

Intraventricular Plus Systemic Antibiotic Therapy for Treating Polymyxin-Resistant *Klebsiella pneumoniae* Ventriculitis: A Case Report

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Background. Treating central nervous system (CNS) infections caused by extensively drug-resistant (XDR) gram-negative bacilli, such as carbapenem-resistant *Klebsiella pneumoniae*, represents a significant clinical challenge. Polymyxin is occasionally used as a salvage treatment for this severe CNS infection. We report here a rare case of polymyxin-resistant *Klebsiella pneumoniae* ventriculitis, which was successfully treated with ventricular injections and intravenous antibiotics.

Methods. A 53-year-old male underwent a decompressive craniectomy and was referred to our hospital with cerebrospinal fluid incisional leakage and persistent fever.

Results. The minimum inhibitory concentration of polymyxin B in this patient increased from 2 to 4 µg/mL during the course of treatment. He was diagnosed with polymyxin-resistant XDR *Klebsiella pneumoniae* ventriculitis. We successfully treated the infection with intravenous ceftazidime/avibactam (CAZ/AVI) combined with ventricular injection of tigecycline according to cerebrospinal fluid microbiological culture.

Conclusions. CAZ/AVI combined with tigecycline may be an effective salvage treatment for CNS infections caused by polymyxin-resistant XDR *Klebsiella pneumoniae*.

Keywords. ceftazidime–avibactam; CNS infection; extensively drug-resistant gram-negative bacillus; *Klebsiella pneumoniae*; polymyxin-resistant.

Multidrug-resistant (MDR) or extensively drug-resistant (XDR) gram-negative bacillus-associated central nervous system (CNS) infections are a serious global health threat and are associated with high mortality rates. Treating such severe CNS infections is challenging due to the limited number of antibiotics that retain susceptibility and reach therapeutic concentrations in cerebrospinal fluid (CSF).

Carbapenem-resistant Enterobacteriaceae, including *Klebsiella pneumoniae* carbapenemase (KPC)–producing strains, can effectively hydrolyze cephalosporins and carbapenems, complicating the treatment of intracranial infections associated with this bacterium [1]. This challenge is even further complicated by

the emergence of KPC-producing XDR Enterobacteriaceae because these isolates are resistant to nearly all antibiotics, except for colistin and tigecycline [2, 3]. Typically, polymyxins such as colistin and/or tigecycline are used to treat CNS infections caused by XDR bacteria. Unfortunately, some bacteria have developed acquired resistance to polymyxins, imposing a global threat [4].

We report a rare case of ventriculitis caused by polymyxin-resistant KPC-producing *Klebsiella pneumoniae*. We eventually eradicated infectious microorganisms from the CNS through a combination of intraventricular (IVT) and systemic antibiotic therapy.

CASE PRESENTATION

A 53-year-old male underwent suboccipital decompression at a local hospital half a month ago for an acute cerebellar infarction. The patient was admitted to our hospital with a CSF incision leakage and persistent hyperpyrexia. Lumbar cistern drainage was performed before transfer to our hospital, and a CSF test confirmed intracranial infection. Physical examination on admission revealed purulent fluid exuding from the skin incision, and a lumbar pool drainage catheter was blocked with purulent CSF. A computed tomography scan of the brain suggested cerebral edema (Figure 1A). Emergent left ventricular external drainage (EVD) was performed first,

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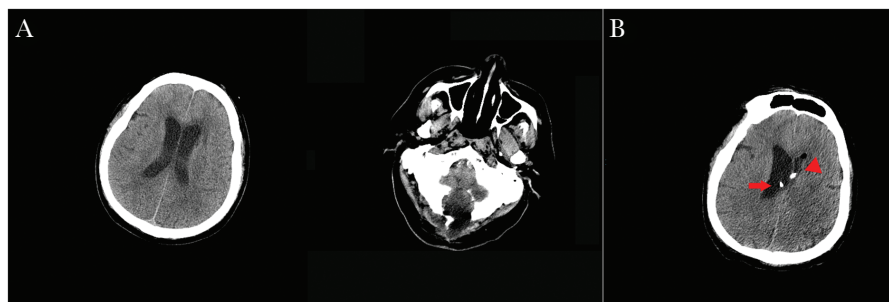


