Infection and Drug Resistance

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ORIGINAL RESEARCH

Epidemiologic analysis and control strategy of *Klebsiella pneumoniae* infection in intensive care units in a teaching hospital of People's Republic of China

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Chunrui Wang[1]
Zhe Yuan[1]
Wenxiang Huang[1]
Li Yan[2]
Jun Tang[3]
Cheng-wei Liu[3]

[1]Department of Infectious Diseases, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, People's Republic of China; [2]Department of Laboratory Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, People's Republic of China; [3]Department of Infectious Diseases, Key Laboratory of Infectious and Parasitic Diseases in Chongqing, Chongqing 400016, People's Republic of China

Background: *Klebsiella pneumoniae* (KP) is the most common pathogen isolated in intensive care units (ICUs) and the most frequently encountered carbapenemase-producing Enterobacteriaceae. Increasing antimicrobial drug resistance, especially in carbapenem-resistant KP (CRKP), can limit the choice of antibiotics used for the treatment of infectious diseases and further poses a negative impact on patient outcome. However, the reason behind this increasing resistance is not well known.

Patients and methods: A retrospective analysis of laboratory records and clinical cases of KP infection in the ICUs of a hospital from January 2013 to December 2017 was conducted. The disk diffusion method and double-paper synergy test were used to test drug sensitivity for extended-spectrum β-lactamase (ESBL) detection. WHONET5.6 and SPSS 21.0 software were used for statistical analysis.

Results: A total of 64.8% (570/847) of patients with KP infection were older than 60 years. The lower respiratory tract was the main infection site, accounting for 70.84% (600/847); the highest rate of ICU admission was for neurosurgery, accounting for 28.69% (243/847). Some 444 multidrug-resistant KP strains were detected, including 69 CRKP and 299 ESBL-producing strains. In the past 5 years, the resistance rate of detected strains to common antibiotics increased to various degrees, particularly carbapenem-resistant strains which increased from 4.76% (9/189) in 2013 to 16.00% (28/175) in 2017. All carbapenem-resistant isolates were resistant to β-lactam antibiotics, and no isolates were resistant to tigecycline.

Conclusion: CRKP and ESBLKP prevalence and resistance rates gradually increased in our ICUs in the past 5 years. The reasons for this are manifold. Regular surveillance of resistance, rational use of antibiotics, and other effective infection control measures need to be strengthened to slow down the production of multidrug-resistant bacteria and prevent their spread in ICU settings.

Keywords: *Klebsiella pneumoniae*, antibiotic resistance, carbapenem resistance, intensive care units

Correspondence: Zhe Yuan
Department of Infectious Diseases, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, People's Republic of China
Tel +86 23 8901 2513
Fax +86 23 8901 2513
Email yuanzhe-1030@163.com

Introduction

In recent years, *Klebsiella* spp. have been among the most common pathogens isolated in intensive care units (ICUs), and *Klebsiella pneumoniae* (KP) is the most frequently encountered carbapenemase-producing Enterobacteriaceae (CRE).[1] The US Centers for Disease Control and Prevention (CDC) bacterial resistance threat report has classified it as having a serious drug resistance level. KP belongs to the Enterobacteriaceae

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Klebsiella, a facultative anaerobic bacterium that is a common pathogen in hospitals. Under the selective pressure generated by the application of broad-spectrum antibacterial drugs, multidrug-resistant KP (MDRKP) strains, including carbapenem-resistant KP (CRKP) and extended-spectrum β-lactamase KP (ESBLKP), strains are increasing,[2] which accounts for substantial increases in illness and death.[1] Few antimicrobial therapy options exist for infections caused by CRKP.[3]

ICUs have been described as a factory for creating, disseminating, and amplifying antimicrobial resistance due to their extremely vulnerable population of critically ill patients, heavy use of invasive procedures, and the frequent application of antimicrobials. ICU stay itself is an independent risk factor for CRKP infection.[4] KP resistance has become a serious problem of clinical concern. As a consequence, epidemiologic and drug resistance analysis of ICU KP is important for controlling nosocomial infections and facilitating the choice and the efficacy of empirical therapy. Additionally, this knowledge is important for the design and the implementation of interventions aiming to prevent the spread of antimicrobial resistance.[5] This study focused on two main points. First, it describes the epidemiological characteristics and drug resistance of KP infection in patients in an ICU setting. Second, it discusses the reasons behind this resistance, including the high extended-spectrum β-lactamase (ESBL) rate and increased CRKP detection.

