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CASE REPORT

Ceftazidime-Avibactam for the Treatment of Central Nervous System Infection Caused by Pan Drug-Resistant Carbapenem-Resistant Klebsiella Pneumoniae: A Case Report

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Background: Central Nervous System (CNS) infections caused by Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) pose a major clinical challenge and are associated with high mortality rates. Polymyxin is used as a salvage treatment for CRKP CNS infection; however, heteroresistance to polymyxin may impact clinical outcomes. In this study, we report a rare case of polymyxin-resistant Klebsiella intracranial infection, which was successfully treated with intravenous and intraventricular antibiotic injections.

Case Presentation: A 46-year-old woman with a 1-day history of post-traumatic disturbance of consciousness and cerebrospinal fluid (CSF) rhinorrhea was referred to our hospital. She underwent external ventricular drainage and decompressive craniectomy, and had a persistent fever. A CSF test confirmed intracranial infection. The minimum inhibitory concentration of polymyxin in this patient was 16 μg/mL. She was diagnosed with polymyxin-resistant pan drug-resistant (PDR) *Klebsiella pneumoniae* (PDR-Kp) intracranial infection. We successfully treated the infection using intravenous ceftazidime/avibactam (CAZ/AVI) and polymyxin B, combined with an intraventricular injection of polymyxin B according to the CSF microbiological culture results.

Conclusion: CAZ/AVI combined with polymyxin B may be an effective salvage treatment for CNS infections caused by polymyxin-resistant PDR-KP.

Keywords: CNS infection, Carbapenem-resistant *Klebsiella pneumoniae*, polymyxin-resistant, ceftazidime/avibactam

Introduction

Central nervous system (CNS) infections caused by extensively drug-resistant (XDR) or pan drug-resistant (PDR) gram-negative bacillus have shown an increasing trend in recent years. PDR occurs when gram-negative bacteria resist all antimicrobial agents, including cephalosporin, carbapenems, enzyme inhibitors, quinolones, and aminoglycosides.[1] The most frequently isolated pathogens in this form of resistance are *Acinetobacter baumannii, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[2] Due to inadequate CSF penetration, sensitive and large doses of antibiotics are often necessary. XDR/PDR infections often have limited treatment options, leading to unfavorable outcomes, and are associated with high fatality rates.

Carbapenem-resistant Enterobacteriaceae, including *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* (KPC-Kp) can effectively hydrolyze carbapenems and cephalosporins, rendering them resistant to nearly all antibiotics except colistin and tigecycline. This poses a significant challenge in treating CNS infections caused by this bacterium.[3] However, some bacteria have developed resistance to polymyxins.[4] This study presents a rare case and reviewed the literature to evaluate the clinical efficacy of ceftazidime/avibactam (CAZ/AVI)-based combination therapy for the treatment of CNS infections caused by polymyxin-resistant KPC-Kp.