Figure 1. Brain CT before and after the first surgery in our hospital. A, CT scan on admission showing cerebral edema. B, Brain CT after the first surgery in our hospital. Red arrows: ommaya capsule; red triangle: ventricular external drainage. Abbreviation: CT, computed tomography.

and a large amount of purulent CSF outflow from the catheter (Supplementary Figure 1). Following right ventricular ommaya capsule implantation, ventricular irrigation was performed (Figure 1B). Additionally, we completely removed the pus, necrotic tissue, and artificial meninges while concurrently harvesting the patient's fascia and adipose tissue to repair defective meninges. Following surgery, the antibiotic regimen included 2 g of cefoperazone/sulbactam intravenously (IV) every 8 hours, 750 000 units of polymyxin IV every 12 hours, and 50 000 units of polymyxin intracerebroventricularly (IVT) every day, as determined by CSF tests performed at a local hospital. On the fourth day of hospitalization, sputum and blood cultures revealed carbapenem-resistant *Klebsiella pneumoniae* (CRKP),

only susceptible to polymyxin, tigecycline, and ceftazidime/avibactam (CAZ/AVI). In addition, CSF culture revealed intracranial infection of CRKP (Table 1). The minimum inhibitory concentration (MIC) of polymyxin against this CRKP was 2 mg/L. Three days after previous anti-infectious treatment with cefoperazone/sulbactam and polymyxin, the patient continued to experience persistent hyperpyrexia, with a hypersensitive C-reactive protein (CRP) level of 137 mg/L. Considering the high MIC of polymyxin and poor clinical effects, the intravenous antibiotic regimen was changed to 2.5 g of CAZ/AVI combined with 4 g of fosfomycin every 8 hours. The intracerebroventricular injection of antibiotic remained polymyxin B, and the dose was doubled, although the polymyxin

Table 1. Microbiological Sensitivity of *Klebsiella pneumoniae* on the Fourth Day of Hospitalization

Drug	MIC, mg/L		
	CSF	Sputum	Blood
Ceftazidime/avibactam	25 mm ^a : S	25 mm ^a : S	25 mm ^a : S
polymyxin	2: S	≤0.5: S	2: S
Tigecycline	0.5: S	0.5: S	0.5: S
Amoxicillin/clavulanate potassium	≥32: R	≥128: R	≥32: R
Piperacillin tazobactam	≥128: R	≥128: R	≥128: R
Cefuroxime sodium	≥64: R	≥64: R	≥64: R
Cefuroxime axetil	≥64: R	≥64: R	≥64: R
Cefoxitin	≥64: R	≥64: R	≥64: R
Ceftazidime	≥64: R	≥64: R	≥64: R
Ceftriaxone	≥64: R	≥64: R	≥64: R
Cefoperazone/sulbactam	≥64: R	≥64: R	≥64: R
Cefepime	≥32: R	≥32: R	≥32: R
Ertapenem	≥8: R	≥8: R	≥8: R
Imipenem	≥16: R	≥16: R	≥16: R
Amikacin	≥64: R	≥64: R	≥64: R
Levofloxacin	≥8: R	≥8: R	≥8: R
Compound sulfamethoxazole	≥320: R	≥320: R	≥320: R
Aztreonam	NA	≥64: R	NA
Meropenem	NA	≥16: R	NA
Tobramycin	NA	≥16: R	NA
Ciprofloxacin	NA	≥4: R	NA
Doxycycline	NA	≥16: R	NA
Minocycline	NA	≥16: R	NA

Abbreviations: CSF, cerebrospinal fluid; MIC, minimum inhibitory concentration.

^aAntibacterial circle diameter: S, susceptible; R, resistant; NA, not available.

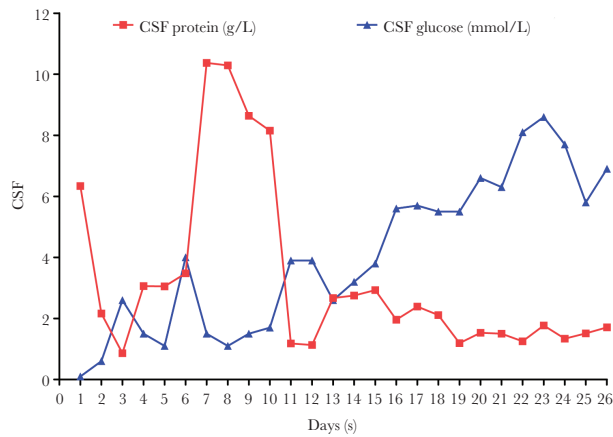


Figure 2. Glucose and protein in cerebrospinal fluid during hospitalization. Abbreviation: CSF, cerebrospinal fluid.

