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Successful Treatment of MDR *Acinetobacter baumannii* Meningitis in a Young Adult Patient With Intraventricular and Intravenous Polymyxin B-Tigecycline Based Combinations: A Case Report

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ABSTRACT

Multiple drug resistance to *Acinetobacter baumannii* infection treatment is a great challenge for neuro-intensivists due to poor drug penetration through the blood–brain barrier (BBB). Fortunately, the intraventricular administration of polymyxin-B and tigecycline seems to be effective; there are few case reports demonstrating the effectiveness of such treatments. Here, we report the case of a 24-year-old male who presented with fever and neck rigidity after intracranial drainage following lung infection caused by MDR *Acinetobacter baumannii*. Due to the presence of turbid CSF, the administration of the intrathecal (ITH) route polymyxin-B and tigecycline is not possible. In this situation, the neuro-intensivist decided to start intraventricular tigecycline and polymyxin-B administration along with IV tigecycline and polymyxin-B via the intraventricular route, which was feasible because the patient had an external ventricular drain (EVD) due to obstructive hydrocephalus caused by the neurosurgeon after excision of the tumor.

JEL Classification: Anesthesia, Acute Medicine, Infectious Diseases

1 | Introduction

Following neurosurgery, intracranial infections are frequent, and most cases have dangerous consequences. There is a 3.8%–30% death rate and an infection rate of approximately 1.50%–6.6% [1, 2]. According to clinical research, ventricular drainage is one of the major risk factors for brain infection following neurosurgery. Other risk factors include trauma, craniotomy, and cerebrospinal fluid (CSF) leakage [3]. Gram negative bacteria are the leading cause of intracranial infection [4]. Among these, intracranial infections caused by *Acinetobacter baumannii* are becoming more common, accounting for 3.6%–11.2% of nosocomial intracranial infection cases [5]. *A. baumannii* cerebral infections can have a fatality rate of up to 71% [6]. Because most medications cannot enter the central nervous system (CNS), intravenous (IV) anti-infective therapy alone is not an effective treatment for intracranial infections.

A recent study on the management of CNS infections indicated that extensively drug-resistant (XDR) *A. baumannii* responded well to intraventricular (IVT) and intrathecal (ITH) antibiotics [2]. All of the pertinent reports available at this time are case

Md Abdur Rahim and Himel Kumar Biswas contributed equally to this work.

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Summary

- Treating *Acinetobacter baumannii* is challenging due to poor blood–brain barrier (BBB) penetration.
- Turbid cerebrospinal fluid limits the use of intrathecal (ITH) polymyxin-B and tigecycline.
- Therefore, intraventricular (IVT) administration of these antibiotics seems effective, offering a viable alternative for overcoming multiple drug resistance in such infections.

studies or small-sample studies. We report the case of a patient who developed an intracranial infection sustained by XDR *A. baumannii* after receiving an external ventricular drain (EVD) placed in situ to remove a space-occupying lesion (SOL). The infection was effectively treated with combination of Polymyxin B and Tigecycline IVT [2].

2 | Case History

A 24-year-old obese (body mass index, 31.6 kg/m^2) male who complained of blurred vision for the last 4 months was brought to our hospital. There was no history of convulsion, nausea, vomiting, fever, headache, loss of consciousness (LOC), or any limb weakness. On admission, his vital parameters were as follows: pulse-88 bpm, blood pressure-130/75 mmHg, temperature-99 F, Glasgow Coma Scale (GCS)-E4V5M6, pupils-2 mm equal, and reacting to light, with adequate urinary output. Magnetic resonance imaging (MRI) with contrast showed a large heterogeneous mass with both solid and cystic components in the right lateral ventricle near the foramen of Monro, resulting in significant dilatation of both lateral ventricles with a mass effect (Figure 1).

