Infection and Drug Resistance

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ORIGINAL RESEARCH

Multicenter Investigation of Drug-Resistance in Burkholderia Cepacia Bloodstream Infections in Hebei Province, China, from 2016 to 2021

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Objective: To compare the epidemiological characteristics and drug resistance of *Burkholderia cepacia* isolated from blood cultures, and to provide data support and a scientific basis for the clinical treatment and detection of hospital infections.

Methods: The Hebei Province Antimicrobial Surveillance Network received 349 *B. cepacia* strains isolated from blood cultures reported by 83 hospitals, from 2016 to 2021. These strains were identified by MALDI-TOF MS and, the antibiotic sensitivity tests were carried out using the VITEK 2 COMPACT system. The 2023 Institute of Clinical and Laboratory Standardization drug-susceptibility breakpoints were used for drug susceptibility testing and the data were analyzed using WHONET5.6 software.

Results: A total of 349 *B. cepacia* strains were isolated from 2016 to 2021, including 68 strains from secondary hospitals and 281 strains from tertiary hospitals. The ratios of male: female patients with *B. cepacia* bloodstream infections in all hospitals, secondary hospitals, and tertiary hospitals were 1.49:1 (209/140), 2.09:1 (46/22), and 1.38:1 (163/118), respectively. Most *B. cepacia* strains were isolated in intensive care units (ICUs), followed by internal medicine departments, accounting for 49.57% (173/349) and 22.92% (80/349), respectively. Regarding the age distribution, most patients were elderly (>65 years, 57.59%, 201/349), with numbers of patients gradually declining with decreasing of age. The resistance rates for levofloxacin, ceftazidime, and sulfamethoxazole decreased over the 6-year period ($P<0.05$), while there were no significant changes in the resistance rates for meropenem, chloramphenicol, and minocycline ($P>0.05$). There was no significant difference in drug-resistance rates between secondary and tertiary hospitals ($P>0.05$).

Conclusion: Attention should be paid to bloodstream infections caused by *B. cepacia*, especially elderly patients and patients admitted to the ICU. The difficult treatment characteristics of *B. cepacia* bloodstream infections mean that laboratories and clinicians should pay careful attention to drug resistance to provide a basis for their prevention and empirical treatment.

Keywords: *B. cepacia*, antimicrobial resistance, secondary hospital, tertiary hospital, multicenter investigation

Introduction

Burkholderia cepacia was initially isolated from decaying onion roots by the American plant pathologist Burkholderia in 1950, and was originally called *Pseudomonas cepacia;*[1] however, following developments in gene-sequencing technology, it was finally renamed *B. cepacia* in 1992.[1] *B. cepacia* is a Gram-negative aerobic bacterium that does not ferment lactose and is commonly found in moist soil, water, and plants. It shows good survival in the natural environment, related to the super-mutation ability of the bacterial genotype and phenotype.[2] *B. cepacia* is an opportunistic pathogen that can cause a variety of nosocomial infections, including sepsis, endocarditis, pneumonia, wound infections, abscesses, and conjunctival diseases.[3–5] Contamination of the dialysate, ultrasonic coupling agent, injection water, and catheter are common causes of hospital outbreaks caused by *B. cepacia*.[6] The isolation rate of *B. cepacia* is highest in patients with cystic fibrosis, in whom it can lead to a severe decline in lung function and multi-organ failure.[7]

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Recent rapid developments in invasive diagnosis and treatment technologies, the extended survival of patients with malignant tumors, population aging, and the improved detection abilities of microbiology laboratories in medical institutions have resulted in a rapid increase in the detection rate of *B. cepacia*. According to the latest data from the Chinese bacterial drug resistance monitoring network (http://www.chinets.com/Data/AntibioticDrugFast), *B. cepacia* has become an important source of clinical infections by non-fermenting bacteria, after P*seudomonas aeruginosa, Acinetobacter baumannii* and *Stenotrophomonas maltophilia*.