MIC was increasing. Following that, the patient's body temperature gradually returned to normal, and CRP levels in his blood decreased rapidly, while his CSF had increased glucose levels and decreased leukocyte levels (Figure 2, Table 2). However, on the seventh day of hospitalization, the patient's CSF drainage from the EVD tube was <100 mL per day, the protein level in

CSF was consistently >5 g/L (Figure 2), and the patient's impairment of consciousness gradually worsened. A cranial computed tomography (CT) scan revealed diffuse brain swelling combined with hydrocephalus and loss of the third ventricle (Figure 3A). On the 13th day of hospitalization, the left EVD and the right ventricular ommaya capsule were removed due to insufficient CSF drainage with blockage of the frontal horn of the left lateral ventricle (Figure 3B), and a new right EVD and continuous lumbar cistern drainage were placed (Figure 3C).

After changing the antibiotic regimen, the patient's blood cultures became negative, but CSF culture remained positive. On the 15th day of hospitalization, sputum and CSF cultures suggested the presence of CRKP, which was sensitive to tigecycline and CAZ/AVI but resistant to polymyxin (Table 3). Because of the synergistic impact of CAZ/AVI and meropenem as reported in the literature [5] and in our susceptibility tests, the antibiotic was adjusted to 2.5 g of CAZ/AVI combined with 2 g of meropenem IV every 8 hours and 50 000 units of polymyxin IVT every 12 hours. On the 16th day of hospitalization, CSF cultures revealed that the bacteria were resistant to polymyxin, with an MIC of 4 mg/L. Intracerebroventricular injection of antibiotics was changed from polymyxin to 5 mg of tigecycline every 12 hours. Six days later (22nd day of hospitalization), CSF

Table 2. Cerebrospinal Fluid Tests and Culture During Hospitalization

Day	CSF RBC Count, cells/mm ³	CSF WBC Count, cells/mm ³	CSF % Neutrophil	CSF Glucose, mmol/L	CSF Protein, g/L	Culture
1	1000	110 000	92	0.1	6.34	NA
2	2017	540	93	0.6	2.16	NA
3	490	140	93	2.6	0.86	NA
4	4000	680	94	1.5	3.06	+
5	4000	3800	92	1.1	3.05	+
6	14 560	5300	94	4.0	3.48	+
7	45	530	90	1.5	10.37	+
8	120	410	88	1.1	10.29	+
9	30	260	92	1.5	8.64	+
10	1050	540	95	1.7	8.15	+
11	400	200	91	3.9	1.18	+
12	350	75	80	3.9	1.13	+
13	7000	1300	90	2.6	2.67	+
14	1319	2083	95	3.2	2.75	+
15	3479	15 155	84	3.8	2.93	+
16	470	360	90	5.6	1.96	+
17	3700	2100	85	5.7	2.39	+
18	420	800	88	5.5	2.11	+
19	200	570	89	5.5	1.19	+
20	2100	1500	89	6.6	1.53	+
21	110	160	91	6.3	1.50	+
22	524	695	92	8.1	1.25	Negative
23	90	50	88	8.6	1.77	Negative
24	620	150	89	7.7	1.34	Negative
25	300	100	90	5.8	1.51	Negative
26	150	45	90	6.9	1.71	Negative

Plus sign indicates *K. pneumoniae*.