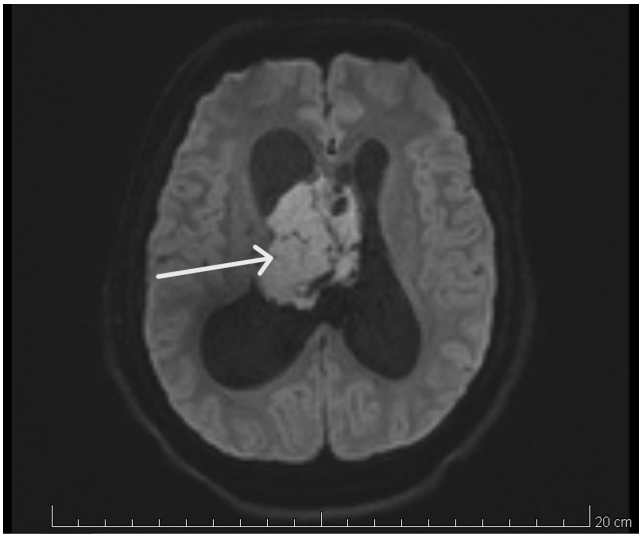

FIGURE 1 | Magnetic resonance imaging (MRI)-contrast enhanced of brain (diffusion-weighted imaging) shows a large heterogeneous mass with both solid and cystic components in the right lateral ventricle near the foramen of Monro, resulting in significant dilatation of both lateral ventricles with a mass effect.

3 | Methods

The Clinical and Laboratory Standards Institute (CLSI) method was used for all bacterial growth measurements except for Tigecycline. Tigecycline breaking point was done by The European Committee on Antimicrobial Susceptibility Testing (EUCAST) method.

4 | Differential Diagnosis, Investigations and Treatment

Right fronto-parietal craniotomy and excision of the right ventricular SOL were performed, and an EVD was placed on the right side. Afterwards, the patient was transferred to the neuro-ICU via the recovery room with mechanical ventilation (MV) support. Consequently, he was extubated on the first post-operative day (POD), as his GCS improved to E4VTM5. Unfortunately, he was intubated again on the same day (just after 4 h) due to worsening of his GCS (E2V2M4) and low oxygen saturation (SpO_2–85%) in room air as well as tachypnea with reduced minute ventilation. Tracheostomy was performed after reintubation on the first POD, and the patient was kept on MV again. Tracheal aspirate and CSF culture and sensitivity (C/S) analysis revealed no bacterial or fungal growth. After the follow-up CT scan of the head was performed on the third POD, the EVD was revised for inadequate drainage. We treated the patient with conventional antibiotics such as cephalosporin, carbapenem and fluroquinolone.

Because the patient's GCS did not improve significantly ($E_3V_TM_4$), on the fifth POD we sent CSF from the EVD, and tracheal aspirates showing no growth (Table 1). Tracheal aspirate on the 16th POD showed moderate growth of Acinetobacter spp. (Table 2), which was extensively drug resistant, and chest X-ray revealed left-sided basal pneumonia (Figure 2).

CSF was sent for C/S again at the time of revision of the EVD (right), which showed profuse growth of *Acinetobacter* spp., which was extensively resistant to drugs (antibiotics) (Table 3). The patient's level of consciousness gradually deteriorated (GCS—E2VTM4, Pupil size 4/4 mm and sluggish reaction to light). Then, according to the CSF C/S report, we started to administer 5 mg tigecycline and 50,000 units of polymyxin-B once daily via EVD beginning on the 21st POD. The patient's GCS score and other vital parameters were monitored closely. On the 23rd POD, as per the neurosurgeon's decision, the right-sided EVD was removed and replaced by a new one along with a left-sided EVD, and CSF was also sent for C/S, fortunately, it showed no bacterial growth at this time.

The patient's level of consciousness started to improve gradually. For this reason, a neurointensivist decided to administer 5 mg of TGC and 50,000 units of poly-B once daily via alternative EVD for 15 days. After antibiotics were administered through the EVD, the cells were blocked for 6 h to reach the maximum concentration of the drug in the CSF. CSF samples collected from the left EVD on the 27th POD and from the right EVD on the 31st POD showed no growth, and the patient's GCS was E4VTM6. Tracheostomy decannulation was performed on the 38th POD.

TABLE 1 | Microorganism growth level.

Serial	Growth level	Measures
1	Scanty growth	< 10 CFU/mL in the plate
2	Moderate growth	> 10 CFU/mL only at primary inoculation site of plate
3	Profuse growth	Numerous CFU/mL at both primary and secondary inoculation site
4	No growth	There is no such growth

TABLE 2 | Tracheal aspirate culture report: including growth level.

