

Successful Treatment of Serious Meningitis Caused by Extremely Carbapenem-Resistant *Enterobacter cloacae* (MIC \geq 16mg/L) with i.v. Meropenem and i.v. Amikacin Plus Intraventricular Amikacin

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Background: Carbapenem-resistant Enterobacteriaceae (CRE) meningitis are associated with poor outcomes and high mortality. Here, we report the first successful treatment case of serious meningitis caused by extremely carbapenem-resistant *Enterobacter cloacae* (minimum inhibitory concentration (MIC) of imipenem \geq 16mg/L) with high-dose prolonged infusion of meropenem and i.v. amikacin plus intraventricular (IVT) amikacin.

Case presentation: A 17-year-old girl developed meningitis from an extremely carbapenem-resistant *Enterobacter cloacae* (MIC of imipenem \geq 16mg/L) as a complication of the removal of a giant central neurocytoma located in bilateral and third ventricles. The patient received four surgeries (one tumor excision and three external ventricular drainages) and was treated with a 70 days course of antibiotics therapy during 100 days hospitalization. Finally, she was safely and successfully treated with the high-dose prolonged infusion of meropenem and i.v. amikacin plus IVT amikacin.

Conclusion: This case report shows the possibility of the antibiotic regimen of high-dose prolonged infusion of meropenem and i.v. amikacin plus IVT amikacin in the successful treatment of CRE meningitis (MIC of imipenem \geq 16mg/L) especially when other antibiotics are unavailable or restricted.

Keywords: carbapenem-resistant enterobacteriaceae, meningitis, *Enterobacter cloacae*, meropenem, intraventricular amikacin

Introduction

For years, infections caused by carbapenem-resistant Enterobacteriaceae (CRE) have been emerging and increasing worldwide during the last decade and antibiotic treatment options for these CRE infections are limited. In 2013, the Centers for Disease Control (CDC) recognized CRE as one of their top 3 “urgent threats”, and data from the CDC showed that the percentage of CRE increased from 1.2% in 2001 to 4.2% in 2011 and in 2017 the CDC listed CRE as one of the highest-level (urgent) drug-resistant threats facing hospitalized patients in the United States. The trends of CRE species were similar in China; the percentage of CRE increased from 5.61% in 2014 to 10.13% in 2017.¹ Although CRE is not as common as other multidrug-resistant (MDR) gram-negative bacteria, the high mortality (up to 50%), limited choice of antibiotic treatment, and increasing prevalence of CRE have led health care professionals around the world to pay high attention to this family of bacteria. Treatment of meningitis caused by CRE is

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a tough and controversial problem due to the presence of multi-resistance and drugs' poor penetration through the blood-brain barrier (BBB). Despite this growing burden, the best treatment for CRE infection remains largely unknown. Here, we report the case of a patient who was successfully treated with a high dose and prolonged-infusion regimen of i.v. meropenem and amikacin plus intraventricular (IVT) amikacin for infection with carbapenem-resistant *Enterobacter cloacae* (minimum inhibitory concentration (MIC) of imipenem ≥ 16 mg/L) in the cerebrospinal fluid (CSF) and blood.

Case Report

A 17-year-old girl weighing 40kg was admitted to our hospital in September 2017 with 1-month history of headache. Neuroimaging showed an occupying lesion located in bilateral and third ventricles (Figure 1A). The patient underwent neuronavigation-assisted IVT tumor excision (Figure 1B) and external ventricular drainage (EVD, right side) on September 27, 2017. Perioperative i.v. antibiotic prophylaxis with cefazolin (2g) was administered. Later, the antibiotic was changed to vancomycin (1g twice daily, Sep 29, Day2 after surgery) and ceftriaxone (2g daily, Oct 3, Day6 after surgery) in view of the possible central nervous system (CNS) infection because she had marked leucocytosis ($20.53 \times 10^9/L$), and the laboratory examination of CSF was abnormal (Table 1, white blood cell (WBC): 826 cells/mm³, glucose: 37mg/dL, protein: 715mg/dL). Ten days from the start of ceftriaxone (Oct 14, Day17 after surgery), she had a sudden-onset of fever and her body temperature was

