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Successful treatment of pan-drug resistant *Acinetobacter baumannii* nosocomial meningitis/ventriculitis by combined intravenous and intrathecal colistin-tigecycline administration: a case series

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SUMMARY

Background: This study aims to evaluate the efficacy of combined intraventricular and intravenous co-administration of colistin and tigecycline in the management of pan-drug resistant *Acinetobacter baumannii* meningitis/ventriculitis.
Methods: In this case series we report 3 patients with healthcare-associated ventriculitis/meningitis caused by pan-drug resistant *Acinetobacter baumannii* that were treated with combined colistin and tigecycline administration through both intraventricular and intravenous routes.
Results: All patients were administered colistin intraventricularly at a dose of 250.000 IU q.d. and intravenously at 9 million IU loading dose, followed after 12 hours by maintenance dose of 4.5 million IU every 12 hours and tigecycline intraventricularly at a dose of 10 mg b.i.d. and intravenously at 200 mg loading dose followed after 12 hours by 100 mg every 12 hours. In patients with a calculated creatinine clearance of less than 60 ml/min, according to the Cockcroft-Gault formula, the maintenance dose of colistin was reduced based on a modified formula. All patients had a favourable clinical and microbiological response with evidence of CSF sterilization.
Conclusions: Taking advantage of the synergistic action of combined colistin and tigecycline through administration both intraventricularly and intravenously may be a promising salvage option for critically ill patients with pan-drug resistant *A. baumannii* CNS infection.

Keywords: Ventriculitis, meningitis, *A. baumannii*, colistin, intraventricular administration.

INTRODUCTION

Hospital-acquired central nervous system (CNS) infections (ventriculitis and meningitis, VM) constitute serious complications of critically-ill neurosurgical patients, especially when attributed to resistant pathogens. The incidence of VM among neurosurgical patients is estimated between 5-7%, whereas it ranges between 1-20% after external ventricular drain (EVD) placement [1, 2]. *Acinetobacter baumannii* (*A. baumannii*) is found in 3.6-11% of CSF cultures [3].
Since VM is a nosocomial infection, multidrug-resistant (MDR) pathogens are usually implicated in its microbial etiology. Resistant *A. baumannii* is

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a difficult-to-treat nosocomial pathogen susceptible to limited therapeutic options, while extended- (XDR) and pan-drug resistant (PDR) *A. baumannii* isolates have emerged because of its constantly evolving resistance mechanisms [3, 4]. Treatment of PDR *A. baumannii* strains is a matter of growing concern associated with high mortality rates, while there are no established therapeutic regimens [5]. To overcome non-susceptibility to all antibiotics, diverse synergistic combinations have been previously tested including high-dose ampicillin/sulbactam with meropenem and colistin, high-dose ampicillin/sulbactam with high-dose tigecycline and colistin or colistin with fosfomycin [5, 6].

We present three patients with healthcare-associated ventriculitis/meningitis by pan-drug resistant *A. baumannii* treated with combined colistin and tigecycline administration through both intraventricular and intravenous routes with favourable clinical and microbiological outcome (Table 1).

CASES PRESENTATION

Definition of A. baumannii PDR phenotype

A. baumannii strains isolated from CSF were identified using Vitek 2 Advanced Expert System (bioMérieux, Marcy L'Étoile, France). Antibiotic susceptibility was performed by the Vitek 2 Advanced Expert System, while MIC to tigecycline was determined by Etest (AB Biodisk) and MIC to colistin by broth microdilution method. Results were interpreted according to EUCAST guidelines (EUCAST, 2022).

A. baumannii's PDR phenotype was defined according to the international expert proposal for Interim standards guidelines [7]. Accordingly, PDR *A. baumannii* isolates were non-susceptible to all agents in all antimicrobial categories, with tigecycline MIC >2 μg/ml. In the latest EUCAST clinical breakpoints (v. 12.0, January 1, 2022) no clinical breakpoint is set for tigecycline due to insufficient evidence [8]. However, previous clinical studies with XDR *A. baumannii* infections, have

Table 1 - Patient demographics, history and type of intervention, clinical and laboratory indications of CNS infection, causative agent, treatment, time to CSF sterilization and outcome. All patients were subjected to the same treatment regimen of colistin intraventricularly at a dose of 250.000 IU q.d. and intravenously at 9 million IU loading dose, followed after 12 hours by maintenance dose of 4.5 million IU every 12 hours and tigecycline intraventricularly at a dose of 10 mg b.i.d. and intravenously at 200 mg loading dose followed after 12 hours by 100 mg every 12 hours.

