Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE REPORT

Combination Therapy with Ceftazidime-Avibactam, Aztreonam, and Topical Polymyxin B for NDM-Producing *Klebsiella pneumoniae* CNS Infection: A Case Report

Guanghong Qi, Wenkai Cong, Mingda Zhang, Shengjie Wang, Zhenwei Bai, Biao Li, Hongwei Chen

Cerebrospinal Fluid Disease Department, Aviation General Hospital, Beijing, People's Republic of China

Correspondence: Hongwei Chen, Email hongwei12@163.com

Background: Central nervous system (CNS)-associated infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) represent a major therapeutic challenge because of limited antibiotic penetration and severe clinical progression. Strains co-producing both *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM) exhibit extensive drug resistance, including reduced susceptibility to ceftazidime–avibactam (CZA), leaving few effective treatment options. Reports of post-neurosurgical CNS infections caused by CZA-resistant, dual-carbapenemase–producing *K. pneumoniae* remain extremely uncommon.

Case Presentation: A 61-year-old man developed a severe postoperative CNS infection following decompressive craniectomy for cerebellar infarction. The initial microbiology report from a previous hospital identified a KPC-positive, NDM-negative *K. pneumoniae* isolate, and treatment with intravenous CZA plus topical polymyxin B irrigation was initiated but proved ineffective. After transfer to our institution, repeat testing using a more sensitive molecular panel revealed that the pathogen actually co-harbored both KPC and NDM and was resistant to CZA, explaining the lack of initial clinical response. Based on these results, the antimicrobial regimen was modified to simultaneous intravenous ceftazidime–avibactam and aztreonam, together with topical polymyxin B irrigation via the surgical drainage catheter. The patient's fever resolved within several days, cerebrospinal fluid parameters progressively normalized, and cultures became negative by treatment day 20. Subsequent complications required external ventricular drainage, neuroendoscopic septostomy, and eventual ventriculoperitoneal shunt placement. No nephrotoxicity or neurotoxicity occurred. At three-month follow-up, no recurrence of infection was observed, although neurological improvement was limited by the underlying brain injury.

Conclusion: This case illustrates the diagnostic importance of repeat carbapenemase testing in refractory CNS infections and suggests that combined ceftazidime–avibactam plus aztreonam, with adjunctive topical polymyxin B, may be a useful therapeutic strategy for CZA-resistant, KPC- and NDM-co-producing *K. pneumoniae* CNS infections.

Keywords: CNS infection, NDM-producing *Klebsiella pneumoniae*, KPC-producing *Klebsiella pneumoniae*, ceftazidime–avibactam, aztreonam, polymyxin B, carbapenem-resistant Enterobacterales

Introduction

In recent years, with the widespread use of carbapenem antibiotics, infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) have resulted in high mortality and disability rates owing to limited antimicrobial options, and a mortality rate of 50% has been reported.[1–3] This mortality rate has been reported primarily in patients with severe healthcare-associated infections, including bloodstream and central nervous system (CNS)-associated infections, particularly in critically ill or post-surgical populations. Compared with other multidrug-resistant Gram-negative pathogens, such as carbapenem-resistant *Acinetobacter baumannii*, CRKP, especially strains harboring multiple carbapenemases, has been associated with similarly high or even higher mortality rates, underscoring its substantial clinical burden. As a novel β-lactam/β-lactamase inhibitor combination, ceftazidime-avibactam sodium exhibits antibacterial activity against KPC-producing CRKP strains,

https://doi.org/10.2147/IDR.S608393
Received: 11 March 2026
Accepted: 6 May 2026
Published: 12 May 2026

particularly against those that produce *K. pneumoniae* carbapenemase (KPC) enzymes.[4] Recent molecular epidemiological studies further highlight the rapid dissemination of carbapenem and colistin resistance genes among nosocomial Gram-negative pathogens. For example, Abbas et al[5] reported a high prevalence of carbapenemase and colistin resistance determinants among multidrug-resistant *Acinetobacter baumannii* isolates in Iraqi hospitals, emphasizing the growing regional and global threat posed by highly resistant Gram-negative organisms. These findings reinforce the urgent need for mechanism-guided therapeutic strategies across different resistant species. However, the emergence of *K. pneumoniae* strains co-harboring multiple carbapenemases, particularly KPC and New Delhi metallo-β-lactamase (NDM), has further complicated antimicrobial therapy. These isolates often exhibit extensive resistance to most available β-lactams and may demonstrate reduced susceptibility or resistance to ceftazidime–avibactam, substantially limiting effective treatment options. Dual-enzyme–producing isolates pose a remarkably greater therapeutic challenge than strains harboring a single carbapenemase, as they combine the broad hydrolytic activity of serine carbapenemases with the potent β-lactam–degrading capacity of metallo-β-lactamases, rendering most β-lactams, including ceftazidime–avibactam, ineffective. Management becomes particularly challenging when such multidrug-resistant organisms cause intracranial infections, as the blood–brain barrier restricts antibiotic penetration and delays in effective therapy can lead to severe neurological sequelae or death. These challenges are amplified in intracranial infections, where the blood–brain barrier (BBB) significantly restricts antimicrobial penetration, achieving therapeutic cerebrospinal fluid (CSF) concentrations is difficult, and even short delays in appropriate therapy can rapidly worsen neurological outcomes. Under physiological conditions, the BBB significantly limits the penetration of many hydrophilic antibiotics, including β-lactams and polymyxins, into the CSF. Although meningeal inflammation may transiently increase BBB permeability, CSF concentrations of several agents often remain lower than corresponding plasma levels and may not consistently exceed the minimum inhibitory concentration for highly resistant pathogens. Furthermore, pharmacokinetic variability in critically ill or post-neurosurgical patients, such as altered CSF circulation, ventricular drainage, or blood–CSF barrier disruption, can further compromise predictable drug exposure in the CNS. These pharmacokinetic constraints complicate the achievement of sustained bactericidal activity in intracranial infections. Aztreonam, which is not hydrolyzed by NDM, is often combined with ceftazidime-avibactam sodium to enhance its efficacy against NDM-producing strains.[4,6] However, aztreonam alone is often ineffective against NDM-producing *K. pneumoniae* because these isolates frequently co-produce other β-lactamases, such as KPC, ESBLs, or AmpC enzymes, which can hydrolyze aztreonam. Avibactam is capable of inhibiting these serine β-lactamases, while lacks activity against metallo-β-lactamases, such as NDM. Therefore, when ceftazidime-avibactam is administered in combination with aztreonam, avibactam inhibits the co-produced serine β-lactamases, thereby protecting aztreonam from enzymatic degradation and allowing aztreonam to retain activity against NDM-producing strains. This complementary mechanism forms the pharmacological basis for the synergistic activity of the ceftazidime-avibactam plus aztreonam combination against NDM-producing *Enterobacterales*. Clinically, this combination is commonly used for NDM-related pulmonary and bloodstream infections with favorable outcomes.[7,8] Management of CRKP intracranial infections remains particularly challenging because several antibiotics demonstrate limited penetration across the BBB. Current therapeutic strategies generally rely on polymyxins, tigecycline, aminoglycosides, or newer β-lactam/β-lactamase inhibitor combinations;[9] however, these regimens are often associated with suboptimal CSF concentrations, significant toxicity, and variable clinical efficacy. Systemically administered polymyxin B demonstrates limited penetration into the CSF, with reported CSF-to-plasma ratios generally remaining low, particularly in the absence of significant meningeal inflammation. As a result, intravenous administration alone may fail to achieve therapeutic intracranial concentrations, especially against pathogens with elevated minimum inhibitory concentrations. For severe or refractory CNS infections caused by multidrug-resistant Gram-negative organisms, intrathecal or intraventricular administration of polymyxin B has been recommended as an adjunctive approach to achieve higher local antimicrobial concentrations.[10] Several clinical case series have demonstrated that intrathecal or intraventricular administration of polymyxin B achieves substantially higher CSF drug concentrations than systemic therapy alone, leading to improved microbiological clearance in ventriculitis and post-neurosurgical meningitis caused by multidrug-resistant Gram-negative organisms. Reported clinical success rates in these settings indicate that adjunctive local polymyxin therapy can remarkably enhance bacterial eradication while maintaining an acceptable safety profile when carefully monitored. Regarding NDM-positive CRKP intracranial infection, systemic therapy alone may fail to achieve sustained bactericidal concentrations within the CSF, particularly in patients with ventricular obstruction or postoperative anatomical alterations. Therefore, adjunctive