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

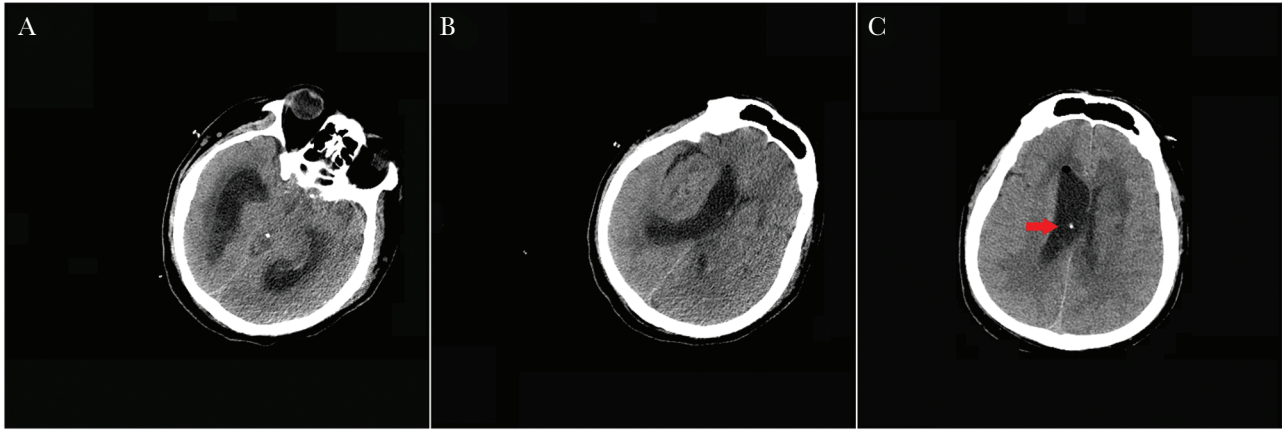


Figure 3. Brain CT before and after the second surgery in our hospital. A, CT revealed diffuse brain swelling combined with hydrocephalus and loss of the third ventricle. B, CT indicated occlusion of the frontal horn of the left ventricle. C, Brain CT after the second surgery in our hospital. Red arrows: ventricular external drainage. Abbreviation: CT, computed tomography.

culture was negative. On the 25th day of hospitalization, the EVD was removed (Figure 4A) and tigecycline was discontinued after repeated negative results from CSF cultures. Additionally, the drainage tube of the lumbar cistern was removed due to a significantly improved CSF test. However, 2 days later, the patient became less conscious and cranial CT revealed worsening hydrocephalus (Figure 4B). On the 30th day of hospitalization, a right EVD was placed, and the drainage tube was placed under a skin tunnel and pulled out under a costal arch to connect to an external drainage device that could be kept for a long time (Figure 5). After repeated negative results upon CSF culture, CAZ/AVI and meropenem were discontinued on the 33rd day of hospitalization. Following that, the patient was transferred to a rehabilitation facility for further treatment. The clinical course of treatment for the patient is summarized in Figure 6.

DISCUSSION

In this case, we describe our experience using a combination of IVT and systemic antibiotic therapy as salvage therapy for intracranial infections caused by XDR *Klebsiella pneumoniae*.

Intraventricular injection of antibiotics is an important therapy for treating XDR gram-negative bacilli-associated ventriculitis, with polymyxin and colistin being one of the most frequent antibiotics for IVT therapy [6]. In the case presented here, a CSF culture at the local hospital suggested CRKP, and a CSF smear collected during surgery at our hospital revealed gram-negative bacteria. He was initially treated with polymyxin injections intravenously and intraventricularly until bacterial susceptibility in his CSF revealed an MIC of 2 µg/mL of polymyxin against *Klebsiella pneumoniae*. For intracerebroventricular injection of antibiotics, the Infectious

Table 3. Microbial Susceptibility of *Klebsiella pneumoniae* in Different Samples

Day	Specimen	MIC, mg/L		
		Polymyxin	Ceftazidime/Avibactam	Tigecycline
2	CSF/sputum/blood	2/≤0.5/2: S	25 mm ^a : S	0.5: S
3	CSF/sputum	2: S	25 mm ^a : S	0.5: S
4	CSF	2: S	25 mm ^a : S	0.5: S
5	Sputum	≤0.5: S	NA	NA
6	CSF	2: S	25 mm ^a : S	0.5: S
7	CSF	2: S	25 mm ^a : S	0.5: S
8	CSF	2: S	25 mm ^a : S	0.5: S
9	Sputum	2: S	NA	NA
10	CSF/sputum	4: R/2: S	23 mm ^a : S/NA	1: S/NA
11	CSF/sputum	4: R/≤0.5: S	23 mm ^a : S/NA	1: S/NA
12	CSF	4: R	23 mm ^a : S	1: S
15	CSF/sputum	4: R	23 mm ^a : S	1: S
16	Sputum	≤0.5: S	NA	≤0.5: S
18	CSF	4: R	4: S	1: S

Abbreviations: CSF, cerebrospinal fluid; MIC, minimum inhibitory concentration.