	Age	*Sex*	*History*	*Intervention*	*CNS infection presentation*	*CSF WBC ($x10^6$/L – PMN Glucose (mg/dl) Protein (mg/dl) Gram*	*Pathogen*	*Treatment*	*Time to CSF sterilization (days)*	*Outcome*
Patient 1	60	Female	aSAH – acute hydrocephalus	Embolization – EVD – VP shunt conversion	Fever – septic shock	450 – 80% 5 68 Gram-negative bacilli	PDR *A. baumannii*	Combined intraventricular - IV colistin / tigecycline	35	Death at 82 days due to carbapenem-resistant *P. aeruginosa* bacteraemia – septic shock
Patient 2	33	Male	SDH – post traumatic hydrocephalus	Craniectomy – bilateral EVD	Fever	1280 – 90% 6 147 Unrevealing	PDR *A. baumannii*	Combined intraventricular – IV colistin / tigecycline	5	Discharged to rehabilitation center
Patient 3	56	Male	aSAH – acute hydrocephalus	Embolization – EVD	Septic shock	2080 – 85% 47 109.5 Gram-negative bacilli	PDR *A. baumannii*	Combined intraventricular – IV colistin / tigecycline	17	Death at 32 days due to massive pulmonary embolism

Abbreviations: aSAH: aneurysmal subarachnoid hemorrhage; SDH: acute subdural hematoma; EVD: external ventricular drain; CSF: cerebrospinal fluid; WBC: white blood cell count; PMN: polymorphonuclear; PDR A. *baumannii:* pan-drug resistant *Acinetobacter baumannii*; IV: intravenous.

shown that when tigecycline MIC is >2 µg/ml, significantly higher therapeutic failures and mortality were observed either when tigecycline was used as monotherapy or as part of combination therapy with colistin [9, 10]. The present study included patients with nosocomial ventriculitis/meningitis caused by carbapenem- and colistin-resistant *A. baumannii* with MIC to tigecycline 4 µg/ml (PDR *A. baumannii* strains).

Treatment regimen

Colistin was administered intraventricularly at a dose of 250.000 IU q.d. and intravenously at 9 million IU loading dose, followed after 12 h by maintenance dose of 4.5 million IU every 12 hours and tigecycline was administered intraventricularly at a dose of 10 mg b.i.d. and intravenously at 200 mg loading dose followed after 12 hours by 100 mg every 12 hours. In patients with a calculated creatinine clearance of less than 60 mL/min, according to the Cockcroft-Gault formula, the maintenance dose of colistin was reduced based on a modified formula from Garonzik et al. (daily maintenance colistin dose [IU] = CL_{CR}/10+2) [11]. The ventricular drainage device was closed for 1 hour after the injection of the antibiotics.

All three patients were admitted and treated in the ICU of our hospital.

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Due to the study's retrospective nature, ethics committee approval was not required.

Case 1

A 60-year-old woman with aneurysmal subarachnoid hemorrhage and acute hydrocephalus was treated with external ventricular drain upon admission; the aneurysm was successfully embolized. Neurological deterioration due to vasospasm led to intubation and ICU admission. During hospitalization a ventriculoperitoneal shunt was placed. On the 33rd post-operative day she developed fever and progressed to septic shock. CSF analysis performed the same day revealed infection by carbapenem and colistin-resistant *A. baumannii* with tigecycline MIC 4 µg/mL (PDR strain). The patient was started on combined colistin and tigecycline intravenously and intrathecally via the VP shunt, as described in the treatment regimen section. The septic shock was reversed within two days, but the patient became afebrile with normal inflammatory markers and negative CSF cultures at 35 days after treatment initiation, whereupon IVT infusions were terminated on the 37th day after treatment initiation. She survived for 82 days in a severe clinical state owing to the subarachnoid hemorrhage and died by sepsis due to carbapenem-resistant *Pseudomonas aeruginosa* bacteremia.