intrathecal polymyxin B may serve as a pharmacologically rational strategy to overcome BBB limitations and rapidly reduce intracranial bacterial load, complementing systemic enzyme-guided therapy. Given the complementary antibacterial mechanisms of ceftazidime-avibactam and aztreonam against strains producing both serine and metallo-β-lactamases, combining these agents with intrathecal polymyxin B may provide both systemic and local antimicrobial activity in the CNS. Nevertheless, evidence supporting this triple-combination strategy for intracranial infection caused by KPC- and NDM-co-producing *K. pneumoniae* remains extremely limited.

Despite the increasing use of ceftazidime-avibactam plus aztreonam for metallo-β-lactamase–producing infections, clinical evidence supporting the addition of intrathecal polymyxin B in the management of intracranial infections caused by KPC- and NDM-co-producing *K. pneumoniae* remains extremely limited. Specifically, there is a lack of detailed case documentation describing treatment strategies, pharmacological rationale, and clinical outcomes in ceftazidime-avibactam–resistant dual-carbapenemase CNS infections. Notably, while combination ceftazidime–avibactam and aztreonam therapy has been reported in systemic infections, evidence supporting its use in CNS infections caused by KPC- and NDM-co-producing strains remains extremely sparse, and successful management of such cases is rarely documented. Therefore, this report aimed to address this gap by presenting a mechanism-guided triple therapeutic approach and its clinical outcome. This report described a case of post-neurosurgical intracranial infection caused by ceftazidime-avibactam-resistant CRKP co-harboring KPC and NDM that was managed with ceftazidime-avibactam plus aztreonam combined with intrathecal polymyxin B, with the aim of providing clinical insight into the potential role of this therapeutic approach. Clinical reports describing the management of intracranial infection caused by *K. pneumoniae* co-producing KPC and NDM, particularly those resistant to ceftazidime–avibactam, remain extremely limited.

Case Presentation

A 61-year-old man was admitted to our hospital on February 7, 2025, who presented with a history of cerebellar infarction requiring posterior fossa decompressive craniectomy approximately five weeks prior to admission and a persistent fever that had lasted for about three weeks. The patient had no history of hypertension, diabetes mellitus, chronic kidney disease, or immunosuppressive disorders, and no prior history of neurosurgical procedures or CNS-associated infections. He was not receiving long-term corticosteroids, immunosuppressive therapy, or chemotherapy before admission. Prior to the onset of the current illness, he was independent in daily activities. Written informed consent for publication of this case and the accompanying images was obtained from the patient's legal representative. Ethics approval for this study was granted by the Ethics Committee of Aviation General Hospital (Beijing, China; Approval No.: HK2025-81).

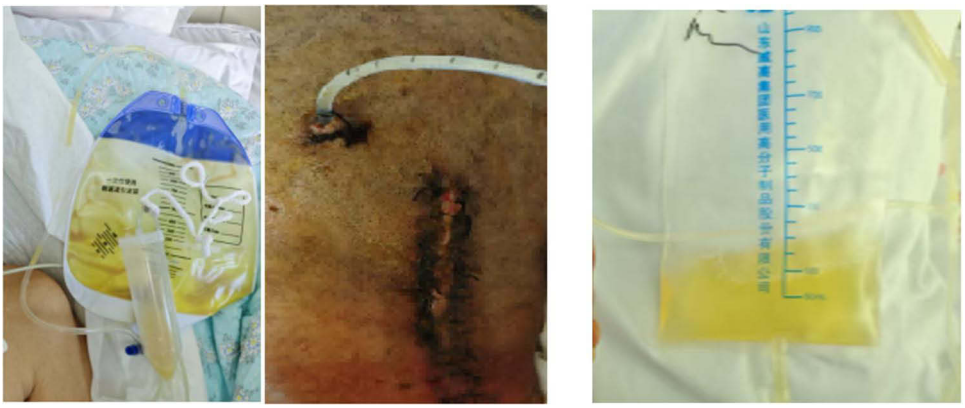
To clarify the clinical timeline, the patient's neurological event and neurosurgical procedures occurred in early January 2025, and he was transferred to our hospital on February 7, 2025, following approximately three weeks of persistent postoperative fever and wound leakage.

Treatment Course at Previous Hospital: On January 1, 2025, the patient developed extensive cerebellar infarction with cerebral herniation and underwent posterior fossa decompressive craniectomy, external ventricular drainage (EVD) and surgical site drainage. Postoperatively, consciousness gradually improved with ability to follow simple commands. On January 16, 2025, the EVD tube was removed and lumbar cistern drainage was performed, yielding clear CSF. On the morning of January 17, 2025, the surgical site drainage tube was removed; however, occipital incision leakage occurred in the afternoon, accompanied by purulent, turbid CSF drainage from the lumbar cistern and fever up to 39.5 C. CSF examination revealed a white blood cell (WBC) count of 50,000 cells/μL and glucose level of 0.02 mmol/L. On January 18, 2025, occipital incision debridement and suturing were performed and a surgical site drainage tube was placed for yellow purulent secretion drainage. On January 20, 2025, the lumbar cistern drainage tube was removed due to obstruction. On January 21, 2025, the patient lapsed into coma, with body temperature fluctuating between 38.0 and 38.5 °C, accompanied by surgical site bulging and persistent incision leakage. Emergency debridement and suturing were repeated, followed by the placement of a surgical site drainage tube and multiple lumbar punctures. Lumbar puncture revealed a CSF WBC count of 6250 cells/μL, and next-generation sequencing (NGS) of the CSF identified *K. pneumoniae* (45,684 reads) and *Acinetobacter baumannii* (1894 reads). Given the remarkably lower sequencing reads for *A. baumannii* and the absence of corresponding organism growth on multiple subsequent CSF and wound cultures, the organism was considered more likely a colonizer or low-level contaminant rather than a true co-pathogen. In contrast, *K. pneumoniae* demonstrated overwhelming dominance in NGS quantification,

