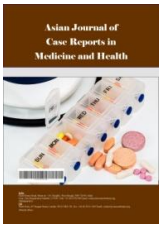

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A Successful Treatment of a Patient Infected with Pan-drug Resistant *Acinetobacter baumannii* Ventriculitis with Intravenous Sulbactam: A Case Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author PK conceptualized validated and wrote the original draft. Authors PN, WL and AU provide the patient data and reviewed edited. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

The post neurosurgical ventriculitis caused by *Acinetobacter baumannii* (*A. baumannii*) is an important problem disorder in neurosurgical patients that can lead to serious medical complications, or even to death. This is because *A. baumannii* frequently can develop multi-drug resistance to several classes of antibiotic, rendering conventional treatment method ineffective. In this case study, we report a case where our patient who is infected with post neurosurgical ventriculitis from *A. baumannii* (pan-drug resistant strain) is successfully treated with 12 grams per day of intravenous sulbactam concurrent with usual dose of intravenous tigecycline and intraventricular colistin. This successful treatment can be another novel adjunctive

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therapy for the treatment of CNS infection caused by A. baumannii (pan-drug resistant) using intravenous non-colistin base plus intraventricular colistin base regimen in post neurosurgical condition.

Keywords: Post neurosurgical ventriculitis; multidrug resistant; Acinetobacter baumannii; intraventricular colistin; intravenous high dose sulbactam.

1. INTRODUCTION

The pan-drug resistant organisms are the cause of several serious nosocomial infections [1-3] such as ventilator-associated pneumonia [4-6] catheter-related blood stream infection [7-9] catheter-associated urinary tract infection [10-12] and surgical site infection (SSI) [13-15]. Especially for the SSI, if it progresses to organ specific SSI, the patient's morbidity and mortality rates can be very high [16,17]. The post neurosurgical ventriculitis, organ specific SSI, caused by pan-drug resistant *Acinetobacter baumanii* (*A. baumanii*) can result in patient's mortality up to 40% - 64% [18,19]. Several studies have reported various modalities to treat this infection such as intrathecal [20], intraventricular [21-23] and/or high dose intravenous prolong drip antibiotics [24-26]. In this case study, we report the clinical course, consequence and treatment modality of a post neurosurgical ventriculitis patient caused by pan-drug resistant *A. baumanii.*

2. CASE PRESENTATION

A 44-year-old Thai woman was transferred from private hospital and admitted at the neurosurgical ward of Prasat Neurological Institute, the specialized neurological hospital of the Ministry of Public Health, with severe headache, nausea, vomiting and insignificant confusion 1 day previously. She had no history of head injury, trauma, central nervous system infections or malignancy. Another related condition includes essential hypertension. However, she denied the receipts any antihypertensive drugs. She also had no fever. The Glasgow Coma Scale (GCS) was 14/15 (E3V5M6) with sign of meningeal irritation. Her blood pressure was 171/110 mmHg with regular heartbeat of 90 beats per minute, heart sounds were clearly auscultated without murmur. She had no edema of her lower limbs. The rest of the physical examination were also normal. On admission, a brain computer tomography image and cerebral angiography were performed and indicated the presence of ruptured anterior communicating artery aneurysm. An emergency right pterional craniotomy procedure was performed for clipping aneurysm and retain a closed suction drainage from the surgical site. A day following the craniotomy, the neurological findings progressively deteriorated because of elevated intracranial pressure (ICP). A spinal drainage was then performed but she still had stupor and right hemiparesis. She had persists high-grade fever (39 - 39.5 Celsius). Two consecutive blood cultures were performed and start empirical antibiotic as ceftazidime intravenous.

On the 3rd day, the blood cultures reported no organism growth, but her fever persisted. The closed suction drainage was removed but there was some pus at the inner tip of catheter. It was sent to microbiologic laboratory for aerobic bacteria culture. The empirical antibiotics therapy was changed to vancomycin and meropenem intravenous injection. Spinal drainage still took place. Three days later, the aerobic bacteria culture from tip of drainage catheter was reported as extended spectrum β lactamase (ESBL) producing *Klebsiella pneumoniae* that was sensitive to almost all antibiotics examined in the laboratory by disk diffusion susceptibility test but resisted to cephalosporin. The vancomycin was stopped but intravenous meropenem injection was continued.

Fig. 1. The yellowish and turbid color CSF before treatment

On the 9th day, the blood culture and cerebrospinal fluid (CSF) specimen were performed again. The CSF examination revealed yellowish and turbid color (Fig. 1) with elevated white blood cell (WBC) count of 756 cells per liter (cells/L), differential count showed 95 percent of lymphocytes (L) and 5 percent of neutrophils (N), reduced blood sugar 40 milligram per deciliter (mg/dl), and elevated protein level 902 milligram per deciliter (mg/dl). The empiric antibiotic therapy was continuing with meropenem.