^aAntibacterial circle diameter: S, susceptible; R, resistant; NA, not available.

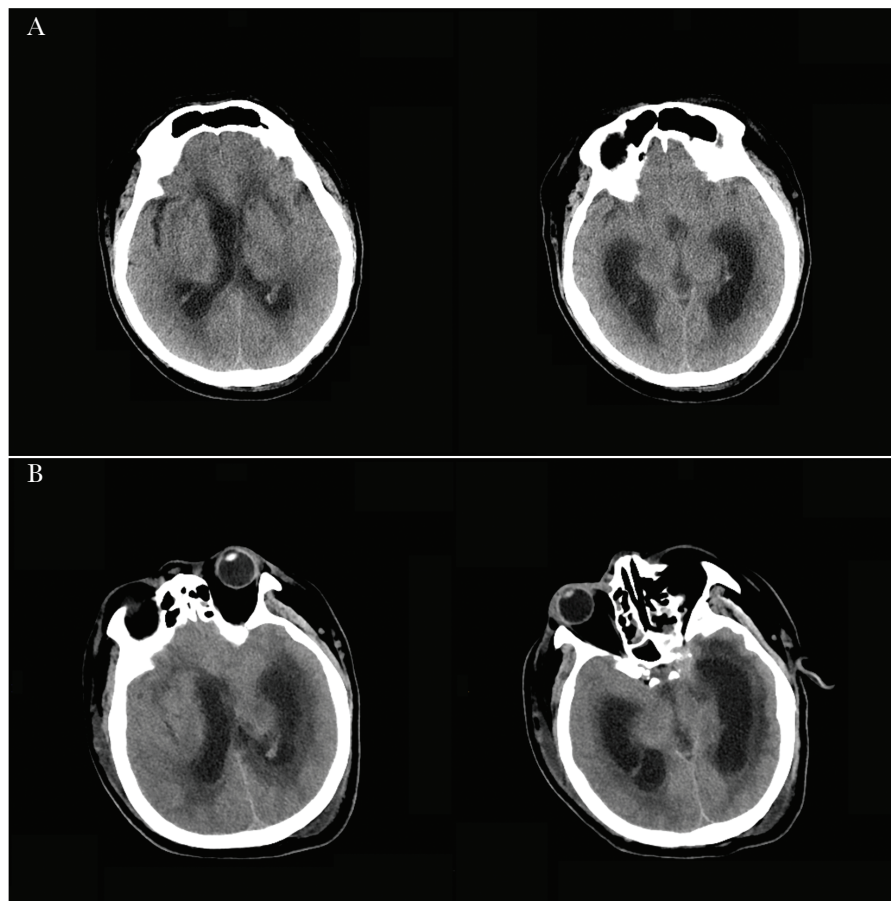


Figure 4. Brain CT on the first and fourth days after removing extraventricular drainage. A, Brain CT demonstrated mild hydrocephalus. B, Brain CT manifested that brain swelling and hydrocephalus were significantly worse than before. Abbreviation: CT, computed tomography.

Diseases Society of America guidelines indicate that a sustained CSF drug concentration >20 times the agent's MIC for an isolated bacterial pathogen is reasonable for sustained CSF sterilization [7]. Although the CSF uptake and disposition of polymyxins in neuronal cells and CNS tissues after IVT delivery remain largely unknown [8], 2 studies have reported on the pharmacokinetics of polymyxins after intracerebroventricular injection in patients [9, 10]. One study showed that when polymyxins were administered at doses >5.22 mg/d, CSF concentrations were >2 mg/L over the entire dosing interval, with trough concentrations ranging between 2.0 and 9.7 mg/L [10]. This patient's sustained CSF drug concentration should exceed 40 $\mu\text{g/mL}$, and his CSF drainage was ~ 150 mL/d, indicating that he should receive >6 mg of polymyxin intracerebroventricularly daily. We adjusted the patient's antibiotic regimen to 50 000 units (5 mg) of polymyxin IVT every 12 hours. This patient did not experience adverse effects such as common neurotoxicity after dose adjustment. CSF culture remained positive, despite improvements in white blood cell counts and biochemical tests of CSF. Besides, subsequent susceptibility results for *Klebsiella pneumoniae* in CSF indicated that bacteria were resistant to polymyxin and only sensitive to tigecycline and CAZ/AVI.