Patients and methods

Study design and population

We retrospectively analyzed laboratory records and clinical cases from January 2013 to December 2017 in the First Affiliated Hospital of Chongqing Medical University, a tertiary university hospital with 3,200 beds in Chongqing, southwest China. Looking up at all KP isolates in ICUs in the hospital in 5 years, and excluding the same isolate from the same patient, patients with the first isolate that was defined as causing infection were included in this study. When two or more kinds of bacteria were cultured in the infected site, the KP infection strain was selected, excluding patients with other concomitant infections. Epidemiological characteristics and drug resistance and treatment outcomes were retrieved from the medical records by two experienced medical doctors. The information about the patient demographics (age, gender), comorbidities (diabetes mellitus, hypertension, coronary atherosclerotic heart disease, cerebrovascular accident, renal failure, heart failure, malignant tumor), and source of infection was collected. Additionally, the general state of patients during KP infection was assessed, such as septic shock and multiple organ dysfunction.

Bacterial identification and drug sensitivity test

Bacterial cultures were processed in the clinical microbiology laboratory. Isolates were identified using the VITEK 2 Compact system or the VITEK MS system (bioMérieux, Lyon, France), and antimicrobial susceptibilities were determined in vitro using a VITEK 2 Compact AST-GN13 card (bioMérieux). The carbapenem-resistant isolates were confirmed manually by the standard broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The CLSI 2014 standard judges resistance, intermediation, and sensitivity.[6] *Escherichia coli* American Type Culture Collection 25922 was used as a quality control strain during the antimicrobial susceptibility testing. Additionally, VITEK 2 compact AST-GN13 cards were used to test the antibiotic susceptibilities of all isolates to ampicillin, ceftazidime, ceftriaxone, cefepime, cefoxitin, cefotetan, ampicillin–sulbactam, piperacillin–tazobactam, cefoperazone–sulbactam, ertapenem, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin, minocycline, and tigecycline. ESBL production was measured by the double-disk synergy test and the disk diffusion method performed on Mueller–Hinton agar supplemented with cloxacillin (250 mg/L).[7]

MDRKP, pan-resistant KP, and CRKP

A strain was judged to be MDRKP if it was nonsusceptible to ≥1 agent in ≥3 antimicrobial categories (including third-generation cephalosporin, aminoglycoside, fluoroquinolone, β-lactamase inhibitors, carbapenems, cephamycins, glycylcyclines, phosphonic acids, polymyxins, and tetracyclines). Extensively drug-resistant strain was nonsusceptible to ≥1 agent in all, but ≤2 categories. Pandrug-resistant strains were nonsusceptible to all antimicrobial agents listed. CRKP strains were resistant to at least one of the carbapenems, including imipenem, meropenem, and ertapenem.[8]

Data collection and definition

Inclusion criteria

Positive pathogen culture in sterile sites such as cerebrospinal fluid, bile, bloodstream, and marrow was considered to show an infectious pathogen. If pathogens were cultivated from a nonsterile site, we distinguished between colonization and infection by estimating the patient's clinical infection symptoms, and laboratory examination including white blood cell count (WBC), neutrophil percentage (NEU), procalcitonin

(PCT), C-reactive protein (CRP), imaging basis (X-ray, computed tomography (CT) ultrasound examination), qualified specimen (sputum culture ≥10^7 cfu/ml; bronchoalveolar lavage fluid culture ≥ 10^5 cfu/ml; urine culture count ≥ 10^5 cells/ml), urine culture count ≥10^5 cells/mL). In addition, the proper time point and site were relative to positive KP culture (retaining specimens before using antibiotics, collecting the first sputum from the deep part of the lung in the early morning, keeping clean middle urine, blood culture in patients with chills).

