Clinical Treatment Options for Carbapenem-resistant Gram-negative Infections in China: a Single Centre Real-world Experience

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Research

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Abstract

Carbapenem-resistant gram-negative bacteria constitute a serious threat to public health worldwide. However, as a result of the complexities of clinical therapy, antibiotic options against carbapenem-resistant pathogens have not yet been fully standardized. Here, we conducted a retrospective study in 65,000 inpatients over a 2-year period that involved a total of 86 patients from whom carbapenem-resistant gram-negative bacteria were isolated. Monotherapy using trimethoprim/ sulfamethoxazole, amikacin, meropenem, and/or doxycycline in our hospital exhibited a clinical success rate of 83.3% for carbapenem-resistant *Klebsiella pneumoniae*, monotherapy using moxifloxacin, piperacillin/tazobactam, cefepime, and/or ceftazidime for carbapenem-resistant *Pseudomonas aeruginosa* exhibited a clinical success rate of 77.7%, and monotherapy using cefoperazone/sulbactam or combination therapy with tigecycline and cefoperazone/sulbactam for carbapenem-resistant *Acinetobacter baumannii* exhibited a clinical success rate of 62.1%. Our findings highlight the clinical strategies used in our hospital to successfully treat carbapenem-resistant gram-negative bacterial infections.

Introduction

Carbapenem-resistant gram-negative bacteria have become increasingly prevalent in recent years, and now constitute a serious threat to public health worldwide. The antibiotic-resistant phenotype of these bacteria leads to more severe clinical outcomes and an increased economic burden because of greater medical costs, longer hospital stays, the need for intensive care units, and increased mortality. In general, carbapenem-resistant gram-negative bacteria include carbapenem-resistant *Klebsiella pneumoniae* (CRKP), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB). CRKP were found in 3.2–7.1% of outpatients, CRPA ranged from 6.6–9.8% of patients on regular wards, and CRAB occurred in 11.5–13.4% of patients in intensive care units [1].

In clinical practice, carbapenem has been identified as a better choice for the systemic treatment of serious gram-negative bacterial infections. Given the high frequency of antibiotic resistance, carbapenem resistance poses a new and difficult challenge in therapeutic decision-making [2]. To date, several retrospective studies have been reported that consider treatment options for carbapenem-resistant gram-negative bacterial infections, and some guidance has been recommended for clinical practice [1, 3, 4]. However, as a result of the complexities of clinical infections, antibiotic therapy needs to be individualized to control carbapenem-resistant pathogens in accordance with different regions [5–8].

In this study, we focused on our hospital's own strategy for treating bacterial infections and tried to identify optimal antibiotic therapeutic strategies to improve clinical efficacy when treating carbapenem-resistant pathogens.

Methods

Study setting

The study was performed at the Songjiang Hospital affiliated to Shanghai Jiao Tong University School of Medicine (Preparatory Stage), the only regional medical centre in Songjiang district of Shanghai, comprising 1035 beds for a population of 2 million people. It is a tertiary facility with up to 3.7 million outpatients and emergency patients, 65,000 inpatients, and 43,000 surgical patients from 2018 to 2019.

Patients

We conducted a retrospective cohort study during the period from January 2018 to December 2019. All patients with clinically-isolated carbapenem-resistant gram-negative bacteria in our hospital were included in the study. A total of 86 consecutive patients were assayed for carbapenem-resistant gram-negative bacteria, of which 44 were infected and 42 were colonized with this organism. Patients were excluded if they tested positive for colonization.

According to the standards of the United States Centers for Diseases Control and Prevention [9], we assayed for healthcare-associated infections and colonization. Briefly, bacterial colonization was defined as a positive culture from a patient without any clinical symptoms of infection, while bacterial infection was characterized by a positive culture from a patient with signs of inflammation. Infectious indices generally refer to body temperature, white blood cell (WBC) count, and C-reactive protein (CRP) and procalcitonin (PCT) levels. Carbapenem-resistant gram-negative bacteria isolated from patients were resistant to both meropenem and imipenem.

The studies involving human participants were reviewed and approved by the research committee of Shanghai Songjiang Clinical Medical College of Nanjing Medical University. The patients/participants provided written informed consent to participate in this study.