Serial	Post-operative day (POD)	Bacteria name	Growth type
1	7th	*Pseudomonas aeruginosa*	Moderate
2	16th	*Acinetobacter* spp.	Moderate
3	25th	*Pseudomonas aeruginosa*	Moderate
4	31st	*Klebsiella pneumonia*	Moderate
5	38th	*Pseudomonas aeruginosa* and *Acinetobacter* spp.	Moderate

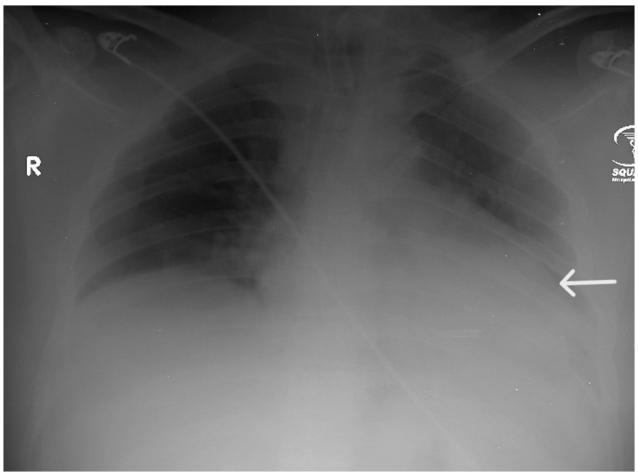

FIGURE 2 | Chest X-ray (anterior–posterior view) shows opacification of a large portion of the left lower lobe.

Furthermore, the neurosurgeon decided to use a ventriculoperitoneal (VP) shunt on the 40th POD, and VP shunt revision was performed on the 43rd POD. Both CSF samples were sent for C/S and showed no growth of organisms (Table 4). On the 45th POD, the patient was transferred to a cabin and being well alert and tolerated oral diet, and further management plans for radiotherapy, such as histopathology revealed central neurocytoma, WHO Grade-II with atypical features (necrosis and increased MIB-1 ~4%), which is a highly radiosensitive tumor.

5 | Discussion

We discussed a patient who underwent IVT tigecycline and polymyxin B therapy for obstructive hydrocephalus and developed XDR *A. baumannii* following the resection of an SOL with EVD in situ. To the best of our knowledge, reports of this treatment have previously been published in other countries but not in Bangladesh. By injecting a medication directly into the ventricle through the EVD, a technique known as the IVT route enables the medicine to enter the CSF by crossing the BBB and quickly reaching its effective concentration. According to the published guidelines, IVT/ITH antibiotics should be taken into consideration, particularly for multidrug-resistant bacteria, if there is no response to IV antibiotics or if the concentrations of CSF do not approach their respective MICs [7]. The patient's intracranial infection in our study; however, was quite critical. IVT antibiotics must be added because IV antibiotics also do not work. Drug-resistant bacteria are more likely to arise in situations involving long-term MV, the use of broad-spectrum antibiotics, and long-term ventricular drainage following the excision of an SOL with EVD in situ because of obstructive hydrocephalus.

Carbapenems are typically the firstline treatment for intracranial infections caused by gram-negative bacilli [8]. In regions where the prevalence of carbapenem-resistant *A. baumannii* is high, carbapenems might not be the treatment of choice due to their yearly increase in resistance [7]. The amount of XDR bacteria is increasing, making treatment more difficult. In many instances, the sole antimicrobial drug that is effective against meningitis pathogens is polymyxin-B [9].

CSF samples were collected multiple times after admission for our investigation, although no organism growth was observed at the beginning of the study. After a few days of mechanical breathing, the patient's GCS score did not improve, and the patient exhibited infection-related symptoms. For these reasons, we sent a tracheal aspirate C/S, which revealed moderately growing XDR Acinetobacter, and a chest X-ray revealed pneumonia. After the

TABLE 3 | Culture and sensitivity of CSF shows profuse growth of *Acinetobacter* spp.