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Case Report

A 46-year-old woman with a 1-day post-traumatic disturbance of consciousness was referred to our hospital. Her condition was complicated by cerebrospinal fluid (CSF) rhinorrhea on admission. Computed tomography (CT) of the brain revealed a left cerebellar hematoma (Figure 1A). The patient presented with severe coagulopathy, and left extra-ventricular drainage (EVD) was performed for external ventricular drainage decompression and continuous monitoring of intracranial pressure. On the 5th day of hospitalization, brain CT indicated increased cerebral edema; hence, craniotomy hematoma removal and decompressive craniotomy (DC) were performed. On the 8th day of hospitalization, the patient developed a fever (her maximum body temperature was 38°C) and leukocytosis. Owing to the presence of CSF rhinorrhea and the retention time of EVD exceeding 5 days, infection was attributed to a CNS source. Lumbar puncture showed a purulent CSF outflow from the catheter. An analysis of the CSF revealed significant leukocytosis and decreased glucose levels, indicating a CNS infection (Table 1). The patient was empirically administered an intravenous (IV) meropenem (2 g) and vancomycin (1 g) 8 hourly while keeping the CSF drainage at 100–150 mL/d. After 24 h of treatment with the above regimen, the patient remained febrile; another CSF test still revealed apparent leukocytosis (Table 1). Based on the epidemiology of common bacteria in our center, 3 g of IV sulbactam was administered every 8 hours. On the 12th day of hospitalization, CSF culture revealed KPC-producing PDR-Kp. The minimum inhibitory concentration (MIC) of polymyxin against PDR-Kp was 16 μg/mL (Table 2). In our hospital, an antimicrobial susceptibility test was performed using the broth dilution method. Carbapenem resistance genes of CRKP (blaKPC, blaNDM, blaOXA-48, blaVIM, and blaIMP) were identified by PCR and sequence analyses. MICs of colistin were interpreted according to the recommendation of the Clinical and Laboratory Standards Institute (CLSI) document M100-S31, with MICs of ≤2 μg/mL and ≥4 μg/mL categorized as intermediate and resistant, respectively.[5,6] The antibiotic therapy was changed to IV meropenem (2 g) 8 hourly, IV polymyxin B (750000 units) 12 hourly, and 50000 units of polymyxin B intracerebroventricularly (IVT) daily. After five post-infusion doses, the sustained plasma concentration of polymyxin B was 3.85 μg/mL, an area under the curve (AUC) (0–24 h) of 92.43 mg*h/L, and CSF drug concentration of 15.86 μg/mL. On the 15th day of hospitalization, the patient had sudden bilateral pupillary dilatation, and brain CT suggested hydrocephalus (Figure 1B). Considering a severe intracranial infection resulting in ventricular adhesions, a right EVD was performed, enhancing CSF drainage to 200 mL per day. The previous anti-infective treatment regimen was maintained. On the 16th day of hospitalization, the CSF showed poor intracranial infection control (Table 1). Subsequently, a CAZ/AVI sensitivity test was performed, showing that the pathogen was sensitive to the drug. Susceptibility tests showed that CAZ/AVI is an effective therapeutic option. Consequently, the antibiotic regimen was adjusted to IV CAZ/AVI (2.5 g) 8 hourly, IV polymyxin B (750000 units) 12 hourly, and IVT polymyxin B (50000 units)