Tigecycline is a broad-spectrum antibiotic with activity against various MDR or XDR pathogens, including *Klebsiella pneumoniae*. There are some cases about tigecycline effective treatment of adult CNS infections caused by MDR/XDR *Klebsiella pneumoniae*. Based on a PubMed search, 5 adult patients with intracranial infections caused by MDR/XDR *K. pneumoniae* have been successfully treated with tigecycline injections (Table 4), including intracerebroventricular (3 cases) and intravenous (2 cases) injections [11–15]. The daily doses of tigecycline used varied widely in these 5 cases, ranging from 4 to 20 mg. Tigecycline concentrations in the CSF were measured in 1 study, and after IVT of 5 mg every 12 hours, tigecycline concentrations in the CSF were 85.155 mg/L at 1 hour and 13.654 mg/L at 12 hours after dosing [13]. We finally chose to administer an intraventricular tigecycline dose of 5 mg every 12 hours based on previous literature. Unlike previous cases, our patient's CSF revealed XDR *Klebsiella pneumoniae* that was only susceptible to tigecycline (MIC, 1 $\mu\text{g/mL}$) and CAZ/AVI after a period of treatment. Based on susceptibility test results, an intravenous CAZ/AVI regimen was employed in conjunction with an intraventricular injection of tigecycline, and the patient's CSF culture eventually became negative.

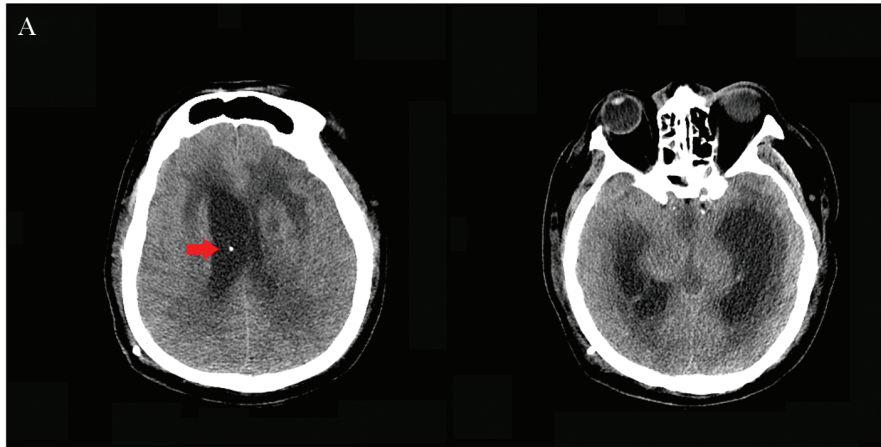


Figure 5. Brain CT after the third surgery. Brain CT on the first day after the third surgery in our hospital. Red arrows: ventricular external drainage. Abbreviation: CT, computed tomography.

CAZ/AVI is a combination of the third-generation cephalosporin ceftazidime and the novel non- β -lactam β -lactamase inhibitor avibactam, which has been approved for treating adults with complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired pneumonia, and other infections caused by aerobic gram-negative organisms in patients with limited treatment options [16]. However, only 6 adult cases of CNS infections caused by MDR/XDR *K. pneumoniae* were effectively treated using CAZ/AVI [17–21]. One case was treated with intravenous CAZ/AVI alone, and 5 cases were treated with CAZ/AVI IV combined with another antibiotic for CNS infection, including ventricular injection or

intravenous antibiotic (Table 5). Although the efficacy of CAZ/AVI combined with other antibiotics for meningitis treatment caused by MDR/XDR gram-negative bacteria remains inconclusive, a study revealed that this combination could synergize and prevent selective drug-resistant mutations in bacteria [22]. Our case received CAZ/AVI combined with another antibiotic intravenously, as well as a ventricular injection of a third antibiotic, encountering no significant adverse effects of this co-administration.

Our case was characterized by an MIC of 2 μ g/mL of polymyxin against XDR *Klebsiella pneumoniae*, which increased to 4 μ g/mL with a period of ventricular polymyxin injection.

