RESEARCH ARTICLE

Application of neuroendoscopic surgical techniques in the assessment and treatment of cerebral ventricular infection

Feng Guan[1],Wei-Cheng Peng[1], Hui Huang[1], Zu-Yuan Ren[2], Zhen-Yu Wang[3], Ji-Di Fu[4], Ying-Bin Li[5], Feng-Qi Cui[6], Bin Dai[1], Guang-Tong Zhu[1], Zhi-Yong Xiao[1], Bei-Bei Mao[1], Zhi-Qiang Hu[1,*]

1 Department of Neurosurgery, Beijing Shijitan Hospital, Capital Medical University, Beijing, China
2 Department of Neurosurgery, Peking Union Medical College Hospital, Beijing, China
3 Department of Neurosurgery, Peking University Third Hospital, Peking University, Beijing, China
4 Department of Neurosurgery, Beijing Tongren Hospital, Capital Medical University, Beijing, China
5 Department of Neurosurgery, the Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China
6 Department of Neurosurgery, Beijing Liangxiang Hospital, Beijing, China

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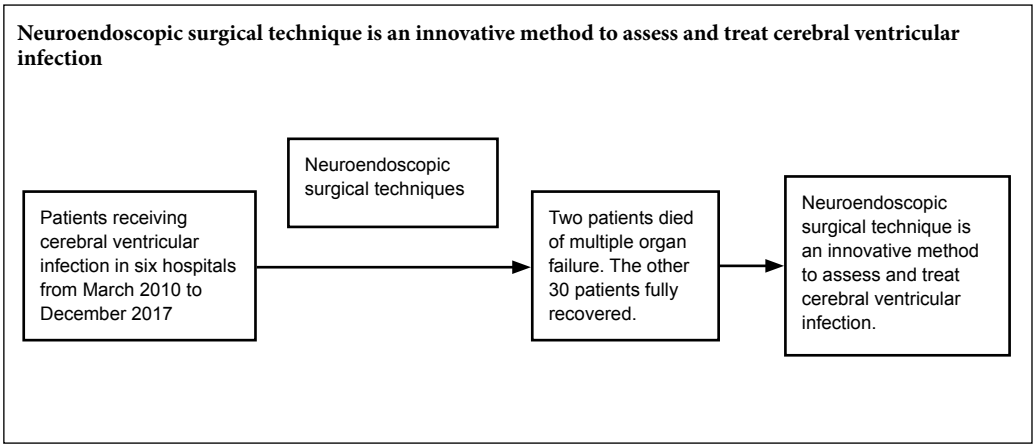
Graphical Abstract



Correspondence to:
Zhi-Qiang Hu, MD,
neuro7777@126.com.

orcid:
0000-0002-0061-1296
(Zhi-Qiang Hu)

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Abstract

Cerebral ventricular infection (CVI) is one of the most dangerous complications in neurosurgery because of its high mortality and disability rates. Few studies have examined the application of neuroendoscopic surgical techniques (NESTs) to assess and treat CVI. This multicenter, retrospective study was conducted using clinical data of 32 patients with CVI who were assessed and treated by NESTs in China. The patients included 20 men and 12 women with a mean age of 42.97 years. NESTs were used to obliterate intraventricular debris and pus, fenestrate or incise the intraventricular compartment and reconstruct cerebrospinal fluid circulation, and remove artificial material. Intraventricular irrigation with antibiotic saline was applied after neuroendoscopic surgery (NES). Secondary hydrocephalus was treated by endoscopic third ventriculostomy or a ventriculoperitoneal shunt. Neuroendoscopic findings of CVI were used to classify patients into Grade I (n = 3), Grade II (n = 13), Grade III (n = 10), and Grade IV (n = 6) CVI. The three patients with grade I CVI underwent one NES, the 23 patients with grade II/III CVI underwent two NESs, and patients with grade IV CVI underwent two (n = 3) or three (n = 3) NESs. The imaging features and grades of neuroendoscopy results were positively related to the number of neurosurgical endoscopic procedures. Two patients died of multiple organ failure and the other 30 patients fully recovered. Among the 26 patients with secondary hydrocephalus, 18 received ventriculoperitoneal shunt and 8 underwent endoscopic third ventriculostomy. There were no recurrences of CVI during the 6- to 76-month follow-up after NES. Application of NESTs is an innovative method to assess and treat CVI, and its neuroendoscopic classification provides an objective, comprehensive assessment of CVI. The study trial was approved by the Institutional Review Board of Beijing Shijitan Hospital, Capital Medical University, China.

Key Words: *nerve regeneration; neuroendoscopy; surgery; cerebral ventricular infection; assessment; treatment; hydrocephalus; irrigation; neural regeneration*

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Introduction

Cerebral ventricular infection (CVI) is one of the most dangerous complications in neurosurgery because of its high mortality and disability rates (Boeer et al., 2011; Guanci, 2013; Davies et al., 2016). CVI is especially prevalent in patients who have undergone external ventricular drainage (EVD) or have an intraventricular stent in place (Sneh-Arbib et al., 2013). CVI can lead to a series of symptoms and side effects, including headaches, consciousness disorders, and even death if treatment is not prompt (Al Shirawi et al., 2006; Fiorella et al., 2015; Glimåker et al., 2015). Although similar conditions such as meningitis and encephalitis have been widely studied (Wang et al., 2014; Chen et al., 2015), there are few studies on CVI (Zheng et al., 2014), despite an urgent need to understand this disease. Currently, the standard assessment of CVI involves imaging (computed tomography [CT], magnetic resonance imaging [MRI]), blood tests, and cerebrospinal fluid (CSF) tests and cultures,. However, the ventricular situation of CVI has not been directly observed and assessed.

Treatment of CVI is also challenging. Currently, the most common treatment of CVI involves an antibiotic treatment that targets the infection (Ng et al., 2014). However, the most effective antibiotics and the optimal treatment strategy remain controversial. In fact, there is evidence that the blood-brain barrier may limit the ability of antibiotics to enter CSF (Warf, 2005). Other factors can influence the efficacy of CVI treatment. Intraventricular and intrathecal medications can be interrupted by subarachnoid adhesion, the intraventricular compartment, an abscess, and artificial implants (Warf et al., 2012). Furthermore, acute CVI that has not been effectively treated may transform into chronic inflammation, thus reducing the optimal treatment window (Gathura et al., 2010; Kulkarni et al., 2010).