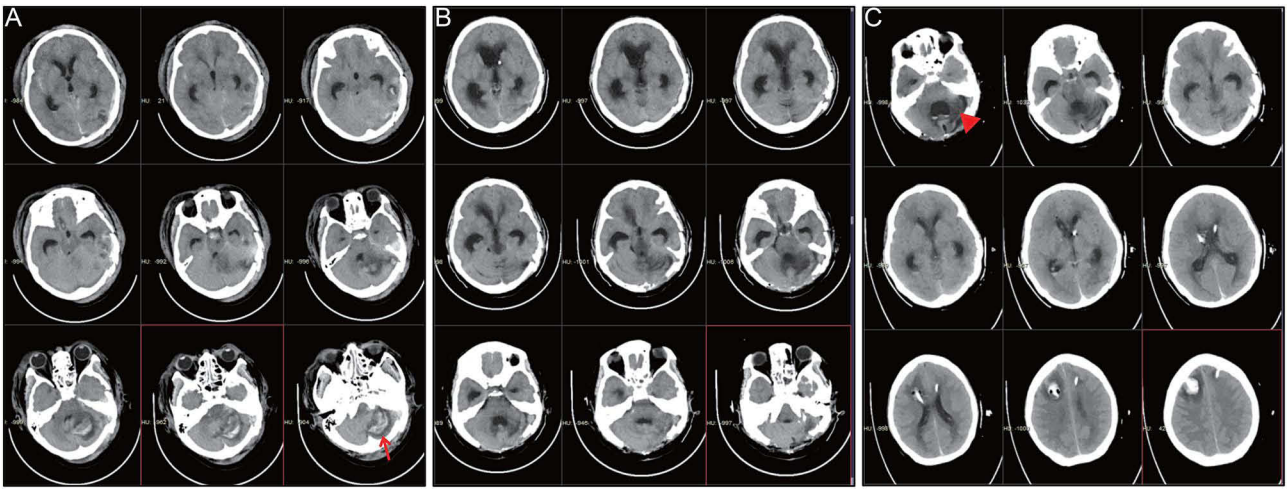

Figure 1 Patient's brain computed tomography. (**A**) The first brain CT in our hospital.Red arrow represents left cerebellar hematoma. **(B)** On the 15th day of hospitalization, the patient had sudden bilateral pupillary dilatation and the brain CT revealed hydrocephalus. **(C)** CSF culture was negative, and the brain CT revealed hydrocephalus relief; however, there was a separation of the fourth ventricles.Red arrow represents the fourth ventricle dilated.

Table 1 Cerebrospinal Fluid Analyses on Different Days

Date	CSF WBC Count, cells/mm3	CSF Glucose, mmol/L	CSF/blood glucose	CSF Protein, g/L	Culture
Day 1	3668	1.8	0.24	3	NA
Day 2	7026	1.4	0.13	3	NA
Day 5	3267	2.5	0.18	3	CRKP
Day 8	11,281	1.2	0.10	3	CRKP
Day 9	2086	3.2	0.21	3	CRKP
Day 10	68	7.0	0.46	1.15	CRKP
Day 11	25	6.0	0.44	0.48	Negative
Day 12	142	7.4	0.36	0.6	Negative
Day 13	108	6.8	0.50	1.19	Negative
Day 15	255	5.0	0.55	1.12	Negative

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cells; CRKP, Carbapenem-resistant *Klebsiella pneumoniae*; NA, not available. Date from diagnosis of intracranial infection.

Table 2 Susceptibility Results for Klebsiella Pneumoniae in Cerebrospinal Fluid

Antibiotic	MIC (μg/mL)	Antibiotic	MIC (μg/mL)
Ceftriaxone	64	Levofloxacin	8
Ceftazidime	64	Compound sulfamethoxazole	320
Cefoxitin	64	Piperacillin/tazobactam sodium	128
Cefepime	32	Cefoperazone/sulbactam	64
Amikacin	64	Aztreonam	64
Ertapenem	8	Minocycline	16
Imipenem	16	Tigecycline	8
Meropenem	16	Polymyxin	16

Abbreviation: MIC, minimum inhibitory concentration.

daily. On the 18th day of hospitalization (11th day of anti-infective treatment), CSF culture was initially negative. The CSF white blood cell count was low; however, CSF glucose levels increased in subsequent CSF tests (Table 1). A head CT revealed hydrocephalus relief; however, the fourth ventricle remained dilated (Figure 1C). After several consecutive negative results from CSF culture, the patient's temperature decreased, indicators of infection decreased, and the CSF became clear. The administration of the antibiotics (CAZ/AVI and polymyxin B) was continued. However, due to the patient's severe brain injury and a poor improvement in consciousness, the family finally decided to discontinue treatment on the 24th day of hospitalization. The CSF test and susceptibility results for PDR-Kp are shown in Table 1 and Table 2, respectively. The clinical course of treatment for this case is summarized in Figure 2.

Discussion

XDR/PDR gram-negative bacteria, particularly associated with CNS infections, pose a substantial global challenge due to severe clinical complications and high rates of morbidity and mortality.[7] An epidemiological study reported a mortality rate of 23.3% for CRKP intracranial infections.[8] Any delay in treatment could contribute to lasting neurological deterioration and increasing fatality rates.

In the current case, the patient experienced CSF rhinorrhea, EVD exceeding 5 days, and DC, which are risk factors for CNS infections. The CSF culture suggested infection with a PDR KPC-Kp. We describe our successful experience using a combination of systemic and IVT antibiotic therapy as a salvage strategy for such severe intracranial infections.