Antibiotics	Sensitivity
Ceftazidime (third)	R
Cefepime (fourth)	R
Gentamycin (10 mcg)	R
Amikacin	R
Trimethoprim/Sulfamethoxazole	R
Levofloxacin	R
Piperacillin/Tazobactam	R
Tetracycline	R
Minocycline	S
Chloramphenicol	R
Meropenem	R
Colistin	S
Tigecycline	S

antibiotic regimen was changed to strengthen its anti-infective properties, the pneumonia considerably improved. Although the patient's level of consciousness did not improve to a tolerable degree and a repeat CT scan revealed ventriculomegaly, the neurosurgeon performed a revision of the EVD and sent CSF for C/S, which revealed profuse growth of Acinetobacter, which is carbapenem resistant.

Since the 1950s, polymyxin has been used widely, but its widespread use has been restricted because of its extreme nephrotoxicity and neurotoxicity, which can cause seizures, chemical meningitis, and ventriculitis. Since there were no other antibiotics available when carbapenem-resistant gram-negative bacteria first emerged and proliferated in the 1990s, polymyxin had to be reintroduced into clinical practice [10]. To better understand the pharmacokinetics (PK), pharmacodynamics (PD), and clinical characteristics of colistin [10], researchers and clinicians have recently found that polymyxin is active against a range of aerobic gram-negative bacteria, particularly strains that are resistant to multiple drugs, such as *A. baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, and that it possesses CNS permeability [11]. Next, we discussed the results of simultaneous IVT polymyxin-B 50,000 IU once daily and TGC 5 mg susceptibility tests with the patient's attendant. Tigecycline and polymyxin B clearly state in their official instructions that they can be used for IVT and ITH.

Patients receive polymyxin-B in its sulfate salt form, which is the active antibacterial agent given directly to them. The primary mode of elimination of polymyxin B is nonrenal clearance, which lowers the risk of nephrotoxicity [12]. When therapy is stopped, polymyxin-induced neurotoxicity is typically reversible. Our study included IVT polymyxin B (50,000 IU) once daily for 15 days. The patient's renal function was thoroughly monitored during this process, and no adverse effects that could be considered nephrotoxic or neurotoxic were noted.

TABLE 4 | CSF study (cell counts with culture and growth type).

Laboratory parameters	Day 5	Day 18	Day 21	Day 23	Day 27	Day 31	Day 40	Day 43	Reference ranges
CSF protein (mg/dL)	251	—	> 300	—	—	> 300	—	> 300	Protein: 12–60 mg/dL
CSF glucose (mg/dL)	63	—	19.8	—	—	75.6	—	48.6	Glucose: 40–70 mg/dL
CSF cell count	—	—	RBC-15000	—	—	RBC- Few	—	—	RBC-0-4 × 10^6 cells/cmm
	—	—	WBC-6700	—	—	WBC-80	—	—	WBC-0-4 × 10^6 cells/cm
	—	—	—	—	—	Lymphocyte-6%	—	—	Lymphocyte-62%
CSF C/S (bacteria and growth level)	No growth	*Acinetobacter* spp. (profuse growth)	*Acinetobacter* spp. (moderate growth)	No growth	No growth	No growth	No growth	No growth	No growth
Site of CSF collection	EVD (right)	EVD (right)	Lumbar puncture	EVD (left)	EVD (left)	EVD (right)	During VP shunt	During VP shunt revision	—

Nevertheless, research has indicated that polymyxin has low permeability to the BBB [13, 14]. In patients receiving only intravenous (IV) treatment for cerebral infections, the CSF contains only 5%–10% polymyxin. ITH administration can increase the amount of drug needed to kill bacteria, in CSF [14]. According to the 2019 International Consensus Guidelines for the Optimal Use of Polymyxins, a daily dose of 50,000 IU (5 mg) of polymyxin-B supplied by ITH/IVT for a mean of 18 days is recommended. According to the 2017 Infectious Diseases Society of America (IDSA) proposal, intracranial infections caused by aerobic gram-negative bacteria should be treated for 21 days, but this should be customized based on the patient's clinical response and should continue for at least three consecutive CSF cultures that yield negative results on different days [7]. The trial involved the administration of IV polymyxin 50,000 units per day and IVT tigecycline 5 mg per day. The treatment was administered for a total of 15 days, during which three consecutive negative CSF cultures were obtained. The therapeutic result was deemed satisfactory.

