AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EPIDEMIOLOGY AND SURVEILLANCE

Epidemiology of Carbapenem-Resistant *Enterobacteriaceae* Infections: Report from the China CRE Network

Yawei Zhang,[a] Qi Wang,[a] Yuyao Yin,[a] Hongbin Chen,[a] Longyang Jin,[a] Bing Gu,[b] Liangyi Xie,[c] Chunxia Yang,[d] Xiaobo Ma,[e] Huayin Li,[f] Wei Li,[g] Xiaoqian Zhang,[h] Kang Liao,[i] Sijin Man,[j] Shifu Wang,[k] Hainan Wen,[l] Binbin Li,[m] Zhusheng Guo,[n] Jinjing Tian,[o] Fengyan Pei,[p] Li Liu,[q] Lijun Zhang,[r] Cuimei Zou,[s] Tongping Hu,[t] Jun Cai,[u] Hong Yang,[v] Jiaming Huang,[w] Xianghong Jia,[x] Wenhui Huang,[y] Bin Cao,[m] Hui Wang[a]

[a]Department of Clinical Laboratory, Peking University People's Hospital, Beijing, China
[b]Department of Clinical Laboratory, Medical Technology Institute of Xuzhou Medical University, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China
[c]Department of Clinical Laboratory, Hunan Provincial People's Hospital, Changsha, Hunan, China
[d]Department of Infectious Diseases and Clinical Microbiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
[e]Department of Clinical Laboratory, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China
[f]Department of Respiratory, Zhongshan Hospital Fudan University, Shanghai, China
[g]Department of Clinical Laboratory, Qilu Hospital of Shandong University, Jinan, Shandong, China
[h]Department of Clinical Laboratory, Henan Province Hospital of TCM, Zhengzhou, Henan, China
[i]Department of Clinical Laboratory, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China
[j]Department of Clinical Laboratory, Tengzhou Central People's Hospital, Tengzhou, Shandong, China
[k]Department of Children's Medical Laboratory Diagnosis Center, Qilu Children's Hospital of Shandong University, Jinan, Shandong, China
[l]Department of Clinical Laboratory, Affiliated Hospital of Chengde Medical University, Chengde, Hebei, China
[m]Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, and National Clinical Research Center for Respiratory Diseases, Beijing, China
[n]Department of Clinical Laboratory, Dongguan Tungwah Hospital, Dongguan, Guangdong, China
[o]Department of Clinical Laboratory, The Second People's Hospital of Liaocheng, Liaocheng, Shandong, China
[p]Department of Clinical Microbiology, Jinan Central Hospital, Jinan, Shandong, China
[q]Department of Clinical Laboratory, The First Hospital of Qiqihar, Qiqihar, Heilongjiang, China
[r]Department of Clinical Laboratory, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
[s]Department of Clinical Laboratory, The First Affiliated People's Hospital of Yinchuan, Yinchuan, Ningxia, China
[t]Department of Clinical Laboratory, The First Affiliated Hospital of Baotou Medical College of Inner Mongolia University of Science and Technology, Baotou, Inner Mongolia, China
[u]Department of Clinical Laboratory, Chongqing Armed Corps Police Hospital, Chongqing, China
[v]Department of Clinical Laboratory, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China
[w]Department of Clinical Laboratory, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, China
[x]Department of Clinical Laboratory, The People's Hospital of Xuchang, Xuchang, Henan, China
[y]Department of Clinical Laboratory, Affiliated Hospital of Qinghai University, Xining, Qinghai, China

ABSTRACT Carbapenem-resistant *Enterobacteriaceae* (CRE) infection is highly endemic in China, but estimates of the infection burden are lacking. We established the incidence of CRE infection from a multicenter study that covered 25 tertiary hospitals in 14 provinces. CRE cases defined as carbapenem-nonsusceptible *Citrobacter freundii*, *Escherichia coli*, *Enterobacter cloacae*, or *Klebsiella pneumoniae* infections during January to December 2015 were collected and reviewed from medical records. Antimicrobial susceptibility testing and carbapenemase gene identification were performed. Among 664 CRE cases, most were caused by *K. pneumoniae* (73.9%), followed by *E. coli* (16.6%) and *E. cloacae* (7.1%). The overall CRE infection incidence

Received 8 September 2017 **Returned for modification** 5 November 2017 **Accepted** 22 November 2017

Accepted manuscript posted online 4 December 2017

Citation Zhang Y, Wang Q, Yin Y, Chen H, Jin L, Gu B, Xie L, Yang C, Ma X, Li H, Li W, Zhang X, Liao K, Man S, Wang S, Wen H, Li B, Guo Z, Tian J, Pei F, Liu L, Zhang L, Zou C, Hu T, Cai J, Yang H, Huang J, Jia X, Huang W, Cao B, Wang H. 2018. Epidemiology of carbapenem-resistant *Enterobacteriaceae* infections: report from the China CRE Network. Antimicrob Agents Chemother 62:e01882-17. https://doi.org/10.1128/AAC.01882-17.

Address correspondence to Bin Cao, caobin_ben@vip.163.com, or Hui Wang, whuibj@163.com.

Y.Z. and Q.W. contributed equally to this work.

per 10,000 discharges was 4.0 and differed significantly by region, with the highest in Jiangsu (14.97) and the lowest in Qinghai (0.34). Underlying comorbidities were found in 83.8% of patients; the median patient age was 62 years (range, 45 to 74 years), and 450 (67.8%) patients were male. Lower respiratory tract infections (65.4%) were the most common, followed by urinary tract infection (16.6%), intra-abdominal infection (7.7%), and bacteremia (7.7%). The overall hospital mortality rate was 33.5%. All isolates showed nonsusceptibility to carbapenems and cephalosporins. The susceptibility rate of polymyxin B was >90%. Tigecycline demonstrated a higher susceptibility rate against *E. coli* than against *K. pneumoniae* (90.9% versus 40.2%). Of 155 clinical isolates analyzed, 89% produced carbapenemases, with a majority of isolates producing KPC (50%) or NDM (33.5%)-type beta-lactamases among *K. pneumoniae* and *E. coli*. The incidence of CRE infection in China was 4.0 per 10,000 discharges. The patient-based disease burden in tertiary hospitals in China is severe, suggesting an urgent need to enhance infection control.