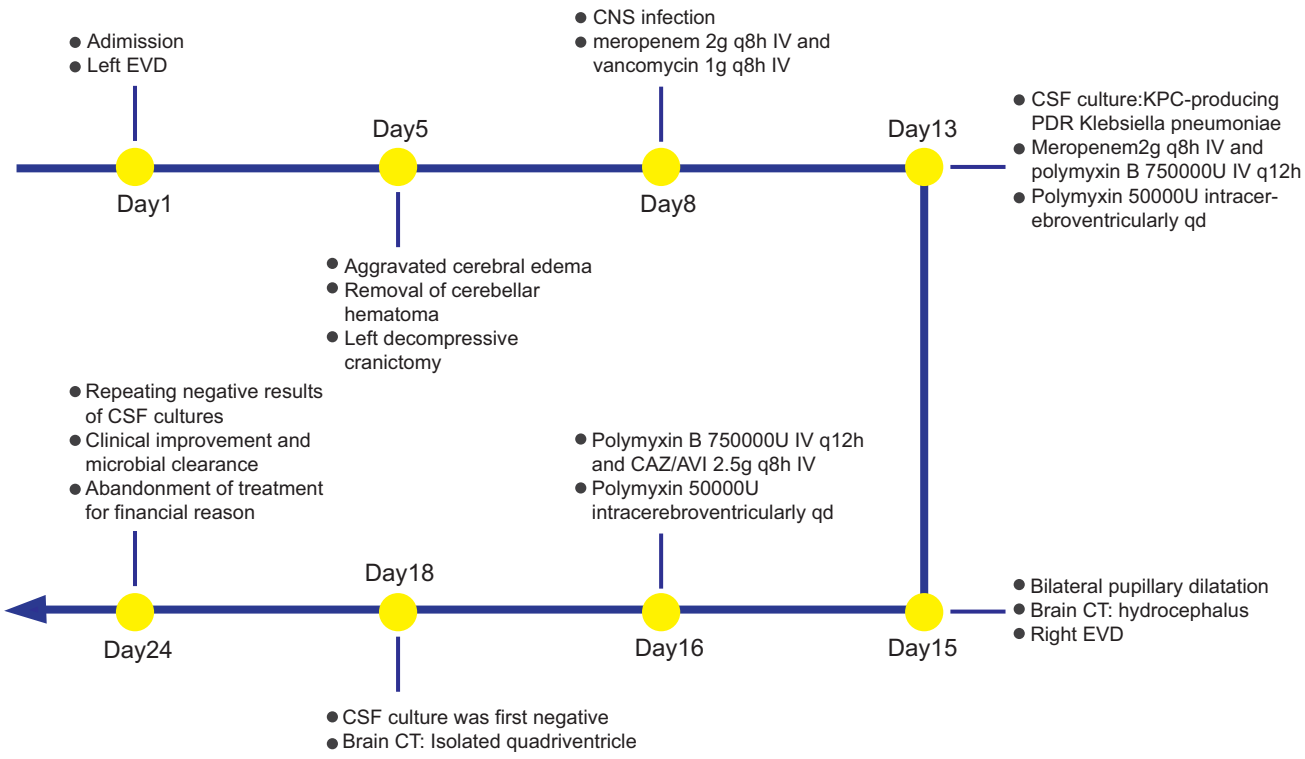

Figure 2 Clinical course of treatment for this case.

