Infection and Drug Resistance

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ORIGINAL RESEARCH

A Clinical Study on the Use of Intraventricular Polymyxin B Supplemented by Continuous External Ventricular Drainage in the Treatment of Drug-Resistant Gram-Negative Bacilli Intracranial Infection

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Purpose: To investigate the clinical effect of ventricular polymyxin B supplemented by continuous external ventricular drainage in the treatment of intracranial infection with multidrug-resistant (MDR) or extensively drug-resistant (XDR) Gram-negative (G-) bacilli following neurosurgery.

Patients and Methods: A retrospective analysis was performed on 28 patients who had G-bacilli intracranial infection following neurosurgery in our department between January 2017 and December 2019. The patients were treated with intraventricular polymyxin B supplemented by continuous external ventricular drainage. The clinical characteristics, treatment process, cerebrospinal-fluid-related indicators, results and prognosis were analysed.

Results: All of 28 patients developed an infection subsequent to neurosurgery, and cerebrospinal fluid (CSF) cultures demonstrated MDR/XDR G- bacilli, including *Acinetobacter baumannii* in 14 cases, *Klebsiella pneumoniae* in 9 cases, *Pseudomonas aeruginosa* in 3 cases, and *Enterobacter cloacae* in 2 cases. The ventricular drainage tube remained unobstructed in all patients during treatment, and intraventricular polymyxin B combined with intravenous antibiotics were administered each day. The duration of treatment with intraventricular polymyxin B was 14.96±4.28 days, and the time required to obtain a negative CSF culture was 8.23±4.02 days. The bacterial clearance rate from cerebrospinal fluid was 92.9% (26/28), and the clinical cure rate was 82.1% (23/28). Among them, 18 patients underwent ventriculoperitoneal shunt insertion for hydrocephalus 82.5 (59.5,114.75) days after the infection was cured, and the mortality rate was 17.6% (5/28). There was no significant change in patient blood creatinine levels before and after treatment. Cured patients were followed up for 4 months to 3 years, and no recurrences were observed.

Conclusion: Treatment of intracranial infection with MDR/XDR G- bacilli using early intraventricular polymyxin B supplemented by continuous external ventricular drainage treatment may be a safe and effective treatment strategy.

Keywords: intracranial infection, drug-resistant, Gram-negative(G-)bacilli, intraventricular polymyxin B, continuous external ventricular drainage

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Introduction

In recent years, due to the abuse of broad-spectrum antibiotics, intracranial infections caused by multidrug-resistant (MDR) or extensively drug-resistant (XDR) Gram-negative (G-) bacilli such as *Acinetobacter baumannii*, *Pseudomonas*

aeruginosa, *Klebsiella pneumoniae*, *Enterobacter cloacae* and Escherichia coli, are increasing year by year,[1] and have become one of the biggest challenges in the clinical management of microbial infections. Effective antibacterial drugs currently available for treating infections caused by these "superbugs" are limited. Studies have demonstrated that polymyxin is a polypeptide antibiotic isolated from Bacillus polymyxa.[2,3] It was abandoned as a treatment in the past due to reports of strong nephrotoxicity, but has been reintroduced into clinical practice to target drug-resistant gram-negative bacteria. Many studies have shown that polymyxin does not easily penetrate the blood-brain barrier to produce anti-infective activity,[4,5] so intraventricular (IVT) and/or intrathecal (ITH) administration may be effective methods for treating G-bacilli intracranial infection. Therefore, the purpose of this study was to retrospectively analyze the clinical efficacy and safety of the treatment based on intraventricular polymyxin B and continuous ventricular drainage in 28 patients with MDR/XDR G- bacillus intracranial infection. The report is as follows.

Materials and Methods

General Information

Patients treated for G-bacilli intracranial infection at the Cerebrospinal Fluid (CSF) Diagnosis and Treatment Center of Beijing Aviation General Hospital of China Medical University from January 2017 to December 2019 were selected. The study was approved by the Medical Science Ethics Committee of the Aviation General Hospital (HK2017-01-04). The Committee waived signature of informed consents by the patients whose records were retrospectively reviewed, as this was a noninterventional, retrospective study with data management processed anonymously. Clinical diagnosis and treatment were collected in the medical records, except patients' names. We have confidential measures for the privacy of patients. This study was conducted in accordance with the Declaration of Helsinki.