Definition of infection

Pneumonia: the fifth point plus one of the items 1) cough with purulent sputum; 2) temperature ≥37.3°C; 3) pulmonary physical signs or moist rales; 4) WBC >10×10^9/L; 5) chest X-ray or chest CT changes. Acute pyelonephritis: fever or backache, with WBC ≥10×10^{12}/L or CRP ≥10 mg/L, accompanied by one of the following urine test indicators: 1) urine routine: WBC >5/high-power field (HP), erythrocytes >3/HP, or clean middle urine WBC >10/HP; 2) urine culture ≥10^5/L. Bloodstream infection: temperature >38°C or <36°C, with chills or combined with one of the following conditions: 1) invasion portals or migration lesions; 2) systemic infection symptoms; 3) rash or bleeding, hepatosplenomegaly, neutrophil increase with left nucleus, and no other explanation; 4) SBP <90 mmHg or decreasing to 40 mmHg below the original level; 5) positive blood culture. Incision infection: 1) the incision was split with pus and pain, temperature ≥38°C; 2) inflammation, swelling, and pain around the incision; pus could be drained from the deep site; 3) secretion culture was positive. Central venous catheter-related infections: one of the following manifestations: 1) puncture site inflammation or with pus; 2) diffuse erythema at the subcutaneous portion of the catheter; 3) fever and no other explanations for the symptoms. Central venous catheter-related infections used the definitions of the US CDC.[9] Relevant demographics and clinical data of the included patients were extracted from the medical records or directly from physicians if needed. The following parameters were recorded: 1) demographics: length of stay (days), age, gender; 2) chronic diseases: diabetes, hypertension, coronary atherosclerotic heart disease, cerebrovascular accident, renal failure, heart failure, malignant tumor; 3) clinical data: fever, WBC >4.0×10^9/L, NEU >75%, PCT >0.05 ng/mL, CRP >10 mg/L; 4) presentation with septic shock or multiple organ dysfunction; 5) source of infection included pneumonia, acute pyelonephritis, bloodstream infection, central venous catheter-related infection, and incision infection (definitions of infection are provided above); 6) specimen source, including sputum, urine, bloodstream, bronchoalveolar lavage fluids, and sterile site (cerebrospinal fluid and bile). Patients ≥60 years old were defined as elderly. Fever was defined as mouth temperature >37.0°C.

Statistical analysis

Statistical analyses were conducted with the statistical package SPSS for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA). The results are listed as the mean (± SD) and median (first–third quartile) for continuous variables with normal and skewed distributions, respectively. Continuous variables were compared using Student's unpaired *t*-test or the Mann–Whitney *U* test. Categorical variables were compared by Pearson's chi-squared test or Fisher's exact test, as appropriate. Associations were given as ORs with a 95% CI. In all analyses, $P<0.05$ was considered significant.

Ethics

The study was approved by the Chongqing Medical University Institutional Review Board and Biomedical Ethics Committee. All patient data were analyzed in anonymity. This retrospective study did not directly interfere with any patient or show the patient's name, medical record number, or other personal information. Moreover, there was no adverse effect on the rights of patients; therefore, the ethics committee waived the need for written informed consent provided by participants.

Results

Strain characteristics and detection rate

According to the inclusion criteria, 847 infected isolates of KP were diagnosed in 2013–2017, including 539 males and 308 females, with an average age of (68±14) years, and those ≥60 years old accounted for 67.30% (570/847). A total of 90% of patients had invasive procedures such as deep vein catheterization, tracheal intubation, gastrointestinal decompression, and long-term application of generally broad-spectrum antibiotics. A total of 847 infected strains were diagnosed. MDRKP strains accounted for 52.42% (444/847), of which ESBL strains were 36.36% (299/847). The detection rates of ESBL strains in 2013–2017 were 33.33% (63/189), 32.67% (49/150), 37.43% (64/171), 33.95% (55/162), and 38.86% (68/175), respectively. CRKP strains accounted for 8.15% (69/847), and the detection rates from 2013 to 2017 were 4.76 (9/189), 4.67% (7/150), 2.92% (5/171), 12.35% (20/162), and 16.00% (28/175), respectively. The difference was statistically significant ($P<0.005$), as shown in Table 1.