Bloodstream infections are serious infections caused by bacteria entering the blood for various reasons. Despite the continuous development of anti-infective drugs and the optimization of treatment methods, these infections are still associated with very high mortality.[8] Studies of the infectious disease burden in China in 2019 and bacterial resistance showed that bloodstream infections were the most deadly type of infection, responsible for 521,392 deaths.[9] Most bloodstream infections caused by *B. cepacia* are individual cases, with a mortality rate of 41%–53.8%,[3,10] and their empirical treatment is essential for improving patient prognosis. *B. cepacia* has a broad spectrum of drug resistance in bloodstream infections, and is naturally resistant to aminoglycosides and polymyxins, and often resistant to beta-lactam antibiotics by inducing changes in chromosomally encoded beta-lactamases and penicillin-binding proteins.[11] The most recent Clinical & Laboratory Standards Institute guidelines, published in 2023, only recommend five antibiotics for *B. cepacia* infections, making antibiotic selection very difficult for clinicians. Meanwhile, the high mortality rate of patients with *B. cepacia*-related bloodstream infections and wide variations in drug-resistance rates among regions highlight the need for regular drug-resistance testing. To the best of our knowledge, there have been no retrospective studies of *B. cepacia* bloodstream infections in any Chinese province, and no large-scale studies have been reported in the literature. Hebei is a large province with a geographical area of 188,800 km^2 and a population of 74.48 million people (as of 2021). According to the data released by the National Bureau of Statistics in May 2021, 13.9% of the population in Hebei province is over the age of 65 years, indicating a mildly aging population. However, there is no comprehensive and specific analysis of patients with *B. cepacia* bloodstream infection in the province. We therefore reviewed and analyzed the antimicrobial resistance data for *B. cepacia* strains isolated from bloodstream infections in Hebei province, China, from 2016 to 2021, to provide evidence for drug resistance and epidemiological data on *B. cepacia* strains isolated from bloodstream infections.

Materials and Methods

General Information

Data from the Hebei Provincial Bacterial Resistance Surveillance Network included 349 *B. cepacia* strains isolated from the blood cultures at 83 secondary and tertiary hospitals in Hebei Province, China, from 2016 to 2021. To avoid duplicate statistics, WHONET 5.6 software was used to ensure that only the first strain from each patient was retained. Figure 1 is a map of Hebei Province.

Inclusion and exclusion criteria

The inclusion criteria were isolates from patients with traceable disease information, including sex, department, age and antibiotic sensitivity test. Isolates without complete information were excluded.

Research Methods

After initial identification of all the strains in the laboratory, the isolates were stored in strain-storage tubes at −20°C, and promptly mailed to the Clinical Laboratory Center of Hebei Province. After receipt, all the strains were immediately inoculated into blood agar at 35°C for 18–24 h and identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (bioMerieux, Paris, France). Strains identified as *B. cepacia* were tested for antibiotic sensitivity using a VITEK 2 COMPACT system (bioMerieux). The bacterial solution was prepared to 0.5 McFarland standards, and 145 μL was added to 3 mL of 0.85% normal saline, after which the cards were added to the mixed bacterial suspension. Finally, the reagent rack was placed into the identification instrument and the drug-sensitivity test results were read 18–24 h later. For the disk diffusion method, 0.5 (McFarland, MCF) bacterial suspensions were inoculated into Mueller-Hinton medium and the drug disks were fixed to the plates according to the Institute of Clinical and Laboratory Standardization