Neuroendoscopic surgical techniques (NESTs) are performed using an endoscope, which is a small telescope-like device equipped with a high-resolution video camera on the end to allow the neurosurgeon to navigate and access the lesion (Du et al., 2018). The advantages of NESTs include less complications and a faster recovery than traditional surgery and minimal scarring. Only a few studies have examined the application of NESTs to assess and treat CVI (Chang et al., 2007; Fehrenbach et al., 2016). Nevertheless, neuroendoscopic surgery (NES) may be an effective approach to provide a panoramic intraventricular view and visual assessment of CVI. Therefore, in the present study, we examined the efficacy of NESTs in assessing and treating CVI in patients who had received NES.

Materials and Methods

Patients

This multicenter, retrospective study was conducted in accordance with the *Helsinki Declaration* of 1975, as revised in 2000. The study has been approved by the Institutional Review Board of Beijing Shijitan Hospital, Capital Medical University, China (**Additional file 1**). All patients or their legal guaidians in this study authorized the release of their medical records and information.

This study included the clinical data of 20 men and 12 women (mean age: 42.97 years, range: 24–60 years) who presented with CVI in six hospitals in China from March 2010 to December 2017 (**Additional Table 1**). These hospitals included the Beijing Shijitan Hospital of Capital Medical University, Peking Union Medical College Hospital, Peking University Third Hospital, Beijing Tongren Hospital of Capital Medical University, the Second Affiliated Hospital of Nanjing Medical University, and Beijing Liangxiang Hospital. The same chief neurosurgeon performed all surgeries in all centers.

All eligible patients enrolled in this study met the following criteria: (1) history of a neurosurgical operation; (2) symptoms of fever, headache, neck/upper back pain, epilepsy, or consciousness disorder; (3) positive meningeal irritation sign; (4) increased leukocytes in the CSF; (5) positive CSF culture; (6) linear enhancement of the ventricular walls and/or intraventricular debris, the intraventricular compartment, or abscesses diagnosed by CT and/or MRI; and (7) intravenous and/or intrathecal antibiotic treatment for 2–4 weeks, but with no improvement.

All cases of CVI were treated by an intravascular approach with/without intrathecal antibiotics for 4 weeks to 6 months before NES. However, the outcomes of these patients were poor. The initiating factors for development of CVI were open surgery (n = 5), endoscopic third ventriculostomy (ETV; n = 5), EVD (n = 7), ventriculoperitoneal (VP) shunt (n = 13), repeated Ommaya taps (n = 1), and pituitary tumor resection by an endoscopic endonasal approach (n = 1). Clinical manifestations included fever (range, 37.5–42°C; n = 32), headache (n = 29), neck/upper back pain (n = 16), dizziness (n = 14), slurred speech (n = 9), intracranial hypertension (n = 21), epilepsy (n = 18), consciousness disorder (n = 8), and meningeal irritation sign (n = 26).

A blood examination showed increased leukocytes (1.51 ± 0.39 × 10^9/L; n = 29), increased procalcitonin levels (10.61 ± 3.61 μg/L; n = 30), and increased C-reactive protein levels (122.15 ± 21.42 mg/L; n = 32). CSF examination showed abnormal (n = 28) and normal CSF appearance (n = 4), positive Pan reaction (n = 32), increased leukocytes (1.63 ± 0.65 × 10^6/L; n = 32), increased protein levels (1.31 ± 0.47 g/L; n = 28), decreased glucose levels (1.58 ± 0.56 mM; n = 29), and decreased chloride levels (68.71 ± 19.74 mM; n = 27).

CSF bacterial culture showed that results were positive in all cases. Pathogens included Staphylococcus epidermidis (n = 14), Staphylococcus aureus (n = 6), Enterococcus faecium (n = 8), Pseudomonas aeruginosa (n = 10), Klebsiellap-neumoniae (n = 5), Enterobacter cloacae (n = 3), and mixed pathogens (n = 14) (**Additional Table 1**).

CT and MRI were performed in all cases before NES. We observed linear ependymal enhancement (n = 32), ventricular dilation (n = 21), intraventricular debris (n = 25), the intraventricular compartment (n = 17), and intraventricular abscesses (n = 6). A single-photon emission CT examination was performed in cases of secondary hydrocephalus as-so-

ciated with CVI (n = 26). The results showed 18 cases of non-obstructive hydrocephalus and eight cases of obstructive hydrocephalus.

Surgical instruments

The MINOP® Modular Neuroendoscopy System (Aesculap, Tuttlingen, Germany) includes a trocar and InVent trocar.

(1) The MINOP trocar with a 6-mm outer diameter and 4 channels: scope channel, 2.8-mm diameter; working channel, 2.2-mm diameter; irrigation channel, 1.4-mm diameter; overflow channel, 1.4-mm diameter. MINOP endoscope with 0° and 30° view directions, a 2.7-mm shaft diameter, and a 180-mm shaft length.

(2) The MINOP InVent trocar with an 8.3-mm outer diameter and 3/4 channels: scope channel, 2.8-mm diameter; irrigation channel, 1.0-mm diameter; two merging channels with a large working/overflow channel of 3.7 × 6.5 mm and a small working/overflow channel of 2.2-mm diameter. MINOP InVent endoscope with 0° and 30° view directions, a 2.7-mm shaft diameter, and a 180-mm shaft length.

NES criterion

(1) Intermittent or continuous hyperthermia, CSF white blood cell count ≥ 10×10^6/L, and positive result of CSF culture through intravenous and/or intrathecal antibiotics for 2–4 weeks (for all patients); (2) imaging data showed obvious ependymal enhancement and/or substantial inflammatory debris on diffusion-weighted imaging (for all patients); (3) imaging data showed intraventricular compartments (optional); (4) imaging data showed intraventricular abscess (for all patients); (5) if EVD was necessary because of CVI secondary to hydrocephalus leading to increased intracranial pressure, neuroendoscopic assessment and treatment were performed according to intraventricular condition during the EVD procedure (for all patients).

Neuroendoscopic classification of CVI

Neuroendoscopic classification of CVI (Grade I–IV) was used for the assessment of CVI in the study. Grade I (early) was classified as clear or yellowish CSF, granular ependymitis, little debris, little pseudomembrane on the ventricular wall, identifiable anatomical landmarks, pink or whitish choroid plexus, a patent foramen of Monro, and a normal third ventricular floor (**Figure 1IA–D**). Grade II (aggressive) was classified as yellowish or light turbid CSF, granular ependymitis, moderate debris, moderate pseudomembrane and pus, identifiable anatomical landmarks, whitish or yellowish choroid plexus, a patent and enlarged foramen of Monro, and a thickened third ventricular floor (**Figure 1IIA–D**). Grade III (severe) was classified as turbid CSF, granular ependymitis, excessive debris and pus, intra-ventricular compartments, difficult to identify anatomical landmarks, membrane-obscured choroid plexus, an enlarged or closed foramen of Monro, a thickened, opaque third ventricular floor, and secondary hydrocephalus (**Figure 1IIIA–D**). Grade IV (excessive) was classified as was Grade III, but was accompanied by an intraventricular abscess (**Figure 1IVA–D** and **Table 1**).