Table 1 Demographic and clinical characteristics of patients with KP infection in ICU in 2013–2017, n (%)

Clinical characteristics	Non-ESBLs/CRKP (n=479)	ESBLKP (n=299)	CRKP (n=69)	KP (N=847)
Length of stay (days)	18.3±16.5	28.7±24.1	34.2±26.5	26.2±22.6
Age (years) ≥60	319 (66.60%)	197 (65.88%)	54 (78.26%)	570 (64.80%)
Male gender	286 (59.71%)	203 (67.89%)	50 (72.46%)	539 (63.63%)
Chronic diseases				
Diabetes	214 (44.68%)	137 (45.82%)	30 (43.47%)	381 (44.98%)
Hypertension	96 (20.04%)	210 (70.23%)	24 (34.78%)	330 (38.96%)
CHD	63 (13.15%)	53 (17.73%)	19 (27.54%)	135 (15.94%)
Cerebrovascular accident	15 (3.13%)	126 (42.14%)	15 (21.74%)	156 (18.42%)
Renal failure	15 (3.13%)	53 (17.73%)	13 (18.84%)	81 (9.56%)
Heart failure	48 (10.02%)	62 (20.74%)	17 (24.64%)	127 (14.99%)
Malignant tumor	82 (17.12%)	48 (16.05%)	8 (11.59%)	138 (16.29%)
Clinical symptoms				
Fever	479 (100.00%)	299 (100.00%)	69 (100.00%)	847 (100.00%)
WBC >4.0×10⁹/L	440 (91.86%)	245 (81.94%)	60 (86.95%)	745 (87.95%)
NEU >75%	409 (85.39%)	244 (81.60%)	58 (84.06%)	711 (83.94%)
PCT >4.0×10⁹/L	464 (96.87%)	283 (94.65%)	64 (92.75%)	811 (95.75%)
CRP >10 mg/L	479 (100.00%)	299 (100.00%)	69 (100.00%)	847 (100.00%)
Outcome				
Septic shock	177 (36.95%)	182 (60.87%)	52 (75.36%)	411 (48.52%)
MOD	132 (27.56%)	143 (47.83%)	46 (66.67%)	321 (37.89%)
Source of infection				
Pneumonia	317 (66.18%)	215 (71.90%)	52 (75.36%)	584 (68.94%)
Acute pyelonephritis	88 (18.37%)	28 (9.36%)	12 (17.40%)	128 (15.11%)
Bloodstream infection	45 (9.39%)	17 (5.69%)	6 (8.70%)	68 (8.03%)
Central venous catheter related	12 (2.51%)	28 (9.36%)	8 (11.60%)	48 (5.67%)
Incision infection	17 (3.55%)	15 (5.02%)	5 (7.25%)	37 (4.37%)
Specimen type				
Sputum	328 (68.48)	210 (70.23%)	46 (66.67%)	584 (70.84)
Urine	73 (15.24)	45 (15.05)	10 (14.49)	128 (6.26)
Bloodstream	34 (5.0)	28 (9.36)	6 (8.69)	68 (5.79)
Bronchoalveolar lavage fluids	16 (3.34)	11 (3.67)	3 (4.34)	30 (3.54)
Sterile site[a]	16 (3.34)	10 (3.34)	2 (2.89)	28 (3.30)

Note: [a]Sterile site included cerebrospinal fluid and bile.

Abbreviations: CHD, coronary atherosclerotic heart disease; CRKP, carbapenem-resistant KP; CRP, C-reactive protein; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; KP, *Klebsiella pneumoniae*; MOD, multiple organ dysfunction; NEU, neutrophil percentage; PCT, procalcitonin; WBC, white blood cell count.

Strain source and distribution in various departments

In the 847 strains, the sputum distribution rate was the highest at 68.94% (584/847), followed by urine at 15.11% (128/847) and blood at 8.03% (68/847). Five ICUs with 110 beds in our hospital were included in this article, of which comprehensive ICU had 30 beds. The Neurology, Neurosurgery, Thoracic surgery, and Respiratory Medicine ICUs had 20 beds each. The Neurosurgical ICU had the highest proportion at 28.69% (243/847), followed by the Neurology ICU at 26.92% (228/847) and the Respiratory Medicine ICU at 18.89% (160/847).