Evaluation of therapeutic efficiency

Global cure was a composite endpoint, which was defined as clinical improvement and microbiological clearance by day 7. Clinical improvement was deemed as being afebrile for ≥ 48 h, having less than 12,000 cells/mm³ or a $\geq 25\%$ reduction in the WBC count, and being hemodynamically stable without the need for vasopressors. Microbiological clearance referred to eradication of the original causative organism from subsequent bacterial cultures upon 7-day therapy, whereas microbiological failure referred to persistence of the original causative organism in the subsequent bacterial cultures by day 7. In the absence of follow-up bacterial culture data, patients who showed clinical improvement were defined as displaying microbiological clearance [10].

Bacterial isolation

Clinical specimens were collected for bacterial culture on or after day 3 of hospitalization. Antimicrobial susceptibility data were obtained before patients received antimicrobial therapy for carbapenem-resistant gram-negative bacteria.

Multiple drug resistant (MDR) refers to the absence of susceptibility to three or more antimicrobial categories. Extensively drug resistant (XDR) refers to the absence of susceptibility to all but two or fewer antimicrobial categories. Pan-drug resistant (PDR) refers to the absence of susceptibility to all antimicrobial categories.

Results

Clinical therapy and the outcome of CRKP infection

Among 12 patients for whom *CRKP* was detected, six were defined as colonization and six were defined as infection. Of note, the infectious indices, which included the WBC count, CRP and PCT levels, from six patients with *CRKP* were significantly elevated (Supplementary Table 1). The *in vitro* antibiotic susceptibility data against *CRKP* infection were summarized in Table 1 and Supplementary Table 2. *CRKP* was resistant to meropenem and imipenem, but highly susceptible to tigecycline, amikacin, and trimethoprim/sulfamethoxazole, with sensitivity rates of 100%, 83.3%, and 50.0%, respectively.

Consistent with our antibiotic susceptibility profile, antibiotic monotherapy in our hospital showed a success rate of 83.3% (5/6) for eliminating *CRKP*, only one case of a urinary tract infection failed treatment with moxifloxacin (Table 2). Five patients were successfully treated with monotherapy, two (one urinary tract and one lung infection) with trimethoprim/sulfamethoxazole, one (lung infection) with doxycycline, one (urinary tract infection) with amikacin, and one (lung infection) with meropenem, which was indicative of a positive clinical outcome. Interestingly, meropenem resistance was established for *CRKP in vitro*, but it showed a better clinical outcome for patients. Taken together, monotherapy with trimethoprim/sulfamethoxazole, amikacin, meropenem and/or doxycycline served as the effective therapeutic strategy for *CRKP* in our hospital.

Clinical therapy and the outcome of CRPA infection

Among 13 patients for whom *CRPA* was detected, four were defined as colonization and nine were defined as infection. As presented in Supplementary Table 3, the infectious indices for nine patients with *CRPA* were significantly elevated. To evaluate the success of antibiotic therapy, we determined the susceptibility rates of these bacteria to antibiotics *in vitro* (Table 3 and Supplementary Table 4). *CRPA* showed resistance to meropenem and imipenem, but was relatively sensitive to cefepime, piperacillin/tazobactam, and ceftazidime at rates of 88.9%, 66.7%, and 66.7%, respectively.

The clinical outcomes exhibited a high success rate (7/9, 77.7%) for eliminating *CRPA* (Table 4). Of the two cases with lung infection for whom treatment failed, one patient was treated with ceftazidime monotherapy and one patient was treated with moxifloxacin and meropenem combination therapy. As a result of their transfer to another hospital, they did not receive the alternative antimicrobial therapy. Among the seven cases that were successfully treated, five patients with a lung infection received therapy with either moxifloxacin (n = 2), piperacillin/tazobactam (n = 2), or ceftazidime (n = 1), and one patient with a urinary tract infection received cefepime monotherapy and one patient with a blood infection

received moxifloxacin monotherapy. Of note, one patient experienced a significant improvement in respiratory symptoms, with initial failure to moxisaxin therapy, followed by ceftazidime administration. Taken together, antibiotic monotherapy with moxifloxacin, piperacillin/tazobactam, cefepime, and ceftazidime exhibited good clinical efficacy against *CRPA* in accordance with our antibiotic susceptibility test.