KEYWORDS carbapenem-resistant *Enterobacteriaceae*, incidence, clinical characteristics, microbiological characteristics, disease burden

Carbapenem-resistant *Enterobacteriaceae* (CRE) is an urgent public health problem worldwide. These multidrug-resistant organisms exhibit resistance to most, if not all, available antibiotics today and are associated with considerable mortality (1). In one study, approximately 32% of patients with bloodstream infections caused by carbapenemase-producing CRE died within 14 days (2). In recent years, significant increases in the prevalence of CRE have been reported in the world (3–5). Since the first report of carbapenemase-producing *K. pneumoniae* isolate in Zhejiang Province, China, in 2007, carbapenem resistance rates in *E. coli* and *K. pneumoniae* have increased from 0% and 0.7% in 2004 to 1.0% and 13.4% in 2014 (6, 7), and CRE has been identified in almost every province in China (8, 9). The rapid spread of CRE is due to the clonal and plasmid-mediated dissemination of clinical carbapenem-resistant strains (5).

Most of previous studies were laboratory based and focused on the molecular characteristics and distribution of CRE in China (7, 9, 10). None of the published studies examined the patient-based disease burden. This dearth of data is notable, because CRE infections are increasingly identified in China with high mortality, but the patient-based CRE burden remains unknown. The epidemiology should be fully understood to inform national prevention and control efforts.

To better understand CRE epidemiology and provide the latest baseline data for the development of infection control protocols for CRE in China, we initiated a surveillance study to assess the burden of CRE infection in a large geographically widespread network of tertiary hospitals in China.

RESULTS

Incidence of CRE cases among inpatients in tertiary hospitals. Table 1 demonstrates the patient-based incidences among different tertiary hospitals and regions. Between 1 January and 31 December 2015, 767 patients with CRE infection were eligible for screening in this study. After application of the exclusion criteria, a total of 664 patients were included. The overall annual CRE infection incidence across the 25 hospitals during 2015 was 4.0 per 10,000 hospital discharges and 4.05 per 100,000 patient-days. The site-specific infection incidence rates varied significantly between different regions, with the highest rate in Jiangsu (14.97 per 10,000 discharges and 14.38 per 100,000 patient-days) and the lowest rate in Qinghai (0.34 per 10,000 discharges and 0.32 per 100,000 patient-days).

Clinical data analysis. Of these 664 individual patients, 214 patients were female (32.2%) and 450 patients were male (67.8%), and the median age was 62 years (interquartile range, 45 to 74 years; Table 2). Regardless of gender, the largest proportion was 65 years or older (304/664 [45.8%]). Of the patients, 37.1% (246/663)

TABLE 1 Basic information of 25 participating tertiary hospitals, CRE cases, and incidence estimates by site in 2015

Region	Hospital	No. of beds	Annual no. of discharges	Bed occupancy	Patient-days[a]	No. of CRE cases[b]	Incidence rate/ 10,000 discharges[c]	Incidence rate/ 100,000 patient-days
Beijing	BJ-1	1,857	71,875	0.92	623,580.6	24	3.34	3.86
	BJ-2	1,415	62,401	0.96	495,816	25	4.00	5.03
	BJ-3	1,770	63,335	0.95	613,747.5	20	3.16	3.25
	Beijing total	5,042	197,611	0.94[d]	1,729,910.2	69	3.49	3.97
Chongqing	CQ-1	924	24,146	0.8	269,808	3	1.24	1.12
	CQ-2	1,346	59,635	1.17	574,809.3	7	1.17	1.22
	Chongqing total	2,270	83,781	0.98[d]	811,979	10	1.19	1.23
Fujian	FJ-1	1,445	54,696	1.04	548,522	1	0.18	0.18
	FJ-2	1,900	74,165	0.99	686,565	49	6.61	7.10
	Fujian total	3,345	128,861	1.02[d]	1,245,343.5	50	3.88	4.02
Guangdong	GD-1	2,458	88,582	0.89	798,481.3	15	1.69	1.88
	GD-2	1,329	46,558	0.89	431,725.7	4	0.86	0.93
	GD-3	1,200	53,776	1.06	464,280	1	0.19	0.22
	Guangdong total	4,987	188,916	0.95[d]	1,729,242.25	20	1.06	1.16
Henan	HN-1	939	26,582	0.83	284,470.1	1	0.38	0.35
	HN-2	2,012	43,340	1.32	969,381.6	38	8.77	3.91
	Henan total	2,951	69,922	1.08[d]	1,163,284.2	39	5.58	3.36
Hebei	HB-1	1,693	50,915	0.98	605,586.1	21	4.12	3.46
Heilongjiang	HLJ-1	2,000	85,036	1.22	890,600	11	1.29	1.24
Hunan	HUN-1	2,625	80,388	0.86	823,987.5	40	4.98	4.85
Inner Mongolia	NMG-1	1,455	47,078	0.90	477,967.5	2	0.42	0.42
Jiangsu	JS-1	4,378	176,968	1.15	1,837,665.5	265	14.97	14.38
Ningxia	NX-1	1,012	26,476	0.88	325,054.4	3	1.13	0.93
Qinghai	QH-1	1,800	59,598	0.96	630,720	2	0.34	0.32
Shanghai	SH-1	2,077	98,784	1.02	773,267.1	54	5.47	7.00
Shandong	SD-1	1,628	44,874	0.84	499,144.8	4	0.89	0.80
	SD-2	1,200	64,833	1.10	481,800	7	1.08	1.45
	SD-3	726	28,082	1.05	278,239.5	19	6.77	6.81
	SD-4	3,555	136,190	1.02	1,323,526.5	29	2.13	2.19
	SD-5	2,381	93,255	1.00	869,065	19	2.04	2.20
	Shandong total	9,490	367,234	1.00[d]	3,463,850	78	2.12	2.25
Total		45,125	1,661,568	0.99	16,305,918.8	664	4.00	4.05