Table 1 Neuroendoscopic classification of cerebral ventricular infection (CVI) (Grades I–IV)

	Grade I (early)	Grade II (aggressive)	Grade III (severe)	Grade IV (excessive)
Cerebrospinal fluid appearance	Clear or yellowish	Yellowish or light turbid	Turbid	Turbid
Granular ependymitis	Yes	Yes	Yes	Yes
Intraventricular debris and pus	Little	Moderate	Excessive	Excessive
Intraventricular compartments	No	No	Yes	Yes
Identifiable anatomical landmarks	Yes	Yes	Yes or no	Yes or no
Choroid plexus	Pink or whitish	Whitish or yellowish	Obscured by membrane	Obscured by membrane
Foramen Monro	Patent	Patent and enlarge	Enlarge or closure	Enlarge or closure
Third ventricle floor	Normal	Thicken	Thicken and opaque	Thicken and opaque
Intraventricular abscess	No	No	No	Yes

Treatment for cerebral ventricular infection

The neuroendoscopic bilateral frontal or unilateral frontal approach with septostomy under general anesthesia was performed in all patients. The purpose of NES was to obliterate intraventricular debris and pus, fenestrate or incise the intraventricular compartment and reconstruct the CSF circulation, remove artificial implant material, and resect or externally drain intraventricular abscesses. Intraventricular irrigation with antibiotic saline (IVIAS) was applied after NES. ETV or VP shunt was performed for secondary hydrocephalus resulting from CVI.

NES procedure

The standard procedure included four or more of the following steps. Neuroendoscopic IVIAS was performed during NES (for all patients). The severity of the ventricular situation with NESTs was assessed (**Figure 1**; for all patients). Debris, sediments, pus, and blood clots were obliterated in the ventricle (**Figure 2A–D**; for all patients). The intra-ventricular compartments were fenestrated or incised (**Figure 2E** & **F**; optional). If the aqueduct of the midbrain was enlarged, the neuroendoscope was placed into the fourth ventricle to assess and treat CVI (**Figure 2G–J**; optional). The intra-endoscopic technique was converted into an extra-endoscopic technique to obliterate a large amount of intra-ventricular debris, pus, and clots with an aspirator (**Figure 2K** & **L**; optional). All intraventricular artificial implants were dissociated and removed (**Figure 2M**; for all patients). The ventricular abscess was resected or drained (optional). The EVD catheter was placed in an optimal site, such as the foramen of Monro or occipital horn, with neuroendoscopic guidance for IVIAS (**Figure 2N**; for all patients). Neuroendoscopic biopsy specimens that were obtained from the debris and pus were detected by hematoxylin-eosin staining.

Repeated NES criterion

Repeated NES was performed when IVIAS after NES had been performed for 2 weeks but the patient still exhibited the following: (1) Intermittent or continuous hyperthermia (≥ 37.5°C); (2) CSF white blood cell count ≥ 10×10^6/L; (3) positive result of CSF culture; and (4) linear enhancement of the ventricular walls and/or intraventricular debris, pus, or compartment confirmed by CT and/or MRI.

Intraventricular irrigation with antibiotic saline after NES

IVIAS was applied either intermittently (Grade I) or continuously (Grade II–IV). IVIAS was applied for 2–6 weeks after NES. Antibiotic saline for irrigating the ventricle was prepared and replaced according to the half-life of the antibiotic. The intraventricular medication included Vancomycin, Gentamicin, and Amicacin (**Additional Table 1**). The intraventricular antibiotic dose was 5–10% of that provided intravenously. Neuroendoscopic intraventricular views were observed before and after IVIAS (**Figure 2O** & **P**; optional).

Discharge and follow-up evaluation

The modified Rankin Scale (mRS) (Reponen et al., 2016; Wilson et al., 2017) was used to evaluate outcomes at discharge and during follow-up. Outpatient follow-up visits were scheduled for the following 6–76 months. An MRI (diffusion weighted imaging sequence and contrast-enhanced) follow-up scan was arranged. Complications associated with surgery and persistence of symptoms during the follow-up period were noted.

Statistical analysis

Descriptive of patients' characters and clinical data were summarized, and continuous variables are presented as the mean ± standard deviation (SD). Association of neuroendoscopic classification with imaging features of cerebral ven-tricular infection was performed under generalized linear regression, in which *t*-tests and *F*-tests were done under a 0.05 statistical significance. All data were analyzed using SPSS version 19.0 statistical software (IBM Corp., Armonk, NY, USA).

Results

Clinical data of patients with CVI that received neuroendoscopic surgical treatment

Two patients (6%) had severe lung infection caused by A baumannii. Both patients were treated with antibacterial and mechanical ventilation, but the efficacy was poor. Ultimately, these two patients died of respiratory failure, 6 weeks and 4 weeks after NES. The other 30 (94%) patients were completely cured. Intracranial hypertension was normalized in 21 patients, disturbance of consciousness was significantly diminished in 5 patients, and meningeal irritation signs disappeared in 26 patients. Among the 26 patients with secondary hydrocephalus, 18 underwent a VP shunt and 8 underwent ETV. ETV failed in one patient and was replaced with a VP shunt. After surgery, cerebral ventricular dilation was normalized in 12 patients, reduced in 5, and unchanged in 4. Among the 32 patients who showed CT/MRI-detected line enhancement of the ventricular wall, 26 showed the disappearance of enhancement and the 6 other patients showed reduced enhancement. Among the 6 patients with an intraventricular abscess, the abscess dis-appeared in 5 patients, and showed linear enhancement with contrast-enhanced CT and MRI in one patient.

Laboratory examinations after NES

Blood examination showed that leukocytes, procalcitonin levels, and C-reactive protein levels were normalized in all patients. CSF appeared normal (n = 24) or light yellow (n = 8). The Pan reaction was negative in all patients (n = 32). The CSF leukocyte count ranged from 0 to 11×10^6/L. CSF chemistry tests showed that total protein levels ranged from 0 to 46 mg/L, glucose levels ranged from 21 to 50 mM, and chloride levels ranged from 110 to 140 mM. CSF culture was negative in all patients.

