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ORIGINAL ARTICLE

Intraventricular antimicrobial therapy in postneurosurgical Gram-negative bacillary meningitis or ventriculitis: A hospital-based retrospective study

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Background: Postneurosurgical Gram-negative bacillary meningitis (GNBM) or ventriculitis is a serious issue. Intraventricular (IVT) therapy has been applied; however, its effectiveness remains controversial, and the adverse drug effects are considerable.
Methods: The demographic data, treatment strategies, and clinical outcomes of patients with postneurosurgical GNBM or ventriculitis were recorded.
Results: From 2003 to 2011, data on 127 episodes of infection in 109 patients were collected, and 15 episodes in 14 patients were treated using a sequential combination of intravenous antibiotics and IVT therapy; others received intravenous antibiotics alone. The average age of patients who received a sequential combination with IVT therapy was 48.9 years, and 71.4% of the patients were men. The regimens used for IVT therapies included gentamicin ($n = 4$), amikacin ($n = 7$), and colistin ($n = 4$). After meningitis had been diagnosed, the average period that elapsed before initiation of IVT therapy was 25.4 days, and the average duration of IVT therapy was 13.3 days. The most frequently isolated pathogen from cerebrospinal fluid (CSF) was *Acinetobacter baumannii*, followed by *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Serratia marcescens*. The cure rate was 73.3%.

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Of note, the mean period to sterilize the CSF after appropriate IVT antibiotic treatment was 6.6 days. There were no incidents of seizure or chemical ventriculitis during this IVT therapy. *Conclusion:* The findings of this study suggest that IVT antibiotic therapy is a useful option in the treatment of postneurosurgical GNBM or ventriculitis, especially for those with a treatment-refractory state.

Introduction

Nosocomial postneurosurgical meningitis is a serious medical issue, particularly in patients with Gram-negative bacillary infection.[1] There is an increasing incidence of postneurosurgical meningitis; this has risen from 12% to 27% of all cases of bacterial meningitis,[2] and the overall mortality for Gram-negative bacillary meningitis (GNBM) has been reported to be high.[1,3] Furthermore, the treatment strategies for GNBM or ventriculitis have become more complex. Multiple bacteria with reduced sensitivity to antibiotics have been emerging[4,5]; moreover, there are limitations to antimicrobial concentrations at the sites of infection.[6] Thus, a combination of intravenous (IV) and intraventricular (IVT) antibiotic administration may be one choice to ensure sterilization of the cerebrospinal fluid (CSF) while minimizing adverse drug effects.[7]

The use of IVT antimicrobial agents remains a challenging intervention due to limited evidence for the efficacy and safety of this treatment. McCracken et al demonstrated a threefold increased relative risk for mortality.[8] Conversely, some studies have reported an overall cure rate of 80% with IVT polymyxins[9] and 100% for those with IVT gentamicin.[10,11] In terms of the controversial option of employing IVT therapy for GNBM, there have been few well-designed studies and clinical trials to verify IVT therapy among adult populations.

In this study, we report our experience with IVT antibiotic therapy in 15 episodes of postneurosurgical GNBM or ventriculitis, and we also made a comparison of the clinical and laboratory data and therapeutic results between patients receiving IVT therapy and those with IV antibiotic treatment alone.

Methods

Patients and setting

From January 2003 to October 2011, we enrolled patients who experienced complications including GNBM and ventriculitis following neurosurgical procedures at the China Medical University Hospital, a 2000-bed medical center in Taiwan. Patients were included when all of the following criteria were met: (1) isolation of Gram-negative bacilli from the CSF, (2) a CSF neutrophil count of >10 cells/μL, (3) clinical features of bacterial central nervous system (CNS) infection (at least one episode of temperature $>37.5^{\circ}$C, headache, or neck stiffness), and (4) neurosurgery within the preceding 2 months.[10] A second episode of meningitis was considered a recurrence if it was due to a organism different from the one causing the initial episode or if it was due to the same organism occurring more than 3 weeks after completion of treatment for the initial episode.[12]

All patients were treated empirically with IV antibiotics, and antibiotic treatment was later adjusted according to the culture report. The CSF analysis and culture were repeated once or twice every week until the CSF culture was negative or until the patient was discharged. Revision or removal of intracranial devices such as external ventricular drainage, a ventriculoperitoneal shunt, or an Ommaya reservoir was decided by the doctor in charge.[7] For patients with persistent bacterial growth in CSF cultures or clinical failure, sequential combination with IVT therapy was undertaken according to procedures outlined in previous studies[7,10,11,15,19] and the practice guidelines of the Infectious Diseases Society of America.[13] All patients were followed up for more than 3 months after completion of antimicrobial treatment. Medical charts were thoroughly reviewed, and any event of IVT therapy-related adverse drug effects was recorded.