[a]The total number of patient days was calculated as average bed occupancy × number of beds × 365.
[b]CRE cases were defined as the first CRE isolate from a patient during hospitalization that met the surveillance definition.
[c]The number of discharges per hospital for the year 2015, including the number who died.
[d]Average bed occupancy.

had acute care hospitalization in the prior year, and 83.8% (554/661) had more than one underlying disease, with a median Charlson comorbidity index of 1 (interquartile range, 0 to 3). Comorbidities include hypertension (281/664 [42.3%]), followed by pulmonary diseases (237/662 [35.8%]), neurological diseases (194/662 [29.3%]), and heart diseases (167/664 [25.2%]). The majority of patients had a urinary catheter (428/661 [64.8%]), and 90.9% had antimicrobial use 30 days prior to culture. Of 592 patients with available detailed antimicrobial use data, most of the patients had the use of multiple antibiotics (355/592 [60%]) prior to culture.

The clinical characteristics and outcomes of the cases are summarized in Table 3. Of the patients, 65.4% (434/664) presented with a lower respiratory tract infection. The majority of the patients demonstrated increased white blood cell count (332/567 [58.6%]) and elevated levels of C-reactive protein (252/320 [78.8%]) and procalcitonin (93/312 [29.8%]). A total of 363 (363/662 [54.8%]) patients were discharged to home, and others were discharged to either a long-term acute facility (7/662 [1.1%]), follow-up

TABLE 2 Demographic characteristics of patients infected with carbapenem-resistant *Enterobacteriaceae*

Characteristic[a]	Data[b]
Female	214/664 (32.2)
Age (median [IQR]) (yr)	62 (45–74)
0–4	57/664 (8.6)
5–17	13/664 (2.0)
18–49	131/664 (19.7)
50–64	159/664 (23.9)
65–79	192/664 (28.9)
≥80	112/664 (16.9)
Travel history to Southeast Asia	5/656 (0.8)
Health care exposure during prior yr	
Acute care hospitalization	246/663 (37.1)
Dialysis	44/661 (6.7)
Long-term acute care facility	47/663 (7.1)
Resident of a long-term-care facility	74/663 (11.2)
Underlying conditions	
Charlson comorbidity index (median [IQR])	1 (0–3)
None	107/661 (16.2)
Cancer[c]	106/661 (16.0)
Diabetes mellitus	140/664 (21.1)
Heart diseases[d]	167/664 (25.2)
Hypertension	281/664 (42.3)
Immunodeficiency[e]	44/663 (6.6)
ICU stay	137/660 (20.8)
Liver diseases[f]	60/663 (9.0)
Neurological diseases[g]	194/662 (29.3)
Pulmonary diseases[h]	237/662 (35.8)
Renal diseases[i]	98/662 (14.8)
Receipt of corticosteroids	99/660 (15)
Receipt of immunosuppressor	8/661 (1.2)
Smoking history	110/664 (16.6)
Indwelling devices prior to culture	
Arterial cannula	38/663 (5.7)
Central venous catheter	265/661 (40.1)
Gastric tube	195/660 (29.5)
Tracheal cannula	260/663 (39.2)
Tracheotomy	161/662 (24.3)
Urinary catheter	428/661 (64.8)
Antimicrobial use prior to culture within 30 days	
None	60/660 (9.1)
Single antimicrobial use	237/592 (40.0)
Multiple antimicrobial use	355/592 (60.0)
Third- or fourth-generation cephalosporin use	214/592 (36.1)
Carbapenem use	191/592 (32.3)

[a]IQR, interquartile range; ICU, intensive care unit.
[b]Data are presented as the number/total number (%), unless otherwise indicated.
[c]Cancer includes malignancy in lung, digestive tract, gynecology, hematological system, and neurological system.
[d]Heart diseases include congestive heart failure, coronary heart disease, valve replacement, and congenital heart disease.
[e]Immunodeficiency includes splenectomy, agranulocytosis, and chemotherapy.
[f]Liver diseases include cirrhosis, hepatitis, liver abscess, hepar adiposum, and hepatic injury.
[g]Neurological diseases include stroke, transient ischemic attack, cerebral palsy, and meningitis.
[h]Pulmonary diseases include chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease, history of pneumonia and tuberculosis, emphysema, respiratory failure, and infection.
[i]Renal diseases include azotemia and chronic kidney disease.

outpatient facility (41/662 [6.2%]), or other hospitals (29/662 [4.4%]). The all-cause hospital mortality rate was 33.5% (222/662).

