread of *CR-ECO*, medical and government agencies need to work together to develop scientific prevention and control measures.

Data Sharing Statement

The data used and/or analyzed in this study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The protocol has been reviewed by the Ethics Committee (IRB) of the First Affiliated Hospital of Hebei North University. Since the project is an observational study and all

Table 4 CR-ECOMIC50 and MIC90 in 2017–2019

Antibiotic Name	Quantity	Break Point	MIC50	MIC90	MIC Range
Tigecycline	159	$S \leq 0.03 R \geq 0.25$	0.5	1	0.025–8
Ertapenem	262	$S \leq 0.5 R \geq 2$	2	8	0.12–32
Cefotaxime	458	$S \leq 1 R \geq 4$	64	64	0.12–128
Piperacillin	719	$S \leq 16 R \geq 128$	128	128	2–256
Tobramycin	743	$S \leq 4 R \geq 16$	16	16	0.5–32
Aztreonam	801	$S \leq 4 R \geq 16$	32	64	0.25–128
Ceftriaxone	996	$S \leq 1 R \geq 4$	64	128	0.25–128
Cefazolin	1092	$S \leq 16 R \geq 32$	32	64	2–128
Ampicillin/sulbactam	1093	$S \leq 8 R \geq 32$	32	64	2–128
Ampicillin	1148	$S \leq 8 R \geq 32$	32	64	2–128
Compound sulfamethoxazole	1149	$S \leq 2 R \geq 4$	8	16	0.25–32
Ceftazidime	1197	$S \leq 4 R \geq 16$	32	64	0.12–128
Ciprofloxacin	1226	$S \leq 1 R \geq 4$	4	4	0.06–32
Meropenem	1227	$S \leq 1 R \geq 4$	8	16	0.06–32
Gentamicin	1227	$S \leq 4 R \geq 16$	16	16	0.5–32
Levofloxacin	1271	$S \leq 2 R \geq 8$	8	16	0.12–16
Piperacillin/tazobactam	1276	$S \leq 16 R \geq 128$	128	128	1–256
Amikacin	1281	$S \leq 16 R \geq 64$	4	64	0.25–128
Cefepime	1284	$S \leq 2 R \geq 16$	32	64	0.12–128
Imipenem	1284	$S \leq 1 R \geq 4$	8	16	0.0625–64

Abbreviations: MIC, minimum inhibitory concentration; MIC50/MIC90, MIC50 and MIC90 can inhibit 50% or 90% of the tested bacteria.

bacterial strains are from strains cultured from residual samples used in clinical diagnosis, it involves the confidentiality of patient data and compliance with the Declaration of Helsinki. Since the data did not affect patient care, it was determined that the exemption criteria were met. After consulting the IRB of the First Affiliated Hospital of Hebei North University, a formal ethical review was approved, and written informed consent from the patient was not required (ethical approval No.: K2019147).

References

- Acevedo R, Bai X, Borrow R, et al. The global meningococcal initiative meeting on prevention of meningococcal disease worldwide: epidemiology, surveillance, hypervirulent strains, antibiotic resistance and high-risk populations. *Expert Rev Vaccines*. 2019;18(1):15–30. doi:10.1080/14760584.2019.1557520
- Aracil-García B, Oteo-Iglesias J, Cuevas-Lobato O, et al. Rapid increase in resistance to third-generation cephalosporins, imipenem and co-resistance in *Klebsiella pneumoniae* from isolated from 7140 blood-cultures (2010–2014) using EARS-Net data in Spain. *Enferm Infecc Microbiol Clin*. 2017;35(8):480–486. doi:10.1016/j.eimc.2016.06.007
- Buetti N, Marshall J, Timsit JF, Atkinson A, Kronenberg A, Sommerstein R. Distribution of pathogens and antimicrobial resistance in bacteraemia according to hospitalization duration: a nationwide surveillance study in Switzerland. *Clin Microbiol Infect*. 2021. doi:10.1016/j.cmi.2021.04.025
- Polemis M, Tryfinopoulou K, Giakkoupi P, Vatopoulos A. Eight-year trends in the relative isolation frequency and antimicrobial susceptibility among bloodstream isolates from Greek hospitals: data from the Greek electronic system for the surveillance of antimicrobial resistance -WHONET- Greece, 2010 to 2017. *Euro Surveill*. 2020;25(34). doi:10.2807/1560-7917.ES.2020.25.34.1900516
- Liu Y, Li R, Xiao X, Wang Z. Antibiotic adjuvants: an alternative approach to overcome multi-drug resistant Gram-negative bacteria. *Crit Rev Microbiol*. 2019;45(3):301–314. doi:10.1080/1040841X.2019.1599813
- Mühlberg E, Umstätter F, Kleist C, Domhan C, Mier W, Uhl P. Renaissance of vancomycin: approaches for breaking antibiotic resistance in multidrug-resistant bacteria. *Can J Microbiol*. 2020;66(1):11–16. doi:10.1139/cjm-2019-0309