Inclusion Criteria and Exclusion Criteria

Inclusion criteria: 1) Age >18 years; 2) CSF culture results showing MDR/XDR G- bacilli;[3] 3) Fulfilment of the criteria for intracranial infection established by the Neurosurgery Branch of the Chinese Medical Association.[6]

Exclusion criteria: 1) Possible colonization or contamination with G- bacilli; 2) A history of intracranial infection before craniotomy; 3) Having received polymyxin B treatment due to intracranial infection or infection at other positions recently (in the past three months); 4) Pregnancy or concurrent malignant tumor in an area other than the central nervous system.

A positive CSF culture was defined by contamination or colonization if the patient did not have clinical symptoms or had normal levels of glucose, protein and nucleated cells.[7,8]

Treatment

After admission, if the patients presented with clinical symptoms of infection and the bacterial culture of CSF indicated MDR/XDR G- bacilli; then, intravenous delivery of antibiotics was performed according to the results of the drug-sensitivity test. If three consecutive bacterial cultures of CSF after admission indicated the same results of MDR/XDR G- bacilli or if MDR/XDR G- bacilli were confirmed as pathogens at other hospitals and the first bacterial culture of CSF at our hospital after admission had the same result as that at another hospital; then, intracerebroventricular delivery of polymyxin B was performed. Intraventricular administration method: first, 5mL of cerebrospinal fluid was withdrawn and discarded, and 5mg polymyxin B was dissolved in 5mL normal saline and injected, after which the tube was clamped for 2 hours. This was done every 24 hours.

To monitor adverse events related to antibiotic therapy, any changes in clinical signs and symptoms that occurred after starting antibiotic therapy and any fluctuations in laboratory findings were recorded.

Testing for CSF Indicators

The Hitachi LABOSPECT 008 AS fully automated biochemical analyzer was used for biochemical analysis of cerebrospinal fluid, mainly including CSF glucose, CSF protein, and CSF chloride. Sysmex XN2000 was used for routine analysis of cerebrospinal fluid. The strain identification and drug susceptibility tests were carried out using the French Biomerieux VITEK 2 Compact fully automated microbiological analysis system. Drug sensitivity results were interpreted according to the 2019 version of the American Clinical and Laboratory Standardization Committee (CLSI) standard M100-S25. The polymyxin sensitivity standards were based on the US Food and Drug Administration (FDA) standards.

Data Collection

A retrospective case investigation method was used to collect clinical data on patients, including age, gender,

main diagnosis, pre-infection craniocerebral surgery, main systemic antibiotics, CSF bacterial culture results, and clinical outcomes. Laboratory test data before and after treatment with intraventricular polymyxin B were collected, including CSF white blood cell count, CSF red blood cells, CSF glucose, CSF chloride, CSF protein levels, as well as liver function and kidney function tests.

Follow-Up and Evaluation Indicators

Clinical cure criteria: 1) Body temperature is normal for more than 3 consecutive days; 2) Improvement or resolution of the original clinical symptoms (meningeal irritation, consciousness); 3) CSF glucose above 2.2 mmol/L on 3 consecutive measurements, white blood cells:red blood cells <1:500; 4) Three consecutive negative CSF bacterial cultures.

Statistical Analysis

SPSS v.23.0 software was used for statistical analysis. Measurement data that conformed to the normal distribution were expressed as mean ± standard deviation, and statistical analysis was performed using a paired *t*-test. Measurement data that did not conform to the normal distribution were calculated as the median (quartile interval), and the Wilcoxon test was used for statistical analysis. The count data were expressed as a percentage, and comparisons were carried out using the $\chi 2$ test. $P < 0.05$ was considered statistically significant.

Results

General Information Regarding the Patients

A total of 28 patients were enrolled in this study, including 23 males and 5 females; the average age was 44.64±17.42 years (range, 16–71 years). All patients were transferred to our hospital following infection at another hospital, and all had undergone neurosurgery before infection. The primary diseases and surgical methods are shown in Table 1.