Drug resistance analysis of KP to common antibiotics

KP resistance to common antibiotics

As shown in Table 2, all isolates were resistant to ampicillin, and no isolates were resistant to tigecycline. The resistance rate to ceftriaxone, ampicillin/sulbactams, aminoglycosides, ciprofloxacin, and minocycline was relatively stable and to other antibiotics increased to different degrees. Among β-lactam drugs, the proportion of isolates that were resistant to ceftriaxone or ampicillin/sulbactams was high: 44.4% or 40.5% of the isolates showed no sensitivity to ceftriaxone or ampicillin/sulbactams, respectively. Low resistance rates to cefotetan,

carbapenem antibiotics, and piperacillin/tazobactam were found (7.0%, 10.4%, and 10.3%, respectively). For aminoglycosides, the resistance rate to gentamicin (31.3%) was higher than that to amikacin (10.9%). Some 24.3% and 30.5% of the isolates were resistant to ciprofloxacin and minocycline, respectively.

ESBL-producing KP resistance to common antibiotics

As shown in Table 3, almost all ESBL strains were resistant to ampicillin and no isolates were resistant to tigecycline. The resistance rates to ceftriaxone, cephamycin, ampicillin, gentamicin, and minocycline remained relatively stable. The resistance rates to other β-lactam antibiotics increased to varying degrees. There was a downward trend for amikacin and ciprofloxacin. The proportion of isolates that were not sensitive to cephalosporins was relatively high: 61.0% and 53.1% of the isolates showed no sensitivity to ceftazidime and cefepime, respectively. For cephamycin, other enzyme inhibitors, excluding ampicillin/sulbactams, and amikacin, ESBLKP maintained a low resistance rate (19.9%, 18.6%,

Table 2 Resistance rates of 847 *Klebsiella pneumoniae* strains to antimicrobial agents (%)

Antimicrobial agent	2013 (n=189)	2014 (n=150)	2015 (n=171)	2016 (n=162)	2017 (n=175)	2013–2017 (N=847)
Ampicillin	100.0	100.0	100.0	100.0	100.0	100.0
Ceftazidime	25.9	26.0	29.2	30.6	28.6	28.1
Ceftriaxone	41.3	40.7	41.5	47.8	50.6	44.4
Cefepime	14.1	14.0	19.6	25.7	32.3	21.2
Cefoxitin	14.4	15.2	16.5	24.7	33.7	25.1
Cefotetan	2.7	2.7	2.4	12.4	14.9	7.0
Ampicillin–sulbactam	50.3	50.7	46.8	53.4	52.0	40.5
Piperacillin–tazobactam	4.8	6.0	6.6	16.8	18.1	10.4
Cefoperazone–sulbactam	3.1	6.6	9.2	18.8	20.7	15.4
Ertapenem	5.4	4.8	3.0	12.6	16.2	8.4
Imipenem	2.1	2.7	2.9	11.8	16.0	7.1
Meropenem	0.0	0.0	3.1	11.9	16.2	10.3
Amikacin	12.3	11.5	4.9	13.6	12.6	10.9
Gentamicin	30.2	28.0	26.9	36.7	34.9	31.3
Ciprofloxacin	25.4	26.7	23.4	24.8	21.7	24.3
Minocycline	27.0	26.6	33.1	28.5	30.0	30.5
Tigecycline	0.0	0.0	0.0	0.0	0.0	0.0

Table 3 Resistance rate of 299 ESBL-producing *Klebsiella pneumoniae* strains to antimicrobial agents (%)

Antimicrobial agent	2013 (n=63)	2014 (n=49)	2015 (n=64)	2016 (n=55)	2017 (n=68)	2013–2017 (n=299)
Ceftazidime	50.8	55.1	59.7	65	74	61
Ceftriaxone	96.8	95.9	100	98.2	98.5	98
Cefepime	46	48.1	56.2	60	64.7	53.1
Cefoxitin	15.7	16.8	21	18.9	19.7	19,9
Cefotetan	1.6	2	0	0	0	0.7
Ampicillin–sulbactam	95.2	93.9	96.9	90.9	94.1	94.3
Piperacillin–tazobactam	7.9	8.2	11.1	12.7	14.7	11.1
Cefoperazone–sulbactam	0	0	14.5	20.4	22.7	18.6
Ertapenem	0	0	0	0	0	0
Imipenem	0	0	0	0	0	0
Meropenem	0	0	0	0	0	0
Amikacin	23.3	21.3	11.1	5.8	11.7	14.5
Gentamicin	52.4	51	62.5	61.8	58.8	57.5
Ciprofloxacin	47.6	46.9	48.4	29	30.9	40.5
Minocycline	55.9	55	56.5	56.6	56.9	56.7
Tigecycline	0	0	0	0	0	0