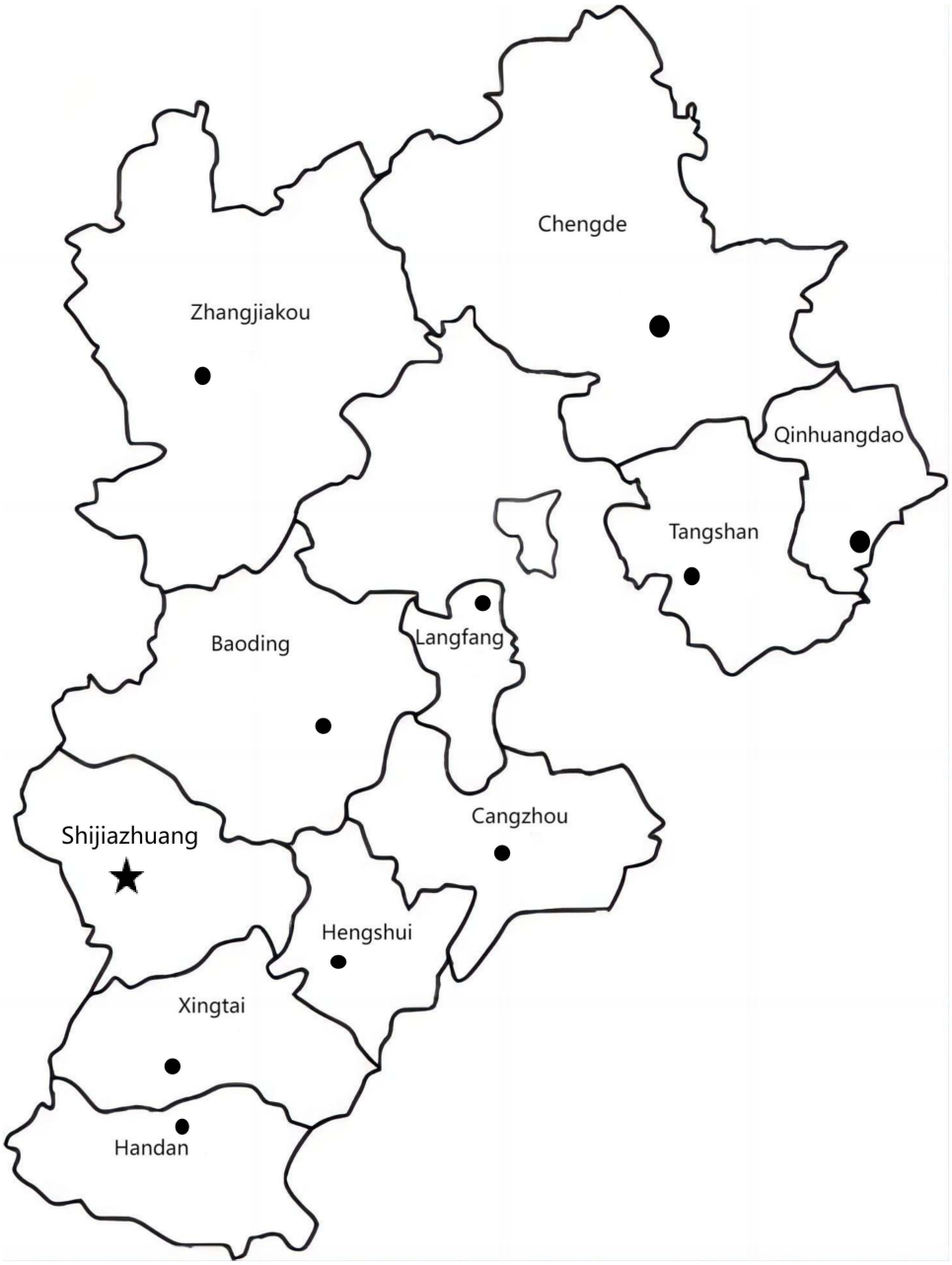

Figure 1 Hebei province map.
Notes: ★: Provincial administrative centre; Hebei Provincial Center for Clinical Laboratories location. ●: Municipal administrative center.

(CLSI), 2022 edition. *Escherichia coli* ATCC25922 and *Pseudomonas aeruginosa* ATCC27853 were used as quality control strains. The antimicrobial susceptibility testing and breakpoint were as recommended by the CLSI (2023).

Statistical Analysis

Data were analyzed using WHONET 5.6 software (World Health Organization, Geneva, Switzerland). Statistical analysis was carried out using SPSS 19.0. Numerical data were analyzed by χ^2 tests, and $P<0.05$ was considered statistically significant.

Results

A total of 349 strains of *B. cepacia* were isolated from blood cultures in Hebei Province, China, from 2016 to 2021. Among these, 67 strains were isolated at secondary hospitals, with a male:female ratio of 2.09:1 (46:22). The equivalent

sex ratio in tertiary hospitals was 1.38:1 (163:118) and the sex ratio in all hospitals in Hebei province was 1.49:1 (209:140). Most strains were isolated from intensive care units (ICUs), accounting for 49.57% (173/349), followed by internal medicine departments, accounting for 22.92% (80/349). The specific data for secondary and tertiary hospitals are shown in Table 1. The age distribution features in hospitals in Hebei province included 201 (57.59%) elderly (>65 years), 67 (19.20%) middle-aged (48–64 years), and 48 (13.75%) young patients (15–47 years), 30 (8.59%) children (28 days to 14 years) and three (0.86%) newborns (<28 days). The detailed information is shown in Table 2. The age distribution was statistically significant (P<0.05).

We first analyzed the resistance rates of *B. cepacia* strains causing bloodstream infections in Hebei province. The resistance rates for levofloxacin, ceftazidime, sulfamethoxazole, meropenem, chloramphenicol, and minocycline were 23.28%, 11.29%, 11.42%, 7.42%, 20%, and 6.59%, respectively.