Definitions

Mixed infection was defined as a patient having two or more bacterial organisms isolated from the initial CSF cultures.[14] Co-infection was defined as a patient having GNBM or ventriculitis with a simultaneous additional infection.

Efficacy was evaluated by both clinical and bacteriologic responses to therapy. In the treatment period, clinical failure was considered to be presentation with deteriorating clinical and laboratory signs of meningitis during appropriate antimicrobial therapy. For the clinical outcome, treatment failure was defined as death due to meningitis, or relapse.[10] Death was considered to be not due to meningitis if all of the following criteria were met: (1) resolving inflammatory parameters; (2) resolution of the clinical signs of meningitis; (3) a serious illness other than meningitis determined to be a more probable cause according to the treating physician; (4) completion of the antibiotic treatment before death; and (5) two negative CSF culture results (if performed) before death as modified by the criteria proposed by Durand et al.[12] Relapse was defined as isolation of the same organism from the CSF or from a CNS lesion within 3 weeks of completing therapy for the initial episode.[12] The criteria for cure proposed by Briggs et al.[3] were modified as follows: resolution of clinical and laboratory signs of meningitis; negative CSF culture results (if performed); and no relapse after withdrawal of

antibiotics. We considered chemical ventriculitis to be present if the white blood cell count in the CSF rose with clinical improvement during IVT therapy.[15]

Appropriate antimicrobial therapy was defined as the isolated bacteria being susceptible *in vitro* to the antimicrobial agents with an ability to achieve potentially therapeutic levels.[16] The period to CSF sterilization was counted from the day when appropriate IV or IVT antibiotic treatment was commenced to the day of the first negative CSF culture report after treatment. The elapsed period was calculated from the day when bacteria were first isolated in the CSF specimen to the day when IVT therapy was initiated.

Microbiology

The CSF specimens were streaked on Trypticase soy agar containing 5% sheep blood (TSA II), Levine EMB agar, and chocolate agar (Becton, Dickinson and Company, Le Pont de Claix, France). The plates were incubated at 35°C for appropriate time periods. Identification of bacteria and tests for susceptibility to various antimicrobial agents were performed with either a disk diffusion test according to the Clinical and Laboratory Standards Institutes or the BD Phoenix Automated Microbiology System (Becton, Dickinson and Company, Le Pont de Claix, France).

Results

From January 2003 to October 2011, there were 301 episodes of culture-proven bacterial meningitis at the China Medical University Hospital. Of these, 249 episodes occurred in patients involved in 16,725 neurosurgical procedures. In total, 127 episodes of GNBM or ventriculitis in 109 patients who fulfilled the criteria were included in this study. Table 1 summarizes the demographical data, clinical and laboratory findings, and therapeutic outcomes for these episodes. Fifteen episodes in 14 patients were treated using a sequential combination of IV and IVT therapy, and patients were followed up for more than 3 months. The remaining 112 episodes in 95 patients were treated using IV antibiotics only.

There was no significant difference in the demographic data, except length of hospital stay, between the patients treated with a sequential combination including IVT therapy and those who received IV antibiotics only. Among the 15 episodes that were treated using a sequential combination of IV and IVT antibiotics, the cure rate was 73.3% (11/15). All four nonsurviving patients died within 2 weeks after completion of therapy. Of these, two had more than two negative CSF culture results before death; however, the treating physician determined that meningitis was the only serious illness that could have been a more probable cause.