7. Zhang J, Xu J, Ma H, et al. Designing an amino-fullerene derivative C(70)-(EDA)(8) to fight superbacteria. *ACS Appl Mater Interfaces*. 2019;11(16):14597–14607. doi:10.1021/acsami.9b01483
8. Wu B, Qi C, Wang L, et al. Detection of microbial aerosols in hospital wards and molecular identification and dissemination of drug resistance of *Escherichia coli*. *Environ Int*. 2020;137:105479. doi:10.1016/j.envint.2020.105479
9. Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in gram-negative bacteria. *Clin Infect Dis*. 2019;69(Suppl 7):S521–S528. doi:10.1093/cid/ciz824
10. Doi Y. Treatment options for carbapenem-resistant gram-negative bacterial infections. *Clin Infect Dis*. 2019;69(Suppl 7):S565–S575. doi:10.1093/cid/ciz830
11. Potter RF, D'Souza AW, Dantas G. Therapeutic spread of carbapenem-resistant *Enterobacteriaceae*. *Drug Resist Updat*. 2016;29:30–46. doi:10.1016/j.drup.2016.09.002
12. Freeman R, Moore LS, Charlett A, Donaldson H, Holmes AH. Exploring the epidemiology of carbapenem-resistant Gram-negative bacteria in west London and the utility of routinely collected hospital microbiology data. *J Antimicrob Chemother*. 2015;70(4):1212–1218. doi:10.1093/jac/duk500
13. Fritzenwanker M, Imirzalioglu C, Herold S, Wagenlehner FM, Zimmer KP, Chakraborty T. Treatment options for carbapenem-resistant gram-negative infections. *Dtsch Arztebl Int*. 2018;115(20–21):345–352. doi:10.3238/arztebl.2018.0345
14. Wang Q, Wang X, Wang J, et al. Phenotypic and genotypic characterization of carbapenem-resistant *Enterobacteriaceae*: data from a longitudinal large-scale CRE study in China (2012–2016). *Clin Infect Dis*. 2018;67(Suppl 2):S196–S205. doi:10.1093/cid/ciy660
15. Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis*. 2019;19(1):56–66. doi:10.1016/S1473-3099(18)30605-4
16. Peri AM, Doi Y, Potoski BA, Harris PNA, Paterson DL, Righi E. Antimicrobial treatment challenges in the era of carbapenem resistance. *Diagn Microbiol Infect Dis*. 2019;94(4):413–425. doi:10.1016/j.diagmicrobio.2019.01.020
17. Wenzler E, Scoble PJ. An appraisal of the pharmacokinetic and pharmacodynamic properties of meropenem-vaborbactam. *Infect Dis Ther*. 2020;9(4):769–784. doi:10.1007/s40121-020-00344-z
18. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant *Enterobacteriaceae*: the impact and evolution of a global menace. *J Infect Dis*. 2017;215(suppl 1):S28–S36. doi:10.1093/infdis/jiw282
19. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of Cefazidime-Avibactam salvage therapy in patients with infections caused by *Klebsiella pneumoniae* Carbapenemase-producing *K. pneumoniae*. *Clin Infect Dis*. 2019;68(3):355–364. doi:10.1093/cid/ciy492
20. Ripabelli G, Sammarco ML, Scutellà M, Felice V, Tamburro M. Carbapenem-resistant KPC- and TEM-producing *Escherichia coli* ST131 isolated from a hospitalized patient with urinary tract infection: first isolation in Molise Region, Central Italy, July 2018. *Microb Drug Resist*. 2020;26(1):38–45. doi:10.1089/mdr.2019.0085
21. Welker S, Boutin S, Miethke T, Heeg K, Nurdjati D. Emergence of carbapenem-resistant ST131 *Escherichia coli* carrying bla(OXA-244) in Germany, 2019 to 2020. *Euro Surveill*. 2020;25(46):doi:10.2807/1560-7917.ES.2020.25.46.2001815
22. Wayne P. The Clinical and Laboratory Standards Institute antimicrobial susceptibility testing standards. *CLSI*. 2019;3:M100–ED29.
23. Diallo OO, Baron SA, Abat C, Colson P, Chaudet H, Rolain JM. Antibiotic resistance surveillance systems: a review. *J Glob Antimicrob Resist*. 2020;23:430–438. doi:10.1016/j.jgar.2020.10.009