Table 1 Demographics of the Patients

Patients	N (%)
Total, N	28
Average age (mean ± sD) (range) (years)	44.64±17.42 (16–71)
Male	23/28 (82.1)
Female	5/28 (17.9)
Primary diagnosis	
ICH	10/28 (35.7)
TBI	9/28 (32.1)
Aneurysm	4/28 (14.3)
Intracranial tumour	3/28 (10.7)
CVM	1/28 (3.6)
SAH	1/28 (3.6)
Surgical patients before infection	28/28 (100.0)
Any surgeries before infection	
LD	21/28 (75.0)
EVD	20/28 (71.4)
More than 2 times EVD	7/28 (25.0)
Craniotomy	19/28 (67.9)
Hematoma evacuation	12/28 (42.9)
Decompressive craniectomy	11/28 (39.3)
VPS	5/28 (17.9)
Intracranial occupying resection	4/28 (14.3)
Ventriculoscopy	3/28 (10.7)
Cranioplasty	3/28 (10.7)
Aneurysm embolization	2/28 (7.1)
Aneurysm clipping	2/28 (7.1)
Ommaya implantation	1/28 (3.6)

Abbreviations: TBI, traumatic brain injury; ICH, intracerebral hemorrhage; CVM, cerebrovascular malformation; SAH, subarachnoid hemorrhage; EVD, external ventricular drainage; LD, lumbar drainage; VPS, ventriculoperitoneal shunt.

Surgical Treatment and Intraventricular Administration for the Patients

Surgical treatment principles, including the existing external ventricular drainage tube for drainage, were kept in place or reinserted, the external lumbar cistern drainage from the previous hospital, the ventriculoperitoneal shunt, the skull repair material, and blocked external ventricular drainage tubes were removed, as shown in Table 2. Intraventricular administration: all patients were given intraventricular polymyxin B 5mg/d, with an average administration time of 14.96±4.28 days (range, 9–23). Table 2

Bacterial results and Systemic Medication

All CSF cultures demonstrated MDR/XDR G- bacilli, including 14 cases of *Acinetobacter baumannii*, 9 cases of *Klebsiella pneumoniae*, 3 cases of *Pseudomonas aeruginosa*, and 2 cases of *Enterobacter cloacae*. The drug resistance analysis of CSF pathogens is shown in Table 3. All patients were treated with systemic antibiotics (based on drug sensitivity results), including tigecycline (n = 7), tigecycline – cefoperazone sodium and sulbactam sodium (n = 7), polymyxin-sulperazon (n = 3), Tigecycline-polymyxin (n = 2), amikacin (n = 2), tigecycline-amikacin (n = 1), tigecycline-gentamicin (n = 1), polymyxin-meropenem (n = 1), levofloxacin and sodium chloride – cefoperazone sodium and sulbactam sodium (n = 1), ceftazidime (n = 1),

Table 2 Surgical Treatment and Local Administration of Intracranial Infection

Variables	N (%)
Operations	
EVD	18/28 (55.9)
Retain the original EVD	16/28 (57.1)
Remove the LD	7/28 (25.0)
Remove the VPS	2/28 (7.1)
Remove the bone repair material	1/28 (3.6)
Intraventricular polymyxin B	28/28 (100.0)
Daily dose of Polymyxin B	
5mg/daily	28/28 (100.0)
Duration of IVT Polymyxin B (mean ± SD) (range)(days)	14.96 ± 4.28 (9–23)

Abbreviations: EVD, external ventricular drainage; LD, lumbar drainage; VPS, ventriculoperitoneal shunt; IVT, intraventricular.

ceftazidime-etimicin (n = 1), Ceftazidime – levofloxacin and sodium chloride (n = 1).

Methods of systemic antibiotics use, including polymyxin B: 50 mg intravenous infusion, once every 12 hours; tigecycline: first dose of 100 mg, then 50 mg intravenous infusion every 12 hours; cefoperazone sodium and sulbactam sodium: 3g intravenous infusion every 8 hours; Amikacin 0.6g intravenous infusion every 12 hours; Meropenem 2g intravenous infusion every 8 hours; Levofloxacin and sodium chloride 0.6g intravenous infusion, once every 12 hours; ceftazidime 2g intravenous infusion, once every 8 hours; etimicin sulfate 150mg, once every 12 hours. Systemic antibiotic treatment lasted for an average of 47.25±20.86 days (range, 19–85 days).

Clinical Symptoms and CSF Laboratory Data for the Patients Before and After Treatment

See Table 4 for details.