persistent recovery from CSF cultures, and concordance with clinical deterioration, supporting its role as the primary causative pathogen. Nonetheless, the initial empirical regimen of vancomycin plus meropenem provided partial coverage against carbapenem-susceptible *A. baumannii*, and tigecycline, introduced later, provides in vitro activity against several multidrug-resistant *A. baumannii* strains. Therefore, although *A. baumannii* was not considered as a major pathogen in this infection, the antimicrobial regimen during the early course still provided sufficient collateral antimicrobial activity. Metagenomic next-generation sequencing of CSF samples was performed by a certified clinical laboratory using a standardized DNA extraction and high-throughput sequencing platform. Sequence reads were aligned against a comprehensive microbial genome database for pathogen identification, and results were interpreted according to the laboratory's validated clinical reporting criteria. The diagnosis of CNS-associated infections was confirmed and antibiotic therapy was escalated to vancomycin and meropenem. This escalation aligned with standard recommendations for post-neurosurgical meningitis, in which meropenem is commonly used for Gram-negative bacilli and vancomycin is recommended for coverage of Gram-positive organisms, including *Staphylococcus aureus* and coagulase-negative staphylococci. On January 22, 2025, carbapenemase typing revealed *KPC*-positive and *NDM*-negative strains, prompting an adjustment in antibiotic therapy to ceftazidime/avibactam sodium and tigecycline via intravenous infusion combined with intermittent polymyxin B irrigation. This adjustment was consistent with available susceptibility data at the referring hospital and with current guidelines suggesting ceftazidime–avibactam as first-line therapy for KPC-producing Enterobacterales CNS infections, with tigecycline or polymyxins considered as adjunctive agents in severe or refractory cases. However, the fever was poorly controlled and yellow purulent secretion persisted from the surgical site drainage tube. Because the referring hospital reported a KPC-positive and NDM-negative isolate, the initial treatment strategy was based on the assumption that the pathogen produced only a serine carbapenemase. However, after transfer to our institution, repeat carbapenemase testing using a more sensitive PCR-based panel demonstrated that the strain actually co-harbored both KPC and NDM. This discrepancy was most likely attributable to methodological differences in testing sensitivity or a false-negative NDM result in the initial assay rather than true strain evolution. The presence of an undetected NDM enzyme explains the patient's poor response to ceftazidime–avibactam monotherapy, as avibactam lacks inhibitory activity against metallo-β-lactamases. Recognition of the dual-carbapenemase profile subsequently guided adjustment to combination therapy with ceftazidime–avibactam plus aztreonam. The patient was transferred to our hospital 17 days after ineffective treatment.

Upon admission, the patient was comatose with stable vital signs, a Glasgow Coma Scale (GCS) score of 5, and a maximum temperature of 38.6 °C. Neurologically, the patient exhibited no spontaneous eye opening (E1), incomprehensible sounds due to intubation (V1), and abnormal extension in response to painful stimuli (M3), corresponding to a total GCS score of 5. Deep brainstem reflexes, including pupillary and corneal responses, were markedly depressed. No limb localization or purposeful movement was found. The patient was intubated and showed no signs of spontaneous eye opening or neck stiffness. The bilateral pupils were approximately 1 mm in diameter with no light reflex. The bilateral Babinski signs were negative, and there were no indications of meningeal irritation. Abundant purulent discharge was noted from the surgical site drainage tube with poor incision healing (Figure 1A). Despite markedly purulent CSF and extremely elevated inflammatory indices, classic meningeal signs, such as neck stiffness, Kernig's sign, and Brudzinski's sign were absent. This presentation is consistent with fulminant post-neurosurgical meningitis, in which prior decompressive craniectomy, CSF diversion, and impaired intracranial pressure regulation can blunt meningeal irritation responses and mask typical physical examination findings. The markedly constricted, nonreactive pupils (approximately 1 mm) indicated significant brainstem dysfunction, most likely involving the midbrain or pontine pupillary pathways. This finding correlated with the patient's deep coma and indicated a combination of mass-effect-related brainstem compression from the prior cerebellar infarction and secondary injury from severe CNS infection. The coexistence of absent meningeal signs and notable pupillary abnormalities therefore reflected advanced neurological injury rather than a mild inflammatory state, demonstrating the severity of the patient's underlying brain damage before and during the infectious process.

Laboratory test results of surgical site secretions on admission indicated WBC count of 130,565 cells/μL, polymorphonuclear cell percentage of 97%, glucose level of 0.25 mmol/L, protein level of 14.7 g/L, and lactate dehydrogenase level of 1319.7 U/L (Table 1). Routine blood test revealed WBC count of 5.3×10^9/L, neutrophil percentage of 69.2%, C-reactive protein (CRP) level of 7.33 mg/L, and procalcitonin (PCT) level of 0.06 ng/mL. Blood biochemistry revealed normal liver and kidney function, fasting blood glucose level of 6.08 mmol/L, and normal electrolytes. Contrast-



A B

Figure 1 (**A**) Abundant purulent secretion from surgical site drainage and poor incision healing on admission; (**B**) On day 10 of treatment, the cerebrospinal fluid (CSF) became pale yellow, with nearly complete resolution of the purulent floccules.

enhanced cranial CT: No significant enhancement was found around the occipital surgical site, and there was no dilation of the bilateral ventricles or the fourth ventricle. A hypodense lesion was observed in the cerebellum (Figure 2A). According to the NGS results and enzyme typing from the previous hospital, the initial regimen in our department consisted of ceftazidime-avibactam sodium 2.5 g IV every 8 h, polymyxin B 500,000 units IV, and surgical site irrigation with polymyxin B 5 mg. CSF, secretions, and blood cultures were sent for analysis, and gram-negative bacilli were identified after 2.8 h; the regimen was not altered.

Antimicrobial susceptibility testing was performed using the broth microdilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. Minimum inhibitory concentrations (MICs) were interpreted according to CLSI breakpoints, except for eravacycline, which was interpreted based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. On the second day of admission, the results confirmed carbapenem-resistant *K. pneumoniae* (Table 2), and antimicrobial susceptibility testing indicated resistance to ceftazidime-avibactam (MIC=8 μg/mL) and aztreonam (MIC>64 μg/mL), and sensitivity to polymyxin B (MIC=1 μg/mL) and eravacycline. Carbapenemase typing revealed KPC- and NDM-positivity (Table 3). These susceptibility results provided a mechanistic explanation for the patient's poor response to ceftazidime–avibactam monotherapy at the previous institution and justified transitioning to combination therapy with ceftazidime–avibactam plus aztreonam, being consistent with enzyme-guided therapy for isolates co-producing serine and metallo-β-lactamases. Carbapenemase genes were detected using polymerase chain reaction (PCR) assays targeting common carbapenemase genes (KPC, NDM, VIM, IMP, and OXA-48), followed by electrophoretic analysis according to the manufacturer's instructions. Because NDM is a metallo-β-lactamase that is not inhibited by avibactam, ceftazidime-avibactam alone is ineffective against isolates co-producing KPC and NDM. However, avibactam can inhibit the co-produced serine β-lactamase (KPC), thereby

Table 1 Results of CSF Examination

Time	CSF White Blood Cells (cells/μL)	CSF Glucose (mmol/L)	CSF Protein (g/L)	CSF Lactate Dehydrogenase (U/L)	CSF Culture
Day 1	130,565	0.25	14.7	1319.7	CRKP
Day 2	175,600	0.20	24.03	2544.7	CRKP
Day 5	80,307	0.20	5.67	1544.6	CRKP
Day 7	7796	2.36	3.28	513.5	CRKP
Day 10	22,993	3.65	3.54	441.3	CRKP
Day 20	51	3.96	1.12	67.1	Negative

Notes: Normal reference ranges: CSF white blood cells: 0–5 $\times 10^6$/L; CSF glucose: 2.5–4.5 mmol/L; CSF protein: 0.15–0.45 g/L; CSF lactate dehydrogenase: <40 U/L; CSF culture: Negative.