Abbreviation: ESBL, extended-spectrum β-lactamase.

and 14.5%, respectively); 40.5% and 56.7% of the isolates were resistant to ciprofloxacin and minocycline, respectively.

CRKP resistance to common antimicrobial drugs

In the past 5 years, 69 CRKP strains and 47 pan-resistant strains were isolated in our ICUs. All isolates were resistant to β-lactam antibiotics, and no isolates were resistant to tigecycline. The resistance rates were 55.6%, 42.9%, 9%, 90%, and 85.7% for amikacin; 77.8%, 85.7%, 20.0%, 90.0%, and 89.3% for gentamicin; 88.9%, 100.0%, 80.0%, 90.0%, and 89.3% for ciprofloxacin; and 22.2%, 14.3%, 60.0%, 15.0%, and 21.4% for minocycline in 2013, 2014, 2015, 2016, and 2017, respectively.

Discussion

To our knowledge, this is the first study in southwest of People's Republic of China to evaluate the clinical characteristics and evolution of antibiotic resistance of CRKP infection in an ICU setting. In this study, we assessed the epidemiology characteristics of KP infection in our ICUs. Our analysis revealed that elderly patients over 60 years old were susceptible to KP infection in the ICU, and most of them had invasive devices and long-term application of generally broad-spectrum antibiotics. Reported risk factors for infection with ESBL are prior use of antimicrobials, ICU stay, indwelling devices, increased illness severity, prolonged hospitalization, emergency intra-abdominal surgery, mechanical ventilation, and residence in nursing homes.[10,11] Our research shows that patients with coma or poor consciousness or without spontaneous respiration were under high risk of infection.

ESBLKP has become a critical issue worldwide, and Asia is no exception.[12] In People's Republic of China, the ESBL-positive rate in KP was between 37.6% and 30.1% from 2011 to 2014.[13] In this research, we found ESBL-positive strain detection rates that ranged from 33.33% in 2013 to 38.86% in 2017. Approximately 61% of ESBLKP strains were resistant to ceftazidime, and >95% were resistant to ceftriaxone, which could be related to the ESBL genotype and use of antibiotics in our hospital. In the past 10 years, CTX-M, especially CTX-M-3 and CTX-M-14 types, accounted for >70% of all genotypes in People's Republic of China, which has high hydrolysis activity to cefotaxime but weak hydrolysis ability to ceftazidime. In addition, the third-generation cephalosporins used in North America are mainly ceftazidime, while ceftriaxone is used commonly in People's Republic of China.[14] The CTX-M type of ESBLKP that decomposes antibacterial drugs is different from the SHV type and TEM type, and there are also differences in antibiotic selection for treatment. It is necessary to strengthen the research on the origin, transmission, and treatment of CTX-M ESBL in People's Republic of China.[15] The increasing prevalence of ESBLKP is contributing to the increased consumption of carbapenems and leading to further increased carbapenem resistance rates in ICUs.