Association of neuroendoscopic classification with imaging features of CVI

The neuroendoscopic bilateral frontal approach was used in 29 patients (Grades II–IV), and the unilateral frontal approach with septostomy was used in 3 patients (grade I). Classification of CVI by NESTs showed 3 Grade I cases, 13 grade II cases, 10 grade III cases, and 6 Grade IV cases. Of these, the 3 patients with Grade I CVI underwent one NES, the 23 patients with Grade II/III underwent two NESs, and patients with Grade IV underwent two (n = 3) or three (n = 3) NESs (**Additional Table 2**). Linear regression analysis showed that the number of NESs significantly increased with an increase in CVI Grade (P = 0.000, **Additional Table 3**). Neuronavigation was applied to 9 Grade II patients, 8 Grade III patients, and 5 Grade IV patients.

For linear regression analysis, four CVI imaging features of ependymal enhancement, intraventricular debris, intra-ventricular compartments, and intraventricular abscess were used as the dependent variables, and neuroendoscopic CVI classification was used as the independent variable. The *F*-test results showed that the associations between imaging features and grades of neuroendoscopic CVI classification were statistically significant (F = 33.146, P = 0.000). Thus, the higher the grade of neuroendoscopic classification of CVI, the more likely it was that a patient would present with imaging features of intraventricular debris, intraventricular compartments, and intraventricular abscess (**Tables 2** and **3**).

Pathological findings of a biopsy specimen of material lining the ventricular wall

Neuroendoscopic biopsy specimens that were obtained from the debris and pus in the ventricle showed edematous changes with scattered hemorrhage and necrosis by hematoxylin-eosin staining. We also observed gliosis, inflammatory cells, proliferation of epithelioid cells, and ependymal thickening (**Figure 3**).

Complications of neuroendoscopic surgical treatment in patients with CVI

Two patients died of multiple organ failure. Less serious

Table 2 Association between neuroendoscopic classification and imaging features of cerebral ventricular infection

	Neuroendoscopic cerebral ventricular infection Classification			
Imaging features	Grade I (n = 3)	Grade II (n = 13)	Grade III (n = 10)	Grade IV (n = 6)
Ependymal enhancement	3	13	10	6
Intraventricular debris	0	9	10	6
Intraventricular comparment	0	5	6	6
Intraventricular abscess	0	0	0	6

Table 3 Regression analysis on imaging features and neuroendoscopic classification of cerebral ventricular infection

Dependent variables	Independent variable	R^2	F	P
Ependymal enhancement	Neuroendoscopic classification	–	–	–
Intraventricular debris	Neuroendoscopic classification	0.364	17.178	0.000
Intraventricular comparment	Neuroendoscopic classification	0.305	13.166	0.001
Intraventricular abscess	Neuroendoscopic classification	0.568	39.414	0.000

complications included seizures (n = 5), subcutaneous effusion (n = 4), subdural effusion (n = 6), intracranial pneumatosis (n = 8), pneumonia (n = 4), and slight intraventricular hemorrhage (n = 5). There were no incision infections, CSF leakages, serious complications associated with ETV, obstructions, infections with rejection of a VP shunt, or ventricular fungal infections.

Follow-up analysis of patients with cerebral ventricular infection that received neuroendoscopic surgical treatment

At discharge, the median mRS score was 3 (range, 0–6). During the 6–76 months of follow-up, there was no recurrence of CVI, and the surgical results for hydrocephalus were satisfactory. The median mRS follow-up score was 2 (range, 0–6).

Case report of cerebral ventricular abscess with neuroendoscopic surgical treatment

A 35-year-old man had an 11-month history of intermittent fever (range, 37–42°C) after undergoing endoscopic endonasal approach for a pituitary tumor. The patient was treated intermittently with intravenous antibiotics (Ceftriaxone sodium and Vancomycin) for approximately 10 months, but with minimal effect. The Glasgow Coma Scale score on admission was 10. The meningeal irritation sign was positive. The pathogen in CSF culture was identified as Pseudomonas Aeruginosa. Sensitive antibiotics were Gentamicin and Amicacin. The patient was treated with IVIAS (Amicacin) after NES for 4 weeks.

Contrast-enhanced MRI showed an annular enhancement signal in the aqueduct and a linear enhancement signal in the fourth ventricle (**Figure 4A–C**). The patient was diagnosed with CVI, intraventricular abscess, and obstructive hydro-cephalus. During NES, we found yellow tissue deposited at the foramen of the aqueduct (**Figure 4D**). A biopsy specimen of the yellow tissue showed inflammatory cellular infiltration. An external catheter for draining the abscess was placed into the third ventricle through the foramen of Monro, and then inserted into the abscess cavity with navigation guidance (**Figure 4E** & **F**). T2-weighted MRI showed that the drainage catheter was inserted into the abscess cavity through the foramen of the aqueduct (**Figure 4G**). Three-dimensional CT reconstruction of the skull showed the drainage catheter in the abscess, as well as the left and right EVD catheters (**Figure 4H–J**).

After 4 weeks of IVIAS following NES, contrast MRI showed that the previous annular enhancement signal of the aqueduct had disappeared and transformed into point-and-line enhanced signals (**Figure 4K–M**). His temperature had returned to the normal range. Blood and CSF tests were normalized, and CSF cultures after NES were negative. The patient was discharged with a favorable outcome after the VP shunt. The follow-up was 54 months, and the patient fully recovered with an mRS score of 0 (**Figure 4N–P**).

Discussion

Efficacy of neuroendoscopic surgical techniques in assessment and treatment of CVI

In the present study, the cure rate (> 90%) and the death rate (6%) of CVI was compared with the cure rate (about 80%) and the death rate (10–30%) of CVI by the treatment of only intravenous and intrathecal antibiotics reported in previous studies (Park et al., 2006; Mori, 2007; Rath et al., 2012; Ziaka et al., 2013; Kumar et al., 2015, 2016; Terada et al., 2016; Satyarthee, 2017; Mahoney et al., 2018; Shang et al., 2018; Yuen et al., 2018). This comparison indicates a satisfactory neural function recovery and regeneration of NEST for CVI. All grade I patients underwent one NES and intermittent IVIAS. Patients with grade II–IV underwent two or three NESs and continuous IVIAS. Linear regression analysis showed that the number of NESs significantly increased with an increase in CVI grade. This indicates that a higher CVI classification is associated with multiple operations. Therefore, the surgical procedure should be rationally designed for higher CVI grades before the first NES, such as incision and unilateral or bilateral approach, to avoid incisional CSF leakage. F-test of regression analysis on the associations between imaging features and grades of neuroendoscopic CVI classification also confirmed that the higher the grade of neuroendoscopic classi-fication of CVI, the more likely a patient was to present with imaging features of intraventricular debris, intraventricular compartments, and intraventricular abscess. An important consideration regarding NEST treatment of CVI is that NES with neuronavigation should be applied in cases