https://doi.org/10.2147/IDR.S608393

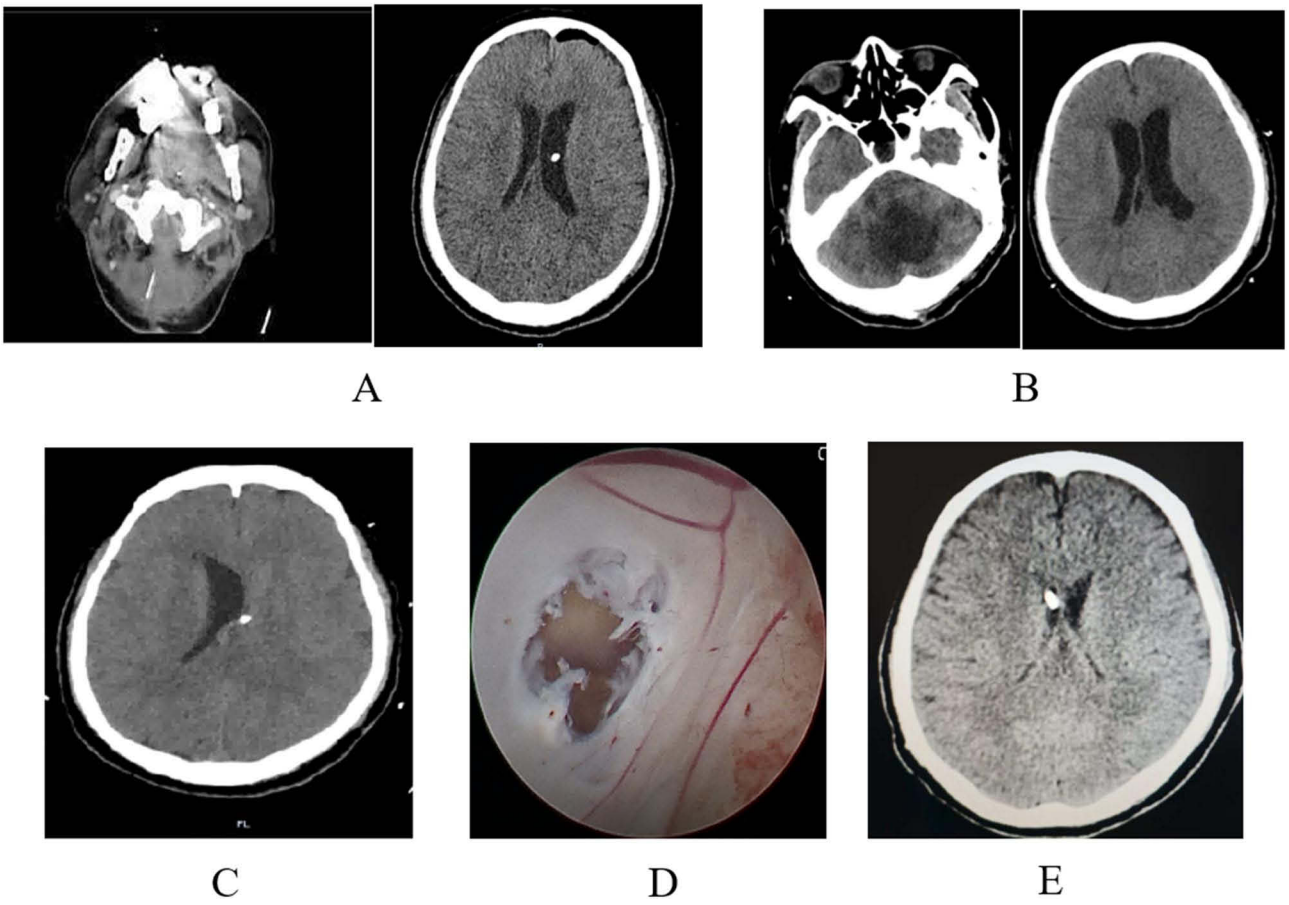


Figure 2 (**A**) No obvious enhancement around the surgical site; (**B**) Ventricular dilation with adhesion to the surgical site, requiring external ventricular drainage; (**C**) Bilateral ventricular adhesion; (**D**) Successful ventriculostomy; (**E**) Satisfactory ventricular morphology after ventriculoperitoneal shunt.

protecting aztreonam from hydrolysis and restoring its activity against NDM-producing strains. Therefore, a combination regimen of ceftazidime-avibactam and aztreonam was selected to overcome the dual-carbapenemase resistance mechanism.

Table 2 Antimicrobial Susceptibility of CSF Isolate (*Klebsiella pneumoniae*)

Antibiotic	Abbreviation	KB Zone (mm)	MIC (μg/mL)	Interpretation	Standard Used
Ticarcillin/Clavulanic Acid	TCC	—	≥128	Resistant	CLSI 2024
Aztreonam	ATM	—	≥64	Resistant	CLSI 2024
Tigecycline	TGC	—	≥8	Resistant	FDA Breakpoints
Minocycline	MNO	—	≥16	Resistant	CLSI 2024
Trimethoprim–Sulfamethoxazole	SXT	—	≥320	Resistant	CLSI 2024
Amikacin	AMK	—	≥64	Resistant	CLSI 2024
Meropenem	MEM	—	≥16	Resistant	CLSI 2024
Imipenem	IPM	—	≥16	Resistant	CLSI 2024
Colistin	COL	—	1	Susceptible	EUCAST 2024
Tobramycin	TOB	—	≥16	Resistant	CLSI 2024
Ceftazidime–Avibactam	CZA	—	8	Resistant	CLSI 2024
Eravacycline	ERV	15	—	Susceptible	EUCAST 2024

Notes: KB = Kirby–Bauer disk diffusion method. Interpretive criteria were applied according to CLSI M100 (34th edition, 2024) unless otherwise specified. Colistin and eravacycline interpretations follow EUCAST 2024 breakpoints. Tigecycline susceptibility was interpreted using FDA breakpoints, as CLSI/EUCAST do not provide breakpoints for Enterobacterales.

https://doi.org/10.2147/IDR.S608393

Table 3 Enzyme Typing Results of CSF Isolate

Subjects	Results	Reference
KPC	Positive	Negative
NDM	Positive	Negative
VIM	Negative	Negative
OXA-48	Negative	Negative
IMP	Negative	Negative