IVT administration of antibiotics can elevate the concentration of drugs within the CSF. This is essential for treating XDR/PDR gram-negative bacilli-associated intracranial infections.[9] Although data pertaining to drug pharmacokinetic and pharmacodynamic properties in the CSF remain scarce, the Infectious Diseases Society of America (IDSA) guidelines indicate that antibiotics for IVT treatment of CNS infections offer sustained CSF sterilization.[10] In cases of CNS infection, the concentration of polymyxin in CSF was only 5% of that in serum after an IV administration of polymyxin B,[11] which could not reach the local effective treatment concentration. Therefore, this treatment should be combined with local administration. The dose of IVT polymyxin varied; a report showed that when polymyxins are administered at doses exceeding 5.22 mg/day, CSF concentrations ranged from 2.0–9.7 mg/L over the entire dosing interval. The MIC of polymyxin against this CRKP was 2 mg/L.

Chinese experts recommend the IVT dose of polymyxin B to be 5 mg/d.[11] Based on relevant literature and guidelines, our patient received a 12-hourly IV polymyxin B (1.5 mg/kg) and a daily 5 mg IVT. After five doses post-infusion, the sustained plasma concentrations of polymyxin B was 3.85 μg/mL, AUC (0–24h)of 92.43 mg*h/L, reaching the guideline-recommended standard.[12]

CAZ/AVI, the combination of a third-generation cephalosporin and a β-lactamase inhibitor with in vitro activity against KPC-Kp, has been approved for treating complicated urinary tract infections, intra-abdominal infections and hospital-acquired pneumonia.[13] However, limited clinical studies and case reports have been published on the efficacy of CAZ/AVI in the treatment of CNS infections.[14–18] Only one experiment conducted on rabbits showed that both ceftazidime and avibactam exhibited a 38% mean CSF penetration, suggesting that CAZ/AVI displays good CSF permeability.[19]

Polymyxin has been revived as one of the last options for treating KPC-Kp. However, polymyxin B can amplify the resistant subpopulation, leading to heteroresistance, which creates barriers to its efficacy and results in poor clinical outcomes. The current case had an MIC of 16 μg/mL for polymyxin against PDR-Kp. Although polymyxin B target concentrations were achieved, initial targeted treatment was not effective. There has been limited research on the efficacy of available antibiotics against heteroresistant strains. A study[20] suggested that the in vitro activity of polymyxin B could

be improved when it is combined with CAZ/AVI. Therefore, delaying or suppressing heteroresistance is potentially valuable for improving the clinical outcome of refractory CRKP infection. Finally, our polymyxin-resistant PDR CRKP intracranial infections were successfully treated with IV CAZ/AVI and polymyxin B, as well as IVT polymyxin B.

There is no consensus on the optimal treatment duration for CNS infection with XDR/PDR CRKP; hence, it needs to be individualized based on the severity of the infection and clinical response. In the current case, the CSF culture was negative on the 5th day of target therapy. During the treatment, CSF was collected several times for examination and culture, indicating that the intracranial infection was gradually controlled, leading to clinical improvement and microbial clearance. On the 18th day of treatment, the head CT showed a dilatation of the fourth ventricle, the cause of which could not be ruled as being caused by infection. Therefore, anti-infective treatment was continued; however, the patient was discharged abruptly, and the specific antibiotic course was not determined. No hepatic or renal injury, epilepsy, diarrhea, skin pigmentation, rash, or other adverse reactions were observed in the patients during treatment.

Conclusions

Based on the reported case in this study and the available literature, IV CAZ/AVI and polymyxin B alongside IVT polymyxin B may be an effective salvage treatment for CNS infections caused by PDR CRKP. This study could not specify the treatment duration and did not perform a therapeutic drug monitoring of CAZ-AVI. Further studies are required to evaluate the efficacy of CAZ/AVI in combination with polymyxin B for treating CNS infections caused by CRKP.

Ethical Statement and Informed Consent

The Ethics Committee of The Second Hospital & Clinical Medical School, Lanzhou University, approved the study. The patient provided written informed consent for publication of this case and the accompanying images.The ethical approval number was2024A-719.

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Author Contributions

All authors made significant contributions to the work reported, whether in the conception, study design, execution, data acquisition, analysis and interpretation, or in all these areas. They participated in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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