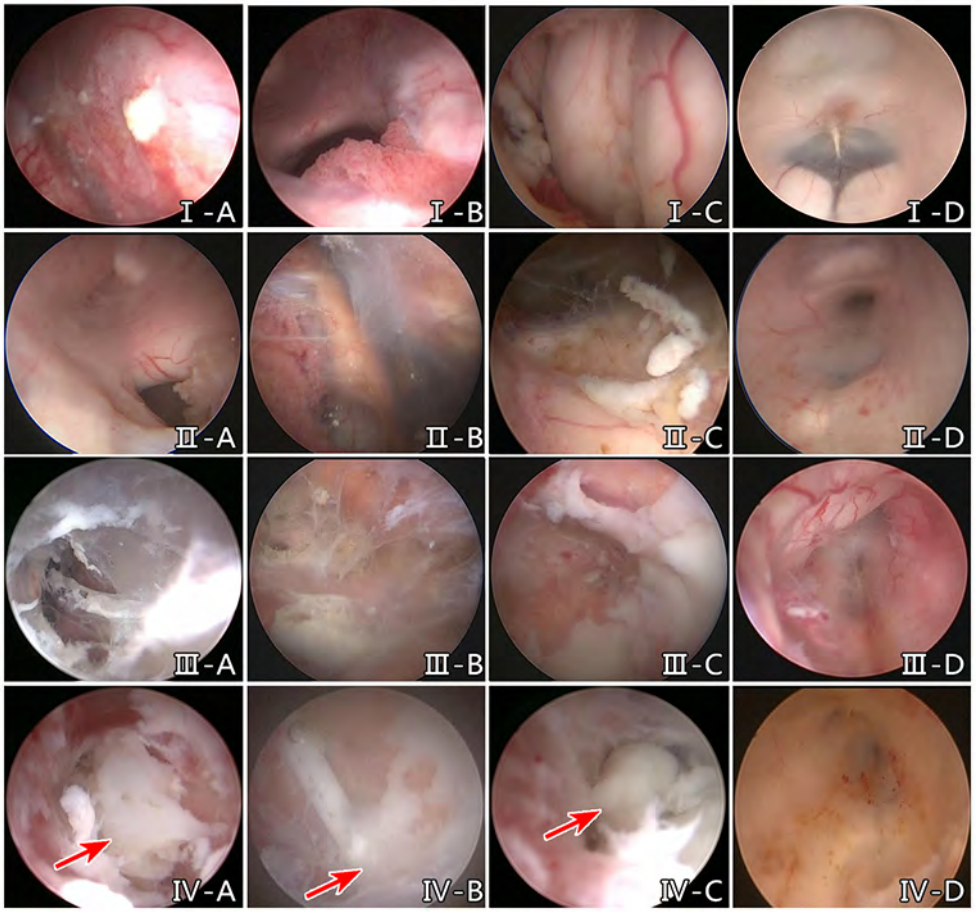

Figure 1 Neuroendoscopic classification of cerebral ventricular infection.
(IA–D) Grade I: Clear or yellowish cerebrospinal fluid (CSF), granular ependymitis, identifiable anatomical landmarks. (IIA–D) Grade II: Yellowish or light, turbid CSF, granular ependymitis, moderate debris and pus, moderate pseudomembrane on the ventricular wall, patent and enlarged foramen of Monro, identifiable anatomical landmarks, and thickened third ventricular floor. (IIIA–D) Grade III: Turbid CSF, granular ependymitis, excessive debris and pus, compartments, difficulty in identifying anatomical landmarks, enlarged or closed foramen of Monro, and thickened and opaque third ventricular floor. (IVA–D) Grade IV: The same as grade III, but accompanied by intraventricular abscesses (red arrows).