Case 2

A 33-year-old male patient was admitted intubated due to severe traumatic brain injury (TBI) with acute subdural hematoma and brain edema. He was treated with craniectomy, drainage of the hematoma and insertion of EVDs bilaterally due to post-traumatic hydrocephalus. On the 42nd post-operative day the patient developed fever; CSF analysis performed the same day indicated infection by PDR *A. baumannii.* The patient was started on colistin and tigecycline intravenously and intrathecally via the EVD drain. CSF cultures became negative at 5 days from treatment initiation with fever resolution and normalization of inflammatory markers, with termination of IVT infusions on the 7th day after treatment initiation. The patient was eventually discharged to continue physiotherapy at the rehabilitation center.

Case 3

A 56-year-old male presented with aneurysmal subarachnoid hemorrhage. He was successfully embolized; on the 1st post-operative day he developed acute hydrocephalus which required an EVD, which was replaced thrice due to malfunction caused by the hemorrhage. On the 11th post-operative day he became septic; CSF samples drawn the same day showed PDR *A. baumannii*. The patient was treated with the described regimen of combined intravenous and intrathecal colistin and tigecycline. CSF was sterilized at 17 days after treatment initiation with gradual clinical and laboratory response. The IVT drug infusions were terminated on the 19th day after treatment initiation. The patient died 32 days later by massive pulmonary embolism.

DISCUSSION

Emergence of colistin resistance in *A. baumannii* has limited our therapeutic armamentarium. MDR *A. baumannii* infections show mortality rates over

60% [5]. Therefore, in severe XDR and PDR infections, it is reasonable to use combination regimens to exploit antibiotic synergism. Different combinations of antibiotics have demonstrated synergistic action against XDR *A. baumannii,* such as colistin combined with rifampicin, tigecycline, sulbactam, vancomycin, and carbapenems combined with colistin, sulbactam, aminoglycosides or rifampicin [6, 12, 13]. The tigecycline-colistin combination was shown to be more synergistic than the tigecycline-rifampicin and colistin–rifampicin combination [14]. However, synergy is not universal and not applicable to every *A. baumannii* strain. Clinically relevant synergy may be less likely for strains with very high MICs [12]. In a recent study from our hospital, 10 patients with PDR *A. baumannii* ventilator-associated pneumonia were administered a triple combination regimen of high-dose ampicillin sulbactam (6/3 g every 8 hours), high-dose tigecycline (200 mg loading dose followed after 12 hours by 100 mg every 12 hours) and combined intravenous and inhaled colistin; resulting in clinical success in nine patients, and microbiological eradication in seven [6].

Poor drug blood-brain barrier permeability is another important obstacle. Combination of intravenous and intrathecal administration of colistin and other antibiotics to enhance drug concentrations at the infection site is often employed. Current choices for intrathecal administration include aminoglycosides, tigecycline and colistin [3, 15, 16]. The combination regimen of colistin and tigecycline used here was an off-label salvage option for our critically-ill patients; there is very limited experience with its application [16]. There were no side effects of this co-administration, including chemical meningitis, seizures or nephrotoxicity.

The most important limitations of our presented cases are:

a) the fact that synergy between colistin and tigecycline was not tested *in vitro*;
b) antibiotic levels were not determined in CSF to compare with respective *in vitro* MICs of *A. baumannii* and
c) the possibility of selection bias always exists in case series, therefore a prospective cohort or RCT is needed to more accurately determine the potential benefit of such treatment.

However, the positive clinical and microbiological response reported herein warrants further investigation, considering the limited therapeutic options and adverse outcomes that are usually encountered in nosocomial VM by PDR *A. baumannii*.

CONCLUSION

Successful CSF sterilization with concomitant clinical response in the above cases indicates that exploiting the synergistic action of combined colistin and tigecycline through administration both intraventricularly and intravenously may be a promising salvage option for critically-ill patients with pan-drug resistant *A. baumannii* CNS infection.

Conflicts of interest
All authors declare no conflict of interest.

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