The causative organisms isolated from CSF culture are listed in Table 2, and the antimicrobial resistance of the pathogens is listed in Table 3. Among the episodes treated using sequential combination with IVT therapy, two patients (14.3%) had mixed infections, one showed methicillin-resistant *Staphylococcus aureus*, and the other was haboring *Candida tropicalis*. In terms of the causative organism, six episodes involving carbapenem-resistant *A. baumannii* (40.0%) and one episode involving carbapenem-resistant *P. aeruginosa* (6.7%) were seen. By contrast, there were more *Enterobacteriaceae* organisms, especially *K. pneumoniae*, in patients who received IV antibiotics alone (41.8% versus 26.7%).

Table 4 details the clinic characteristics, microorganisms, antibiotic treatment, and outcome for 15 IVT episodes in 14 patients with postneurosurgical GNBM or ventriculitis. The regimens used for IVT therapies were diverse and included amikacin ($n = 7$), gentamicin ($n = 4$), and colistin ($n = 4$). All IVT antibiotics were administered once daily and had *in vitro* activity against pathogens isolated from CSF. The daily IVT antibiotic dosage and duration varied. IVT therapy was added sequentially because of persistent bacterial growth in the CSF cultures ($n = 13$) or as a result of clinical failure ($n = 2$). The elapsed period from when bacteria were first isolated in the CSF specimens to the initiation of IVT therapy was 25.4 ± 17.6 (range 5—63) days, and the average duration of IVT therapy was 13.3 ± 6.7 (range 3—27) days. In this study, no adverse drug effects, seizures, or chemical ventriculitis were observed during the IVT therapy. Of the four patients in the IVT therapy group who died, *P. aeruginosa* infection was the most common, accounting for 75% (3/4) of instances. By contrast, the mortality rate was 42.9% (12/28) for all cases of *P. aeruginosa* causing CNS infection in this study.

Discussion

Mortality and morbidity rates for GNBM or ventriculitis in postneurosurgical patients remain unfavorably high.[1,3] To optimize antimicrobial concentrations in CSF, IVT therapy should be considered for patients infected with drug-resistant microorganisms or with those it is hard to eradicated.[7,9–11] However, clinicians have previously been wary of the IVT treatment modality because of concerns about IVT treatment-related adverse drug effects; careful preparation and delivery are required to avoid contamination. In addition, the effectiveness of IVT antibiotics in bacterial meningitis is controversial, and this treatment is often reserved for either seriously ill or treatment-refractory patients.

In this study, we analyzed 127 episodes of GNBM or ventriculitis in 109 patients who received neurosurgical procedures over an 8-year period. The cure rate for patients who received a sequential combination with IVT therapy in our study was similar to those observed in previous studies, which ranged from 71.4% to 100%.[7,10,11,15,19]

In the present study, IVT therapy was added sequentially for patients with persistent bacterial growth in CSF cultures or who exhibited clinical failure. The findings of this study suggest that IVT antibiotic use in postneurosurgical GNBM or ventriculitis treatment may be able to shorten the period to CSF sterilization, especially in those with a treatment-refractory state. This is important, because delayed sterilization of the CSF is associated with adverse neurologic outcomes.[20]

Conversely, the mean period that elapsed before the initiation of IVT therapy in our study was much longer than that in previous studies.[10,19] These variations in the time of

Table 1 Demographic and laboratory data for 127 episodes of Gram-negative bacillary meningitis or ventriculitis in 109 postneurosurgical patients