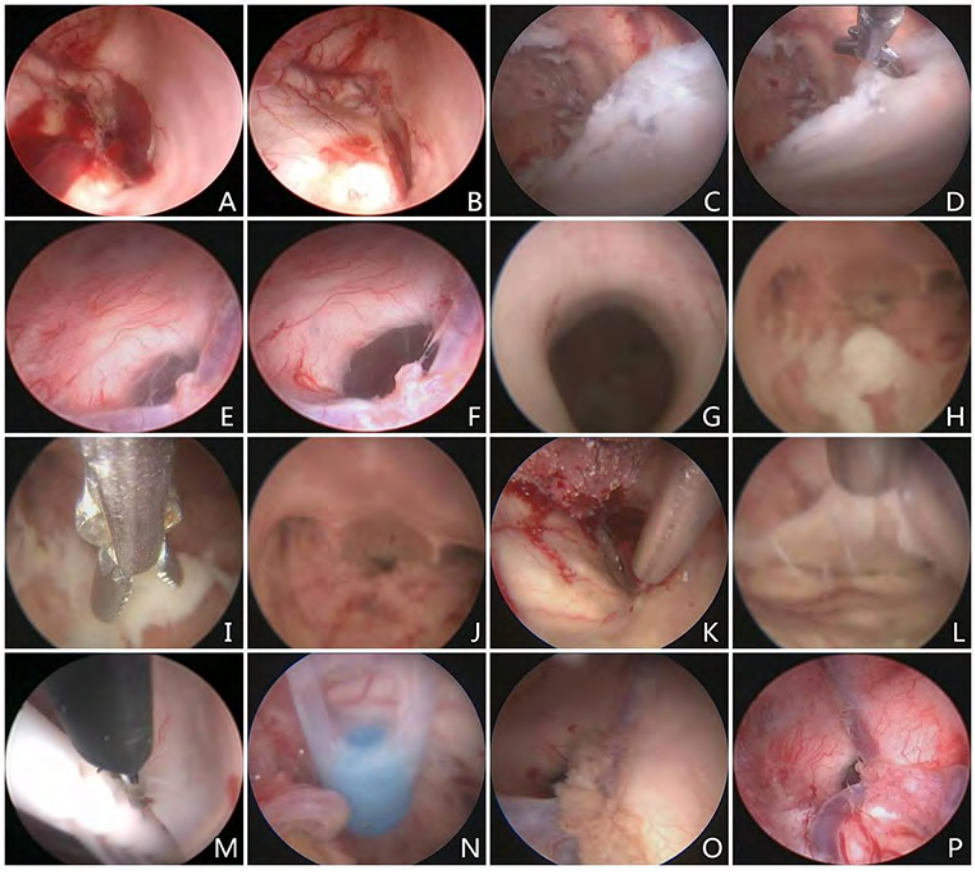

Figure 2 Application of neuroendoscopic surgical techniques to treat cerebral ventricular infection.
(A, B) Before (A) and after (B) obliteration of blood clots in the right occipital horn of the lateral ventricle. (C, D) Before (C) and after (D) obliteration of debris and pus in the right lateral ventricle. (E, F) Before (E) and after (F) fenestration of the membrane over the foramen of Monro. (G-J) The enlarged aqueduct of the midbrain (G), assessment of the infection state in the fourth ventricle (H), before (I) and after (J) obliteration of debris and pus in the fourth ventricle. (K, L) Conversion of the intra-endoscopic technique to the extra-endoscopic technique to obliterate a large amount of intraventricular debris, pus, and clots with an aspirator. (M) Dissociation of artificial implants attached to the ventricular wall. (N) To place the external ventricular drainage catheter at the optimal location by neuroendoscopic guidance. (O, P) Intraventricular views before (O) and after (P) intraventricular irrigation with antibiotic saline. Two weeks after intraventricular irrigation with antibiotic saline, blood vessels on the ventricular wall were obviously dilated and hyperemic.

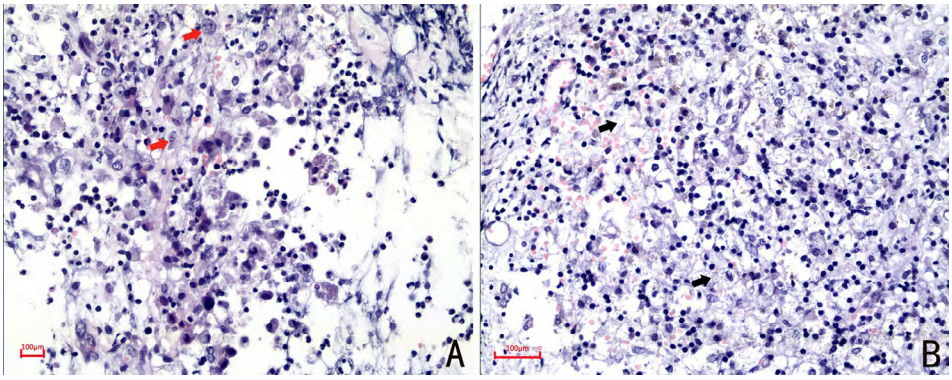

Figure 3 Hematoxylin-eosin staining of a biopsy specimen of material lining the ventricular wall.
(A, B) The edematous changes with scattered hemorrhage and gliosis (red arrows), necrosis (black arrows), inflammatory cells, proliferation of epithelioid cells, and ependymal thickening can be seen (original magnification, A, 100×; B, 200×). Scale bars: 100 μm.

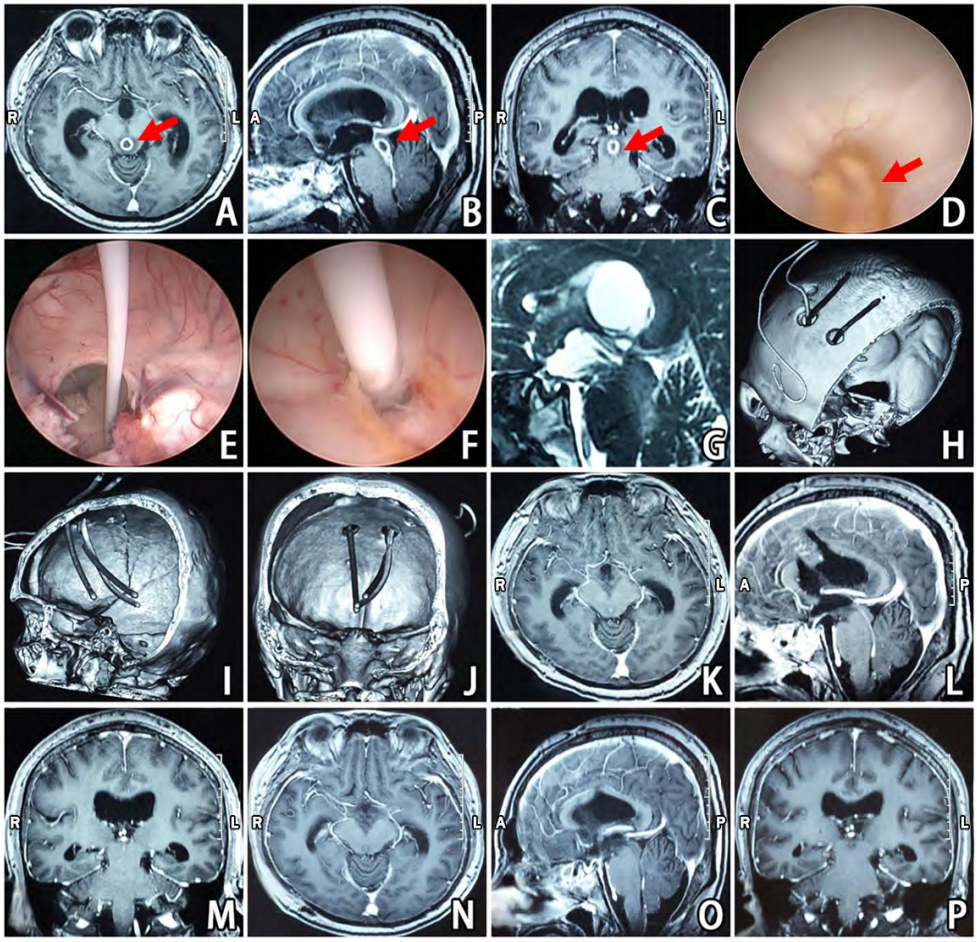

Figure 4 Medical images and scenarios of neuroendoscopic surgery (NES) for cerebral ventricular infection.
(A–C) Contrast-enhanced magnetic resonance imaging (MRI) shows an enhanced annular signal in the aqueduct (red arrow) and an enhanced linear signal in the fourth ventricle. (D) During NES, yellow tissue (red arrow) was deposited at the foramen of the aqueduct. (E) The catheter used for external drainage of the abscess was placed in the third ventricle through the foramen of Monro. (F) An external drainage catheter was inserted into the abscess cavity. (G) T2-weighted MRI showed that the catheter was in the abscess cavity. (H–J) Three-dimensional computed tomography reconstruction of the skull shows the drainage catheter in the abscess, as well as the left and right external ventricular drainage catheters. (K–M) Contrast-enhanced MRI showed that the previous annular enhanced signal had disappeared and been replaced by point-and-line signals in the aqueduct and fourth ventricle 4 weeks after NES. (N–P) Contrast-enhanced MRI at one year of follow-up. A: Anterior; P: posterior; R: right; L: left.

