

# Treatment of Carbapenem-Resistant Multidrug-Resistant Gram-Negative Bacilli with Intracerebroventricular Injection of Polymyxin B: A Retrospective Study

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**Purpose:** We evaluated the efficacy and administration time of intraventricular (IVT) polymyxin B in the treatment of carbapenem-resistant and multidrug-resistant/extensively drug-resistant (MDR/XDR) Gram-negative bacilli in central nervous system (CNS) infections and investigated prognostic factors.

**Patients and Methods:** This retrospective analysis comprised 41 post-surgical carbapenem-resistant CNS infections from October 2016 to October 2021. All patients were treated with effective intravenous antibiotics and IVT polymyxin B. Patient characteristics, therapeutic procedure, symptoms, cerebrospinal fluid (CSF) examination, laboratory tests, and complications were recorded. The effectiveness of IVT polymyxin B was evaluated using temperature, Glasgow Coma Scale, CSF contents, bacterial clearance rate, cure rate, and mortality. Mortality between early (7 days) and late administration of IVT polymyxin B was compared. Prognostic factors were evaluated using the pupillary light reflex and multiloculated hydrocephalus.

**Results:** The 41 patients acquired carbapenem-resistant MDR/XDR bacteria, including 24 *Klebsiella pneumoniae*, 15 *Acinetobacter baumannii*, 3 *Pseudomonas aeruginosa*, and 1 *Enterobacter cloacae*. The bacterial clearance rate was 32/41 (78.0%), and 9 patients (22.0%) with uncured bacterial infections died. Adverse events included 1 case of skin pigmentation. Among the 32 cured patients, 31 received a ventriculoperitoneal shunt, and 1 patient had an extraventricular drainage tube removed. Mortality in the late (>7 days) group was higher (39.1% vs 0%,  $P < 0.05$ ). The group without pupillary light reflex showed a higher death rate (41.2% vs 8.3%;  $P < 0.05$ ). The multiloculated hydrocephalus group had a higher mortality rate than that of the normal group (34.8% vs 5.6%,  $P < 0.05$ ). All 32 cured patients were followed up for 9 to 66 months, and all survived without recurrent infections.

**Conclusion:** Intraventricular polymyxin B is an effective treatment for carbapenem-resistant MDR/XDR Gram-negative bacilli, with a 78% cure rate and significant mortality reduction if administered within 7 days of bacterial identification. Multiloculated hydrocephalus and the pupillary light reflex may be used as prognostic indicators of mortality.

**Keywords:** polymyxin B, intracerebroventricular injection, central nervous system infections, cerebrospinal fluid, prognosis

## Introduction

Treatment of infections of the central nervous system (CNS) is particularly challenging due to the limited permeability of the blood-brain barrier. Insufficient treatment may lead to increased morbidity and mortality as well as extended hospital stays. One study found that the risk of CNS infection following craniotomy was 1.5–5.5%, which increased to 9.6–15% if external ventricular drainage was inserted.<sup>1–5</sup> Infections caused by multidrug-resistant/extensively drug-resistant (MDR/

XDR) Gram-negative bacilli, such as *Acinetobacter baumannii* and *Klebsiella pneumoniae*, are difficult to treat because of the scarcity of effective drugs.<sup>6</sup> Furthermore, carbapenem resistance is strongly correlated with death from meningitis.<sup>7</sup> Fortunately, adjuvant intrathecal or intraventricular (ITH/IVT) colistin treatment may help patients with a CNS infection caused by MDR/XDR gram-negative bacilli isolates.<sup>8–10</sup>

Because the cerebrospinal fluid (CSF) lacks opsonins and has ineffective phagocytosis, bactericidal dosages of antibiotics are required to guarantee the removal of infection, unlike in other bodily compartments.<sup>11</sup> Polymyxins are regarded as the most effective antibiotics and can eradicate Gram-negative bacteria. Polymyxins primarily target bacterial membranes, causing their disruption and cell death.<sup>12</sup> Polymyxins also shuffle phospholipids, mediate hydroxyl radical death pathways, counterbalance endotoxins, and affect normal cell reproduction and respiration.<sup>13</sup> According to a study that evaluated 40,625 isolates, resistance to polymyxin compounds was uncommon, and the highest polymyxin B resistance rates were observed for *Klebsiella spp.* (1.4%), followed by *Acinetobacter spp.* (0.8%) and *Pseudomonas aeruginosa* and *Escherichia coli* (both at 0.1%).<sup>14</sup> It has even been suggested that polymyxin B is currently used as a “last-line” treatment for multidrug-resistant Gram-negative bacteria.<sup>15</sup> However, as a result of their polycationic structure and high molecular weight, polymyxins have difficulty penetrating the blood-brain barrier when administered intravenously.<sup>16</sup> Due to the blood-brain barrier, intravenous (IV) polymyxin B cannot reach the effective concentration in the CSF needed to treat an infection in the brain. IV injection results in a concentration of colistin in the CSF that is only 5–10% that of the blood level.<sup>17</sup> Only intracerebroventricular injection resulted in CSF colistin concentrations above the minimum inhibitory concentration of 0.5 g/mL and penetration rates that were 11% greater than 7% compared to IV administration alone.<sup>18</sup> IVT polymyxins may be the only way to quickly and effectively reach the bactericidal concentration.

The Standards and Practice Guidelines of the Infectious Diseases Society of America (IDSA) state that IVT injection in conjunction with IV polymyxin B or colistin is advised for the treatment of intracranial MDR gram-negative bacterial infections.<sup>19</sup> IVT+IV colistin or polymyxin B is the best treatment for MDR/XDR Gram-negative CNS infections, according to multiple studies.<sup>20–22</sup> Unfortunately, IVT polymyxin B is often used as a remedial treatment but is not recommended as an initial treatment for carbapenem-resistant MDR/XDR Gram-negative bacilli, and there have been few clinical studies on the correlation between the timing of IVT polymyxin administration and mortality.<sup>23</sup> The IDSA guidelines also do not provide a possible effective start time window for IVT polymyxin B. This study aimed to determine the efficacy and administration time of IVT polymyxin B in the treatment of carbapenem-resistant and MDR/XDR Gram-negative bacilli in CNS infections and to investigate prognostic factors.