Regarding *B. cepacia* isolated from secondary hospitals in Hebei province during 2016–2021, the resistance rate for levofloxacin gradually decreased from 2016, except in 2019 (P<0.05). The resistance data for other drugs are shown in Table 3.

Regarding *B. cepacia* isolated from tertiary hospitals in Hebei province during 2016–2021, there was a slight downward trend in levofloxacin resistance from 2016 to 2020, with a sudden increase to 29.2% in 2021, but a resistance rate of 0% in 2018. The resistance rate for sulfamethoxazole also declined steadily during this period (P<0.05). Resistance rates of ceftazidime and meropenem seemed to decrease while resistance to chloramphenicol seemed to increase between 2016 and 2021, but the differences were not significant. The drug-resistance data are shown in Table 4.

Regarding the analysis of drug resistance of *B. cepacia* in all hospitals in Hebei province, we further learned the comparison of drug resistance rates of levofloxacin, ceftazidime, and sulfamethoxazole had statistical significance (P<0.05) and the drug-resistance rates gradually decreased, while the resistance rates of the other three drugs fluctuated and showed no obvious trends (Table 5 and Figure 2).

Table 1 Departmental and Hospital Distribution of B. Cepacia in Hebei Province

Department Classification	Secondary Hospital	Tertiary Hospital	Total Numbers of Hebei Province
	N (%)	N (%)	N (%)
ICU	34 (50.78)	139 (49.29)	173 (49.57)
Medicine	13 (19.40)	67 (23.76)	80 (22.92)
Surgery	7 (10.45)	28 (9.93)	35 (10.03)
Pediatrics	9 (13.43)	18 (6.38)	27 (7.74)
Outpatient	2 (2.99)	15 (5.32)	17 (4.87)
Obstetrics and Gynecology	0 (0)	6 (2.13)	6 (1.72)
Others	2(2.99)	9(3.19)	11 (3.15)
Total	67 (100)	282 (100)	349 (100)

Abbreviation: N, number.

Table 2 Age-Related Distribution of B. Cepacia in Hebei Province

	Newborn (<28 days)	Children (28 days–14 years)	Young People (15–47 years)	Middle-aged People (48–64 years)	Older People (>65 years)	P value
Secondary hospital	1	8	7	14	37	<0.001
Tertiary hospital	2	22	41	53	164	<0.001
Total numbers	3	30	48	67	201	<0.001

Table 3 Drug Resistance of B. Cepacia in Secondary Hospitals in Hebei Province

Drug	Antibiotic Class	2016		2017		2018		2019		2020		2021		P value
		N	R(%)	N	R(%)	N	R(%)	N	R(%)	N	R(%)	N	R(%)	
Lev (N=67)	Fluoroquinolones	9	77.8	14	28.6	15	20	5	80	14	14.3	10	10	0.002
Caz (N=68)	Cephalosporin	10	20	14	7	15	40	5	0	14	0	10	0	0.014
Sxt (N=60)	Compound sulfanilamide	9	22.2	12	16.7	15	26.7	5	0	10	0	9	0	0.28
Mem (N=64)	Carbapenems	7	14.7	14	14.3	15	13.3	5	0	14	0	9	0	0.586
Cl (N=23)	Chloramphenicol	–	–	3	33.3	12	41.7	–	–	5	20	3	33.3	0.909
Mh (N=10)	Tetracycline	–	–	–	–	–	–	–	–	5	0	5	20	1.000

Abbreviations: N, number of strains; R, drug-resistance rate; -, no data; Lev, levofloxacin; Caz, ceftazidime; Sxt, sulfamethoxazole; Mem, meropenem; Cl, chloramphenicol-(Chloramphenicol); Mh, minocycline.