24. Patil S, Chen H, Zhang X, Lian M, Ren PG, Wen F. Antimicrobial resistance and resistance determinant insights into multi-drug resistant gram-negative bacteria isolates from paediatric patients in China. *Infect Drug Resist*. 2019;12:3625–3634. doi:10.2147/IDR.S223736
25. Spaziani M, Venditti C, Butera O, et al. Importance of surveillance of new Delhi metallo-beta-lactamase *Klebsiella pneumoniae*: molecular characterization and clonality of strains isolated in the Lazio Region, Italy. *Infect Drug Resist*. 2021;14:3659–3665. doi:10.2147/IDR.S318717
26. Wang YLH, Zhang L, Sun B. Application of modified carbapenem inactivation method and its derivative tests for the detection of carbapenemase-producing *Aeromonas*. *Infect Drug Resist*. 2021;2021(14):3949–3960. doi:10.2147/IDR.S330115
27. El-Badawy MF, Abdelwahab SF, Alghamdi SA, Shohayeb MM. Characterization of phenotypic and genotypic traits of carbapenem-resistant *Acinetobacter baumannii* clinical isolates recovered from a tertiary care hospital in Taif, Saudi Arabia. *Infect Drug Resist*. 2019;12:3113–3124. doi:10.2147/IDR.S206691
28. Cheng P, Li F, Liu R, et al. Prevalence and molecular epidemiology characteristics of carbapenem-resistant *Escherichia coli* in Heilongjiang Province, China. *Infect Drug Resist*. 2019;12:2505–2518. doi:10.2147/IDR.S208122
29. Pruthi Vishree BS, Vinodh Kumar OR, Sinha DK, et al. Spatial molecular epidemiology of carbapenem-resistant and New Delhi metallo-beta-lactamase (blaNDM)-producing *Escherichia coli* in the piglets of organized farms in India. *J Appl Microbiol*. 2017;122(6):1537–1546. doi:10.1111/jam.13455
30. Gurung S, Kafle S, Dhungel B, et al. Detection of OXA-48 gene in carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* from urine samples. *J Infect Drug Resist*. 2020;13:2311–2321. doi:10.2147/IDR.S259967
31. Guh AY, Bulens SN, Mu Y, et al. Epidemiology of carbapenem-resistant *Enterobacteriaceae* in 7 US communities, 2012–2013. *JAMA*. 2015;314(14):1479–1487. doi:10.1001/jama.2015.12480
32. Johnson JK, Robinson GL, Pineles LL, et al. Carbapenem MICs in *Escherichia coli* and *Klebsiella* species producing extended-spectrum beta-lactamases in critical care patients from 2001 to 2009. *Antimicrob Agents Chemother*. 2017;61(4):doi:10.1128/AAC.01718-16
33. Tang X, Xiao M, Zhuo C, Xu Y, Zhong N. Multi-level analysis of bacteria isolated from inpatients in respiratory departments in China. *J Thorac Dis*. 2018;10(5):2666–2675. doi:10.21037/jtd.2018.04.46
34. Hu FP, Guo Y, Zhu DM, et al. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005–2014. *Clin Microbiol Infect*. 2016;22(Suppl 1):S9–14. doi:10.1016/j.cmi.2016.01.001
35. Johnston BD, Thuras P, Porter SB, et al. Activity of cefiderocol, ceftazidime-avibactam, and eravacycline against carbapenem-resistant *Escherichia coli* isolates from the United States and international sites in relation to clonal background, resistance genes, core resistance, and region. *Antimicrob Agents Chemother*. 2020;64(10):451. doi:10.1128/AAC.00797-20
36. Garcia-Effron G. Rezafungin: mechanisms of action, susceptibility and resistance: similarities and differences with the other echinocandins. *J Fungi (Basel)*. 2020;6(4):67. doi:10.3390/jof6040262
37. Alatoon A, Elsayed H, Lawlor K, et al. Comparison of antimicrobial activity between ceftolozane-tazobactam and ceftazidime-avibactam against multidrug-resistant isolates of *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. *Int J Infect Dis*. 2017;62:39–43. doi:10.1016/j.ijid.2017.06.007

UNDER PEER REVIEW