	IV antibiotics plus sequential IVT therapy	IV antibiotics alone	*p*
	n = 14 (%)	*n* = 95 (%)	
Age (mean, y)	48.9 ± 20.5	53.8 ± 20.2	0.408
Male (%)	10 (71.4)	62 (65.3)	0.769
APACHE II score[a]	13.3 ± 5.4	13.1 ± 5.8	0.970
Laboratory data[a]			
WBC (/μL)	14,207.3 ± 4942.9	12,990.7 ± 6337.1	0.500
CRP (mg/dL)	6.4 ± 6.0	10.1 ± 10.4	0.210
ESR (mm/1 h)	42.0 ± 38.8	60.0 ± 39.3	0.221
BUN (mg/dL)	20.5 ± 15.0	19.4 ± 18.3	0.828
Creatinine (mg/dL)	1.2 ± 1.5	0.9 ± 0.7	0.054
CSF RBC (/μL)	10,353.4 ± 30753.0	29,912.6 ± 73730.7	0.308
CSF WBC (/μL)	7205.6 ± 18883.2	6579.0 ± 24254.5	0.931
CSF PMN (%)	70.1 ± 30.2	72.0 ± 29.0	0.757
CSF glucose (mg/dL)	36.4 ± 16.0	52.4 ± 40.2	0.056
CSF protein (mg/dL)	483.3 ± 671.1	377.8 ± 755.0	0.622
CSF lactate (mg/dL)	67.7 ± 30.5	71.3 ± 47.4	0.870
Underlying conditions			
DM	2 (14.3)	23 (24.2)	0.516
Liver cirrhosis	0 (0)	6 (6.3)	1.000
ESRD	0 (0)	3 (3.2)	1.000
Cancer	0 (0)	4 (4.2)	1.000
Steroid using	0 (0)	13 (13.7)	0.212
CNS disease			
Intracranial tumor	2 (14.3)	3 (3.2)	0.123
Traumatic brain injury	4 (28.6)	27 (28.4)	1.000
Brain infarction	2 (14.3)	6 (6.3)	0.273
ICH[b]	2 (14.3)	30 (31.6)	0.777
Other[c]	4 (28.6)	29 (30.5)	0.870
Mixed infection	2 (14.3)	8 (8.4)	0.614
Bacteremia[a]	3 (21.4)	14 (14.7)	0.455
Co-infection	3 (21.4)	29 (30.5)	0.754
Pneumonia	2 (14.3)	15 (15.8)	1.000
UTI	2 (14.3)	16 (16.8)	1.000
Outcome[a]			
Cure	11 (73.3)	74 (66.0)	0.870
Death	4 (26.7)	34 (30.4)	1.000
Relapse	0 (0)	4 (3.6)	1.000
Length of hospital stay (mean, d)[a]	122.5 ± 43.7	79.1 ± 49.9	0.002
Period to CSF sterilization (mean, d)[a]	6.6 ± 4.6	12.9 ± 7.6	0.004

[a] The denominator was set as episodes: *n* = 15 for IV antibiotics plus sequential IVT therapy, and *n* = 112 for IV antibiotics alone.
[b] Intracranial hemorrhage related to traumatic brain injury was excluded.
[c] Hydrocephalus or increased intracranial pressure without the above cause.
BUN = blood urea nitrogen; CNS = central nervous system; CRP = C-reactive protein; CSF = cerebrospinal fluid; DM = diabetes mellitus; ESR = erythrocyte sedimentation rate; ESRD = end-stage renal disease; ICH = intracranial hemorrhage; IV = intravenous; IVT = intraventricular; PMN = polymorphonuclear neutrophil granulocytes; RBC = red blood cell; UTI = urinary tract infection; WBC = white blood cell.

addition of IVT therapy to systemic antibiotic treatment may be related to the variable mortality rate in those studies.[19] For this reason and because of the bacteriological cure rate for the patients in this study, we suggest that timely implementation of effective IVT therapy might increase the clinical cure rate for postneurosurgical GNBM or ventriculitis.

In the past, the major concern related to IVT therapy with antimicrobials was the possibility of adverse drug effects such as seizure, chemical ventriculitis, or hearing loss.[21] In the present study, hearing loss was not assessed because of the variable consciousness of these post-neurosurgical patients. In previous reports, the incidence of these adverse effects varied from 13% to 60% for chemical

Table 2 Causative organisms of 127 episodes of Gram-negative bacillary meningitis or ventriculitis in 109 postneurosurgical patients

	IV antibiotics plus sequential IVT therapy	IV antibiotics alone	Total
	$n = 15$ (%)	$n = 112$ (%)	$n = 127$ (%)
Glucose non-fermenting GNB			
Acinetobacter spp.[a]	7 (46.7)	13 (11.6)	20 (15.7)
Pseudomonas spp.[b]	3 (20.0)	30 (26.8)	33 (26.0)
Stenotrophomonas maltophilia	(0.0)	8 (7.1)	8 (6.3)
Other[c]	1 (6.7)	7 (6.3)	8 (6.3)
Glucose-fermenting GNB			
Enterobacteriaceae	4 (26.7)	48 (42.9)	52 (40.9)
Escherichia coli[d]	2 (13.3)	9 (8.2)	11 (8.7)
Klebsiella pneumonia[e]	1 (6.7)	17 (14.6)	18 (14.2)
Serratia marcescens	1 (6.7)	5 (4.6)	6 (4.7)
Citrobacter spp.	0 (0.0)	2 (1.8)	2 (1.6)
Enterobacter spp.	0 (0.0)	10 (8.2)	10 (7.1)
Other[f]	0 (0.0)	5 (4.6)	5 (3.9)
Oxidase-positive GNB[g]	0 (0.0)	6 (5.5)	6 (4.7)