38.4°C with symptoms of nausea, emesis and apathy. On the days that followed, CSF cultures showed carbapenem-resistant *Enterobacter cloacae* infection, and MIC to imipenem ≥ 16 mg/mL (Table 2, Oct 17, Day20 after surgery). Blood culture was positive too. So we immediately removed the drainage tube of external ventricular and the catheter was cultured as well. The patient was then switched to tigecycline i.v. (100mg loading dose, then 50mg twice daily) and amikacin i.v. (600mg daily). But on the night of the same day, the patient suffered cardiac and respiratory arrest due to herniation of the brain, and we were forced to place another EVD (right side) for her (Figure 1C). Considering the poor BBB penetration of tigecycline, after one day therapy, we adjusted the antibiotics (Oct 19, Day22 after surgery) to meropenem i.v. (2g thrice daily, prolonged infusion ≥ 3 hrs) and amikacin i.v. (600mg daily), in addition to cotrimoxazole (sulfamethoxazole 0.4g and trimethoprim 0.08g per pill, 2 pills per day). However, cotrimoxazole was used only once as the patient was allergic to it. After antibiotic treatment, the patient still had fever and the highest temperature was 38.8°C. The state of consciousness gradually deteriorated into lethargy, while CSF cultures still showed carbapenem-resistant *Enterobacter cloacae* infection. Therefore, given the poor permeability of the BBB to antibiotics, off-label IVT amikacin was given as a feasible treatment option. After the patient signed the informed consent, amikacin was administered IVT at a dose of 30 mg/d (Oct 21, Day24 after surgery). The dosage and usage of amikacin were as follows: 5mL normal saline containing 30mg amikacin was

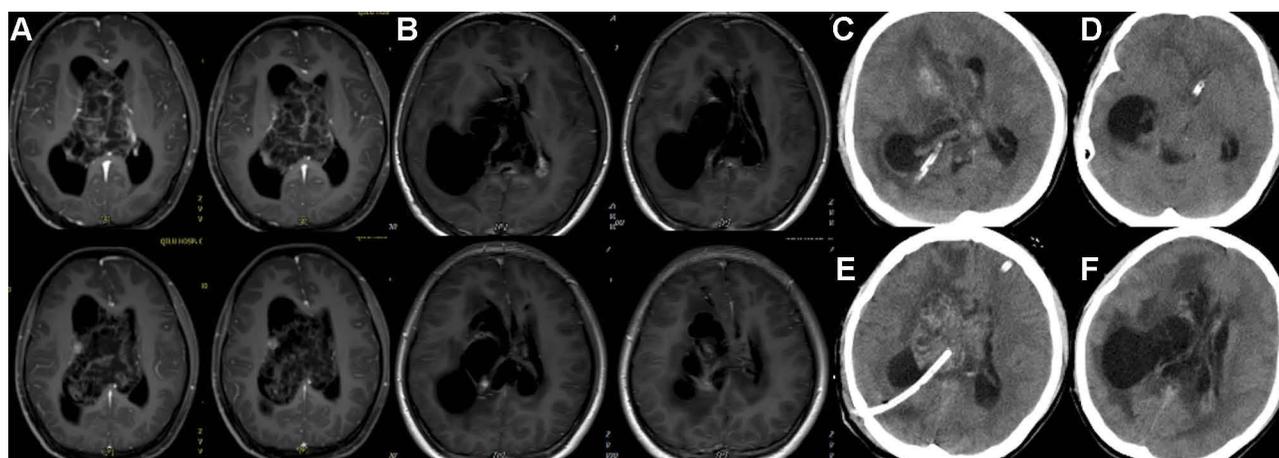


Figure 1 Imaging data during the hospitalization of the patient.

Notes: (A) Contrast-enhanced T1-weighted MRI showed the occupying lesion of bilateral and third ventricles before surgery; (B) contrast-enhanced T1-weighted MRI on the 1st day after surgery; (C) EVD (right side) because of cerebral hernia on the 20th day after surgery; (D) EVD (left side) because of the right side catheter inadvertently slipping off on the 29th day after surgery; (E) EVD (right side) because of the worsening hydrocephalus on the 32th day after surgery; (F) ventricular catheters were removed on the 48th day after surgery.