Table 4 Drug Resistance of B. Cepacia in Tertiary Hospitals in Hebei Province

Drug Name	Antibiotic Class	2016		2017		2018		2019		2020		2021		P value
		N	R(%)	N	R(%)	N	R(%)	N	R(%)	N	R(%)	N	R(%)	
Lev (N=279)	Fluoroquinolones	35	28.6	35	34.3	21	0	58	17.2	58	13.8	72	29.2	0.005
Caz (N=291)	Cephalosporin	39	20.5	40	22.5	22	4.5	58	10.3	59	5.1	73	9.6	0.053
Sxt (N=251)	Compound sulfanilamide	37	13.5	35	25.7	18	22.2	49	6.1	42	9.5	70	4.3	0.012
Mem (N=260)	Carbapenems	39	7.7	36	13.9	22	9.1	51	5.9	50	4	62	8.1	0.656
Cl (N=86)	Chloramphenicol	9	0	11	18.2	9	22.2	28	10.7	6	16.7	23	21.7	0.634
Mh (N=92)	Tetracycline	10	0	8	12.5	4	25	22	9.1	19	5.3	29	3.4	0.408

Abbreviations: N, number of strains; R, drug-resistance rate; -, no data; Lev, levofloxacin; Caz, ceftazidime; Sxt, sulfamethoxazole; Mem; meropenem; Cl, chloramphenicol; Mh, minocycline.

Table 5 Drug Resistance of B. Cepacia in All Hospitals in Hebei Province

Drug Name	Antibiotic Class	2016		2017		2018		2019		2020		2021		P value
		N	R(%)	N	R(%)	N	R(%)	N	R(%)	N	R(%)	N	R(%)	
Lev (N=346)	Fluoroquinolones	44	38.6	49	32.7	36	8.3	63	22.2	72	13.9	82	26.8	0.005
Caz (N=359)	Cephalosporin	49	20.4	54	27.3	37	18.9	63	9.5	73	4.1	83	8.4	0.019
Sxt (N=311)	Compound sulfanilamide	46	15.2	47	23.4	33	24.2	54	5.6	52	7.7	79	3.8	0.001
Mem (N=324)	Carbapenems	46	8.7	50	14	37	10.8	56	5.4	64	3.1	71	7	0.325
Cl (N=109)	Chloramphenicol	9	0	14	21.4	21	33.3	28	10.7	11	18.2	26	23.7	0.277
Mh (N=102)	Tetracycline	10	0	8	12.5	4	25	22	9.1	24	4.2	34	5.9	0.484

Abbreviations: N, number of strains; R, drug-resistance rate; -, no data; Lev, levofloxacin; Caz, ceftazidime; Sxt, sulfamethoxazole; Mem; meropenem; Cl, chloramphenicol; Mh, minocycline.

A comparison of the 6-year data between secondary and tertiary hospitals showed no significant differences ($P > 0.05$). The drug-resistance rates were 30.3% vs 21.6% for levofloxacin and 34.8% vs 16.04% for chloramphenicol. Other results are shown in Table 6.

We compared drug resistance among the departments with the top three isolates. Among these, levofloxacin resistance was significantly higher in ICU isolates compared with medical and surgical isolates (31.5% vs 16.2% vs 8.1%) ($P<0.05$). The resistance rates for co-trimoxazole, meropenem, and minocycline were lower in ICU isolates compared with the other two departments, but the difference was not significant. The specific values are shown in Table 7.

Discussion

A total of 349 *B. cepacia* strains isolated from bloodstream infection were analyzed in this study. Significantly more strains were isolated from tertiary compared with secondary hospitals (282/67). This difference may have been due to the

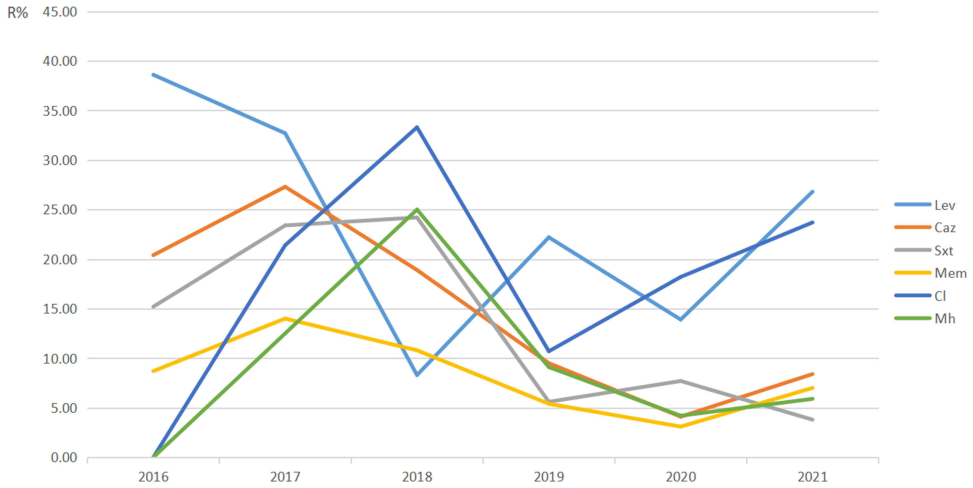

Figure 2 Drug resistance of *B. cepacia* in all hospitals in Hebei province.
Note: R%, drug resistance rate.