## Materials and Methods

### Selection and Exclusion Criteria

We retrospectively collected data from 41 patients with CNS infections from October 2016 to October 2021 in the Department of Neurosurgery of Beijing Aviation General Hospital. Selection criteria were: (1) clinical and radiographic evidence supported the diagnosis of CNS infections; (2) biochemical and routine examinations of the CSF suggested an intracranial infection; (3) two consecutive CSF bacterial cultures contained Gram-negative bacilli, and carbapenem-resistant strains were screened; (4) in addition to IV antibiotic, simultaneous IVT injection of polymyxin B was performed; (5) clinical data were complete. The exclusion criteria were: (1) patients developed CNS infection prior to neurosurgery; (2) patients with false-positive CSF cultures, which may have been caused by contamination from the trial process and sampling; (3) immunocompromised patients; (4) incomplete clinical data.

### Microbial Culture Methods

CSF was collected and injected into Columbia blood AGAR culture flasks and then shaken at 35 °C for 24 h with a BACT/ALERT3D120 blood culture apparatus. After a few days, when the bacterial culture was positive, the bacterial suspension was standardized and placed in a VITEK2 for bacterial identification and to obtain drug sensitivity results. For polymyxin B drug sensitivity testing, bacterial suspensions were placed on MacConkey agar and test strips were used (E test method, BIO-KONT company, CHN). The polymyxin drug sensitivity results were evaluated according to the latest Clinical and Laboratory Standards Institute standards from 2015 to 2021 (<https://clsi.org/meetings/susceptibility-testing-subcommittees>).

## Clinical Treatment

Among the 41 patients with CNS infection, 22 were transferred from other hospitals without identifying the pathogenic bacteria in the CSF, but the clinical manifestations, CSF examination, and imaging supported CNS infection. Empirical IV antibiotic therapy and CSF culture results were obtained. After the bacterial identification and drug susceptibility results were obtained, the original CSF drainage tube or ventricle shunt tube was immediately removed and a new CSF external drainage tube was inserted. Sensitive antibiotics were administered intravenously to fight infection, and 5 mg polymyxin B (XGEN PHARMACEUTICALS, US) was injected into the ventricle daily. The other 19 cases were transferred with bacterial identification, and the drug susceptibility results of CSF were obtained from another hospital. After admission, the original CSF drainage tube or ventricular shunt tube was immediately removed and a new ventricular shunt tube was placed. For the treatment of CNS infection, sensitive antibiotics were administered intravenously, and polymyxin B (5 mg/day) was administered intraventricularly. During anti-infective treatment, head CT was reviewed once a week to monitor ventricular adhesion and multiloculated hydrocephalus. When multiloculated hydrocephalus or isolated ventricle with peripheral brain tissue was compressed and clinical symptoms appeared, one or more ventricular drainages were performed.

## Infection Cure Criteria and Management

The criteria for cure of infection were as follows. (1) The patient showed relief of symptoms and indicators of CNS illness, such as fever, neck stiffness, and changes in mental status, with meningeal irritation being the typical manifestation. (2) Biochemical and routine CSF levels returned to normal. Normal CSF was clear and colorless and levels of protein were 50–150 mg/L, glucose 2.5–4.5 mmol/L, leukocytes (0–5)  $\times 10^6$ /L, and chloride 120–130 mmol/L. The bacteria in the CSF were continuously cultured three times without bacterial growth. (4) To evaluate the symptoms and imaging manifestations of patients with hydrocephalus, the ventricle drainage tube was replaced and drainage continued, and the duration of CSF purification was recorded. When the standard conditions for ventriculoperitoneal shunt were reached, it was performed. If the infection had been cured and the diagnosis of hydrocephalus was excluded, the drainage tube outside the ventricle was removed.

## Clinical Outcomes

The data collected included clinical characteristics such as age, gender, primary disease, previous surgical procedures, and implants. The course of treatment included bacterial isolates, drug susceptibility, concomitant infections, empirical systemic antibiotics, IV antibiotics, and the duration of IV antibiotic administration. The pupil reflex and Glasgow Coma Scale (GCS) score before IVT polymyxin B, delay period (DP) from bacterial identification to IVT injection of polymyxin B, usage and dosage of IVT injection of polymyxin B, bacterial clearance time, body temperature, GCS score after bacterial clearance, presence of the multiloculated hydrocephalus, location of the isolated ventricles, number of drainage tubes placed in the ventricles, CSF purification time (time between bacterial identification in CSF and routine and biochemical normalization), CSF examination (bacterial culture, drug sensitivity, appearance, leukocytes, glucose, and protein), serum creatinine, and screening for adverse reactions including epilepsy, acute kidney injury, and skin pigmentation. All cured patients were followed up from 9 to 66 months. Prognostic factors were evaluated using the pupil light reflex and multiloculated hydrocephalus for mortality rates.

## Statistics

The patients were grouped for statistical analysis by the DP of IVT polymyxin B, with  $DP \leq 7$  days for the early IVT injection group and  $DP > 7$  days for the late IVT injection group. The effectiveness of IVT polymyxin B was evaluated comparing the abovementioned indicators using paired samples *t*-tests and the independent samples Mann–Whitney *U*-Test. The chi-square test and Fisher's exact test were used to compare mortality rates between the early and late groups. Statistical analysis was performed using SPSS (version 26.0). Numeric data with a normal distribution were represented as the mean  $\pm$  standard deviation, and paired sample *t*-tests were used to compare pre-treatment and post-treatment variables. Non-normally distributed data were expressed as median (lower quartile, upper quartile).  $P < 0.05$  was considered statistically significant.

## Results

A total of 41 patients with CNS infections between October 2016 and October 2021 were selected for this study. A total of 41 major pathogenic bacterial strains were isolated, including 24 cases of *K. pneumoniae*, 15 *A. baumannii*, 3 *Pseudomonas aeruginosa*, and 1 *Enterobacter cloacae*, all of which were MDR/XDR strains. In terms of drug resistance, the carbapenem resistance rate was 100%, polymyxin B resistance rate was 0%, and tigecycline resistance rate was 18.2%–33.3%. The results are presented in Table 1.