On the 13th day, the high-grade fever still persisted and poor clinical responses were observed. The prior blood cultures for aerobic bacterial were reported no organism growth but the CSF aerobic bacterial culture positive for *Acinetobacter baumanii* (few growth) that resisted to nearly all antibiotics except tigecycline. There was no sensitivity test of colistin. Nevertheless, meropenem was stopped and changed to tigecycline 100 mg intravenous loading, then 50 mg intravenous every 12 hours, cefoperazone plus sulbactam 3 grams (cefoperazone 2 grams plus sulbactam 1 gram) intravenous drip in 4 hours every 6 hours (total sulbactam 4 grams per day) and colistin 10 mg intrathecal (IT) once daily. Further semi-quantitative bacterial sensitivity test by Epsilometer test (E-test) were request immediately and reported the next day. The minimal inhibitory concentration (MIC) of meropenem was > 32 microgram per milliliter (µg/ml), the MIC of colistin was 2 µg/ml and the MIC of sulbactam was 24 µg/ml (Table 1).

On the 15th day, the spinal drain was removed because it obstructed and external ventricular drainage was applied. The tracheostomy was done in the same operation. So, we changed the route of colistin administration from intrathecal to intraventricular. The CSF aerobic bacterial culture was positive for *Acinetobacter baumanii* again. On the next day, we received the single preparation of sulbactam sodium and switch cefoperazone plus sulbactam to sulbactam 3 g (in single preparation) intravenous drip in 4 hours every 6 hours for 2 days and then sulbactam 12 g intravenous continue drip 24 hours. The antibiotic timeline as shown in Fig. 2. Three days later, fever began to subside and afebrile. The CSF aerobic bacterial culture was done again and reported no growth of microorganisms. The patient received all antibiotics in this regimen for about 2 weeks.

On the 30th day, the external ventricular drainage was removed, and the surgical team had performed left ventriculoperitoneal shunt. Level of consciousness and overall condition improved gradually. She began to wean off mechanical respirator and could spontaneous breathing without oxygen supplement. She was discharged from our hospital in totally dependent status on the next month. The GCS on discharge was E4VtM4.

Table 1. The antimicrobial susceptibility pattern of *Acinetobacter baumanii* in CSF

Antimicrobial	Disc diffusion test	MIC (ug/ml) by E-test
Ampicillin	Resist	-
Amoxicillin/Clavulanic acid	Resist	-
Cefazolin	Resist	-
Cefotaxime	Resist	-
Ceftazidime	Resist	-
Cefoperazone/Sulbactam	Resist	-
Meropenem	Resist	> 32
Gentamicin	Resist	-
Amikacin	Resist	-
Levofloxacin	Resist	-
Ofloxacin	Resist	-
Ciprofloxacin	Resist	-
Cotrimoxazole	Resist	-
Piperacillin/Tazobactam	Resist	-
Tigecycline	Sense	-
Ertapenem	Resist	-
Colistin	-	2.0
Sulbactam	-	24