greater number of beds in tertiary hospitals than in secondary hospitals in Hebei province, and the significantly larger numbers of patients with severe infections. Alternatively, the discrepancy may have been due to differences in laboratory testing levels. Further analyses are needed to determine the specific reason. We analyzed the drug-resistance rates in the different types of hospitals and found no significant differences for the six studied antibiotics. Notably however, the resistance rate for levofloxacin in tertiary hospitals fluctuated greatly from 2016 to 2021, and the rate in 2018 was 0%, which was significantly different from the resistance rates in other years. In contrast to our results, El et al[9] and Chang

Table 6 Drug-Resistance Rates of B. Cepacia in Secondary and Tertiary Hospitals in Hebei Province

Drug Name	Antibiotic Class	Secondary hospitals		Tertiary hospitals		P value
		N	R(%)	N	R(%)	
Lev (N=346)	Fluoroquinolones	67	30.3	279	21.6	0.184
Caz (N=359)	Cephalosporin	68	13.4	291	10.8	0.698
Sxt (N=311)	Compound sulfanilamide	60	13.6	251	10.9	0.741
Mem (N=324)	Carbapenems	64	7.9	260	7.3	0.793
Cl (N=109)	Chloramphenicol	23	34.8	86	16.0	0.074
Mh (N=102)	Tetracycline	10	3.8	92	6.9	1

Abbreviations: N, number of strains; R, drug-resistance rate; -, no data; Lev, levofloxacin; Caz, ceftazidime; Sxt, sulfamethoxazole; Mem; meropenem; Cl, chloramphenicol; Mh, minocycline.

Table 7 Drug Resistance of B. Cepacia in Different Departments

Drug Name	Antibiotic Class	ICU		Medicine		Surgery		P value
		N	R(%)	N	R(%)	N	R(%)	
Lev	Fluoroquinolones	168	31.5	68	16.2	37	8.1	0.003
Caz	Cephalosporin	170	10.6	70	15.7	39	5.1	0.229
Sxt	Compound sulfanilamide	149	9.2	58	17.2	34	11.8	0.289
Mem	Carbapenems	150	6	64	12.5	34	8.8	0.277
Cl	Chloramphenicol	50	20	23	30.4	11	18.2	0.58
Mh	Tetracycline	49	4.1	27	11.1	10	10	0.485

Abbreviations: N, number of strains; R, drug-resistance rate; -, no data; Lev, levofloxacin; Caz, ceftazidime; Sxt, sulfamethoxazole; Mem; meropenem; Cl, chloramphenicol; Mh, minocycline.

et al[1,12] found resistance rates of *B. cepacia* to levofloxacin in bloodstream infections of 12%–74.9%, while we found that all 21 B. cepacia isolates from tertiary hospitals in 2018, including isolates from 15 different tertiary hospitals, were susceptible to levofloxacin. To clarify the reasons for this phenomenon, we telephoned the heads of these laboratories and found that none of the patients had received quinolone antibiotics before developing their bloodstream infections, which may have contributed to the low resistance to levofloxacin.

Severe underlying diseases, old age, prolonged bed rest, multiple organ failure, immune damage, prolonged antibiotic exposure, immunosuppressive agents, and invasive surgery are potential risk factors for bloodstream infections caused by *B. cepacia*.[3,6,13–15] ICU patients are at particularly high risk of *B. cepacia* bloodstream infection, and most strains were accordingly isolated from ICUs in the current study (173/49.57%), consistent with studies from other regions.[3,6,16] The route by which *B. cepacia* enters the blood system to cause infection is not fully understood. It may enter the blood via the urinary tract, respiratory tract, or damaged intestinal mucosa. It is therefore necessary to strengthen nursing care and regulate the intestinal flora in ICU patients, in addition to treating their underlying disease, to reduce the risk of *B. cepacia* blood infection.