[a] Six CR *Acinetobacter baumannii* for IV antibiotics plus sequential IVT therapy, and four for IV antibiotics alone.
[b] One CR *Pseudomonas aeruginosa* for IV antibiotics plus sequential IVT therapy.
[c] Including *Achromobacter*, *Chryseobacterium*, *Delftia*, and *Sphingobacterium*.
[d] One *Escherichia coli* ESBL strain for IV antibiotics plus sequential IVT therapy, and four for IV antibiotics alone.
[e] Five *Klebsiella pneumoniae* ESBL strain for IV antibiotics alone.
[f] Including *Morganella*, *Proteus*, and *Salmonella*.
[g] Including *Aeromonas* and, *Moraxella*.
CR = carbapenem-resistant; ESBL = extended-spectrum beta-lactamase; GNB = Gram-negative bacilli; IV = intravenous; IVT = intraventricular.

ventriculitis, and from 4% to 20% for treatment-associated seizures.[15,19] Several recent reports have suggested that the intrathecal or IVT administration of agents such as polymyxin B, colistin, and vancomycin is not associated with severe or irreversible adverse IVT drug effects.[21] Similarly, we report no incidents of seizure or chemical ventriculitis during IVT therapy. This indicates that IVT therapy is safe, but further well-designed studies are required to provide further evidence on this.

Of the causative organisms, the pathogens most frequently isolated from the CSF cultures in our study were *Pseudomonas* species (26.0%). This finding is similar to those of some studies,[2,17,18] whereas other reports have differed.[3,16] Furthermore, we found that *P. aeruginosa* was the major cause of mortality in patients who received sequential combination with IVT therapy. Although this correlation has not been previously reported in adult populations, some studies have reported that *P. aeruginosa* is a predictor of unfavorable outcomes in neonates and children.[22,23] For the above condition, we suggest that more aggressive interventions and earlier IVT therapy application for *P. aeruginosa* meningitis should be considered.

There are two limitations to this study. First, we did not enroll enough patients who had received a sequential combination of IV and IVT therapy to analyze the efficacy of IVT for different causative organisms. Second, with

Table 3 Antimicrobial resistance of causative organisms from cerebrospinal fluid in 15 episodes of postneurosurgical Gram-negative bacillary meningitis and ventriculitis treated with sequential intraventricular therapy

Antimicrobial agent	*Acinetobacter baumannii*	*Escherichia coli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Serratia marcescens*	*Sphingobacterium multivorum*	Total
	$n = 7$ (%)	$n = 2$ (%)	$n = 1$ (%)	$n = 3$ (%)	$n = 1$ (%)	$n = 1$ (%)	$n = 15$ (%)
Ceftazidime	7 (100)	1 (50.0)		0 (0)	0 (0)	1 (100)	9 (60.0)
Cefotaxime	7 (100)	1 (50.0)	0 (0)		0 (0)		8 (53.3)
Cefepime	7 (100)	1 (50.0)	0 (0)	0 (0)	0 (0)	1 (100)	9 (60.0)
Carbapenem	6 (85.7)	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	7 (46.7)
Gentamicin	4 (57.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (26.7)
Amikacin	4 (57.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (26.7)
Colistin	0 (0)	0 (0)					0 (0)

Table 4 Clinical characteristics and microorganisms isolated from cerebrospinal fluid (CSF) and treatment and outcomes for 15 episodes of postneurosurgical Gram-negative bacillary meningitis and ventriculitis treated with sequential intraventricular therapy (IVT)