There is currently little experience with ITH/ITV polymyxin B. According to Pan et al., the ITH/ITV polymyxin B had a good therapeutic effect on cerebral XDR *A. baumannii* infections, with a death rate of only 8.70%. Among the trial participants, there were no cases of acute renal injury or neurotoxicity [15]. It is evident from this that IVT polymyxin B is reasonably safe.

The average CSF sterilization time in the literature was 4 days, which was significantly less (range 1–18 days) than the 15 days (range 8–48 days) that we found. This discrepancy can be attributed to how most published cases and our definitions of CSF sterilization criteria differ. Treatment was further complicated by the patient's XDR bacterial infection in our study. A viable option for treating cerebral infections is IVT polymyxin B, a gram-negative bacterium that is resistant to many drugs. However, information about the PK of polymyxin B (such as inhalation, ITH/IVT) and other methods outside IV injection is currently lacking. A glycylcycline-based antibiotic is called tigecycline. Tests conducted both in vitro and in vivo have verified that TGC typically demonstrates strong antibacterial activity against gram-positive and gram-negative bacteria that are resistant to other antibiotics [15, 16]. The penetration rate of tigecycline in the CSF is only 11% as a result of its lack of penetration into the CNS, and patients with intracranial infection do not significantly benefit from IV injection. Consequently, patients are not advised to receive traditional IV tigecycline therapy.

As a result, we mixed IV TGC with IVT, which could be a possible course of treatment for patients. For the first time, XDR *A. baumannii* cerebral infection was successfully treated with IVT tigecycline in 2016 [6]. In our research, IV tigecycline was continued, and the IVT dosage was 5 mg/day. The course of antibiotic treatment was stopped after 15 days of treatment when the patient's CSF cultures became negative three times in a row.

IVT-tigecycline appeared to be a safe course of therapy. Our study was supported by prior studies that revealed successful patient application of IVT and the ITH tigecycline [17].

To treat XDR bacteria, tigecycline can be used in conjunction with colistin or polymyxin B. According to in vitro antibiotic investigations, tigecycline and polymyxin B may work synergistically to treat carbapenem-resistant *A. baumannii*, with up to 70% of these strains exhibiting such synergistic effects [18]. However, antibacterial activity in vitro does not always translate into in vivo activity. The effectiveness of TGC and polymyxin in clinical settings has been questioned, and additional clinical research is required to support the management of XDR *A. baumannii* [19].

6 | Conclusion

Treatment for *A. baumannii* intracranial infections that are generally resistant to drugs involves the use of IVT tigecycline in conjunction with polymyxin-B. For XDR *A. baumannii*, IVT injection of tigecycline and polymyxin-B appears to be a safe therapy of choice. As this is a case report with only one patient reported our results lacks of external validity on effectiveness and safety of this treatment. Since our hospital is presently unable to quantify the quantity of tigecycline or polymyxin-B in serum and CSF, there are no PK data available for our study. Thus, additional research is needed to demonstrate the therapeutic efficacy of the program.

If IVT, tigecycline and polymyxin-B prove to be safe and successful in the future, they may also be used as first-line treatments for XDR intracranial infection.

Author Contributions

Md Abdur Rahim: conceptualization, data curation, formal analysis, investigation, project administration, resources, supervision, validation, writing – review and editing. **Himel Kumar Biswas:** conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, visualization, writing – original draft, writing – review and editing. **Md Abdul Kader Zilani:** investigation, project administration, resources. **Rama Biswas:** investigation, project administration, supervision, validation, visualization, writing – review and editing. **Sirazul Haque Ershad:** data curation, formal analysis, investigation, project administration, supervision, validation, visualization.

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Ethics Statement

As per Institutional Review Board (IRB) of Square Hospital, Dhaka Bangladesh, guideline- case reports do not require ethics approval.

Consent

The patient's written approval was received prior to the publishing of this case report and its related photographs.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All the required information is available in the manuscript itself.

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