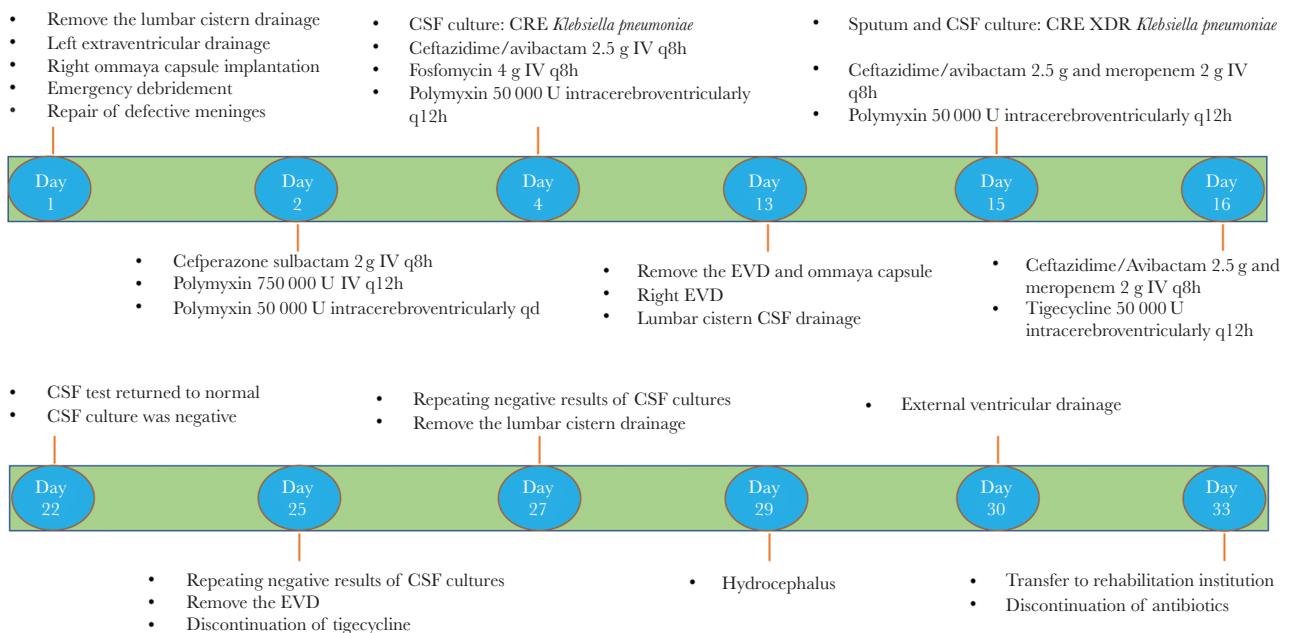


Figure 6. Schematic presentation of the clinical treatment process. Abbreviations: CRE, ; CSF, cerebrospinal fluid; EVD, emergent ventricular drainage; IV, intravenous; XDR, extremely drug-resistant.

Table 4. Summary of Tigecycline used for CNS Infections Caused by MDR/XDR *K. pneumoniae*

	Patient 1 [11]	Patient 2 [12]	Patient 3 [13]	Patient 4 [14]	Patient 5 [15]
Country	Greece	Mexico	China	Jordan	America
CSF cultures	XDR <i>K. pneumoniae</i>	MDR <i>Klebsiella oxytoca</i>	MDR <i>K. pneumoniae</i>	ESBL-positive <i>Klebsiella pneumoniae</i>	<i>K. pneumoniae</i>
MIC, mg/L	Colistin \leq 0.5; tigecycline = 1 and amikacin = 16	Tigecycline < 2	NA	NA	Tigecycline = 1
IVT therapy (duration)	colistin 125 \times 10 ³ IU qd (11 d) and tigecycline 4 mg qd (9 d)	Tigecycline 5 mg qd (11 d)	Tigecycline 10 mg q12h (39 d)	None	None
IV therapy (duration)	Colistin and tigecycline (16 d)	Meropenem 6 g qd and amikacin 1500 mg qd (NA)	Tigecycline 40 mg (39 d)	Tigecycline 50 mg q12h (14 d)	Tigecycline 100 mg q12h (4 wk) and meropenem 1 g q8h (4 wk)
Outcome	Cured	Cured	Cured	Cured	Cured

Abbreviations: CSF, cerebrospinal fluid; ESBL, extended-spectrum β -lactamase; IV, intravenously; IVT, intraventricularly; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; NA, not available; XDR, extensively drug-resistant.