Abbreviation: EVD, external ventricular drainage.

Table 1 CSF Analyses for *Enterobacter cloacae*

Treatment (Day After Surgery/Date)	Color and Appearance	CSF WBC Count (Cells/mm ³)	CSF RBC Count (cells/mm ³)	CSF % Neutrophils	CSF Protein (mg/dL)	CSF Glucose (mg/dL)
Day 2 (Sep. 29)	Red/hazy	826	60,000	66	715	37
Day 8 (Oct. 5)	Red/hazy	1986	35,200	74	327	53
Day10 (Oct. 7)	Light red/hazy	954	13,500	69	432	49
Day 17 (Oct. 14)	Yellow/slightly hazy	2202	872	85	370	42
Day 21 (Oct. 18)	Pale yellow/hazy	2907	212	88	519	34
Day 24 (Oct. 21)	Pale yellow/hazy	4742	100	90	697	21
Day 26 (Oct. 23)	Colorless/clear	2550	45	57	275	35
Day 31 (Oct. 28)	Colorless/clear	1520	79	72	428	56
Day 35 (Nov. 1)	Colorless/clear	760	88	39	324	46
Day 37 (Nov. 3)	Colorless/clear	194	23	41	NA	NA
Day 40 (Nov. 6)	Colorless/clear	28	12	0	NA	NA
Day 43 (Nov. 9)	Colorless/clear	36	3	0	NA	NA
Day 48 (Nov. 14)	Colorless/clear	9	27	0	NA	NA
Day 70 (Dec. 6)	Colorless/clear	2	5	0	131	59

Abbreviations: WBC, white blood cell; RBC, red blood cell; NA, not available.

Table 2 CSF Culture Susceptibilities for *Enterobacter cloacae*

Blood and CSF <i>Enterobacter cloacae</i> Susceptibilities					
Antibiotics	MIC (mg/L) ^a	Interpretation	Antibiotics	MIC (mg/L) ^a	Interpretation
Amikacin	≤2	S	Ceftriaxone	≥64	R
Gentamicin	≤1	S	Aztreonam	≥64	R
Trimethoprim-sulfamethoxazole	≤20	S	Cefazolin	≥64	R
Tigecycline	≤0.5	S	Cefoxitin	≥64	R
Levofloxacin	4	I	Cefalotin	≥64	R
Amoxicillin-clavulanic acid	≥32	R	Imipenem	≥16	R
Cefepime	≥64	R	Ciprofloxacin	≥4	R

Note: ^aSusceptibilities and MICs determined by an automated platform using broth microdilution.

Abbreviations: S, susceptible; R, resistant; I, Intermediary; CSF, cerebrospinal fluid.

slowly injected into the ventricle. After each injection, the CSF drainage tube was temporarily closed for 1 hr to prevent premature drug outflow. After 2 days of IVT amikacin therapy (Oct 23, Day26 after surgery), routine CSF results showed an elevated WBC count (2550 cells/mm³, with 57% neutrophils). CSF culture was persistently positive with the carbapenem-resistant *Enterobacter cloacae* in the following two results on the 26th and 28th day after surgery. In the meantime, we underwent EVD for her on the left (Oct 26, Day29 after surgery) and right side (Oct 29, Day32 after surgery) because of the drainage (right side) inadvertently slipping off and hydrocephalus, respectively (Figure 1D and E). The CSF culture was negative (Nov 2, Day36 after surgery) after the above treatment. And IVT treatment was well tolerated by the patient. After the CSF culture was negative for 3 consecutive times, the ventricular drainages were removed successively (Left side: Nov 6,

Day40 after surgery; Right side: Nov 14, Day48 after surgery, Figure 1F) and the IVT amikacin was discontinued (Nov 12, Day46 after surgery). On Dec 6 (Day71 after surgery), the CSF culture of the patient had been continuously negative for 9 times, and the indicators of CSF were basically normal (Table 1); we stopped meropenem and amikacin.