Antimicrobial susceptibility testing and microbiological characteristics. Most of the infections were caused by *K. pneumoniae* (491/664 [73.9%]), followed by *E. coli*

TABLE 3 Clinical characteristics and outcomes of patients infected with carbapenem-resistant *Enterobacteriaceae*

Characteristic	Data[a]
Infection types[b]	
Bacteremia	51/664 (7.7)
Intra-abdominal infection	51/664 (7.7)
Lower respiratory tract infection	434/664 (65.4)
Meningitis	10/664 (1.5)
Urinary tract infection	110/664 (16.6)
Wound infection[c]	9/664 (1.4)
Other infections[d]	12/664 (1.8)
APACHE II score (median [IQR])[e]	17 (12–23)
Septic shock	58/664 (8.7)
Laboratory findings	
White blood cells/mm^3	
Median (IQR)	10,000 (5,925–14,165)
Subgroup	
<4,000	26/567 (4.6)
>10,000	332/567 (58.6)
C-reactive protein >10 mg/liter	252/320 (78.8)
Procalcitonin	
0.5 to 2 ng/ml	73/312 (23.4)
>2 ng/ml	93/312 (29.8)
Clinical outcomes	
Length of stay (median [IQR]) (days)	29 (16–48)
ICU admission	378/664 (56.9)
Length of ICU stay (median [IQR]) (days)	5 (0–15)
Discharge disposition	
Home	363/662 (54.8)
Long-term acute facility	7/662 (1.1)
Follow-up outpatient	41/662 (6.2)
Transfer to other hospitals	29/662 (4.4)
Mortality	
In-hospital mortality	222/662 (33.5)
Bacteremia-associated mortality	22/51 (43.1)
Intra-abdominal infection-associated mortality	13/50 (26)
Lower respiratory tract infection-associated mortality	148/425 (34.8)
Urinary tract infection-associated mortality	30/99 (30.3)

[a]Data are presented as the number/total number (%), unless otherwise indicated.
[b]Patients with multiple diagnoses were listed under more than one category, so total numbers may be larger than the number of patients.
[c]Wound infection includes wound infection and surgical site infection.
[d]Other infections include skin and soft tissue infection and other infections.
[e]APACHE II, Acute Physiology and Chronic Health Evaluation II.

(110/664 [16.6%]), *E. cloacae* (47/664 [7.1%]), and *C. freundii* (16/664 [2.4%]). Available antimicrobial susceptibility testing results were collected from local clinical laboratories. Antimicrobial susceptibility results for CRE of various species from sterile or nonsterile sites are listed in Table 4. All isolates showed nonsusceptibility to carbapenems and cephalosporins. For the antimicrobial agents that served as candidates for the treatment of CRE, aminoglycosides displayed better activity than fluoroquinolones, with susceptibility rates of >60% and <11% for sterile isolates, respectively. Polymyxin B retained excellent activity, with a susceptibility rate of >90%, regardless of species. However, tigecycline demonstrated relatively higher performance against *E. coli* than with *K. pneumoniae* isolates (susceptibility rate of 90.9% versus 40.2%, respectively).

Of the 155 CRE isolates submitted for an investigation of resistance mechanisms, KPC-type enzymes were the most common carbapenemase and were identified in 78 isolates (78/155 [50.3%]). In *E. coli*, the most frequently detected carbapenemase was the NDM-type enzymes (29/39 [74.4%]), with NDM-5 being identified in 51.3%

TABLE 4 Antimicrobial susceptibility testing results of CRE isolates based on local clinical laboratories

Antimicrobial agent	% (no. of susceptible isolates/no. of isolates tested)				
	By site		By organism		
	Isolated from sterile site (n = 242)	Isolated from nonsterile site (n = 422)	*Klebsiella pneumoniae* (n = 491)	*Escherichia coli* (n = 110)	*Enterobacter cloacae* (n = 47)
Ertapenem	0 (0/57)	0 (0/29)	0 (0/54)	4.2 (1/24)	0 (0/7)
Meropenem	4.4 (11/249)	7.9 (14/177)	4.7 (14/301)	9.2 (7/76)	5.4 (2/37)
Imipenem	0.5 (2/419)	2.1 (5/237)	0.6 (3/487)	2.8 (3/106)	0 (0/47)
Ceftazidime	2.5 (7/280)	2.4 (5/205)	1.2 (4/335)	2.2 (2/91)	13.6 (6/44)
Ceftriaxone	0.9 (3/347)	1.1 (2/186)	1.0 (4/399)	0 (0/81)	5 (2/40)
Cefotaxime	0 (0/114)	1.4 (1/70)	1.7 (2/119)	0 (0/41)	0 (0/20)
Aztreonam	3 (11/364)	8.1 (17/210)	2.3 (10/429)	12.4 (12/97)	21.2 (7/33)
Cefepime	1.7 (7/416)	3.9 (9/233)	1.6 (8/485)	2.8 (3/108)	12.5 (5/40)
Piperacillin-tazobactam	2.9 (12/414)	9 (21/233)	3.1 (15/485)	4.7 (5/107)	25.6 (10/39)
Ciprofloxacin	6.4 (26/409)	11.4 (25/219)	7.8 (37/477)	5 (5/101)	22.2 (8/36)
Levofloxacin	10.4 (42/404)	15.1 (32/212)	10.3 (48/467)	9.3 (9/97)	42.1 (16/38)
Gentamicin	14.1 (54/384)	26 (57/219)	15.2 (67/441)	22.5 (23/102)	40.9 (18/44)
Tobramycin	11.4 (34/298)	21.3 (34/160)	11 (38/344)	26 (19/73)	25 (7/28)
Amikacin	63 (266/422)	61.2 (145/237)	58.2 (284/488)	75.9 (82/108)	72.3 (34/47)
Trimethoprim-sulfamethoxazole	26.3 (110/419)	39.3 (92/234)	32.6 (158/484)	26.4 (28/106)	46.8 (22/47)

of isolates (Table 5). In *K. pneumoniae* isolates, the most prevalent enzyme was KPC-2, with 77.0% of isolates being PCR positive (Table 6). No KPC-3 was found in this study. IMP-4, IMP-26, NDM-1, and NDM-6 were detected in *C. freundii* and *E. cloacae*. IMP-type enzymes were found in only a small proportion (8/155 [5.2%]) of isolates, but interestingly, not in *E. coli*. Multilocus sequence typing (MLST) results showed that the most prevalent sequence type (ST) among *K. pneumoniae* and *E. coli* was ST11 (75/100 [75%]) and ST167 (10/39 [25.6%]), respectively (Table 5 and 6). Furthermore, most CRE isolates (more than 90%) were susceptible to colistin and tigecycline. However, colistin and tigecycline nonsusceptibility was identified in three and nine isolates, respectively. For these three colistin-resistant isolates, only one had the *mcr-1* gene. One isolate that co-carried $bla_{\text{NDM-5}}$ and *mcr-1* was identified in this study. Fig. S1 shows the MIC distributions of meropenem, tigecycline, and polymyxin based on KPC-2 and NDM.