The age of the 41 patients was 37.7±19.1, and 70.7% were male. The primary diseases included intracerebral hemorrhage in 12 cases (29.3%), traumatic brain injury and CSF leakage in 9 cases (22.0%), traumatic brain injury in

**Table 1** Drug Susceptibility Results of 41 MDR/XDR Gram-Negative Bacilli

Antibiotic		KP (N=22)		AB(N=15)		PA(N=3)		ES(N=1)	
		n	n%	n	n%	n	n%	n	n%
Polymyxin B	R	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	I	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	≤0.5/S	22	100.0%	15	100.0%	3	100.0%	1	100.0%
Meropenem	≥16/R	22	100.0%	15	100.0%	3	100.0%	1	100.0%
	I	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	≤1/S	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Imipenem	≥16/R	22	100.0%	15	100.0%	3	100.0%	1	100.0%
	I	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	≤1/S	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Tigecycline	≥8/R	4	18.2%	4	26.7%	1	33.3%	0	0.0%
	=4/I	2	9.1%	2	13.3%	1	33.3%	0	0.0%
	≤2/S	16	72.7%	9	60.0%	1	33.3%	1	100.0%
Tobramycin	≥16/R	19	86.4%	12	80.0%	1	33.3%	0	0.0%
	=8/I	1	4.5%	0	0.0%	1	33.3%	0	0.0%
	≤1/S	2	9.1%	3	20.0%	1	33.3%	1	100.0%
cotrimoxazole	≥320/R	15	68.2%	8	53.3%	3	100.0%	1	100.0%
	I	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	≤20/S	7	31.8%	7	46.7%	0	0.0%	0	0.0%
Minocycline	≥16/R	15	68.2%	9	60.0%	2	66.7%	0	0.0%
	=8/I	0	0.0%	2	13.3%	0	0.0%	0	0.0%
	≤4/S	7	31.8%	4	26.7%	1	33.3%	1	100.0%
Piperacillin	≥128/R	22	100.0%	15	100.0%	2	66.7%	1	100.0%
	I	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	≤4/S	0	0.0%	0	0.0%	1	33.3%	0	0.0%
Piperacillin-tazobactam	≥32/R	21	95.5%	15	100.0%	2	66.7%	1	100.0%
	I	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	≤8/S	1	4.5%	0	0.0%	1	33.3%	0	0.0%
Cefepime	≥64/R	22	100.0%	15	100.0%	2	66.7%	1	100.0%
	I	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	≤1/S	0	0.0%	0	0.0%	1	33.3%	0	0.0%
Ciprofloxacin	≥4/R	21	95.5%	13	86.7%	2	66.7%	1	100.0%
	=2/I	0	0.0%	0	0.0%	1	33.3%	0	0.0%
	≤0.5/S	1	4.5%	2	13.3%	0	0.0%	0	0.0%
Levofloxacin	≥8/R	21	95.5%	10	66.7%	2	66.7%	1	100.0%
	=4/I	0	0.0%	3	20.0%	1	33.3%	0	0.0%
	≤1/S	1	4.5%	2	13.3%	0	0.0%	0	0.0%
Gentamicin	≥16/R	16	72.7%	11	73.3%	1	33.3%	0	0.0%
	=8/I	0	0.0%	1	6.7%	0	0.0%	0	0.0%
	≤21/S	6	27.3%	3	20.0%	2	66.7%	1	100.0%

**Abbreviations:** AB, *Acinetobacter baumannii*; KP, *Klebsiella pneumoniae*; PA, *Pseudomonas aeruginosa*; ES, *Enterobacter sulcus*; S, susceptible; I, intermediate; R, resistant.

8 cases (19.5%), brain aneurysm in 6 cases (14.6%), brain tumors in 4 cases (9.8%), chronic subdural hematoma in 1 case (2.4%), and hydrocephalus in 1 case (2.4%). The previous surgical procedures and conditions included decompressive craniectomy, intracerebral hemorrhage, external ventricular drainage, lumbar cisterna drainage, traumatic brain injury, evacuation of intracranial hematoma, excision of brain abscess, excision of intracranial tumor, intracranial aneurysm clipping, and Ommaya tube placement. The implants included extraventricular drainage tubes, lumbar cistern drainage tubes, subdural drainage tubes, and Ommaya tubes. These data are presented in Table 2.

**Table 2** Clinical Characteristics of Patients Enrolled in the Study

Case	Age	Gender	Primary Disease	Surgeries	Foreign Body
1	59	M	TBI	EICH+DC+VP+EVD	EVD
2	52	M	TBI	EICH+DC+EVD	EVD
3	61	F	TBI	EBA+EICH	NA
4	15	M	Brain aneurysm	EICT+EVD+LCD+OTP	EVD+LCD+OTP
5	64	F	Brain aneurysm	EICH+DC+EVD	LCD
6	51	M	ICH	EICH+EVD	EVD
7	18	M	Brain tumors	EICT+EVD+LCD+OTP	EVD+LCD+OTP
8	56	F	ICH	EICH+DC+LCD	LCD
9	57	M	ICH	EICH+DC+EVD	EVD
10	46	M	TBI+CFL	EICH+DC+LCD	LCD
11	65	M	Chronic subdural hematoma	EVD	EVD
12	58	M	TBI	EICH+DC+LCD+LCD	EVD+LCD
13	62	M	Brain aneurysm	EICH+DC+EVD	EVD+LCD
14	33	M	ICH	EICH+DC+EVD	EVD
15	17	F	TBI+CFL	EICH+DC+LCD	LCD
16	16	F	Hydrocephalus	EVD+LCD	EVD+LCD
17	33	M	Brain aneurysm	EICH+DC+ICAC+VP+EVD+LCD	EVD+LCD
18	53	M	ICH	EICH+ICAC+EVD+DC	EVD
19	42	F	ICH	EICH+EVD+LCD	EVD+LCD
20	15	M	TBI+CFL	EICH+DC+LCD	LCD
21	71	M	TBI+CFL	EICH+DC+EVD	EVD
22	25	M	ICH	EVD	EVD
23	33	M	TBI+CFL	EICH+DC+LCD	LCD
24	2	F	Brain tumors	EICT+EVD	EVD
25	59	F	ICH	EVD	EVD
26	20	M	TBI	EICH+VP+EVD	EVD
27	39	M	Brain aneurysm	ICAC+EICH+DC+LCD	EVD
28	55	M	ICH	EICH+DC+LCD+EVD	EVD
29	31	M	TBI+CFL	EICH+DC+EVD	EVD
30	33	M	TBI	EICH+DC+EVD+LCD	LCD
31	26	F	Brain tumors	EICT+EVD+LCD	LCD
32	57	F	Brain aneurysm	EICH+DC+LCD	LCD
33	25	M	TBI	EICH+DC+LCD	EVD+LCD+OTP
34	27	M	TBI	EVD+LCD	EVD
35	24	F	TBI+CFL	EICH+DC+VP+EVD+LCD	LCD
36	16	M	ICH	EICH+DC+VP+EVD+LCD	EVD+LCD
37	56	M	ICH	EICH+DC+VP+EVD+LCD	EVD
38	18	M	TBI+CFL	EICH+DC+EVD+LCD	EVD+LCD
39	30	M	TBI+CFL	EICH+DC+EVD+LCD	LCD
40	2	M	Brain tumors	EICT+EVD	EVD
41	24	F	ICH	LCD+VP+EVD	EVD