Clinical therapy and the outcome of CRAB infection

Among 61 patients for whom *CRAB* was detected, 32 were defined as colonization and 29 were defined as infection. As presented in Supplementary Table 5, the infectious indices for 29 patients with *CRAB* were significantly elevated. As presented in Table 5 and Supplementary Table 6, *CRAB* exhibited resistance to meropenem and imipenem, but was relatively sensitive to tigecycline (89.6%), cefoperazone/sulbactam (55.1%), and piperacillin/tazobactam (33.5%).

The clinical outcomes exhibited a relatively high success rate (18/29, 62.1%) for eliminating *CRAB* infection upon monotherapy or combination therapy (Table 6). First, monotherapy was administered to 19 patients. Of the twelve patients who received cefoperazone/sulbactam monotherapy, nine (eight lung and one blood infection) showed clinical improvement and three (two lung and one urinary tract infection) showed clinical failure. Of the four patients who received piperacillin/tazobactam monotherapy, two (lung infection) showed clinical improvement and two (lung infection) showed clinical failure. One patient (lung infection) was treated with imipenem/cilastatin monotherapy and showed clinical improvement. Two patients (lung infection) were treated with trimethoprim/sulfamethoxazole and/or meropenem monotherapy and showed no clinical improvement. Second, combination therapy was administered to 10 patients. Of the six patients who received cefoperazone/sulbactam and tigecycline combination therapy, three (two lung and one abdominal cavity infection) showed clinical improvement and three (lung infection) showed clinical failure. Of the two patients who received imipenem/cilastatin and tigecycline combination therapy, one (lung infection) showed clinical improvement and one (lung infection) showed clinical failure. One patient treated for a lung infection with meropenem and tigecycline combination therapy and one patient treated for a urinary tract infection with trimethoprim/sulfamethoxazole and levofloxacin showed clinical improvement. Taken together, cefoperazone/sulbactam monotherapy, or combination therapy with cefoperazone/sulbactam and tigecycline, were the better treatment options for *CRAB* in our hospital.

Discussion

Our aim was to identify treatment regimens for infections caused by carbapenem-resistant gram-negative bacteria in our hospital. In this study, a total of 44 patients who infected with carbapenem-resistant gram-negative were found in 65,000 inpatients over a 2-year period, indicative of a very low infectious rate. Furthermore, monotherapy (trimethoprim/sulfamethoxazole, amikacin, meropenem, and doxycycline) was an effective antibiotic regimen for the treatment of *CRKP* infection; monotherapy of moxifloxacin, piperacillin/tazobactam, cefepime, and ceftazidime was the preferred antibiotic choice for *CRPA*

infection; and cefoperazone/sulbactam monotherapy or tigecycline combination therapy could effectively treat *CRAB* infections.

Carbapenem is the treatment option for patients who develop serious infections with MDR, XDR, and PDR gram-negative bacilli, but unfortunately the resistance to carbapenem significantly compromises this treatment choice [11]. Consequently, carbapenem resistance among gram-negative bacteria is disseminating worldwide, which poses a serious threat to current medical practices. Similar to previous reports [12, 13], *CRAB* isolates in our study were XDR strains, showing susceptibility to only one and/or two antibiotics *in vitro*. Unlike previous reports [12, 13], *CRKP* and *CRPA* isolates in our study were MDR, indicative of a better antibiotic choice *in vitro*.

In fact, the antibiotic susceptibility determined by *in vitro* culture does not always correlate with the success of clinical therapy *in vivo* [11]. Exact antibiotic doses and bacterial inocula can be easily assessed on agar plates, but this may not be replicated in patients. As a result, despite many *in vitro* studies of bacterial infection, the findings do not always translate into successful treatment in clinical studies. In this study, we observed that the implementation of antibiotic regimens in *CRKP* and *CRPA*-infected patients were consistent with *in vitro* activity. However, a minor difference was found in *CRAB*-infected patients. Of the 29 patients with *CRAB*, resistance to empirical antibiotics piperacillin/tazobactam (2/2, 100%) and imipenem/cilastatin (1/1, 100%) was shown *in vitro* but patients effectively recovered, and in 20 cases resistance to cefoperazone/sulbactam was shown but clinical efficacy was evident for most patients. This discrepancy maybe attributed to the different environments *in vivo* and *in vitro*, the minimum inhibitory concentrations, as well as the clinical efficacy of the cefoperazone/sulbactam combination [14, 15].