MIC: minimal inhibitory concentration, ug/ml: microgram per milliliter

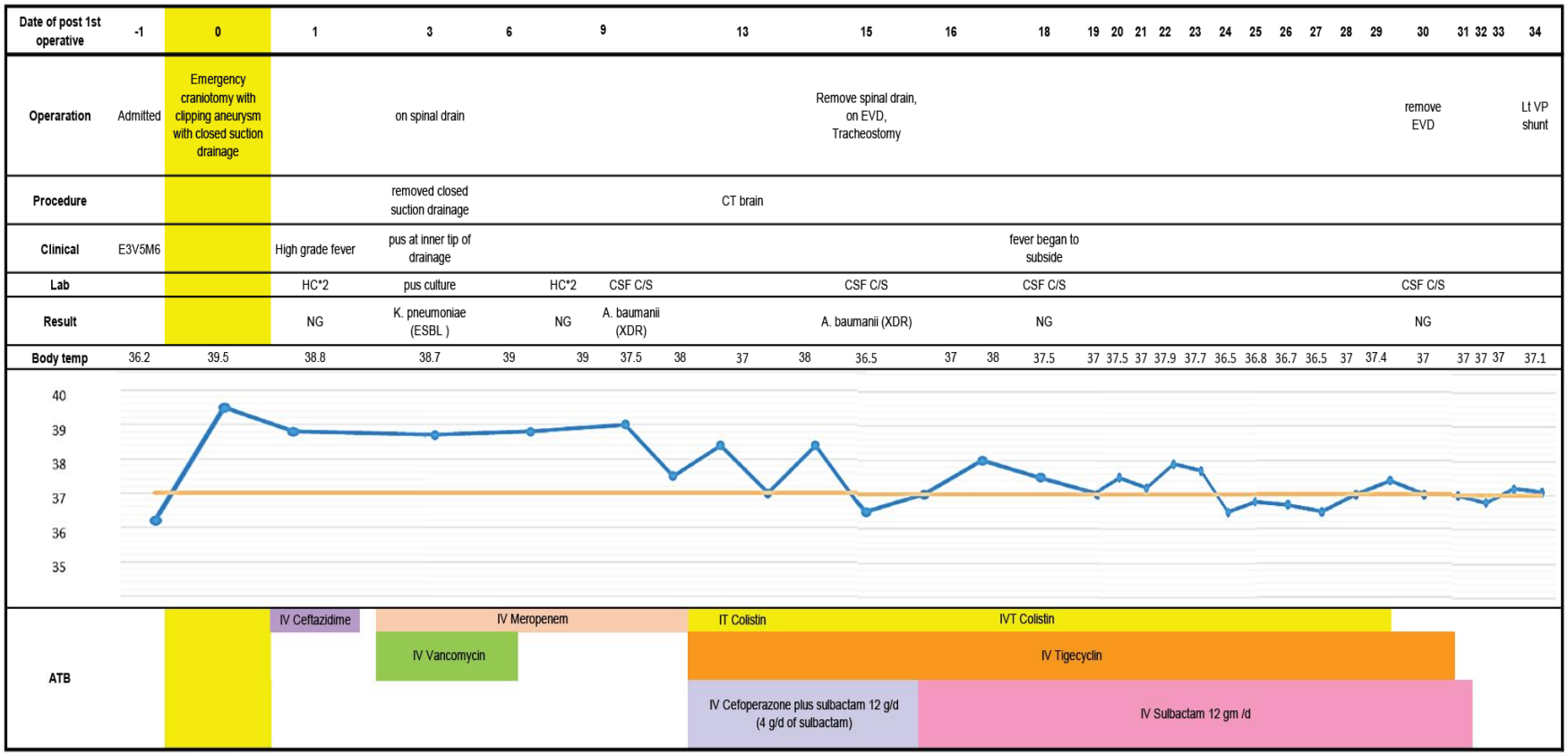

Fig. 2. The timeline of clinical, operation, procedure and antibiotics course

*Abbreviation: HC*2; hemoculture 2 specimens in 30 min apart. NG; no growth. IV; intravenous. K.pneumoniae; Klebseilla pneumoniae. ESBL; extended spectrum beta lactamase. CSF; cerebrospinal fluid. C/S;culture. A.baumanii; Acinetobacter baumannii. XDR; pan-drug resistant. CT; computerized tomography. IT; intrathecal. IVT; intraventricular. EVD; external ventricular drainage. VP shunt; ventriculoperitoneal shunt. D/C; discharge*

3. DISCUSSION

The post neurosurgical procedure *Acinetobacter baumanii* (pan-drug resistant) ventriculitis have high mortality rate in general situations. Even supposing, there were already isolates of A. baumanii that resistant to almost all available antibiotics, we were looking for the other antibiotic options for these infections, such as direct intrathecal or intraventricular antibiotic administration, high dose and/or prolong drip of antibiotic that guide by Minimal Inhibitory Concentration (MIC), pharmacokinetic/ pharmacodynamic and combination of several drugs.

However microbiological lab was not report sensitivity of *A. baumanii* to colistin, but the MIC of colistin was 2 µg/ml that suggest *A. baumanii* sensitive. Then, we give intrathecal and intraventricular colistin as current effective treatment of post neurosurgical pan-drug resistant A. baumanii ventriculitis [27-32]. Nevertheless, apprehension about acute kidney injury from concurrent high dose intravenous colistin injection, we decided to administer intravenous tigecycline as the only an antibiotic reported sensitive to *A. baumanii* in our case instead of intravenous colistin.

Aimed at the most effective regimen for *A. baumanii* (pan-drug resistant), we desire to add sulbactam intravenous by means of triple therapy as cefoperazone plus sulbactam 3 grams (cefoperazone 2 grams plus sulbactam 1 gram) intravenous drip in 4 hours every 6 hours as total sulbactam dosage 4 grams per day until we received the sulbactam in single preparation. So, the sulbactam dose was increased to 12 grams per day because the MIC of sulbactam was 24 µg/ml that was rather high [33].

Nevertheless, there was one interesting study that assesses the probability of target attainment (PTA) for sulbactam in patients with severe sepsis caused by A. baumannii following administration of sulbactam in several doses regimen [34]. Up to our knowledge, the sulbactam limited reaches CSF concentrations of approximately 30% of those found in serum with inflamed meninges [35]. The other studies suggest CSF penetration measured by the ratio of trough concentrations (CSF/serum) was 13.4%±5.3% for cefoperazone and 106.5%±87.5% for sulbactam [36,37,38]. Compare with our case, the MICs of *A. baumanii* to sulbactam was 24 µg/ml that finally we decided to use the sulbactam 12 grams per day intravenous continuous drip as per the MIC 32 µg/ml.

4. CONCLUSION

The pan-drug resistant *A. baumannii* CNS infection in post neurosurgical patients was an extremely serious complication. We report a case of our patient who successfully be treated with high dose intravenous sulbactam 12 grams per day continuous drip concurrent with intravenous tigecycline and intraventricular colistin. This successful treatment method in our patient can be another novel modality to decrease morbidity and mortality of CNS infection from pan-drug resistant *A. baumannii* in post neurosurgical conditions.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report.

ETHICAL APPROVAL

As per international standard, written ethical approval has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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