**Abbreviations:** DC, decompressive craniectomy; ICH, intracerebral hemorrhage; EVD, external ventricular drain; LCD, lumbar cisterna drainage; TBI, traumatic brain injury; EICH, evacuation intracranial hematoma; EBA, excision of brain abscess; EICT, excision of intracranial tumor; ICAC, intracranial aneurysm clipping; OTP, Ommaya tube placement; CFL, cerebrospinal fluid leakage; F, female; M, male.

Among the 41 major pathogenic bacteria, 28 were single infections and 13 were associated with concomitant infections, most of which were associated with Gram-positive cocci and some Gram-negative bacilli. Empirical systemic therapy or subsequent systemic therapy was performed prior to the identification of drug susceptibility results, including meropenem, vancomycin, cefoperazone sulbactam sodium, ceftriaxone, levofloxacin, ceftazidime, amikacin, piperacillin, tazobactam, and tigecycline. After identification of drug susceptibility results, 41 sensitive IV antibiotics were selected accordingly. The main antibiotics used in the 41 patients were tigecycline ( $n = 26$ ), amikacin ( $n = 5$ ), ceftazidime ( $n = 2$ ), fosfomycin ( $n = 2$ ), polymyxin ( $n = 2$ ), levofloxacin ( $n = 1$ ), ciprofloxacin ( $n = 1$ ), cefoperazone ( $n = 1$ ), and tobramycin ( $n = 1$ ). In some severe cases, a second sensitive antibiotic was administered intravenously. The durations of IV antibiotic administration are listed in Table 3.

The ventricle was injected daily with 5 mg polymyxin B. The median DP of IVT polymyxin B administration was 10.0 (5.0–26.0), the median time for continuous intraventricular polymyxin B injection was 19 (13, 27), the median time for bacterial clearance was 6.0 (5.0–10.0), and the median time for CSF purification was 83 (40–119). The bacterial clearance times of *K. pneumonia* and *A. baumannii* were 8.0 (6.0–12.0) days and 5.0 (4.0–7.0) days, respectively, and there was a significant difference between them ( $P < 0.05$ ). Due to limited sample sizes, *P. aeruginosa* and *E. cloacae* were removed from the analysis. The comparison of the delay periods of the death group with those of the cured group showed that both were statistically significant ( $P < 0.05$ ). These results are listed in Table 3.

The body temperature and GCS scores of all patients before and after bacterial clearance were significantly different ( $P < 0.05$ ). Nonmetric tests before and after bacterial clearance, leukocytes, and glucose and protein levels were all significant ( $P < 0.05$ ). These data are presented in Table 4.

The bacterial clearance rate was 78.0%, and all 9 patients without bacterial clearance died. Thirty-two patients (78.0%) were cured, and 9 patients (22.0%) died, of which the 30-day mortality rate was 1/41 (2.4%), the 90-day mortality rate was 8/41 (19.5%), and the hospital mortality rate was 9/41 (22.0%). Adverse events included 0 cases of epilepsy, 0 cases of acute kidney injury, and 1 case of skin pigmentation (Figure 1). Among the 32 cases of infection cured, 31 cases received ventriculoperitoneal shunt, 1 case had the extraventricular drainage tube removed, and 18 cases developed multiloculated hydrocephalus. All 32 cured patients were followed up for 9 to 66 months, and all survived without recurrent infections (Table 5).

Among the 41 patients, one ventricular drainage tube was indwelled in 24 cases (58.5%), two tubes in 13 cases (31.7%), three tubes in three cases (7.3%), and four tubes in one case (2.4%) (Figure 1).

Compared to the early (DP  $\leq 7$  days) IVT polymyxin B group, mortality in the late (DP  $> 7$  days) group was higher (39.1% vs 0%,  $P < 0.05$ ). However, there was no statistical difference in the IVT polymyxin B delay period (days) between patients with multiloculated hydrocephalus and normal ventricles in the non-parametric test [13 (7, 26) vs 6 (3, 26);  $P < 0.05$ ].

The pupil reflexes of 41 patients before IVT polymyxin B were evaluated; 24 (58.5%) were present and 17 (41.5%) vanished. Compared with the group with a pupillary light reaction before polymyxin B intraventricular injection, the group without a reflex had a higher death rate (41.2% vs 8.3%;  $P < 0.05$ ). The multiloculated hydrocephalus group had a higher mortality rate than the normal ventricle groups (34.8 vs 5.6%,  $P < 0.05$ ), as shown in Table 6.

## Discussion

Based on how the 3163 strains of bacteria found in CSF samples by CHINET in 2021 were split, 11.3% were *A. baumannii*, 9.1% were *K. pneumonia*, 1.6% *Pseudomonas aeruginosa*, and 1.6% *E. cloacae*. In terms of drug resistance, the resistance rate of *K. pneumoniae* to meropenem increased from 2.9% in 2005 to 26% in 2022, and the resistance rate of *A. baumannii* to meropenem increased from 31% in 2005 to 76.6% in 2022 (see <http://www.chinets.com>). Carbapenem antibiotics are effective drugs for CNS infections because of their good blood-brain barrier permeability. Due to the lack of sensitive and high-permeability drugs, the rate of carbapenem-resistant MDR bacteria is increasing. Carbapenem-resistant Gram-negative bacteria are a leading cause of hospitalizations and deaths.<sup>24</sup> In contrast to patients infected with carbapenem-susceptible *K. pneumoniae*, those with purpose-carbapenem-resistant *K. pneumoniae* have a higher mortality rate.<sup>25</sup> Resistance to carbapenem may increase the mortality risk for patients with *A. baumannii* infection.<sup>26</sup> Therefore, the detection rate of carbapenem-resistant Gram-negative bacteria is increasing each year and is closely related to high mortality. Intracranial