B. cepacia-related bloodstream infections are difficult to treat, and the mortality rate varies from 16%–53.8%.[3,12,17,18] This may be related to the limited choice of clinical drugs due to the specific drug-resistance phenotype. *B. cepacia* is naturally resistant to most β-lactam antibiotics, as well as aminoglycosides and colistin antibiotics. Meropenem, levofloxacin, and sulfamethoxazole are the first-line drugs for the clinical treatment of infections caused by *B. cepacia*. We analyzed the six antibiotics recommended by CLSI and found that the resistance rate to sulfamethoxazole was 11.42%, which was higher than in Taiwan[1] and the United States[12] (5% and 6%, respectively). This may be because the patients included in this study were all critically ill patients with bloodstream infections and the use of antibiotics was thus more advanced, resulting in an increase in the resistance rate to sulfamethoxazole. The resistance mechanism of *B. cepacia* to sulfamethoxazole involves high expression of efflux pump genes such as RND3 and RND4[19,20] and mutation of antibiotic target genes.[21] Sulfamethoxazole is one of the most commonly used antibiotics for the treatment of *B. cepacia*, and an increase in resistance will result in the failure of most clinical empirical treatments, thus increasing patients' physical and mental stress. The main mechanism of *B. cepacia* resistance to meropenem involves overexpression of class A β-lactamase caused by mutations in the *penA* gene located on chromosome 2, and mutation or modification of this gene by key amino acid residues reduces the susceptibility of *B. cepacia* to cephalosporins and meropenem.[22,23] Our research showed that the resistance rate to meropenem was 7.42%, which was lower than the 22.2–52% reported in other regions,[17,18,24] suggesting that meropenem should be considered for the empirical treatment of bloodstream infections caused by *B. cepacia* in Hebei province, China. Comparing the bacterial resistance rates among departments showed that the rate of levofloxacin-resistant isolates was significantly higher in the ICU compared with the medical and surgical departments ($P<0.05$). Further inquiries revealed that the frequency of fluoroquinolone use in the ICU of the hospital where one researcher worked was very high; however, we could not obtain information on the antibiotic use situation for every hospital in Hebei Province, including for each ICU, and we were therefore unable to determine if the levofloxacin-resistance rate in the ICU in Hebei Province was related to the excessive use of fluoroquinolones. We speculated that this phenomenon may have occurred because ICU patients frequently have low immunity, undergo invasive operations, and use many, high-strength antibiotics, and the ICU environment in terms of multiresistant bacteria is complex and diverse, leading to bacterial resistance as a result of cross transmission. The Sanford Guidelines for Antimicrobial Therapy, 46th edition,[25] recommend cotrimoxazole as the preferred drug and chloramphenicol as a candidate drug for the treatment of patients with cystic pulmonary fibrosis caused by B. cepacia, and clearly points out the need for culture and drug sensitivity results to guide treatment. However, these guidelines did not provide any guidance for bloodstream infections caused by *B. cepacia*. The current study showed that ceftazidime and meropenem had relatively low resistance rates and high drug safety, and could thus be used as empirical drugs for bloodstream infections caused by *B. cepacia*. However, timely culture and drug sensitivity results are an indispensable basis for treatment.

This study had some limitations. The hospitals included in this study were all members of the Hebei Provincial Bacterial Resistance Surveillance Network, which included various specialized hospitals as well as general hospitals, which may have led to a slight bias in the drug-resistance data. In addition, we did not collect further case information for patients with *B. cepacia* bloodstream infections. Further studies are therefore needed to collect strains and patients' case information simultaneously from large general hospitals, to obtain more accurate epidemiological and drug-resistance data.

In summary, aging of the population and stay in the ICU have led to an increase in the incidence of bloodstream infections caused by *B. cepacia*. Ceftazidime and meropenem may offer good empirical treatment, with low drug resistance rates; however, bacterial culture and drug sensitivity tests are essential to guide patient treatment. Notably, information on bloodstream infections caused by *B. cepacia* is scarce due to its high fatality rate, indicating the need to strengthen the surveillance of resistance to *B. cepacia*.

Ethical Approval Statement

Ethical approval was obtained from the Institutional Review Board of the Affiliated Hospital of Chengde Medical University. All the clinical samples were part of the routine hospital laboratory procedure and there was no additional burden on patients. We obtained verbal consent from all patients or their guardians regarding, and strict confidentiality was maintained for all patient information. We declare that our study complied with the Declaration of Helsinki.

Author Contributions

All authors made significant contributions to the work reported, in terms of the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed to submission to the journal; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests in this work.

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