During the follow-up period, the patient's mental status improved, and her fever gradually subsided. The meningitis was effectively and safely treated without evidence of nephrotoxicity or seizures. Neurologically, she did not have any focal deficits. Additionally, the patient's pathologic result confirmed central neurocytoma and she was transferred to receive radiotherapy and rehabilitation. And the patient received third ventriculostomy and septostomy of the septum pellucidum because of obstructive hydrocephalus after three months. So far, she has made a full recovery and is leading a normal life.

Discussion

To our knowledge, this is the fourth clinical report of a successful treatment case for CRE meningitis, but it is the first case with high dose and prolonged-infusion regimen of i.v. meropenem and amikacin plus IVT amikacin for serious carbapenem-resistant *Enterobacter cloacae* (MIC of imipenem ≥ 16 mg/L) in the CSF and blood.² To review and summarize this case, the patient received four surgeries (one tumor excision and three EVDs) and was treated with a 70 days course of antibiotics therapy during 100 days hospitalization. We believe that our experience, such as practices in route, frequency and dose of administration, can help manage these fatal infections.

CRE is one of the highest levels of drug-resistance threats due to limited antibiotic treatment regimens and high mortality. Currently, the CDC defines CRE as a type of Enterobacteriaceae that is resistant to any carbapenems (i.e., with ertapenem MIC ≥ 2 mg/L or an imipenem, meropenem or dorepenem MIC ≥ 4 mg/L) or carbapenemases was detected to produce.¹ Enterobacteriaceae resistant to carbapenems can be mainly attributed to either carbapenemase production or porin loss coupled with β -lactamases (extended-spectrum β -lactamases (ESBLs) or cephalosporinases). The carbapenemases include *K. pneumoniae* carbapenemases (KPCs), metallo- β -lactamases (MBLs), and oxacillinases (OXAs),³ in which the production of KPC enzymes is the most common mechanism of resistance among CRE. The optimal treatment of infection because of carbapenemase-producing organisms is uncertain and antibiotic options are limited. Treatment recommendations on CRE are mostly focused on KPC-*Klebsiella pneumoniae* (KPC-Kp) and are mainly based on expert opinion, as most studies are characterized by multiple biases (retrospective nature, small sample sizes, high heterogeneity, and differences in local epidemiology and in antibiotic use).

The CRE active antibiotics administered intravenously in the United States in 2016 included ceftazidime-avibactam, polymyxins, dual carbapenems, aminoglycosides and tigecycline,³ while ceftazidime-avibactam and polymyxins are unavailable in China. Unfortunately, key factors associated with these antibiotics complicate their use for the treatment of CRE-related meningitis or ventriculitis. Among these antibiotics, meropenem remains the empiric therapy for patients with CRE meningitis as pharmacokinetic data suggest that $T > MIC$ targets can be achieved using high-dose prolonged-infusion meropenem when carbapenem MICs are relatively low (< 4 mg/L) or

even moderately elevated (8–16 mg/L).^{3,4} In a review of 20 clinical studies, the mortality rate in the carbapenem-containing regimen was lower than that in the noncarbapenem-containing regimen (18.8% vs. 30.7%).⁵ When the MIC is higher than 16 mg/L, carbapenem excluding combination therapy should be performed considering in-vitro activity of antimicrobials.^{3,6} Pharmacokinetic data have found that high-dosed, prolonged (continuous or extended) infusion of meropenem could achieve adequate exposures (40% C_{trough} time $> MIC$) in 100%, 75%, and 40% of septic patients infected with KPC-Kp isolates with MICs of 4, 8, and 16 mg/L, respectively.^{3,4} As Tumbarello⁷ reported, the combined regimen, including meropenem, had a survival rate of 87% at meropenem MICs less than 4 mg/L, 75% under 8 mg/L, and 65% over 16 mg/L, better than the overall survival rate reported in the study (58%). Besides, dual carbapenems may be a treatment choice for this patient. In addition, the double-carbapenem regimen (ertapenem and high-dose meropenem or doripenem) has shown to enhance efficacy over either agent alone in previous in-vitro and in-vivo studies and has been recently considered a possible therapeutic strategy in KPC-Kp with high carbapenem MIC or colistin resistance.⁸ In the Cprek and Gallagher⁸ retrospective chart-based studies, 39% of patients with carbapenem-resistant *K. pneumoniae* infections achieved clinical success after treatment with dual carbapenems, but there were no cases of CNS meningitis in these patients.