**Table 3** Cerebrospinal Fluid (CSF) Culture and Treatment Strategies for Each Patient

Case	CSF Isolate	Drug Susceptibility	Concomitant Infection	Antibiotics Before CSF Culture	IV Sensitive Antibiotics	Duration of IV (Days)	IVT Polymyxin B Delay Period	IVT Polymyxin B (mg, qd)	Duration of IVT Polymyxin B (Days)	CSF Bacterial Clearance Days	Multiloculated/ Normal Ventricle	Ventricular Segment Counts	Isolated Ventricular	CSF Purification Time	Outcome	Survival Follow-Up Period (Months)
1	KP	CR	NO	CRO	AK	35	3	5	14	6	N	1	NO	254	Cure	Alive/62
2	KP	CR	NO	CAZ	PB	31	3	5	13	6	M	2	TA	93	Cure	Alive/32
3	KP	CR	NO	AK	TGC	16	3	5	19	12	N	1	NO	95	Cure	Alive/16
4	KP	CR	AB	AK	TGC	32	3	5	27	6	N	1	NO	56	Cure	Alive/22
5	AB	CR	NO	MEM	TGC	23	3	5	10	5	N	1	NO	46	Cure	Alive/57
6	AB	CR	NO	LEV	TGC	14	3	5	12	5	N	1	NO	37	Cure	Alive/64
7	KP	CR	NO	MEM+VA	TGC	83	3	5	25	14	M	2	TA	178	Cure	Alive/44
8	AB	CR	NO	MEM+VA	FOS	5	3	5	12	5	M	3	TA+FV	100	Cure	Alive/11
9	AB	CR	Se	CAZ	TGC	66	5	5	19	7	N	1	NO	48	Cure	Alive/36
10	KP	CR	NO	LEV	TGC	24	5	5	18	8	N	1	NO	102	Cure	Alive/35
11	KP	CR	NO	LEV	CIP	32	5	5	21	14	N	1	NO	40	Cure	Alive/10
12	KP	CR	NO	LEV	TGC	12	5	5	20	8	N	1	NO	96	Cure	Alive/52
13	AB	CR	NO	MEM+VA	TOB	13	6	5	10	3	M	2	TA	70	Cure	Alive/66
14	KP	CR	NO	CRO	TGC	58	7	5	21	8	M	1	TA	124	Cure	Alive/17
15	KP	CR	NO	CAZ	TGC	48	7	5	27	14	N	1	NO	97	Cure	Alive/57
16	AB	CR	EC	CFPs	TGC	40	7	5	18	7	M	1	FV	106	Cure	Alive/51
17	KP	CR	NO	LEV	TGC	32	7	5	10	3	M	1	TA+FV	236	Cure	Alive/30
18	KP	CR	NO	MEM	TGC	19	7	5	13	5	M	4	TA+LRLV	170	Cure	Alive/38
19	KP	CR	NO	Biapenem	TGC	20	8	5	20	NA	M	2	LLV+RLV	NA	Death	Death
20	KP	CR	NO	CRO	FOS	46	9	5	26	12	N	1	NO	50	Cure	Alive/9
21	AB	CR	NO	LEV	TGC	38	10	5	9	3	M	2	FV	50	Cure	Alive/43
22	AB	CR	NO	CFPs	TGC	57	11	5	12	5	N	1	NO	70	Cure	Alive/45
23	AB	CR	NO	TGC	TGC	78	13	5	30	10	M	2	TA	51	Cure	Alive/57
24	AB	CR	NO	TGC	PB	73	13	5	13	4	M	2	TA	119	Cure	Alive/32
25	EC	CR	Se	TGC	AK	15	13	5	27	9	M	1	LLV+RLV	12	Cure	Alive/51
26	KP	CR	NO	TGC	TGC	39	20	5	33	NA	M	1	LLV+RLV	NA	Death	Death
27	KP	CR	AB	TGC+PB	TGC	86	20	5	35	NA	M	3	TA+LRLV	NA	Death	Death
28	AB	CR	NO	TGC	TGC	19	20	5	18	6	M	1	FV	12	Cure	Alive/64
29	AB	CR	NO	TGC	CFPs	7	25	5	15	NA	M	3	TA+FV	NA	Death	Death
30	PA	CR	Se	TGC	AK	10	25	5	13	5	N	1	NO	203	Cure	Alive/62
31	AB	CR	E.faecium	LEV	LEV	63	26	5	35	NA	M	2	LLV+RLV	NA	Death	Death
32	KP	CR	E.faecalis	TGC	TGC	6	26	5	22	10	N	1	NO	14	Cure	Alive/37
33	KP	CR	NO	TGC	TGC	88	30	5	18	6	N	1	NO	30	Cure	Alive/60
34	AB	CR	NO	TGC	TGC	3	30	5	23	NA	M	2	LLV+RLV	NA	Death	Death
35	AB	CR	BC	AK	AK	23	30	5	26	NA	N	1	NO	NA	Death	Death
36	KP	CR	Se	TGC	TGC	26	30	5	14	5	M	2	TA	17	Cure	Alive/64
37	KP	CR	NO	TGC	TGC	5	37	5	35	NA	M	2	LLV+RLV	NA	Death	Death
38	KP	CR	SM	TGC	TGC	48	40	5	38	NA	M	2	TA	NA	Death	Death
39	PA	CR	NO	CAZ	CAZ	159	45	5	19	6	N	1	NO	147	Cure	Alive/54
40	PA	CR	SC	CAZ	CAZ	34	97	5	30	14	M	2	TA	47	Cure	Alive/56
41	KP	CR	Se	TGC	AK	44	192	5	28	15	N	1	NO	83	Cure	Alive/38

**Abbreviations:** AB, *Acinetobacter baumannii*; KP, *Klebsiella pneumoniae*; PA, *Pseudomonas aeruginosa*; ES, *Enterobacter sulcus*; EC, *Escherichia coli*; Se, *Staphylococcus epidermidis*; E. faecium, *Enterococcus faecium*; BC, *Burkholderia cepacia*; SM, *Serratia marcescens*; SC, *Staphylococcus caprae*; CR, carbapenem resistance; IVT, intraventricular; IV, intravenous; CRO, Ceftriaxone; CAZ, ceftazidime; CAZ, Ceftazidime-avibactam; MEM, Meropenem; VA, Vancomycin; LEV, Levofloxacin; TGC, Tigecycline; TOB, Tobramycin; AK, Amikacin; CAZ, Ceftazidime; CFPs, Cefoperazone/sulbactam; PB, Polymyxin B; CFPs, Cefoperazone sulbactam sodium; CIP, Ciprofloxacin; FOS, Fosfomycin; CST, Compound sulfamethoxazole tablets; GN, Gentamicin; TA, Temporal angle; FV, Fourth ventricle; N, Normal; M, Multiloculated; LLV, Left lateral ventricle; RLV, Right lateral ventricle.