In accordance with the Sanford Guide to Antimicrobial Therapy and supporting literature indicating that aztreonam 8 g/day, in combination with ceftazidime-avibactam sodium 7.5 g/day via continuous or 2-hour infusion, achieves complete bacterial eradication and inhibition of resistance, the following regimen was determined, considering the patient's clinical condition, antimicrobial susceptibility results, and the pharmacokinetics of drug penetration into the CSF: 1) Ceftazidime-avibactam sodium 2.5 g IV every 8 h; aztreonam 2 g IV every 8 h; both administered simultaneously via a Y-type tube at a constant rate over 2 h; 2) Polymyxin B was prepared by dissolving 5 mg of polymyxin B in 10 mL of sterile normal saline (final concentration 0.5 mg/mL) and was administered slowly through the surgical site drainage catheter once daily. After administration, the drainage tube was clamped for approximately 2 h to allow local drug retention before reopening for continuous drainage. Topical polymyxin B irrigation was continued for 20 days until CSF parameters improved and cultures became negative. In addition, given the limited penetration of several antibiotics into the CNS and the susceptibility of the isolate to polymyxin B, topical administration through the surgical drainage tube was used to achieve higher local drug concentrations at the site of infection. The off-label administration of polymyxin B via local irrigation was conducted in accordance with institutional policies and was approved by the hospital's clinical ethics committee, with full oversight throughout the patient's treatment. On day 3, the patient's fever was resolved (temperature 36.0–38.0°C), in which the positive culture time of purulent secretion was prolonged by 6.5 h, and there was reduced purulent drainage. The patient exhibited a rigid response to pain, without spontaneous eye opening. On day 10, the temperature was stabilized at 36.0–37.5 °C; the positive culture time was prolonged by 8.0 h, and the CSF turned pale yellow with nearly complete resolution of purulent floccules (Figure 1B). The patient achieved spontaneous eye opening and remained comatose, with muscle contraction in response to pain. On day 19, the patient's coma deepened and cranial CT revealed ventricular dilation (Figure 2B). External ventricular drainage was performed, yielding clear CSF, and repeated CSF cultures were negative with normal biochemical and routine indices. The ventricular catheter was connected to a closed drainage system with the drainage chamber positioned 10–15 cm above the external auditory canal. The drainage volume and CSF characteristics were monitored daily to guide infection control and intracranial pressure management. On day 20, the patient was afebrile with no obvious drainage from the surgical site tube, which was removed one month. Continuous CSF purification and drainage were performed. On day 38, bilateral ventricular adhesions were observed during CSF drainage (Figure 2C). Irrigation with urokinase (20,000 units) failed to correct the ventricular asymmetry. External ventricular drainage was performed via a right frontal approach using a standard ventricular catheter connected to a closed drainage system. The drainage height was maintained at approximately 10–15 cm above the external auditory canal to regulate CSF outflow. Surgical site drainage was maintained to evacuate purulent secretions and monitor wound infection. A neuroendoscopic septostomy was performed on day 53 (Figure 2D), which resulted in satisfactory ventricular symmetry (Figure 2E). On day 116, a ventriculoperitoneal shunt was placed after normalization of the CSF indices. Despite successful infection control, the patient remained comatose at discharge (GCS score, 9) because of severe pre-admission brain damage. CSF examination, antimicrobial susceptibility, and enzyme typing results are summarized in Tables 1–3. The treatment course is shown in Figure 3.

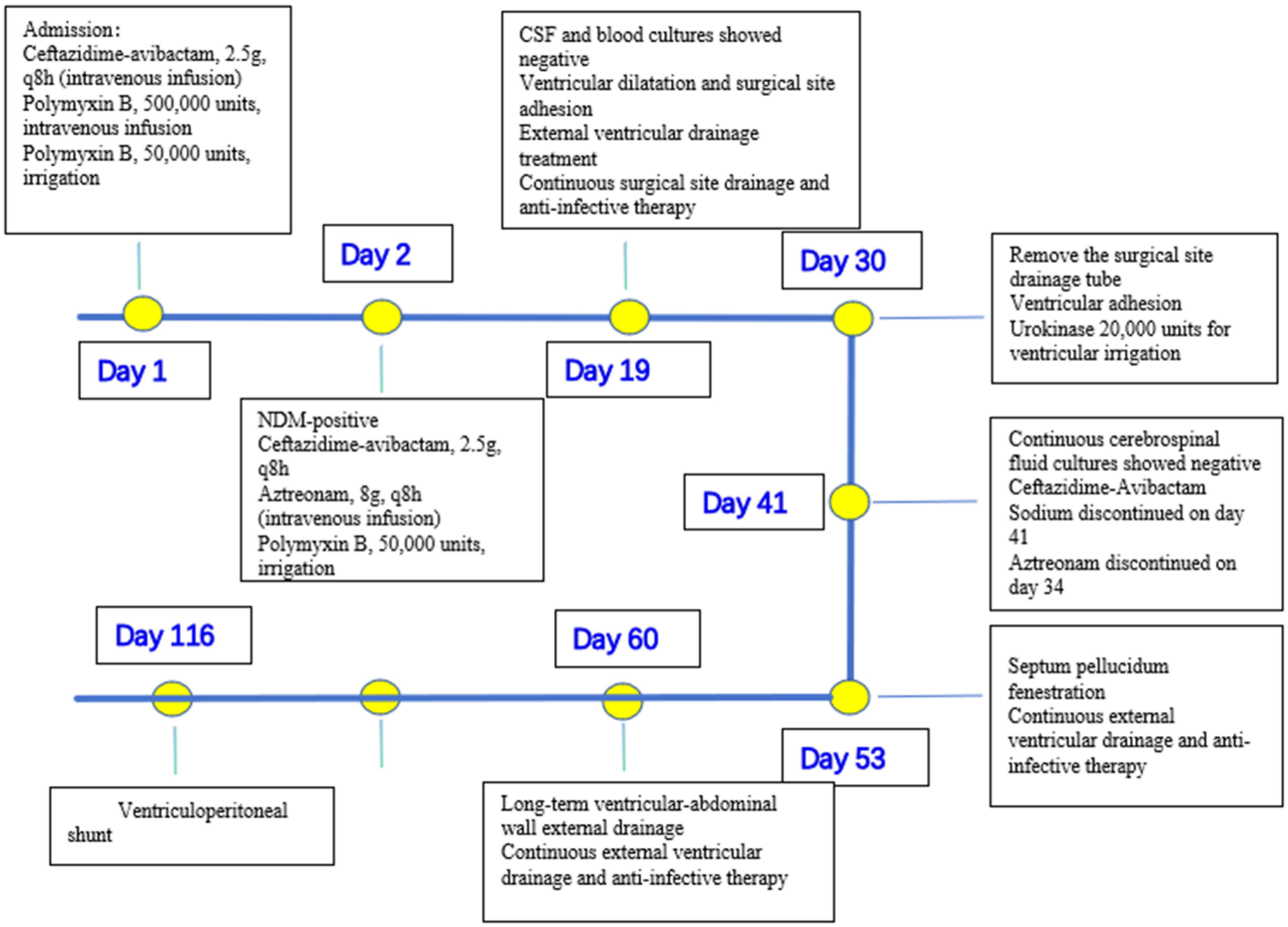


Figure 3 Flowchart of the treatment over time.

Discussion

The treatment of intracranial infections caused by CRKP is challenging. Epidemiological studies have reported a 28-day mortality rate of up to 50% for intracranial CRKP infections,[9] particularly when strains co-produce KPC and NDM enzymes, rendering traditional regimens ineffective.[10] This case highlights the effectiveness of enzyme typing-guided combination antimicrobial therapy for optimizing treatment outcomes and provides valuable insights for managing similar complex cases. Because these findings derive from a single case, they should be interpreted as preliminary clinical evidence rather than definitive proof of therapeutic superiority. The findings indicate a potential benefit of enzyme guided combination therapy, while further studies are required to validate its broader applicability. The present case is particularly noteworthy because it describes the successful management of a post-neurosurgical CNS-associated infection caused by a highly resistant CRKP strain co-producing both KPC and NDM carbapenemases. The successful use of enzyme-typing–guided triple combination therapy consisting of ceftazidime-avibactam, aztreonam, and adjunctive local polymyxin B provides practical clinical evidence for managing infections caused by dual-carbapenemase–producing organisms, which are often associated with extremely limited therapeutic options.