Current guidance for the treatment of carbapenem-resistant gram-negative bacterial infections relies on antibiotic therapy based on polymyxins (including colistin or polymyxin B), aminoglycosides, and tigecycline [16, 17]. Emerging retrospective clinical studies show that antibiotic options have not yet been fully standardized, and that treatments may need to be individualized to control carbapenem-resistant pathogens depending on different regions [1]. Papst *et al.* showed that in Israel, monotherapy was the preferred choice for treating *CRPA* and *CRAB* infections, whereas in all other countries, combination therapy with two drugs was standard [11]. Ceftazidime/avibactam was commonly used for the treatment of *CRKP*-infected patients in the USA, whereas ceftolozane/tazobactam was often used in Spain, Italy, France, and the USA [11]. Chen *et al.* reported that both monotherapy of colistin and combination therapy of colistin and carbapenem showed high cure rates of *CRAB* and *CRKP* [18]. Our study showed that our hospital's antibiotic treatment strategies, which included monotherapy of trimethoprim/sulfamethoxazole, amikacin, meropenem, and/or doxycycline therapy for *CRKP*, monotherapy of moxifloxacin, piperacillin/tazobactam, cefepime, and/or ceftazidime for *CRKP*, and monotherapy of cefoperazone/sulbactam or combination therapy with cefoperazone/sulbactam and tigecycline for *CRAB*, according to standard guidance, led to a high cure rate.

Carbapenem resistance mechanisms are most commonly associated with carbapenemase production, porin loss, drug efflux, and target alteration [19]. In China, KPC-2 and NDM gene were identified as the main resistance mechanism of CRKP to carbapenem [20, 21]. Han et al reported that the carbapenemase gene among CRKP were KPC-2 (64.6%, 457/709), NDM (21.1%, 150/709) and OXA-232 (9.3%, 66/709), while only 9 strains were positive for multiple carbapenemases [21]. Additionally, carbapenem-resistance gene OXA-23 played a critical role in carbapenem-resistance of CRAB [22], and metallo- β -lactamase IMP-45 may contribute to CRPA resistance to carbapenem [23, 24].

In summary, our study collates the successful treatment regimens for infections caused by carbapenem-resistant gram-negative bacteria in our hospital. In the future, it will be of great interest to elucidate the molecular mechanisms of carbapenem resistance. It will also be important to further identify optimal antibiotic treatment strategies through a multi-centre study involving a greater number of patients in Shanghai.

Declarations

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Author contributions

Z.Y. designed the study. R.S., X.W., Y.H., and J. L. analysed data and wrote the manuscript. All authors reviewed the manuscript.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tables

Table 1. *In vitro* susceptibility test of the antibiotics against *CRKP* infection in clinical therapy

Strain	KB (mm)	MIC values (mg/L)				Biological source of isolation
	MEM	SXT	AMK	DOX	MFX	
1	6	>16	<2	NA	NA	Sputum
2	6	2	<2	NA	NA	Sputum
3	6	>16	<2	NA	NA	Sputum
4	14	<1	<2	NA	NA	Urine
5	6	>16	>64	NA	NA	Urine
6	6	>16	<2	NA	NA	Urine

MEM, Meropenem; SXT, Trimethoprim-Sulfamethoxazole; DOX, Doxycycline; AMK, Amikacin; MFX, Moxifloxacin; NA, not available; MIC, Minimal inhibitory concentration; KB, Kirby-Bauer