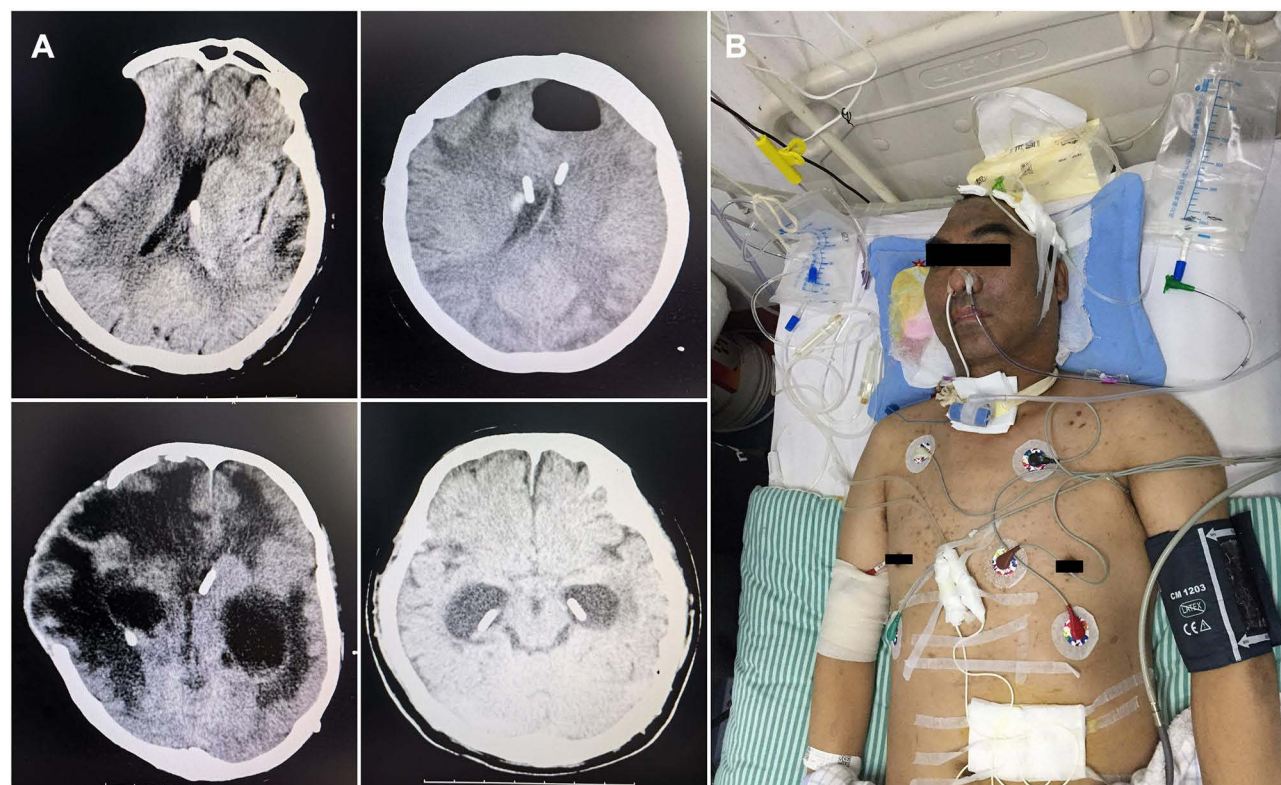
**Table 4** Clinical Symptoms and Laboratory Data in Patients

Variable	Before IVT Polymyxin B	After IVT Polymyxin B	p
Temperature (°C)	38.2±0.45	37.0±0.65	0
GCS score	7.54±3.36	8.49±3.78	0.03
Serum Creatinine (μmol/L)	65.10±16.12	63.45±14.78	0.08
<b>CSF</b>			
Leukocytes (cells/μL)	1848 (280, 4244)	4 (2, 9)	0
Glucose (mmol/L)	0.58 (0.45, 1.90)	3.61 (3.20, 3.97)	0
Protein (g/L)	0.44 (0.20, 0.97)	3.00 (1.00, 4.50)	0

**Abbreviations:** CNS, central nervous system; GCS, Glasgow Coma Scale; CSF, cerebrospinal fluid.

infections caused by carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *A. baumannii* have become difficult to solve in clinical practice.

Carbapenem-resistant strains should be treated with colistin sodium or polymyxin B according to the IDSA Standards and Practice Guidelines (strong, moderate).<sup>19</sup> Patients with post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria have been shown in observational studies to benefit from the addition of ITH/IVT antimicrobial therapy, which is associated with a lower risk of mortality and a higher microbiological clearance rate and only mild adverse effects.<sup>23</sup> The current standard of care for MDR/XDR *A. baumannii* ventriculitis/meningitis is IVT/ITH colistin, which provides a novel, relatively safe, and effective form of therapy.<sup>27</sup> Therefore, IVT polymyxin B may be an effective treatment for CNS infections with MDR/XDR Gram-negative bacteria.



**Figure 1** Multiloculated hydrocephalus and skin pigmentation in carbapenem-resistant MDR/XDR gram-negative central nervous system infections. **(A)** CT indicated multiloculated hydrocephalus in 23 carbapenem-resistant MDR/XDR gram-negative central nervous system infections. **(B)** One patient developed hyperpigmentation after receiving 50 mg q12h intravenous Polymyxin B for 31 days.