In recent years, the global incidence of CRKP infections has increased significantly, and NDM has become one of the most widely distributed carbapenemase genes.[11] Similarly, carbapenemase-encoding genes have been reported across multiple nosocomial pathogens, including *Burkholderia cepacia* and *Aeromonas sobria*, further highlighting the expanding distribution and clinical impact of carbapenemase producers in hospital settings.[12] The uniqueness of this case lies in the strain co-producing KPC and NDM enzymes, whose combined resistance mechanisms led to failure of the initial therapy (ceftazidime-avibactam sodium + intermittent polymyxin B irrigation). Several factors likely contributed to the

treatment failure at the referring hospital. Firstly, ceftazidime-avibactam combined with tigecycline and intermittent polymyxin B irrigation was suboptimal for a strain co-producing both KPC and NDM, because ceftazidime-avibactam cannot inhibit metallo-β-lactamases such as NDM, resulting in persistent ceftazidime hydrolysis and inadequate β-lactam activity. Secondly, the use of polymyxin B through intermittent and low-frequency irrigation may not have achieved sustained therapeutic drug concentrations within the surgical cavity, limiting its bactericidal effectiveness. Thirdly, the initial carbapenemase typing at the referring hospital incorrectly identified the isolate as NDM-negative, delaying the recognition of dual carbapenemase production and leading to the continuation of an ineffective antimicrobial regimen. Together, these factors explain the patient's lack of clinical improvement prior to transfer and highlight the importance of accurate and timely enzyme typing, appropriate drug selection, and rational optimization of local antimicrobial administration. Previous Chinese research has demonstrated high carriage rates of blaKPC-2 and blaNDM in CRKP isolates,[13] emphasizing the importance of comprehensive enzyme typing in clinical management. Timely and accurate enzyme typing not only guides targeted antimicrobial therapy, but also provides critical data for molecular epidemiological tracking. The pharmacokinetic and pharmacodynamic rationale for the selected regimen is critical in the context of CNS-associated infections, where adequate antibiotic exposure in the CSF is essential for therapeutic success.[13] Both ceftazidime and aztreonam demonstrate moderate penetration across the inflamed BBB, achieving approximately 10–30% of plasma concentrations in the CSF, which can reach therapeutic levels when high-dose, prolonged infusion regimens are used.[4,14] Although data on avibactam's independent CSF penetration are limited, pharmacokinetic modeling and clinical observations suggest that, when dosed as ceftazidime-avibactam 2.5 g q8h and administered by an extended 2-hour infusion, avibactam exposure in CSF is sufficient to inhibit target β-lactamases.[15–18] Simultaneous infusion of aztreonam (2 g q8h) with ceftazidime-avibactam via a Y-type tube optimizes plasma and CSF concentrations of both agents, facilitating synergistic action against organisms expressing both serine (KPC) and metallo-β-lactamases (NDM).[14] This approach is supported by recent hollow-fiber infection model data and clinical reports indicating that concurrent, extended infusion maximizes pharmacodynamic target attainment, particularly for pathogens with high MICs or reduced susceptibility.[14,19] Furthermore, the dosing regimens applied in this case reflect recommended practice for severe Gram-negative CNS infections, balancing adequate CNS penetration and bactericidal activity with the need to minimize neurotoxicity risk.[20] As such, this pharmacologic strategy is rational and consistent with published evidence for maximizing antimicrobial exposure and efficacy in the treatment of multidrug-resistant intracranial infections.[4,13,18] These results therefore suggest, rather than confirm, the potential utility of this regimen for managing infections caused by dual-carbapenemase–producing organisms.

In this case, the coexistence of KPC and NDM created a combined resistance phenotype that rendered ceftazidime-avibactam ineffective. Although avibactam potently inhibits serine β-lactamases, such as KPC, it has no activity against metallo-β-lactamases, such as NDM, allowing NDM to continue hydrolyzing ceftazidime even in the presence of avibactam. This dual-enzyme configuration generates a cooperative resistance mechanism, in which NDM efficiently hydrolyzes the ceftazidime component despite inhibition of KPC by avibactam, thereby maintaining effective β-lactam degradation. At the same time, the presence of KPC and other accompanying β-lactamases can further compromise the activity of cephalosporins and contribute to elevated ceftazidime-avibactam minimum inhibitory concentrations. As a result, the simultaneous production of serine carbapenemases and metallo-β-lactamases establishes parallel hydrolytic pathways that collectively abolish the antibacterial activity of ceftazidime-avibactam. Similar resistance mechanisms have been described in dual-carbapenemase–producing *Enterobacterales*, where isolates harboring both KPC and NDM frequently demonstrate reduced susceptibility or resistance to ceftazidime-avibactam and are associated with therapeutic failure.[4,10,16] This explains the observed ceftazidime-avibactam resistance (MIC = 8 μg/mL) in our isolate. An important clarification is required regarding the carbapenemase profile. At the previous hospital, initial carbapenemase testing indicated a KPC-positive/NDM-negative phenotype, which guided the early therapeutic choices. However, repeat testing at our institution, which was performed using a different PCR panel with higher analytical sensitivity, confirmed the presence of both KPC and NDM genes. Thus, the earlier NDM-negative result likely reflected a false-negative finding rather than a true discrepancy in pathogen characteristics. The dual-enzyme profile identified at our center was therefore considered the definitive result and served as the basis for therapeutic decision-making. The synergistic rationale for the ceftazidime-avibactam plus aztreonam regimen arises from the complementary roles of the two agents: avibactam inhibits KPC and thereby protects aztreonam from KPC-mediated

hydrolysis, while aztreonam itself remains intrinsically stable in the presence of NDM. When administered simultaneously, this dual blockade restores effective β-lactam activity against strains co-producing serine and metallo-β-lactamases. For CRKP infections that were positive for both KPC and NDM, ceftazidime-avibactam sodium was administered in combination with aztreonam via intravenous infusion. This combination demonstrated a clear synergistic mechanism: aztreonam was resistant to hydrolysis by NDM, whereas avibactam in ceftazidime-avibactam sodium (CAZ-AVI) inhibited KPC enzymes, effectively covering strains with coexisting NDM and other resistance mechanisms.[11,12] Notably, the infusion strategy, involving simultaneous administration via a Y-type tube for over 2 h, was derived from existing literature, indicating improved bacterial clearance and resistance suppression.[13–15] Several recent studies have reported the successful use of ceftazidime-avibactam combined with aztreonam for infections caused by metallo-β-lactamase–producing *Enterobacterales*.[12,19] However, most published cases involve bloodstream infections, pneumonia, or intra-abdominal infections, while reports describing CNS infections remain extremely limited. In addition, only a small number of cases have documented CRKP strains co-producing both KPC and NDM enzymes,[11] and evidence regarding optimal treatment strategies for these dual-carbapenemase-producing isolates in the CNS is scarce. Only a few CNS infections caused by KPC- and NDM-co-producing CRKP have been reported in the literature,[9,14] and most were treated using limited two-drug combinations, such as tigecycline with polymyxins or high-dose carbapenems, often with suboptimal outcomes and prolonged microbiological persistence. Several cases required repeated surgical interventions or developed severe neurological sequelae despite aggressive therapy, reflecting the difficulty of achieving adequate CNS antimicrobial exposure in this setting. Importantly, none of the previously published cases utilized the complete triple-agent strategy employed in our patient—namely ceftazidime-avibactam plus aztreonam administered simultaneously via a Y-type tube, combined with targeted local polymyxin B irrigation. In contrast to earlier reports, this regimen achieved rapid clinical stabilization, clearance of CSF infection by day 20, and effective local source control without systemic toxicity. The favorable outcome observed here suggests that a synergistic, enzyme typing–guided triple-combination strategy may offer superior microbiological and clinical efficacy compared with previously described regimens for intracranial infections caused by dual carbapenemase–producing CRKP. Compared with previously reported cases, the present case demonstrates successful microbiological clearance using a combined strategy of ceftazidime-avibactam plus aztreonam with adjunctive local polymyxin B administration, guided by enzyme typing and antimicrobial susceptibility testing. This case therefore provides additional clinical evidence supporting the feasibility of this combination regimen for treating severe intracranial infections caused by KPC- and NDM-co-producing CRKP.