Due to the low penetration of current treatment antibiotics for CRE meningitis, the combination of IVT and i.v. antibiotics is a good choice. Antimicrobial therapy with IVT should be considered in patients with healthcare-associated ventriculitis and meningitis in which only systemic antimicrobial therapy responds poorly to infection.⁹ Although polymyxins and aminoglycosides have bactericidal activities, they both have disadvantages of renal toxicity and poor pharmacokinetic, including low penetration of CSF; i.v. and IVT use of these antibiotics may overcome these shortcomings.¹⁰ In one study, IVT gentamicin combined with intravenous meropenem was used to treat neurosurgical gram-negative ventriculitis and meningitis without recurrence. However, there are few studies on the pharmacokinetic, optimal dosage and clinical application of IVT aminoglycoside drugs. Recent studies revealed that IVT antimicrobials therapy, especially amikacin, could be a successful option for the treatment of severe MDR intracranial bacterial infections.^{9,11} However, daily IVT amikacin doses of 10–50 mg appear to achieve bacteriologic

sterilization. On the basis of 2 review articles, the daily dose of amikacin was selected as 30mg IVT.¹⁰ Additionally, recent years IVT injection of tigecycline was considered as an effective drug against CNS infection of MDR. IVT injection of tigecycline is an option when intravenous antibiotic therapy for a life-threatening CNS infection has failed and no alternative treatment is available.¹² In view of the above-mentioned studies and the antibiotics available in China, we eventually chose the regimen of a high dose and prolonged-infusion regimen of i.v. meropenem and amikacin plus IVT amikacin to treat this serious meningitis patient for extremely carbapenem-resistant *Enterobacter cloacae* (MIC of imipenem \geq 16mg/L). Despite meropenem being resistant (MIC of imipenem \geq 16mg/L) to *Enterobacter cloacae*, the chosen treatment protocol cured the patient eventually.

Our patient had a high risk for CRE meningitis due to multiple neurosurgical operations, mechanical ventilation, EVD, prolonged treatment in intensive care unit and exposure to various antibiotics, including carbapenems and cephalosporins. The combination of meropenem and amikacin was selected based on previous studies on the combination of IVT and i.v. antibiotics and other antibiotics with anti-CRE activity that had poor permeability to CSF, as well as limited clinical experience with meropenem alone for meningitis.

The treatment course of CNS infection caused by severe drug-resistant bacteria is still controversial. After appropriate antimicrobial therapy, patients with repeated positive CSF culture should continue to be treated for 10–14 days after the last positive culture.⁹ In this case, the reason that we decided to use antibiotics for a long time was mainly due to the severity of the patient's infection, the strong resistance of the pathogenic bacteria of infection, and the difficulty in controlling the source of infection caused by removing or replacing the external ventricular drainage. Additionally, the operation of EVD reduces intracranial pressure effectively and improves clinical symptoms, and it also wins more precious time for the success of anti-infective treatment.

Despite limited treatment options for CRE-related CNS meningitis and the patient's complex medical conditions, she was eventually treated with high-dose prolonged meropenem and amikacin combined with IVT amikacin successfully. After 2 weeks of treatment, the microbe was finally eradicated and the patient's clinical symptoms were improved enough to be transferred to a subacute care facility for radiotherapy.

Conclusion

This case report shows the possibility of the antibiotic regimen of high-dose prolonged infusion of meropenem and i.v. amikacin plus intraventricular amikacin in the successful treatment of CRE meningitis (MIC of imipenem \geq 16mg/L) especially when other antibiotics are unavailable or restricted. Continued research is critically needed to determine the most appropriate treatment of CRE meningitis.

Ethics Statement

Written informed consent has been provided by the patient for the publication of this case report and any accompanying images, and the institutional approval was not required to publish the case details.

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Disclosure

Zheng He and Chengcheng Wang are co-first authors. The authors report no conflicts of interest in this work.

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