DISCUSSION

Carbapenem-resistant *Enterobacteriaceae* presents a particularly critical problem worldwide due to rapidly rising resistance rates and subsequent high mortality. Prior to this study, only the percentage of CRE strains among clinical isolates was reported in China. In this multicenter retrospective research, we first demonstrated an overall CRE infection incidence rate of 4.0 per 10,000 discharges. Previous studies reported the CRE incidences in the United States and the European countries, which

TABLE 5 Molecular characteristics of *E. coli* isolates submitted for testing

Region[a]	No. of carbapenemase-producing isolates/no. of isolates submitted for testing	Carbapenemase-producing isolates (no. [%])				Sequence type (no. [%])			
		KPC-2	NDM-1	NDM-5	NDM-6	ST167	ST405	ST410	Others
Beijing	4/7	0	0	4 (57.1)	0	2 (28.6)	0	0	5 (71.4)
Fujian	1/1	0	0	1 (100)	0	0	0	0	1 (100)
Guangdong	5/6	0	0	4 (66.7)	1 (16.7)	1 (16.7)	0	0	5 (83.3)
Henan	2/3	1 (33.3)	0	1 (33.3)	0	1 (33.3)	1 (33.3)	0	1 (33.3)
Hunan	5/7	0	4 (57.1)	1 (14.3)	0	0	1 (14.3)	1 (14.3)	5 (71.4)
Jiangsu	2/2	0	2 (100)	0	0	1 (50)	0	0	1 (50)
Ningxia	1/1	0	0	1 (100)	0	1 (100)	0	0	0
Shandong	10/12	0	0	8 (66.7)	2 (16.7)	4 (33.3)	0	2 (16.7)	6 (50)
Total	30/39	1 (2.6)	6 (15.4)	20 (51.3)	3 (7.7)	10 (25.6)	2 (5.1)	3 (7.7)	24 (61.5)

[a]Chongqing, Hebei, Heilongjiang, Hubei, Inner Mongolia, Qinghai, and Shanghai did not submit any *E. coli* isolates for molecular characterization.

TABLE 6 Molecular characteristics of *K. pneumoniae* isolates submitted for testing

Region[a]	No. of carbapenemase-producing isolates/no. of isolates submitted for testing	Carbapenemase-producing isolates (no. [%])					Sequence type (no. [%])	
		IMP	KPC-2	NDM-1	NDM-5	NDM-6	ST11	Others
Beijing	32/37	1 (2.7)[b]	29 (78.4)	0	0	2 (5.4)	31 (83.8)	6 (16.2)
Fujian	9/9	0	9 (100)	0	0	0	9 (100)	0
Guangdong	9/10	0	7 (70)	0	0	2 (20)	6 (60)	4 (40)
Henan	9/9	0	9 (100)	0	0	0	9 (100)	0
Hebei	1/1	0	1 (100)	0	0	0	1 (100)	0
Hunan	5/5	1 (20)[b]	0	4 (80)	0	0	0	5 (100)
Inner Mongolia	2/2	0	2 (100)	0	0	0	1 (50)	1 (50)
Shandong	27/27	0	20 (74.1)	0	1 (3.7)	6 (22.2)	18 (66.7)	9 (33.3)
Total	94/100	2 (2)	77 (77)	4 (4)	1 (1)	10 (10)	75 (75)	25 (25)

[a]Heilongjiang, Jiangsu, Ningxia, Qinghai, and Shanghai did not submit any *K. pneumoniae* isolates for molecular characterization.
[b]The types of IMP in Beijing and Hunan were IMP-1 and IMP-4, respectively.

were 2.93 per 100,000 population and 1.3 per 10,000 hospital admissions, respectively (11, 12).

Variation by site for the incidence of CRE per 10,000 hospital discharges was observed, ranging from 14.97 in Jiangsu to 0.34 in Qinghai. The percentage of CRE in Jiangsu was considerably higher in 2015 than the other hospitals. However, this is likely due to a CRE outbreak in the hospital at the time of data collection. Furthermore, the incidence of CRE infection per 100,000 patient-days ranged from 14.38 in Jiangsu to 0.32 in Qinghai, with an average of 4.05 across all Chinese participating sites.

Previous studies showed that hospitalization and cumulative antibiotic exposure history, especially for previous use of beta-lactams and carbapenems, were considered as risk factors associated with CRE infections (13, 14). In this study, 90.9% of patients had antimicrobial therapy prior to culture, with a total of 214/592 (36.1%) and 191/592 (32.3%) of patients being exposed to third- or fourth-generation cephalosporins or carbapenems.

The mortality rates from CRE bacteremia have ranged from approximately 20% to 70% (15–18); however, fewer studies have reported the hospital mortality rates of CRE nonbloodstream infections. Carbapenem-resistant *K. pneumoniae* nonbacteremic infections were associated with 24.3% mortality, and 40% of patients with lower respiratory tract infections eventually died (19). Urinary tract infections were reported to have limited mortality (19–21). For carbapenem-resistant *K. pneumoniae* infections, pneumonia and bloodstream infections were related to high mortality risks, while urinary tract infections showed no excess mortality (21). Bacteremia presented a high death rate in this study, with an overall mortality of 43.1%. However, contrary to previous studies, urinary tract infection had a relatively high mortality rate (30.3%); the potential reason for this is that we assessed the all-cause mortality, and since most patients (83.8%) had underlying diseases in this study, they likely died of their comorbidities.