Therapeutic efficacy was confirmed by both laboratory and clinical improvements; the patient's temperature was maintained below 37.5 °C, and the GCS score increased from 5 to 9 by day 5; CSF culture returned negative on day 20; and there was significant improvement in CSF indices (Table 1).

In such cases, the role of polymyxin B in surgical site irrigation is critical. This route of administration was selected because the infectious focus was confined to the postoperative surgical cavity rather than the ventricular system, making surgical site irrigation a more targeted and less invasive strategy compared with intraventricular catheterization. To avoid misunderstanding, it is important to emphasize that polymyxin B in this case was delivered solely through local surgical site irrigation, and no intraventricular or intrathecal administration was performed at any stage. Local administration effectively circumvents the blood-brain barrier and ensures therapeutic drug concentrations at the site of infection.[16,20] Additionally, a 2025 study conducted at our center reported the efficacy and safety of intraventricular polymyxin B for CRKP related CNS infections.[21] Although this evidence supports the broader role of local polymyxin B therapy in refractory intracranial infections, in the present case, polymyxin B was not administered intraventricularly but exclusively via surgical site irrigation, being consistent with the patient's postoperative anatomy. Consistent with previous research,[16] drainage from the surgical site changed from purulent to pale yellow, and no adverse reactions such as nephrotoxicity or neurotoxicity were identified. Although polymyxin B can achieve high local antimicrobial concentrations when administered intrathecally or via surgical site irrigation, its use carries well-documented risks, including nephrotoxicity and neurotoxicity. Published data indicate that systemic polymyxin therapy may cause acute kidney injury in up to 40–60% of patients, and intrathecal administration has been associated with seizures, chemical meningitis, and radiculitis in rare cases. Even though no such adverse effects were found in our patient, these risks must be recognized when considering polymyxin-based strategies, particularly in critically ill individuals. Previous clinical reports and consensus guidelines[22,23] demonstrate that intraventricular or intrathecal polymyxin B doses ranging from 5–10 mg/

day can achieve bactericidal CSF concentrations; however, these dosing recommendations pertain to intraventricular therapy and were not applied in the present case. Instead, our patient received 5 mg once daily via surgical site irrigation, a route selected to achieve high local drug exposure while minimizing systemic and neurotoxic risk. In the present case, a dose of 5 mg once daily was selected to balance antimicrobial efficacy with the risk of neurotoxicity, particularly given the patient's severe neurological status and prolonged infection course. The surgical site drainage tube was temporarily clamped for 2 h following administration to facilitate adequate local drug exposure. During therapy, renal function, neurological status, and potential adverse reactions were closely monitored, and no evidence of polymyxin B–related nephrotoxicity or neurotoxicity was observed.

Another key aspect of treatment is the management of complications following infection control. The patient developed ventricular adhesions and hydrocephalus (Figure 2B and C), which were addressed using a phased surgical approach. It involved initial external ventricular drainage, followed by neuroendoscopic septostomy (Figure 2D), and ultimately, placement of a ventriculoperitoneal shunt after normalization of CSF. This systematic approach successfully restored CSF circulation. Despite the persistence of coma (GCS score, 9) due to severe pre-admission brain damage, both the infection and hydrocephalus were effectively managed, and no recurrence was found during three-month follow-up. The unfavorable neurological outcome was likely multifactorial. The patient had already developed extensive cerebellar infarction with cerebral herniation prior to infection, which resulted in substantial primary brain injury. In addition, the prolonged course of intracranial infection, persistent inflammation, and subsequent complications including ventricular adhesions and hydrocephalus may have further contributed to secondary neurological damage. Previous studies have shown that poor baseline neurological status, delayed infection control, and structural brain injury are important predictors of unfavorable functional outcomes in patients with post-neurosurgical CNS infections.

Nevertheless, several limitations should be acknowledged. Firstly, this report described a single case, and therefore the findings could not be generalized to all patients with CRKP-associated CNS infections. Secondly, although the favorable outcome indicated potential synergy among ceftazidime-avibactam, aztreonam, and locally administered polymyxin B, the relative contribution of each component of the regimen could not be definitively determined. Larger clinical studies are required to further evaluate the safety, optimal dosing strategies, and therapeutic efficacy of this combination approach in patients with intracranial infections caused by dual-carbapenemase–producing organisms.

Conclusions

This single case highlighted several practical considerations for managing complex intracranial infections caused by carbapenem-resistant *K. pneumoniae*. Firstly, timely and comprehensive carbapenemase typing could remarkably guide the selection of targeted antimicrobial combinations, particularly when initial therapy failed. Secondly, for infections involving NDM-producing strains, the combined use of ceftazidime-avibactam and aztreonam could be regarded as a therapeutic option, and adjunctive local polymyxin B administration exhibited to be beneficial when surgical-site or CSF exposure was limited. Thirdly, careful attention to the infusion strategy, including simultaneous administration and extended infusion duration, may optimize drug exposure. Finally, clinicians should remain vigilant for treatment-related complications such as ventricular adhesions or hydrocephalus, as timely neurosurgical management is essential for restoring CSF circulation and improving overall outcomes. While broader conclusions cannot be drawn from a single case, these observations may assist clinicians facing similarly resistant pathogens in post-neurosurgical CNS infections.

Ethics Statement for Case Report on Infection and Drug Resistance

This case report has been conducted in accordance with the ethical principles of the Declaration of Helsinki and the guidelines for medical research involving human subjects. Written informed consent for publication of this case and the accompanying images was obtained from the patient's legal representative. Ethics approval for this study was granted by the Ethics Committee of Aviation General Hospital (Beijing, China; Approval No. HK2025-81). In addition, the Ethics Committee confirmed whether institutional approval was required for publication of the case details, and all necessary approvals were obtained. The patient (or legal guardian) was fully informed of the purpose, process, potential risks, and benefits of the case report including the use of clinical information and relevant test results for academic exchange and

publication. The patient (or legal guardian) voluntarily agreed to participate and signed an informed consent form that was retained in the medical records of the hospital for future reference.

To protect the patient's privacy and confidentiality, all identifying information (including name, medical record number, contact information, address, and any other personal identifiers) was de-identified and anonymized in this case report. No information that could lead to patient identification was disclosed. All clinical data and test results used in this report are accurate, true, and have been obtained through standardized clinical procedures, without any fabrication or falsification.

The authors confirm that the publication of this case report does not violate any ethical norms, does not cause any potential harm to the patient, and fully respects the patient's autonomy, privacy, and right to provide informed consent. The authors declare no conflict of interest related to this case report.

Funding

This study was sponsored by Chronic Disease Management Research Project in 2025 (Grant No. GWJJMB202510041112).

Disclosure

The authors declare that there is no conflicts of interest in this work.