Finally, we were able to successfully treat this uncommon case of polymyxin-resistant XDR *Klebsiella pneumoniae* ventriculitis with intravenous CAZ/AVI and meropenem, as well as ventricular injection of tigecycline. Although intracerebroventricular administration of polymyxin is an important treatment for central CRKP infections, there is still a need to monitor MIC values and to adjust the regimen promptly. In addition, the potential for induced resistance to polymyxin requires vigilance. Finally, intracerebroventricular administration of tigecycline is a salvage treatment in case of failure of polymyxin therapy. The optimal treatment duration for CNS infections caused by MDR/XDR gram-negative bacilli has not been established, and we recommend that the duration of therapy for this serious infection be individualized according to the patient's clinical response. We previously successfully treated 3 patients with MDR/XDR gram-negative meningitis, and this is the first patient with a severe intracranial infection resistant to polymyxins

that we successfully treated [18]. We administered antibiotics to each of these 4 patients until their CSF returned to normal and at least 3 CSF cultures (>1 day between sampling) were negative. In addition, rapid removal of abscess and unobstructed CSF drainage (EVD or lumbar cistern drainage) are critical.

There are some shortcomings in this article. First, the drug concentrations in brain tissue and CSF following IVT of antibiotics are unknown. Studies are needed to obtain information on pharmacokinetic and drug concentrations after IVT of polymyxin or tigecycline for optimal IVT treatment. Second, we are unsure whether IVT of polymyxin or tigecycline at other doses is safe and effective in the treatment of CNS infections associated with XDR gram-negative bacteria. In addition, it is unclear whether this combination of drugs will cause other side effects in brain tissue and in the patient. Due to the limited numbers, we did not identify any other adverse events during the course of treatment in this patient.

Table 5. Summary of Ceftazidime–Avibactam Utilized for CNS Infections Caused by MDR/XDR *K. pneumoniae*

First Author	Country	Numbers	CSF Cultures	Drugs	MIC, mg/L	Outcome
Amanda Holyk	USA	1	MDR <i>K. pneumoniae</i>	CAZ/AVI 2.5 g IV 21 d and gentamicin 15 d intraventricularly	Gentamicin = 1, polymyxin B, tigecycline = 1	Cured
Sophie Samuel	USA	1	KPC-producing MDR <i>K. pneumoniae</i>	CAZ/AVI 2.5 g IV q6h 14 d	NA	Cured
Natalie Gofman	USA	1	Carbapenem-resistant <i>K. pneumoniae</i> and <i>Pseudomonas aeruginosa</i>	Intrathecal amikacin 30 mg qd 4 wk and CAZ/AVI 2.5 g IV q8h 6 wk	Amikacin \leq 4, ceftazidime = 2, avibactam = 1	Cured
Mohamad Yasmin	USA	1	KPC-producing MDR <i>K. pneumoniae</i>	CAZ/AVI 2.5 g IV q8h 10 d and intrathecal amikacin	Meropenem = 4, CAZ/AVI = 0.75, amikacin = 4	Cured
Qian Zhou	China	1	KPC-producing XDR <i>K. pneumoniae</i>	Meropenem 2 g and CAZ/AVI 2.5 g IV q8h 26 d	Polymyxin \leq 0.5, tigecycline = 2, CAZ/AVI = 21 mm ^a	Cured
Qian Zhou	China	1	MDR <i>K. pneumoniae</i> and XDR <i>K. pneumoniae</i>	CAZ/AVI 2.5 g IV q8h and amikacin 400 mg IV qd 27 d	Polymyxin = 1, tigecycline = 2, CAZ/AVI = 4	Cured

Abbreviations: CAZ/AVI, ceftazidime/avibactam; CSF, cerebrospinal fluid; IV, intravenously; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; XDR, extensively drug-resistant.

^aAntibacterial circle diameter.

CONCLUSIONS

We successfully treated a patient with polymyxin-resistant XDR *Klebsiella pneumoniae*-associated CNS infection with intravenous CAZ/AVI combined with ventricular injection of tigecycline. CAZ/AVI combined with tigecycline may be an effective salvage treatment for CNS infections caused by XDR gram-negative bacteria. However, additional research and clinical trials are required to determine the efficacy and safety of this combination in CNS infections.

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Author contributions. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Patient consent. Written informed consent has been obtained from the patient involved in the case report. Ethics approval is not needed for Case Reports according to our local Research Ethics Board.

Availability of data. All data generated during this study are included in the tables.

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