of abnormal intraventricular structures identified by CT and MRI. This may avoid injury caused by blind grasping, fistulas, and suction. Because of gravity and positioning, the debris, pus, and blood clots are often deposited in the third ventricle, occipital areas, and temporal horn of the lateral ventricle. These areas may be assessed and cleared during NES (Mori, 2007). Application of NESTs may also be used to reconstruct the CSF circulation, which is beneficial for IVIAS after NES. Furthermore, artificial implants are usually surrounded by bacteria and adhere to the ventricular wall or choroid plexus. During NES, artificial implants can be identified visually and removed to avoid secondary intracranial hemorrhage. With endoscopic guidance, a 14 Fr EVD catheter for IVIAS can be placed at the ideal site (*e.g.*, foramen of Monro, the occipital horn of the lateral ventricle) to avoid adhesion to the choroid plexus and ventricular wall. During NES, two methods may be applied to treat an intraventricular abscess, as follows: (1) complete removal of the abscess when it is around the shunt or in a non-essential functional area; and (2) draining of the abscess when it is in close proximity to an important anatomical structure (*e.g.*, the brainstem), or when the cyst of the abscess cannot be completely removed.

Finally, when there is excessive intraventricular debris, pus, and abscesses, the intra-endoscopic technique may be converted to an extra-endoscopic technique, which can effectively accelerate the surgical process and ensure the safety

and efficacy of NES. Our specific procedure was as follows. First, the neuroendoscope was placed into the lateral ventricle *via* the neuroendoscopic access or cortical fistula as an observation tool. A closed adjustable pressure aspirator was placed into the lateral ventricle *via* the neuroendoscopic access or cortical fistula. When the aspirator was near debris, sediments, and pus, the aspirator was opened to remove the inflammatory substances. The depth and direction of the aspirator were controlled by the surgeon, and the intensity of the aspirator was adjusted according to the quantity of the inflammatory substances.

Role of intraventricular irrigation with antibiotic saline after NE

Although intraventricular debris and pus are removed by NESTs, ependymitis is not fundamentally cured. Therefore, IVIAS is applied after NES to consolidate the NES (Terada et al., 2016; Yuen et al., 2018). In our study, intermittent IVIAS was conducted in patients with Grade I CVI (early stage), whereas continuous IVIAS was applied in patients with Grade II–IV CVI (aggressive, severe, and excessive stages, respectively). Kumar et al. (2015, 2016) reported that endoscopic lavage may be helpful in improving the outcome of CVI patients. In any patient with ventriculitis, if CSF sterilization is not achieved within 7–14 days of intravenous and/or intrathecal antibiotics, endoscopic lavage (2 weeks or longer) must be seriously considered because it may help to expedite the clearance of infection. Compared with the intravascular and intrathecal route, antibiotics can be applied directly to the ventricle by IVIAS (Terada et al., 2016; Yuen et al., 2018). IVIAS also maintains a stable concentration of medication in the CSF, which provides a reasonable and effective sterilization level that can cure CVI. Additionally, IVIAS replaces inflammatory or hemorrhagic CSF, debris, and inflammatory mediators in the ventricle. Nevertheless, in our study, obviously dilated, hyperemic blood vessels were found in the ventricular wall during IVIAS in 8 patients (which indicated a potential risk of intra-ventricular bleeding.

There are several important considerations that should be made when using IVIAS. An antibiotic should be selected according to evidence-based medicine and the susceptibility of the bacteriological culture. If a patient had NES treatment and 2 weeks of IVIAS, after which their temperature was still > 37.5°C and they had abnormal CSF test results, the location of EVD catheter needed to be changed for continued IVIAS. Furthermore, during the procedure, neuroendoscopic inspection was used to evaluate the therapeutic effect of CVI, and relict sediment or inflammatory deposits can be cleaned up. The drainage catheter must also be fluent during IVIAS, and the temperature of the antibiotic saline should be consistent with body temperature (36–37°C) to avoid chills. Finally, drugs (Depakine, 20–30 mg/kg per day) are required to prevent epilepsy.

Strategies for treating secondary hydrocephalus associated with CVI

CVI can easily cause midbrain aqueduct adhesion, stenosis or atresia, and obstruction of the fourth ventricle outlet leading to obstructive hydrocephalus. ETV is feasible for treating secondary obstructive hydrocephalus associated with CVI if the imaging data confirms obstruction of the CSF pathway (Mohan et al., 2012). ETV should be performed after CVI is completely cured so that the CVI cannot spread to the cerebral and spinal subarachnoid spaces. There are also some considerations that should be made for CVI during ETV. First, CVI usually leads to abnormal intraventricular anatomical structures, which makes it difficult to identify anatomical landmarks (Wang et al., 2017). In the present study, we found inflammatory thickening of the third ventricular floor in five cases. Application of neuronavigation is strongly recommended to ensure the safety and efficacy of ETV. Second, a stoma should be shaped to avoid closure. Finally, the basilar cistern should be further observed and assessed through the stoma of the third ventricular floor.

However, in some patients, CVI with obstructive hydrocephalus is also accompanied by communicating hydrocephalus. In the present study, ETV failed in one patient with midbrain aqueduct atresia, and it was replaced with a VP shunt. The reason for ETV failure was that CVI caused CSF absorption dysfunction, which led to communicating hydrocephalus. Therefore, if the imaging data confirm that the ventricular system is dilated and there is no specific CSF pathway obstruction, a VP shunt should be performed as soon as possible. A VP shunt is an optimal choice for non-obstructive hydrocephalus. When the CSF culture is continuously negative (at least 3 consecutive times), and the patient's temperature and blood and CSF leukocyte and protein levels are normalized after ceasing IVIAS, a VP shunt should be considered. We suggest that subsequent intravascular antibiotic treatment should been performed for 1–2 weeks after the VP shunt (Husain et al., 2007; Wang et al., 2017). In our study, CVI and secondary hydrocephalus were cured and there was no recurrence.

Limitations

Multicenter studies with more extended follow-up periods should be designed for further optimization of the neuro-endoscopic classification of CVI and identifying the safe and effective dose of IVIAS.