References

1. Zhi-Wen Y, Yan-Li Z, Man Y, Wei-Jun F. Clinical treatment of pandrug-resistant bacterial infection consulted by clinical pharmacist. *Saudi Pharm J*. 2015;23(4):377–380. PMID: 27134538; PMCID: PMC4834688. doi:10.1016/j.jsps.2015.01.001
2. Chan LM, Lok DYL, Wong RCW, et al. Antimicrobial susceptibility testing of the combination of aztreonam and avibactam in NDM-producing *Enterobacterales*: a comparative evaluation using the CLSI and EUCAST methods. *Antibiotics*. 2025;14(7):675. PMID: 40723978; PMCID: PMC12291778. doi:10.3390/antibiotics14070675
3. Seeberger PH, Pereira CL, Khan N, et al. A semi-synthetic glycoconjugate vaccine candidate for carbapenem-resistant *Klebsiella pneumoniae*. *Angew Chem Int Ed Engl*. 2017;56(45):13973–13978. PMID: 28815890; PMCID: PMC5819008. doi:10.1002/anie.201700964
4. Zhang W, Guo Y, Li J, et al. In vitro and in vivo bactericidal activity of ceftazidime-avibactam against Carbapenemase-producing *Klebsiella pneumoniae*. *Antimicrob Resist Infect Control*. 2018;7(1):142. PMID: 30479755; PMCID: PMC6249859. doi:10.1186/s13756-018-0435-9
5. Abbas DA, Al-Ouqaili MTS, Alfeehan MJ. Molecular and bacteriological characterization of colistin and carbapenem-resistant nosocomial isolates of *Acinetobacter baumannii* isolated from different Iraqi hospitals. *J Infect Public Health*. 2026;19(3):103118. ISSN 1876-0341. doi:10.1016/j.jiph.2025.103118
6. Emeraud C, Escaut L, Boucly A, et al. Aztreonam plus clavulanate, tazobactam, or avibactam for treatment of infections caused by Metallo-β-Lactamase-producing gram-negative bacteria. *Antimicrob Agents Chemother*. 2019;63(5):e00010–19. PMID: 30858212; PMCID: PMC6496057. doi:10.1128/AAC.00010-19
7. Alghoribi MF, Alqurashi M, Okdah L, et al. Successful treatment of infective endocarditis due to pandrug-resistant *Klebsiella pneumoniae* with ceftazidime-avibactam and aztreonam. *Sci Rep*. 2021;11(1):9684. PMID: 33958683; PMCID: PMC8102575. doi:10.1038/s41598-021-89255-8
8. Sieswerda E, van den Brand M, van den Berg RB, et al. Successful rescue treatment of sepsis due to a pandrug-resistant, NDM-producing *Klebsiella pneumoniae* using aztreonam powder for nebulizer solution as intravenous therapy in combination with ceftazidime/avibactam. *J Antimicrob Chemother*. 2020;75(3):773–775. PMID: 31789378; PMCID: PMC7021014. doi:10.1093/jac/dkz495
9. Hu H, Wang H, Yu M, et al. Clinical and microbiological characteristics of carbapenem-resistant Enterobacteriaceae causing post-operative central nervous system infections in China. *J Glob Antimicrob Resist*. 2023;35:35–43. PMID: 37611894. doi:10.1016/j.jgar.2023.08.006
10. Xia Y, Zhou P, Gao H, et al. Co-production of KPC-2 and NDM-5 in a carbapenem-resistant *Klebsiella pneumoniae* clinical isolate: genetic insights and risks. *Infect Drug Resist*. 2025;18:3329–3341. PMID: 40635769; PMCID: PMC12239901. doi:10.2147/IDR.S523271
11. Al-Ouqaili MTS, Hussein RA, Kanaan BA, Al-Neda ATS. Investigation of carbapenemase-encoding genes in *Burkholderia cepacia* and *Aeromonas sobria* isolates from nosocomial infections in Iraqi patients. *PLoS One*. 2025;20(8):e0315490. doi:10.1371/journal.pone.0315490
12. Lin D, Chen J, Yang Y, Cheng J, Sun C. Epidemiological study of carbapenem-resistant *Klebsiella pneumoniae*. *Open Med*. 2018;13(1):460–466. PMID: 30426083; PMCID: PMC6227897. doi:10.1515/med-2018-0070
13. Lemon JK, Jankowsi-Romano C, Duong S, Juretschko S, Streva VA. Evaluation of gradient strip diffusion for susceptibility testing of aztreonam-avibactam in metallo-β-lactamase-producing Enterobacterales. *J Clin Microbiol*. 2024;62(11):e0064924. PMID: 39345139; PMCID: PMC11559034. doi:10.1128/jcm.00649-24
14. Balbuena JP, Cordova E, Mykietiuk A, et al. Carbapenem-resistant Gram-negative bacilli bacteremia in Argentina (EMBARCAR): findings from a prospective, multicenter cohort study. *Clin Infect Dis*. 2025:ciaf259. PMID: 40393137. doi:10.1093/cid/ciaf259
15. Lodise TP, Smith NM, O'Donnell N, et al. Determining the optimal dosing of a novel combination regimen of ceftazidime/avibactam with aztreonam against NDM-1-producing Enterobacteriaceae using a hollow-fibre infection model. *J Antimicrob Chemother*. 2020;75(9):2622–2632. PMID: 32464664; PMCID: PMC8444334. doi:10.1093/jac/dkaa197
16. Sree RA, Gupta A, Gupta N, et al. Ceftazidime-avibactam alone or in combination with Aztreonam versus Polymyxins in the management of carbapenem-Resistant *Klebsiella pneumoniae* nosocomial Infections (CAPRI study): a retrospective cohort study from South India. *Infection*. 2024;52(2):429–437. PMID: 37697224; PMCID: PMC10954914. doi:10.1007/s15010-023-02094-9
17. Shi Q, Yin D, Han R, et al. Emergence and recovery of ceftazidime-avibactam resistance in blaKPC-33-harboring *Klebsiella pneumoniae* sequence type 11 isolates in China. *Clin Infect Dis*. 2020;71(Suppl 4):S436–S439. PMID: 33367577. doi:10.1093/cid/ciaa1521

18. Venditti C, Butera O, Meledandri M, et al. Molecular analysis of clinical isolates of ceftazidime-avibactam-resistant *Klebsiella pneumoniae*. *Clin Microbiol Infect*. 2021;27(7):1040.e1–1040.e6. PMID: 33775814. doi:10.1016/j.cmi.2021.03.001
19. Pérez-Nadales E, Fernández-Ruiz M, Natera AM, et al; REIPI/INCREMENT-SOT Study Group. Efficacy of ceftazidime-avibactam in solid organ transplant recipients with bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae*. *Am J Transplant*. 2023;23 (7):1022–1034. PMID: 37028515. doi:10.1016/j.ajt.2023.03.011
20. Eskenazi A, Lood C, Wubbolts J, et al. Combination of pre-adapted bacteriophage therapy and antibiotics for treatment of fracture-related infection due to pandrug-resistant *Klebsiella pneumoniae*. *Nat Commun*. 2022;13(1):302. PMID: 35042848; PMCID: PMC8766457. doi:10.1038/s41467-021-27656-z
21. Li X, Zhou L, Huang H. Dynamic evolution of KPC-230-mediated resistance to ceftazidime-avibactam during the treatment of carbapenem-resistant Klebsiella pnenmoniae. *Drug Resist Updat*. 2025;79:101205. PMID: 39889330. doi:10.1016/j.drup.2025.101205
22. Karampatakis T, Antachopoulos C, Iosifidis E, Tsakris A, Roilides E. Molecular epidemiology of carbapenem-resistant *Klebsiella pneumoniae* in Greece. *Future Microbiol*. 2016;11(6):809–823. PMID: 27206024. doi:10.2217/fmb-2016-0042
23. Cong W, Qi G, Wang S, Bai Z, Wang L, Chen H. Efficacy of ceftazidime-avibactam for the treatment of central nervous system infection caused by carbapenem-resistant *Klebsiella pneumoniae* after neurosurgery. *Front Neurol*. 2025;16:1604045. PMID: 41200442; PMCID: PMC12585989. doi:10.3389/fneur.2025.1604045