Episode	Age (y) /sex	CSF culture	Concurrent IV antibiotics	IVT therapy			Medical condition	APACHE II score	Length of hospital stay (d)	Outcome
				Daily dose	IVT duration (d)	Elapsed period[b] (d)				
1[a]	79/F	*Acinetobacter baumannii*	Imipenem	Amikacin 50 mg	9	32	Brain infarction s/p Ommaya	6	213	Cured
2	28/M	CR *Acinetobacter baumannii*	Meropenem	Amikacin 30 mg	11	10	ICH s/p EVD	10	139	Cured
3	39/M	CR *Acinetobacter baumannii*[c]	Meropenem/colistin	Amikacin 10 mg	18	21	Hydrocephalus s/p VP shunt AIDS	9	136	Cured
4	31/M	CR *Acinetobacter baumannii*	Imipenem/colistin	Colistin 6.4 mg	27	28	TBI/ICH s/p EVD	11	116	Cured
5	70/F	CR *Acinetobacter baumannii*	Imipenem/sulbactam/ colistin	Colistin 3.2 mg	20	23	Brain infarction s/p VP shunt	18	98	Death
6	60/M	CR *Acinetobacter baumannii*	Meropenem/colistin	Colistin 16 mg	7	30	ICH s/p VP shunt	16	83	Cured
7	15/M	CR *Acinetobacter baumannii*	Meropenem/colistin	Colistin 2 mg	10	14	Hydrocephalus s/p EVD Hypertensive nephrosclerosis	21	98	Cured
8	53/M	*Escherichia coli*[d]	Cefepime/ceftazidime	Gentamicin 10 mg	3	19	TBI/ICH s/p EVD	14	177	Cured
9[a]	79/F	*Escherichia coli* (ESBL)	Imipenem	Amikacin 10 mg	3	48	Brain infarction s/p VP shunt	6	81	Cured
10	57/M	*Klebsiella pneumoniae*	Ceftriaxone	Amikacin 30 mg	17	5	Hydrocephalus s/p EVD DM	22	128	Cured
11	77/F	*Pseudomonas aeruginosa*	Ceftazidime	Amikacin 10 mg	15	12	Intracranial tumor s/p VP shunt	19	172	Death
12	48/F	*Pseudomonas aeruginosa*	Cefepime	Amikacin 50 mg	10	13	Communicated hydrocephalus s/p Ommaya	7	66	Death
13	25/M	CR *Pseudomonas aeruginosa*	Ceftazidime Meropenem	Gentamicin 4 mg	15	55	TBI/ICH s/p craniotomy	9	147	Death
14	68/M	*Serratia marcescens*	Ceftazidime/cefepime	Gentamicin 8 mg	14	8	ICH s/p EVD	15	59	Cured
15	35/M	*Sphingobacterium multivorum*	Imipenem/ trimethoprim/ sulfamethoxazole	Gentamicin 8 mg	21	63	TBI/ICH s/p VP shunt	16	124	Cured

[a] Two separate episodes in one patient.
[b] Period from when bacteria were first isolated in the CSF specimen to the initiation of IVT therapy.
[c] Mixed infection with *Candida tropicalis*.
[d] Mixed infection with methicillin-resistant *Staphylococcus aureus*.
AIDS = acquired immune deficiency syndrome; CR- = carbapenem-resistant; DM = diabetes mellitus; ESBL = extended-spectrum beta-lactamase; EVD = external ventricular drain; ICH = intracranial hemorrhage; IV = intravenous; s/p = status post; TBI = traumatic brain injury; VP shunt = ventriculoperitoneal shunt.

a retrospective study, it is difficult to define the optimal regimens, dosage, duration, and indications in IVT antimicrobial therapy for postneurosurgical patients with GNBM or ventriculitis. All of these would influence the treatment response to IVT therapy. For the above reasons and because of the high mortality rate among those who received IV antibiotic treatment alone for postneurosurgical GNBM, further large-scale prospective studies are needed.

In conclusion, this study details the clinical aspects of postneurosurgical GNBM or ventriculitis and outlines experiences of sequential combination with IVT therapy. The findings of this study suggest that IVT antibiotic use can be one of the options for postneurosurgical GNBM or ventriculitis treatment, especially for those with a treatment-refractory state. Further prospective randomized studies are needed to determine whether this treatment modality could shorten the time to CSF sterilization, and thus improve patients' outcomes.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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