**Table 5** Clinical Outcomes and Complications

Outcome/Complication	No. Cases(%)
Bacterial clearance rate	32 (78.0%)
Cured rate	32 (78.0%)
Mortality	9 (22.0%)
30-day mortality	1 (2.4%)
90-day mortality	8 (19.5%)
<b>Adverse events</b>	
Epilepsy	0 (0%)
Acute kidney injury	0 (0%)
Skin hyperpigmentation	1 (2.4%)
<b>Sequelae of infection</b>	
Hydrocephalus and VP	31 (75.6%)
Remove the drainage tube	1 (2.4%)
Multiloculated ventricle	18 (43.9%)

**Table 6** Clinical Factors and Mortality

Variable	Cure	Death	p
<b>DP of IVT Polymyxin B</b>			0.002
Early IVT group	18 (100%)	0 (0%)	
Late IVT group	14 (60.9%)	9 (39.1%)	
<b>Pupil light reflex</b>			0.021
Presence	22(91.7%)	2(8.3%)	
Disappeared	10 (58.8%)	7(41.2%)	
<b>Multiloculated hydrocephalus</b>			0.005
Multiloculated	15 (65.2%)	8(34.8%)	
Normal	17 (94.4%)	1(5.6%)	

**Note:** DP, delay period; DP ≤7 days for the early IVT injection group; DP >7 days for the late IVT injection group.

## The Effectiveness of IVT Polymyxin B

The IDSA guidelines recommend 5 mg/day for 10–21 days of IVT polymyxin B.<sup>11</sup> In the International Consensus Guidelines for the Optimal Use of Polymyxins, the dose for IVT polymyxin B is 5 mg/day for 18 days.<sup>28</sup> Nevertheless, the quality of evidence is low, as stated in the guidelines. Despite the success of IVT + IV polymyxin B treatment, there are few clinical reports of other IV antibiotics combined with IVT polymyxin B. In our study, domestic polymyxin B was costly and not easily obtainable in China until 2018, so the majority of cases did not use the IV+IVT polymyxin B program recommended by the guidelines because of cost concerns. Therefore, IV antibiotics, such as tigecycline, amikacin, and fosfomycin, according to the drug susceptibility results, were used in combination with IVT polymyxin B (5 mg/day), with continuous IVT injection of polymyxin B for a median of 19 days (13, 27). According to published data, the bacterial clearance rate of IVT polymyxin B as an adjunct to standard IV treatment differed among studies: 65.2%,<sup>29</sup> 25%,<sup>8</sup> 66.7%,<sup>30</sup> 25%,<sup>31</sup> 78%,<sup>21</sup> 67%,<sup>32</sup> and 67.6%.<sup>33</sup> In our study, the bacterial clearance rate reached 78%, which is slightly higher than the bacterial clearance rate reported in the literature. The review and meta-analysis of Maria et al concluded that IVT antibiotics improved eradication rates for Gram-negative ventriculitis and meningitis, but they were not statistically significant.<sup>34</sup> But, in carbapenem-resistant Gram-negative ventriculitis and meningitis, the effect was significant (10 times).<sup>34</sup> However, the evidence was very poor. Further prospective large-scale studies are required to validate these findings.<sup>34</sup>

Some CSF management techniques may be helpful in improving bacterial clearance during treatment procedures. First, many reports believe that extracellular ventricular drainage and lumbar cisternectomy are high risk factors for intracranial infection,<sup>35–37</sup> and the infection rate can reach 23.2%.<sup>36</sup> Moreover, it has been reported that after the bacterial

clearance of CSF, even if there are no bacteria in the bacterial culture of CSF, the fixed value bacteria in the extracellular ventricular drainage tube can still be detected by electron microscopy and PCR.<sup>38</sup> In our treatment procedure, the temporary external ventricular drainage tube was removed immediately after bacterial clearance of IV antibiotics + IVT polymyxin B and a new ventricular drainage tube was inserted, which could prevent recurrence of infection caused by bacteria fixed in the drainage tube and improve the cure rate. Second, continuous ventricular drainage of CSF gradually cleared the CSF after placing a new extracellular ventricular drainage tube.<sup>39,40</sup> In our study, CSF biochemistry and routine results also indicated gradual improvement to normal. Third, IVT polymyxin B can bypass the blood-brain barrier and higher concentration accumulates in the CSF than with IV antibiotics alone, reaching a minimum inhibitory concentration of 0.5 g/mL.<sup>18</sup> IVT polymyxin B combined with continuous extraventricular drainage can drain inflammatory CSF while clearing bacteria to reduce the bacterial load of intracranial infection. Adequate long-term IV sensitive antibiotics have an effective therapeutic effect after an infection-induced increase in blood-brain barrier permeability.<sup>41</sup>

In this study, the median number of days of continuous intracerebroventricular injection of polymyxin B was 19 (13, 27), which was consistent with the guideline-recommended duration of continuous intracerebroventricular injection (10–21 or 18 days).<sup>19,28</sup> The median bacterial clearance time in days was 6.0 (5.0–10.0). The nonparametric test in this study compared the bacterial clearance times of *K. pneumoniae* and *A. baumannii* and found that the median bacterial clearance time for *K. pneumoniae* was 8.0 (6.0–12.0), and that for *A. baumannii* was 5.0 (4.0–7.0), and the difference was statistically significant ( $P < 0.05$ ). We believe that compared with the intracerebroventricular injection time for carbapenem-resistant *K. pneumoniae*, that for carbapenem-resistant *A. baumannii* should be appropriately extended by at least more than 8 days, which can reduce bacterial recurrence and improve the bacterial clearance rate.

Based on the clinical symptoms and laboratory results, we believe that the combination of IV-sensitive antibiotics and IVT polymyxin B can effectively control ventricular inflammation, improve GCS score, and have no effect on renal function.

## Mortality

According to the literature, the mortality rates reported by studies using antibiotic IVT+IV treatment regimens varied and were 36.4%, 75%,<sup>27</sup> 34.9%,<sup>28</sup> 55.5%,<sup>13</sup> 20%,<sup>29</sup> and 32.4%.<sup>30</sup> The mortality rate of intracranial infections caused by MDR/XDR Gram-negative bacteria using only IV antibiotics in different studies were 56.2%,<sup>12</sup> 77.8%,<sup>13</sup> 72.7%,<sup>30</sup> 37.9%,<sup>8</sup> 91.6%,<sup>7</sup> 55.3%,<sup>14</sup> and 33.3%.<sup>29</sup> In our study, 32 patients (78.0%) were cured, and 9 patients (22.0%) died, of which the 30-day mortality rate was 1/41 (2.4%), the 90-day mortality rate was 8/41 (19.5%), and the hospital mortality rate was 9/41 (22.0%). Our findings are consistent with other literature reports on cure and mortality, with slightly better results than those of other studies.