Treatment Results and Complications

The CSF bacterial clearance rate in the 28 patients was 92.9% (26/28), and the average time from application of IVT polymyxin B to negative CSF culture was 8.23±4.02 days (range, 3–16 days). Twenty-three cases were clinically cured, and the cure rate was 82.1% (23/28), of which 18 cases (64.3%) underwent ventriculoperitoneal shunt due to the presence of hydrocephalus 82.5 (59.5,114.75) days after infection had been controlled. The overall mortality rate was 17.6% (5/28), and the mortality rate due to infection was 7.1% (2/28). Analysis of causes, including 2 patients had purulent CSF with multiple brain abscesses at the time of admission, suggesting extensive brain parenchymal infection. After intraventricular polymyxin B treatment, intraventricular CSF culture was negative, but the drainage fluid of the abscess cavity remained culture positive. One case died in the hospital, and 1 case died after giving up treatment and returning home; 2 cases suffered spontaneous ventricular hemorrhage after a negative CSF result and, as their condition worsened, the 2 patients gave up treatment and died after returning home; 1 case had a massive secondary cerebral infarction after a negative CSF and died after giving up treatment and returning home. All cured patients were followed up for 4 months to 3 years, and no recurrences were noted. See Table 5 for details.

Safety Evaluation

The blood creatinine of patients before and after intraventricular polymyxin was (44.75±16.68) μmol/L and (48.64 ±13.01) μmol/L, and the differences were not statistically significant (P = 0.115). Renal function was not impaired. No epileptic seizures, neurotoxicity or neuromuscular block occurred during intraventricular administration or within 2 hours of administration.

Table 3 Analysis of Cerebrospinal Fluid Pathogenic Bacteria and Drug Resistance in 28 Patients with Intracranial Infection by G-Bacilli

Antimicrobial Agent	*Acinetobacter baumannii* n =14	*Klebsiella pneumoniae* n=9	*Pseudomonas aeruginosa* n=3	*Enterobacter cloacae* n=2	Total n =28 (%)
Amikacin	14	9	1	0	24/28 (85.7)
Carbapenem	13	8	3	1	25/28 (89.3)
Cephalosporin	14	8	2	2	26/28 (92.9)
Levofloxacin	14	7	2	2	25/28 (89.3)
Tigecycline	5	2	3	0	10/28 (35.7)
Cefoperazone sodium and sulbactam sodium	10	7	1	2	20/28 (71.4)
Gentamicin	12	8	1	2	23/28 (82.1)
Polymyxin B	0	0	0	0	0/28 (0.0)

Table 4 Clinical Symptoms and Laboratory Data in Patients

Laboratory Values	Before IVT Initiation	After Discontinuing IVT	P-value
Temperature >38°C	28/28 (100.0%)	5/28 (17.9%)	0.000
Neck stiffness	23/28 (82.1%)	14/28 (50.0%)	0.011
GCS			
≥12	4/28 (14.3%)	9/28 (32.1%)	
8–12	4/28 (14.3%)	7/28 (25.0%)	
≤8	20/28 (71.4%)	12/28 (42.9%)	0.031
MRS			
>4	24/28 (85.7%)	16/28 (57.1%)	
≤4	4/28 (14.3%)	12/28 (42.9%)	0.018
Creatinine	44.75±16.68 (19.5–91)	48.64±13.01 (27.3–80.8)	0.115
CSF leukocyte count			
Median (IQR), cells/*10-6/L	1610 (223,7480)	13 (8,84)	0.000
CSF glucose			
Mean ±SD, mmol/L (range)	1.14±0.83 (0.01–2.69)	3.58±1.24 (0.51–6.2)	0.000
CSF chloride			
Mean ±SD, mmol/L (range)	113.00±8.80 (92.5–125.2)	117.41±6.07 (99.6–126.1)	0.027
CSF protein			
Mean ±SD, g/L (range)	3.00±1.43 (0.35–6.10)	1.30±0.54 (0.18–2.47)	0.000

Abbreviations: GCS, Glasgow Coma Scale; IVT, intraventricular; MRS, Modified Rankin Scale; CSF, cerebrospinal fluid.

Table 5 Outcomes and Complications

Variables	N (%)
Clinical cure	23/28 (82.1)
Etiological validity	26/28 (92.9)
Time from application of polymyxin B to negative CSF culture (mean ± SD) (range), days	8.23±4.02 (3–16)
Death	5/28 (17.6)
SVH	2/28 (7.1)
Extensive brain parenchymal infection	2/28 (7.1)
Massive secondary cerebral infarction	1/28 (3.6)
Complications	
Hydrocephalus	18/28 (55.9)
VPS	18/28 (55.9)
Time from negative CSF cultures to VPS (Median)(IQR), days	82.5 (59.5,114.75)
Epilepsy	0/28 (0.0)

Abbreviations: SVH, spontaneous ventricular hemorrhage; VPS, ventriculoperitoneal shunt; CSF, cerebrospinal fluid.