Table 2. Clinical data for the six *CRKP* infections treated with antibiotics

Patient	age(y)	sex	infection site	antibiotics	doses	ATD	MO	CO	AST
1	73	F	lung	MEM	1.0g ivgtt q8h	8days	E	Recovered	R
2	46	M	lung	SXT	0.96g po q12h	11days	E	Improved	S
3	89	F	lung	DOX	0.1g ivgtt q12h	12days	E	Recovered	NA
4	71	M	Urine	AMK	0.4g ivgtt qd	7days	E	Recovered	S
5	81	M	Urine	SXT	0.96g po q12h	38days	P	Improved	R
6	90	F	Urine	MFX	0.4g ivgtt qd	13days	P	Failed	NA

Y, Year; F, Female; M, male; E, Eradication; P, Persistence; MO, Microbiological outcome; CO, Clinical outcome; AST, Antimicrobial susceptibility test; ATD, Antibiotic treatment duration; NA, not available; S, Susceptible; I, Intermediate; R, Resistance

Patient 6: *In vitro* susceptibility test of MFX is not available, but CIP and LVX show resistance.

Table 3. *In vitro* susceptibility test of the antibiotics against *CRPA* infection in clinical therapy

Strain	MIC values (mg/L)				KB (mm)	
	MFX	CAZ	FEP	TZP	MEM	Biological source of isolation
1	NA	16	8	64	12	blood
2	NA	>64	32	64	10	Sputum
3	NA	4	2	8	12	Sputum
4	NA	16	8	16	12	Urine
5	NA	32	8	16	10	Sputum
6	NA	2	4	<4	15	Sputum
7	NA	8	4	<4	12	Sputum
8	NA	8	8	<4	13	Sputum
9	NA	>64	32	>128	12	Sputum

Table 4. Clinical data for the nine *CRPA* infections treated with antibiotics

Patient	age(y)	sex	infection site	antibiotics	doses	ATD	MO	CO	AST
1	88	M	blood	MFX	0.4g ivgtt qd	14days	E	Improved	NA
2	77	M	lung	MFX	0.4g ivgtt qd	8days	E	Recovered	NA
3	79	M	lung	CAZ	1.5g ivgtt bid	13days	E	Recovered	S
4	67	M	Urine	FEP	2.0g ivgtt bid	8days	E	Recovered	S
5	78	M	lung	TZP	4.5g ivgtt q8h	5days	E	Recovered	S
6	81	M	lung	MEM+MFX	0.5g ivg q6h +0.4g ivg qd	11days	P	Failed	R+R
7	78	M	lung	TZP	4.5g ivgtt q8h	3days	E	Improved	S
8	78	M	lung	CAZ	1.5g ivg bid	14days	P	Failed	S
9	91	M	lung	MFX	0.4g ivgtt qd	9days	P	Improved	NA

Patient 1: *In vitro* susceptibility test of MFX is not available, but CIP and LVX show susceptible.

Patient 2: *In vitro* susceptibility test of MFX is not available, but CIP and LVX show resistance.

Patient 9: *In vitro* susceptibility test of MFX is not available, but CIP and LVX show susceptible.

Table 5. *In vitro* susceptibility test of the antibiotics against *CRAB* infection in clinical therapy

Strain	MIC values (mg/L)			KB (mm)				Biological source of isolation
	IPM	SXT	LVX	CSL	TGC	MEM	TZP	
1	>16	16	4	11	19	6	6	Sputum
2	>16	0.5	4	15	11	8	8	Sputum
3	>16	16	>8	21	17	8	10	Sputum
4	>16	1	>8	21	15	9	10	Sputum
5	> 16	16	4	14	20	6	8	Sputum
6	>16	>16	>8	17	14	6	6	Sputum
7	>16	16	>8	19	16	10	10	Sputum
8	>16	1	>8	15	16	10	6	Abdominal fluid
9	>16	1	4	12	17	6	6	Sputum
10	> 16	<1	4	15	16	8	6	Sputum
11	>16	1	4	11	14	6	6	Sputum
12	>16	< 1	4	11	18	10	10	Sputum
13	>16	>16	>8	18	17	8	10	Sputum
14	> 16	<1	>8	12	17	7	10	Sputum
15	>16	>16	>8	21	16	11	10	Sputum
16	>16	>16	>8	8	16	6	9	Sputum
17	>16	<1	4	17	13	6	6	Blood
18	>16	<1	>8	21	16	8	8	Sputum
19	>16	<1	4	14	16	7	6	Sputum
20	>16	>16	>8	15	8	8	9	Sputum
21	>16	<1	4	16	18	8	9	Sputum
22	>16	<1	4	14	16	8	6	Sputum
23	>16	>16	>8	21	14	10	9	Sputum
24	>16	<1	4	15	16	10	10	Sputum
25	>16	<1	4	16	16	8	6	Sputum
26	>16	< 1	4	10	17	8	6	Urine
27	>16	>16	>8	21	16	11	9	Sputum
28	>16	>16	>8	22	16	8	12	Urine
29	>16	>16	>8	19	16	6	8	Sputum