The China Antimicrobial Surveillance Network report in 2017 showed that the resistance rate of CRKP had increased rapidly from 6.4% in 2014 to 9.0% in 2017. The highest detection rate was 26.9% in some provinces. Detection rates of CRKP in the elderly, children, and adults were 10.2%, 9.1%, and 7.8%, respectively.[16] The incidence of ICU CRKP in Taiwan increased from 1.2% in 2003 to 11.9% in 2011, indicating an elevation over time.[17] In this study, CRKP prevalence between 2013 and 2017 was from 4.8% to 16.0%, indicating a higher detection and faster growth rate. The reasons behind this growth may be related to the complex carbapenem resistance mechanism. The two main mechanisms are acquisition of carbapenemase genes, such as clavulanic acid-inhibited β-lactamases (Ambler class A families: KPC, NMC, IMI, SME, and GES), metallo-β-lactamases (Ambler class B families: IMP, VIM, NDM-1, GIM, SPM, and SIM), and expanded-spectrum oxacillinases (Ambler class D family: OXA-48), and a decrease in the uptake of antibiotics by a qualitative and/or quantitative deficiency of porin expression in association with overexpression of β-lactamases that possess very weak affinity for carbapenems.[18,19] In recent years, although the blaKPC-2 gene was prevalent among KP isolates in most parts of People's Republic of China, blaNDM was the major resistance gene detectable in several regions in southern China.[20] In addition, OXA-producing KP, which are mainly found in isolated strains of children, was reported in People's Republic of China.[21] Detection of carbapenemase genes in CRKP strains in clinical laboratories should be improved in People's Republic of China, which will be helpful for establishing its own epidemiological data and further research.

Above all, the KP infection and resistance rates in ICU patients are significantly increasing due to the extremely vulnerable population (reduced host defenses with deregulated immune responses), increased risk of becoming infected through multiple procedures and use of invasive devices that distort the anatomical integrity–protective barriers of patients (intubation, mechanical ventilation, vascular access, etc), prolonged hospital stays, and excessive use of broad-spectrum antimicrobial agents.[10,22] In contrast to developed

countries, antibiotic overuse or misuse is still universal in People's Republic of China, particularly in rural areas.[23] People living in impoverished regions have a stronger need for antimicrobial therapy, and poverty can encourage shorter courses of treatment or use of lower-quality drugs. Next, resistance for KP is consequently emerging in the ICU settings, especially through the production of ESBLs and carbapenemases, of which the KPC, NDM, and OXA carbapenemases have emerged in recent years as the most concerning.[24] ESBLs are encoded by transferable conjugative plasmids, which also often encode resistant determinants to other antibiotics.[25] Bla_{KPC} and bla_{OXA} are transmitted by plasmids, and bla_{NDM} is transmitted by transposons. Their potential for transfer makes effective control and treatment difficult, which has resulted in endemic and epidemic outbreaks.[26] The high incidence of ESBL-producing bacteria in Chinese communities is partly caused by the high incidence of these bacteria in animals. Resistant bacteria of animal origin can be transmitted to humans through the environment, food products, or direct contact with livestock.[27] Furthermore, due to the large populations in general hospitals, it is difficult to implement hospital infection management measures effectively, including implementation of multimodal infection prevention and control strategies, hand hygiene compliance for the control of CRE, contact precautions, patient isolation, environmental cleaning, and surveillance cultures of the environment for MDRKP.[28] The prevention and control of multidrug-resistant hospital infections need to be strengthened, improving the level of prevention and control of multidrug-resistant infections in People's Republic of China.

We acknowledge several limitations to this study. First, our analysis was retrospective, and it is possible that there may have been some degree of misclassification of the source of infection. Second, we do not distinguish between health care-associated infections and community-acquired infections. The likelihood that the isolated organism is a colonizing bacterium may be considered in such studies. We minimized this possibility through the inclusion criterion that a patient had to have a suspected infection; therefore, certain observations may not be applicable to other settings.

Conclusion

In summary, CRKP and ESBLKP prevalence and resistance rates have gradually increased in ICUs in the past 5 years. The reasons driving the high ESBL rate and increase in CREKP are various. Regular surveillance of resistance patterns in each country, or each hospital, is warranted to establish its own epidemiological data such as the molecular typing of isolates. Finally, further implementation of infection control policies, including appropriate use of antibiotics based on drug sensitivity tests, slowing down the production of multidrug-resistant bacteria, and preventing the spread of drug-resistant bacteria, would be effective in decreasing the damage of antibiotic-resistant bacteria. Prevention and control of drug-resistant bacteria is not insurmountable, but will require a shift in behavior and attitudes among senior managers and, ultimately, all health care workers providing patient care.

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Author contributions

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

Disclosure

The authors report no conflicts of interest in this work.

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