Discussion

Intracranial infection is a serious complication with a high rate of disability and mortality after neurosurgery.[9,10] The incidence rate is 1–10%.[11] In recent years, the incidence of G-bacilli intracranial infections, with *Acinetobacter baumannii* and *Klebsiella pneumoniae* in particular, has significantly increased,[12,13] accounting for more than 30% of cases.[12] Furthermore, drug resistance rates are gradually increasing,[1] resulting in extreme difficulties for clinical treatment. In terms of treatment of G-bacilli intracranial infection, carbapenem antibiotics are usually preferred, especially high-dose meropenem as the initial treatment, but the current rate of resistance of G- bacilli to carbapenems has been increasing yearly.[14] In this study, the rate of resistance of the bacteria identified the CSF test to carbapenems was as high as 89.3% (25/28) when the patients were admitted to our hospital. The reason for such a high rate may be related to the fact that this group of patients had received large doses of high-grade antibiotics in the previous hospital based on prior experience, which may have caused drug resistance. Due to the high degree of resistance, treatment of MDR and even XDR G-bacilli is fraught with challenges and the prognosis is poor. This requires a clinical search for an antibiotic that is not drug-resistant for treatments to be completed.

Polymyxin B, as a drug with rapid bactericidal activity, has good activity against most G- bacteria,[15] which is consistent with the results of this study. Many studies have shown that polymyxin B has a significant effect on various serious nosocomial infections caused by MDR G- bacilli

such as bacteremia, urinary tract infections, abdominal infections and wound infections.[14,16,17] However, due to various reasons, such as its large molecular weight and difficulty in penetrating the blood-brain barrier to achieve effective bacteriostatic concentrations in CSF, there is limited research on the application of polymyxin B in the treatment of intracranial infections in China and globally.

The 2017 guidelines of the American Society for Infectious Diseases (IDSA) recommended that IVT and/or ITH therapy is a treatment for intracranial infections, especially when systemic intravenous medication is not effective.[18] Because this route of administration can bypass the blood-brain barrier and directly act on the site of infection, the effect is more direct and precise, and at the same time, the toxic reactions of systemic drugs can be avoided.[19] However, many antibiotics are currently not approved for intraventricular and/or intrathecal use, such as meropenem, ceftazidime and tigecycline. Therefore, the intracerebroventricular and/or intrathecal use of these antibiotics is off-label use and involves safety issues. Polymyxin B is an antibiotic whose official instructions clearly state that it can be used for IVT/ITH administration. Moreover, Polymyxin B, compared to Polymyxin E, shows superior PK characteristics in the human body, reducing the potential for nephrotoxicity. Therefore, this study used only polymyxin B in the ventricles. Studies have shown that polymyxin B alone is less effective in treating G- bacilli,[20] and when combined with other antibiotics, its efficacy can be significantly enhanced.[21] At present, there is no uniform standard for the clinical treatment cycle of severe intracranial infection, but generally, the course of treatment is relatively long, often requiring 4–8 weeks. A total of 28 patients with MDR/XDR G- bacilli intracranial infection after neurosurgery were included in this group. Intraventricular polymyxin B was used for 14.96±4.28 (range, 9–23) days, supplemented with intravenous administration of various sensitive antibiotics for 47.25±20.86 (range, 19–85) days, the CSF bacterial clearance rate was as high as 92.9% (26/28), and the clinical cure rate was 82.1% (23/28). The results showed that intraventricular polymyxin B can effectively remove MDR/XDR G- bacilli in the CSF, but, even though the effects are clear, intravenous antibiotics may have played a synergistic role. Recently, Shang et al reported that intraventricular lavage combined with daily polymyxin E can effectively improve the neurological symptoms and CSF laboratory indicators in patients with severe ventricular inflammation.[22] In this study, intraventricular polymyxin B has also been used to achieve the same effect.