Carbapenem resistance as a result of carbapenemase production is the most prevalent mechanism in CRE globally. This is supported by epidemiological data that highlight the changes in resistance mechanisms (10, 22). In this study, at least one KPC-producing CRE isolate has been reported from all participating sites. As previously reported, the majority of the KPC-producing *K. pneumoniae* isolates in China belong to a common sequence type, ST11 (23), which was different from that in the United States (with a predominance of ST258) (24). While KPC remains the predominant carbapenemase in most regions in China, NDM was detected in 71.4% of CRE isolates in Hunan. Most of the KPC-2- and NDM-producing isolates demonstrated a moderate MIC level of meropenem resistance (see Fig. S1 in the supplemental material).

To the best of our knowledge, this study was the first of its kind in China; however,

several limitations exist. First, information on clinical characteristics and outcomes could not be completely acquired because of the limitations of a retrospective study. Second, although hospitals in a broad geographic distribution of China were recruited in this study, not all hospitals in China participated in this study. Third, for the strains submitted to the Center Laboratory, the antimicrobial susceptibility profiles of carbapenems had a high accordance with those tested by participating hospitals. However, variations in detection platforms and technique skills may exist between hospitals, although they have good external quality control. Therefore, there might be an overestimation of CRE incidence due to the lack of confirmation of CRE through centralized testing of all isolates. Fourth, given the lack of available medical data for ascertainment of all infections, our data likely overestimated the proportion of lower respiratory and urinary tract infections.

In conclusion, the overall incidence of CRE infection was 4.0 per 10,000 discharges among 25 tertiary hospitals in China, which indicated high patient-based disease burden in tertiary hospitals in China, suggesting an urgent need to enhance infection control measures and clinical awareness. Our study also highlights the importance of conducting a prospective study with more participating hospitals and isolates to further understand the CRE burden in China.

MATERIALS AND METHODS

Setting. A retrospective epidemiologic surveillance study of CRE infection was conducted within the network of tertiary hospitals from January to December 2015. A total of 25 hospitals in 14 provinces contributed data to this study. All sites were tertiary hospitals with more than 700 beds, equivalent quality control, skilled facilities, and qualified specialties. All the participating hospitals pass the regional or national external quality assessment for bacterial identification and antimicrobial susceptibility testing, which is carried out and analyzed by the Local or National Center for Clinical Laboratories external quality assessment service annually. Geographic locations and basic information, including the number of beds, annual number of discharges, and average bed occupancy of the participating hospitals are shown in Fig. 1 and Table 1, respectively. The study was reviewed and approved by the research ethics board of Peking University People's Hospital and was also in accordance with institutional policies of the participating hospitals. Informed consent was not required, as all data in this study were anonymized.

Study population. Inpatients with CRE from clinical culture were selected at each site by a review of microbiology reports. Patients with clinical symptoms and positive culture from either respiratory tract secretions, urine, or surgical wounds were evaluated for CRE infection according to the Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) criteria (25). Hospital-acquired CRE infection is defined as an infection that occurred after more than 48 h of hospitalization. If a patient has the following health care-associated risk factors, such as surgery, residence in a long-term-care facility, or hospitalization during the previous year, a positive culture within 48 h is defined as a health care-associated infection. For this study, patients with clinically significant hospital-acquired infection and health care-associated infection due to CRE were eligible. Exclusion criteria were community-acquired infection, missing key data, isolates with colonization only, screening samples, and subsequent episodes in the same patient.

A CRE case was defined as the first clinical culture with carbapenem-nonsusceptible (imipenem, meropenem, or ertapenem) organism of the *Enterobacteriaceae* family, which includes *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, or *Klebsiella pneumoniae* for each individual patient. CRE isolates were identified by local diagnostic laboratories in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines (26). Notably, all participating hospitals are tertiary hospitals and have standardized protocols for CRE identification and antimicrobial susceptibility testing, with strict quality control and high external detection quality.

Data collection. Medical records of all cases were reviewed to collect clinical and epidemiologic data, including sample date, location of culture collection, specimen source, patient demographics, nosocomial or community acquisition, location in the hospital, travel history to Southeast Asia, health care exposures during the prior year, underlying medical conditions, indwelling devices and antimicrobial therapy exposures 30 days prior to culture, infection types, clinical manifestations, treatment, and outcomes. Identification of organisms and susceptibility testing were done at each participating center. The results of antimicrobial susceptibility testing for all isolates were also obtained.

Isolate collection and microbiological investigation. All participating hospitals were required to submit CRE isolates to the Center Laboratory in Peking University People's Hospital for further microbiological investigation involving the detection of resistance mechanisms. Each center submitted all the strains they kept, but only a minority of isolates were submitted to the Center Laboratory for resistance gene screening, because not all CRE isolates were routinely stored in every site.

FIG 1 Distribution of participating hospitals (red dots) in this study.

The MICs of the following antimicrobials, including ceftriaxone (Roche, Shanghai, China), ceftazidime, cefoxitin, cefepime, and amikacin (National Institutes for Food and Drug Control, Beijing, China), piperacillin-tazobactam and tigecycline (Pfizer, NY, USA), imipenem (MSD, Hangzhou, China), meropenem (Sumitomo Pharmaceuticals, Suzhou, China), ciprofloxacin (Bayer, Leverkusen, Germany), and colistin (Amresco, Solon, OH, USA), were determined by agar and broth dilution methods, according to CLSI guidelines (27). The results were interpreted based on CLSI breakpoints (26). The interpretive criteria for tigecycline were based on the breakpoints of the Food and Drug Administration (FDA).