We found that mortality was associated with the pupil response to light, administration time of IVT polymyxin B, and multiloculated hydrocephalus. First, patients with lost pupillary reflex before treatment had a higher mortality rate, indicating that the degree of brain injury is related to mortality and that the loss of optical reflex is a prognostic indicator. Second, we found that patients with delayed injection of IVT polymyxin B had a higher mortality rate. Instead of being utilized as an initial treatment, IVT injection is typically employed as a corrective treatment after systemic medication fails.<sup>31</sup> However, when to initiate IVT treatment is not clear in the guidelines and depends more on clinical experience. It is widely accepted that IVT therapy is added sequentially to the treatment regimen for patients who exhibit persistent bacterial growth in CSF cultures or are clinically failing. IVT antibiotic use in ventriculitis treatment may be able to shorten the period of CSF bacterial clearance, especially in patients in a treatment-refractory state. Conversely, delayed bacterial clearance from the CSF is associated with adverse neurologic outcomes.<sup>31,42</sup> Furthermore, delayed ITH/IVT colistin therapy contributed to mortality.<sup>43</sup> This is consistent with our results. For carbapenem-resistant CNS infections, IVT polymyxin B should be initiated as soon as the bacteria are isolated. An effective time window for initiating therapy is generally within 7 days of bacterial identification and IVT polymyxin B therapy should be administered as soon as possible.

Lastly, multiloculated hydrocephalus is also called compartmentalized hydrocephalus or ventricular septations. Inflammation of the ependyma supports subependymal glial tissue development, where exudates and debris form fibroglial webs. Once the ependymal lining is disturbed, glial tufts create septations.<sup>44</sup> It has been reported that VP

patients with intracranial infection with Gram-negative bacilli have a higher probability of multiloculated hydrocephalus, with an incidence of approximately 32%.<sup>44</sup> In our study, carbapenem-resistant MDR Gram-negative bacilli caused a higher mortality rate in ventricular compartmentalization patients with central nervous system infection. A possible reason is that compartmentalization may affect the distribution of CSF in the subarachnoid space and the ventricle, leading to the failure to kill bacteria completely, the infection does not heal, and even an asymmetrically dilated ventricle, causing acute cerebral hernia.

In our study, repeat CT scans following IVT polymyxin B + IV sensitive antibiotic therapy found multiloculated hydrocephalus. Regarding the cause, it has been hypothesized that the IVT administration of antibiotics may be a factor.<sup>45</sup> In addition, it has been claimed that the delayed beginning of IVT irrigation and the administration of antibiotics contributed to an increased prevalence of multiloculated hydrocephalus.<sup>46</sup> However, our study found no statistical difference in IVT polymyxin B DP between the patients with multiloculated hydrocephalus and those with normal ventricles. In addition, there was no indication of chemical ventriculitis after IVT polymyxin B administration. Therefore, more studies are required to determine the connection between multiloculated hydrocephalus and IVT polymyxin B.

## Adverse Events

There were no instances of epilepsy or acute kidney injury. The only side effect in our study was skin hyperpigmentation in one patient who received 50 mg IV polymyxin B every 12 h for 31 days. The patient developed head and neck symptoms after 3 days of systemic polymyxin B treatment, and the color of the head and neck became dark brown after 10 days. (Figure 1). At the patient's cervicothoracic junction, an interface of dark and light colors was visible. We call this phenomenon the "neck-thorax junction sign", when other parts of the body's skin are normal. After 31 days of continuous systemic administration of polymyxin B, the patient recovered and survived. Head and neck skin pigmentation partially recovered 3 months after drug discontinuation. Unfortunately, dermoscopy and dermatopathology were not performed in this patient.

The incidence of skin hyperpigmentation after IV polymyxin B treatment is approximately 8%, and it is assumed that this is related to an inflammatory process and melanocyte activation.<sup>47</sup> Melanocytes are more abundant in the head and neck.<sup>48</sup> High adnexal and nerve density is also characteristic of the head skin. The number of sebaceous glands on the head is 400–900/cm<sup>2</sup>.<sup>49,50</sup> Polymyxin B usage may activate them, causing a non-uniform pigmentation distribution.

## Limitations

This study had several limitations. (1) This was a single-center retrospective study, and prospective or retrospective multicenter randomized investigations are needed. (2) Our study had a small sample size ( $n = 41$ ). (3) All carbapenem-resistant MDR/XDR Gram-negative bacilli isolated in this study were from critically ill patients who were treated with IVT polymyxin B + IV sensitive antibiotics. A strictly IV drug group was not used as the control group. (4) Polymyxin B was expensive and not easily obtainable in China until 2018; therefore, instead of using the IVT+IV polymyxin B regimen recommended by the guidelines, a systemic IV regimen based on susceptibility results was selected. An imbalance in a comparison study may have led to different results.

## Conclusion

Intraventricular polymyxin B is an effective treatment for carbapenem-resistant multidrug-resistant Gram-negative bacilli, with a 78% cure rate and capacity to significantly reduce mortality if administered within 7 days after bacterial identification. Multiloculated hydrocephalus and the pupillary light reflex may be used as prognostic indicators of mortality.

## Abbreviations

CNS, central nervous system; CSF, cerebrospinal fluid; DP, delay period; GCS, Glasgow Coma Scale; IDSA, Infectious Diseases Society of America; ITH, intrathecal; IV, intravenous; IVT, intraventricular; MDR/XDR, multidrug-resistant /extensively drug-resistant.

## Ethical Statement

The study protocol was approved by Aviation General Hospital Medical Ethics Committee. (Protocol Number: KY2022-073-02). The study was conducted in accordance with the revised Helsinki Declaration in 2013. Written informed consent was obtained from patients or guardians of patients with coma, a parent or legal guardian of patients under 18 years of age. Written informed consent was obtained from the patient or guardian to have the case details and any accompanying images published.

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

## Disclosure

The author reports no conflicts of interest in this work.

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