According to reports, the mortality rate associated with intracranial infections caused by MDR/XDR G- bacilli is as high as 26–71%.[22–24] The total mortality rate in this study was 17.6% (5/28), and the mortality rate directly caused by infection was 7.1% (2/28), which was lower than that reported in the literature. This may be related to the timely use of intraventricular polymyxin B following the identification of MDR/XDR G- bacilli in the patients in this study. In the past, intraventricular administration has been considered an alternative option when intravenous treatment was ineffective. Two patients in this group were given high-dose intravenous antibiotics in the hospital where they had received treatment previously and no effects were observed, and they already had severe diffuse infection of the brain parenchyma when they were admitted to our hospital. Although they were treated with intraventricular polymyxin B, their infection could not be controlled in the end. Wang et al also showed that timely and effective IVT treatment may improve the cure rate of intracranial infection after neurosurgery.[23]

According to reports, polymyxin has strong side effects such as nephrotoxicity, neurotoxicity and neuromuscular blockage. However, recent studies have confirmed that the incidence and severity of nephrotoxicity are rare and mild,[25] and are reversible after the drug is withdrawn.[26] In addition, the neurotoxic effects caused by polymyxin B are generally mild and can be resolved once drug treatment is stopped. Recent studies have shown that patients with renal insufficiency do not need drug dose adjustment when using polymyxin B.[27] Other studies have shown that intraventricular antibiotic treatment may cause seizures.[28] None of the above-mentioned adverse reactions occurred during treatment in this group of patients, which suggests that intraventricular polymyxin B is adequately safe in the treatment of MDR/XDR G- bacilli intracranial infection.

Studies have shown that artificial materials related to infections should be completely removed as soon as possible during intracranial infections.[6,18] In addition, smooth and continuous CSF drainage is essential for the treatment of severe intracranial infection,[22] usually using external ventricular drainage or lumbar cistern drainage. Most researchers believe that lumbar cistern drainage is more effective at reducing the recurrence of intracranial infections. However, as MDR/XDR G- bacteria CSF is mostly cloudy, turbid, and even purulent, the drainage tube outside the lumbar cistern can be easily blocked, leading to

a higher possibility of infection. In this study, unobstructed external ventricular drainage tubes were used for the treatment of inflammatory CSF and intraventricular drug delivery. The lumbar cistern drainage tube from previous hospitals, ventriculoperitoneal shunt and skull repair materials were removed, but the external ventricular drainage tube from previous hospitals was not removed due to its unobstructed flow. It is suggested that during the treatment of intracranial infection, continuous and unobstructed cerebrospinal fluid drainage can effectively drain CSF with bacteria to the outside of the body, and there is no need to replace it prematurely or too frequently, which can help avoid secondary damage to brain tissues and the nervous system, and any intracranial bleeding that may occur as a result.

The mortality rate of hydrocephalus caused by intracranial infection is as high as 50%, and the prognosis is poor in 70% patients,[29,30] which is mainly due to the fact that white blood cells, protein and other indicators in CSF cannot return to their normal value within a short time after the bacteria in CSF are cleared, and shunting treatment performed at this moment probably fails, so the final shunt operation cannot be performed. For such patients, continuous CSF drainage technology can be used to continue drainage and purify inflammatory CSF. This method can effectively extend the time of tube placement, reducing the possibility of intracranial infection.[31] During drainage, patients should undergo weekly cerebrospinal fluid routine tests, biochemical tests and bacterial cultures. After three consecutive satisfactory CSF results, the ventriculoperitoneal shunt is placed. In this study, 18 cases had hydrocephalus, after CSF bacteria were cleared, and they were switched to continuous drainage of CSF. Postoperative drainage was performed by intraventricular shunt for 47.25±20.86 days. There was no further infection during drainage. They were followed up for 4 months to 3 years, and no cases of recurrence were noted.

Conclusion

In cases of MDR/XDR G- bacilli intracranial infection, early intraventricular polymyxin B supplemented by continuous ventricular drainage treatment has a clinical cure rate of 82.1%, with no change in renal function post-treatment, and is thus a safe and effective treatment strategy. However, these findings are yet to be confirmed by large-scale research.

This study also has the following limitations: (1) The number of cases is relatively small. (2) This study was a single-center retrospective design, which lacked a simple intravenous infusion control. There existed certain limitations in proving or disproving the efficacy or safety of any intervention. A multi-center randomized controlled trial is required to verify the findings of the present study in the future. (3) This study did not comprehensively investigate important characteristics such as CSF drug concentrations and optimal dosage of polymyxin B.

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Disclosure

The authors report no conflicts of interest in this work.

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