PCR was used to detect the presence of carbapenemase genes (bla_{NDM}, bla_{KPC}, bla_{IMP}, and bla_{VIM}), other β-lactamase genes (bla_{CTX-M}, bla_{TEM}, bla_{SHV}, bla_{DHA}, and bla_{CMY}), and the mobilized colistin resistance gene (*mcr-1*), as previously described (28, 29). Multilocus sequence typing (MLST) was performed according to the protocol described on the Pasteur Institute MLST website (http://bigsdb.pasteur.fr/klebsiella/klebsiella.html) for *K. pneumoniae* and the MLST websites for *E. coli* (http://mlst.warwick.ac.uk/mlst/dbs/Ecoli), *E. cloacae* (https://pubmlst.org/ecloacae/), and *C. freundii* (https://pubmlst.org/cfreundii/).

Statistical analyses. Annual incidence rates for CRE infections were calculated as the number of CRE cases divided by the number of discharges in the participating hospitals in 2015. CRE infection incidence was also reported as the number of CRE cases per 100,000 hospital patient-days.

Descriptive statistics were used to summarize the clinical and epidemiologic characteristics of CRE infections. The Charlson comorbidity index score was calculated. Continuous variables were presented as medians with the interquartile range. For categorical variables, the percentage of patients or isolates in each category was calculated. All analyses were performed using Whonet (version 5.6), GraphPad Prism (version 5), and the SPSS software (version 18.0).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01882-17.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

ACKNOWLEDGMENTS

This study was partly supported by the National Natural Science Foundation of China (grant no. 81625014 and 81661138006).

We thank Thamarai Schneiders in the University of Edinburgh for her suggestions on our manuscript.