Table 6. Clinical data for the 29 *CRAB* infections treated with antibiotics

Patient	age(y)	sex	infection site	antibiotics	doses	ATD	MO	CO	AST
1	61	M	lung	CSL	3.0g ivgtt q8h	9 days	E	Recovered	R
2	71	M	lung	CSL	3.0g ivgtt q8h	19 days	P	Failed	R
3	65	M	lung	CSL	1.5g ivgtt q8h	18 days	E	Recovered	M
4	90	M	lung	TZP	4.5g ivgtt q8h	19 days	E	Improved	R
5	76	M	lung	IMP/CS	1.0g ivgtt q8h	4 days	E	Recovered	R
6	91	M	lung	CSL	3.0g ivgtt q8h	10 days	P	Improved	M
7	84	M	lung	TZP	4.5g ivgtt q8h	2 days	P	Failed	R
8	35	M	Abdominal cavity	CSL+TGC	3.0g ivgtt q12h+50mg ivgtt qd	8 days	P	Improved	R+S
9	88	F	lung	TZP	4.5g ivgtt q8h	11 days	E	Recovered	R
10	89	F	lung	IMP/CS+TGC	1.0g ivgtt q8h+50mg ivgtt q12h	17 days	E	Improved	R+S
11	91	F	lung	TZP	4.5g ivgtt q8h	9 days	P	Failed	R
12	88	M	lung	SXT	0.96g po q12h	6 days	P	Failed	S
13	68	M	lung	CSL	3.0g ivgtt q8h	14 days	P	Failed	M
14	71	M	lung	IMP/CS+TGC	1.0g ivgtt q8h+50mg ivgtt q12h	15 days	P	Failed	R+S
15	92	M	lung	CSL	3.0g ivgtt q12h	19 days	E	Improved	S
16	83	M	lung	CSL+TGC	3.0g ivgtt q8h+50mg ivgtt q12h	14 days	P	Failed	R+S
17	80	F	Blood	CSL	3.0g ivgtt q8h	7 days	E	Recovered	M
18	47	M	lung	CSL	3.0g ivgtt q8h	6 days	E	Recovered	S
19	71	M	lung	CSL+TGC	3.0g ivgtt q12h+50mg ivgtt q12h	9 days	E	Recovered	S+S
20	88	M	lung	CSL+TGC	3.0g ivgtt q12h+50mg ivgtt q12h	8 days	P	Failed	R+R
21	72	M	lung	CSL+TGC	3.0g ivgtt q8h+50mg ivgtt q12h	8 days	P	Improved	M+S
22	65	M	lung	MEM	1.0g ivgtt q8h	10 days	P	Failed	R
23	66	F	lung	CSL	1.5g ivgtt q8h	7 days	E	Recovered	S
24	56	M	lung	CSL	3.0g ivgtt q8h	10 days	E	Recovered	R
25	79	F	lung	MEM+ TGC	1.0g ivgtt q8h+50mg ivgtt q12h	11days	E	Recovered	R+S
26	71	F	Urine tract	SXT+LVX	0.96g po tid+500mg ivgtt qd	12 days	E	Recovered	S+M
27	64	M	lung	CSL	3.0g ivgtt q12h	5 days	P	Improved	S
28	74	F	Urine tract	CSL	3.0g ivgtt q12h	6 days	P	Failed	S
29	36	M	lung	CSL+TGC	3.0g ivgtt q6h+50mg ivgtt q12h	8 days	P	Failed	M+S

CS, Cilastatin sodium.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable.docx](#)