We declare no conflicts of interest.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). 2013. Vital signs: carbapenem-resistant *Enterobacteriaceae*. MMWR Morb Mortal Wkly Rep 62:165–170.
2. Tamma PD, Goodman KE, Harris AD, Tekle T, Roberts A, Taiwo A, Simner PJ. 2017. Comparing the outcomes of patients with carbapenemase-producing and non-carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* bacteremia. Clin Infect Dis 64:257–264. https://doi.org/10.1093/cid/ciw741.
3. Cantón R, Akóva M, Carmeli Y, Giske CG, Glupczynski Y, Gniadkowski M, Livermore DM, Miriagou V, Naas T, Rossolini GM, Samuelsen Ø, Seifert H, Woodford N, Nordmann P, European Network on Carbapenemases. 2012. Rapid evolution and spread of carbapenemases among *Enterobacteriaceae* in Europe. Clin Microbiol Infect 18:413–431. https://doi.org/10.1111/j.1469-0691.2012.03821.x.
4. Gupta N, Limbago BM, Patel JB, Kallen AJ. 2011. Carbapenem-resistant *Enterobacteriaceae*: epidemiology and prevention. Clin Infect Dis 53:60–67. https://doi.org/10.1093/cid/cir202.
5. Nordmann P, Naas T, Poirel L. 2011. Global spread of carbapenemase-producing *Enterobacteriaceae*. Emerg Infect Dis 17:1791–1798. https://doi.org/10.3201/eid1710.110655.
6. Xiao YH, Wang J, Li Y, MOH National Antimicrobial Resistance Investigation Net. 2008. Bacterial resistance surveillance in China: a report from Mohnarin 2004–2005. Eur J Clin Microbiol Infect Dis 27:697–708. https://doi.org/10.1007/s10096-008-0494-6.
7. Hu FP, Guo Y, Zhu DM, Wang F, Jiang XF, Xu YC, Zhang XJ, Zhang CX, Ji P, Xie Y, Kang M, Wang CQ, Wang AM, Xu YH, Shen JL, Sun ZY, Chen ZJ, Ni YX, Sun JY, Chu YZ, Tian SF, Hu ZD, Li J, Yu YS, Lin J, Shan B, Du Y, Han Y, Guo S, Wei LH, Wu L, Zhang H, Kong J, Hu YJ, Ai XM, Zhuo C, Su DH, Yang Q, Jia B, Huang W. 2016. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005–2014. Clin Microbiol Infect 22(Suppl 1):S9–S14. https://doi.org/10.1016/j.cmi.2016.01.001.
8. Wei ZQ, Du XX, Yu YS, Shen P, Chen YG, Li LJ. 2007. Plasmid-mediated KPC-2 in a *Klebsiella pneumoniae* isolate from China. Antimicrob Agents Chemother 51:763–765. https://doi.org/10.1128/AAC.01053-06.
9. Zhang R, Chan EW, Zhou H, Chen S. 2017. Prevalence and genetic characteristics of carbapenem-resistant *Enterobacteriaceae* strains in China. Lancet Infect Dis 17:256–257. https://doi.org/10.1016/S1473-3099(17)30072-5.
10. Xu A, Zheng B, Xu YC, Huang ZG, Zhong NS, Zhuo C. 2016. National epidemiology of carbapenem-resistant and extensively drug-resistant Gram-negative bacteria isolated from blood samples in China in 2013. Clin Microbiol Infect 22(Suppl 1):S1–S8. https://doi.org/10.1016/j.cmi.2015.09.015.
11. Guh AY, Bulens SN, Mu Y, Jacob JT, Reno J, Scott J, Wilson LE, Vaeth E, Lynfield R, Shaw KM, Vagnone PM, Bamberg WM, Janelle SJ, Dumyati G, Concannon C, Beldavs Z, Cunningham M, Cassidy PM, Phipps EC, Kenslow N, Travis T, Lonsway D, Rasheed JK, Limbago BM, Kallen AJ. 2015. Epidemiology of carbapenem-resistant *Enterobacteriaceae* in 7 US communities, 2012–2013. JAMA 314:1479–1487. https://doi.org/10.1001/jama.2015.12480.
12. Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasević AT, Cantón R, Carmeli Y, Friedrich AW, Giske CG, Glupczynski Y, Gniadkowski M, Livermore DM, Nordmann P, Poirel L, Rossolini GM, Seifert H, Vatopoulos A, Walsh T, Woodford N, Monnet DL, European Survey of Carbapenemase-Producing *Enterobacteriaceae* (EuSCAPE) Working Group. 2017. Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE): a prospective, multinational study. Lancet Infect Dis 17:153–163. https://doi.org/10.1016/S1473-3099(16)30257-2.
13. Patel N, Harrington S, Dihmess A, Woo B, Masoud R, Martis P, Fiorenza M, Graffunder E, Evans A, McNutt LA, Lodise TP. 2011. Clinical epidemiology of carbapenem-intermediate or -resistant *Enterobacteriaceae*. J Antimicrob Chemother 66:1600–1608. https://doi.org/10.1093/jac/dkr156.
14. Wang Q, Zhang Y, Yao X, Xian H, Liu Y, Li H, Chen H, Wang X, Wang R, Zhao C, Cao B, Wang H. 2016. Risk factors and clinical outcomes for carbapenem-resistant *Enterobacteriaceae* nosocomial infections. Eur J Clin Microbiol Infect Dis 35:1679–1689. https://doi.org/10.1007/s10096-016-2710-0.
15. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. 2014. Deaths attributable to carbapenem-resistant *Enterobacteriaceae* infections. Emerg Infect Dis 20:1170–1175. https://doi.org/10.3201/eid2007.121004.
16. Fraenkel-Wandel Y, Raveh-Brawer D, Wiener-Well Y, Yinnon AM, Assous MV. 2016. Mortality due to bla_{KPC} *Klebsiella pneumoniae* bacteraemia. J Antimicrob Chemother 71:1083–1087. https://doi.org/10.1093/jac/dkv414.
17. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, Spanu T, Ambretti S, Ginocchio F, Cristini F, Losito AR, Tedeschi S, Cauda R, Bassetti M. 2012. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. Clin Infect Dis 55:943–950. https://doi.org/10.1093/cid/cis588.
18. Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, Stefanou I, Sypsa V, Miriagou V, Nepka M, Georgiadou S, Markogiannakis A, Goukos D, Skoutelis A. 2014. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother 58:2322–2328. https://doi.org/10.1128/AAC.02166-13.
19. Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M, Losito AR, Bartoletti M, Del Bono V, Corcione S, Maiuro G, Tedeschi S, Celani L, Cardellino CS, Spanu T, Marchese A, Ambretti S, Cauda R, Viscoli C, Viale P, ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva). 2015. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother 70:2133–2143. https://doi.org/10.1093/jac/dkv086.
20. Qureshi ZA, Syed A, Clarke LG, Doi Y, Shields RK. 2014. Epidemiology and clinical outcomes of patients with carbapenem-resistant *Klebsiella pneumoniae* bacteriuria. Antimicrob Agents Chemother 58:3100–3104. https://doi.org/10.1128/AAC.02445-13.
21. Hauck C, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, Watkins RR, Scalera NM, Doi Y, Kaye KS, Evans S, Fowler VG, Jr, Bonomo RA, van Duin D, Antibacterial Resistance Leadership Group. 2016. Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infections. Clin Microbiol Infect 22:513–519. https://doi.org/10.1016/j.cmi.2016.01.023.
22. Yang Q, Wang H, Sun H, Chen H, Xu Y, Chen M. 2010. Phenotypic and genotypic characterization of *Enterobacteriaceae* with decreased susceptibility to carbapenems: results from large hospital-based surveillance studies in China. Antimicrob Agents Chemother 54:573–577. https://doi.org/10.1128/AAC.01099-09.
23. Qi Y, Wei Z, Ji S, Du X, Shen P, Yu Y. 2011. ST11, the dominant clone of KPC-producing *Klebsiella pneumoniae* in China. J Antimicrob Chemother 66:307–312. https://doi.org/10.1093/jac/dkq431.
24. Giani T, Pini B, Arena F, Conte V, Bracco S, Migliavacca R; AMCLI-CRE Survey Participants, Pantosti A, Pagani L, Luzzaro F, Rossolini GM. 2013. Epidemic diffusion of KPC carbapenemase-producing *Klebsiella pneumoniae* in Italy: results of the first countrywide survey, 15 May to 30 June 2011. Euro Surveill 18:pii=20489. http://www.eurosurveillance.org/docserver/fulltext/eurosurveillance/18/22/art20489-en.pdf?expires=1512179861&id=id&accname=guest&checksum=54EF2E779EA3823E1746DC3A7AFB18D2.
25. Horan TC, Andrus M, Dudeck MA. 2008. CDC/NHSN surveillance defini-

tion of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 36:309–332. https://doi.org/10.1016/j.ajic.2008.03.002.
26. Clinical and Laboratory Standards Institute. 2015. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 10th ed. CLSI document M07-A10. Clinical and Laboratory Standards Institute, Wayne, PA.
27. Clinical and Laboratory Standards Institute. 2016. Performance standards for antimicrobial susceptibility testing, 26th ed; approved standard M100S. Clinical and Laboratory Standards Institute, Wayne, PA.
28. Wang X, Xu X, Li Z, Chen H, Wang Q, Yang P, Zhao C, Ni M, Wang H. 2014. An outbreak of a nosocomial NDM-1-producing *Klebsiella pneumoniae* ST147 at a teaching hospital in mainland China. Microb Drug Resist 20:144–149. https://doi.org/10.1089/mdr.2013.0100.
29. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, Doi Y, Tian G, Dong B, Huang X, Yu LF, Gu D, Ren H, Chen X, Lv L, He D, Zhou H, Liang Z, Liu JH, Shen J. 2016. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 16:161–168. https://doi.org/10.1016/S1473-3099(15)00424-7.