Conclusions

Application of NESTs to assess and treat CVI is an innovative method. Neuroendoscopic classification of CVI (grades I–IV) provides an objective, comprehensive assessment of CVI. IVIAS is also a necessary procedure for the permanent cure of CVI. NESTs should be applied more extensively for assessing and treating CVI.

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Additional files:

Additional file 1: *Ethics Approval Documentation (Chinese).*

Additional file 2: *Open peer review report 1.*

Additional Table 1: *Patients' characteristics and details.*

Additional Table 2: *Relation between neuroendoscopic classification of cerebral ventricular infection and the number of neuroendoscopic surgeries.*

Additional Table 3: *Linear regression analysis results of Additional Table 2.*

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Additional Table 1 Patients' characteristics and details

Patients Number	Age (years) /sex	Primary diagnosis	Surgery before neuroendoscopic surgery	Cerebrospinal fluid culture (pathogen)	Intrathecal sensitive antibiotic	Duration of intravenous/intrathecal antibiotic before surgery (weeks)	Glasgow coma scale before surgery	Glasgow coma scale Grade	Cerebrospinal fluid culture after surgery	Duration of intravenous antibiotic after surgery (weeks)	Duration of Intraventricular irrigation with antibiotic saline (weeks)	Long -term cerebrospinal fluid diversion	Follow -up duration (months)	Modified Rankin Scale at discharge	Modified Rankin Scale last follow-up	Outcome
1	33/M	Hydrocephalus	Ventriculoperit-oneal shunt	SE	Vancomycin	2	14	Ⅱ	Sterile	3	3	—	34	2	2	Survived
2	45/M	Hydrocephalus	Endoscopic third ventriculostomy	SE, EF	Vancomycin	2	13	Ⅰ	Sterile	3	2	Ventriculoperito-neal shunt	8	2	1	Survived
3	26/F	Head injury	Open surgery	PA	Gentamicin, Amicacin	24	8	Ⅳ	Sterile	6	4	Ventriculoperito-neal shunt	—	—	—	Died
4	24/M	Head injury	Ventriculoperiton-eal shunt	SE, EF	Vancomycin	4	12	Ⅲ	Sterile	3	3	Endoscopic third ventriculostomy	40	4	4	Survived
5	36/F	Intraventricular hemorrhage	External ventricular drainage	KP	Gentamicin, Amicacin	3	13	Ⅲ	Sterile	3	3	—	20	3	3	Survived
6	55/F	Hydrocephalus	Ventriculoperit-oneal shunt	SA	Vancomycin	4	10	Ⅳ	Sterile	6	5	Ventriculoperito-neal shunt	12	5	4	Survived
7	60/M	Hydrocephalus	Endoscopic third ventriculostomy	SE, KP	Vancomycin, Gentamicin	5	13	Ⅲ	Sterile	4	3	Ventriculoperito-neal shunt	17	4	3	Survived
8	45/M	Intraventricular hemorrhage	External ventricular drainage	SE, EC	Vancomycin, Gentamicin, Amicacin	2	15	Ⅰ	Sterile	2	2	Endoscopic third ventriculostomy	6	1	1	Survived
9	34/F	Head injury	Open surgery	SE	Vancomycin	3	11	Ⅲ	Sterile	5	4	Ventriculoperito-neal shunt	34	3	3	Survived
10	47/M	Aneurysm subarachnoid hemorrhage	Ventriculoperit-oneal shunt	SA	Vancomycin	4	13	Ⅱ	Sterile	3	3	—	35	3	2	Survived
11	35/F	Pituitary adenoma	Transnasal pituitary tumor resection	PA	Gentamicin, Amicacin	3	10	Ⅳ	Sterile	5	4	Ventriculoperito-neal shunt	54	3	0	Survived
12	27/M	Hydrocephalus	Ventriculoperit-oneal shunt	SE, EC	Vancomycin Gentamicin,	6	12	Ⅱ	Sterile	4	3	Ventriculoperito-neal shunt	60	3	2	Survived

					Amicacin											
13	55/M	Hydrocephalus	Endoscopic third ventriculostomy	EF	Vancomycin	4	14	II	Sterile	3	3	Endoscopic third ventriculostomy	6	2	1	Survived
14	50/F	Intraventricular hemorrhage	External ventricular drainage	PA	Gentamicin, Amicacin	3	13	II	Sterile	4	3	Ventriculoperito-neal shunt	23	1	1	Survived
15	47/M	Intraventricular hemorrhage	External ventricular drainage	SE, EF	Vancomycin	2	11	II	Sterile	4	3	Endoscopic third ventriculostomy failure, Ventriculoperito-neal shunt	17	2	2	Survived
16	50/F	Hydrocephalus	Ventriculoperit-oneal shunt	SA	Vancomycin	4	12	II	Sterile	3	**3**	—	30	2	2	Survived
17	39/M	Aneurysm SAH	Ventriculoperit-oneal shunt	SA	Vancomycin	6	12	III	Sterile	4	3	Ventriculoperito-neal shunt	46	3	2	Survived
18	46/M	Hydrocephalus	Ventriculoperit-oneal shunt	SE, PA	Vancomycin, Gentamicin, Amicacin	3	11	III	Sterile	4	4	—	27	3	3	Survived
19	36/M	Intraventricular hemorrhage	Repreated ommaya taps	EF, PA	Gentamicin, Amicacin	5	9	IV	Sterile	6	6	Endoscopic third ventriculostomy	6	4	4	Survived
20	54/F	Head injury	Ventriculoperit-oneal shunt	PA, KP	Gentamicin, Amicacin	2	13	II	Sterile	4	3	Ventriculoperito-neal shunt	15	3	2	Survived
21	45/F	Hydrocephalus	Ventriculoperit-oneal shunt	KP	Gentamicin, Amicacin	3	15	II	Sterile	4	3	Ventriculoperito-neal shunt	8	1	1	Survived
22	45/M	Aneurysm	Open surgery	SE, EC	Vancomycin, Gentamicin, Amicacin	4	11	II	Sterile	4	3	Ventriculoperito-neal shunt	35	3	2	Survived
23	38/F	Intraventricular tumor	Ventriculoperit-oneal shunt	PA	Gentamicin, Amicacin	2	13	I	Sterile	2	2	—	6	1	0	Survived
24	31/M	Hydrocephalus	Ventriculoperit-oneal shunt	PA	Gentamicin, Amicacin	4	12	II	Sterile	4	3	Ventriculoperito-neal shunt	60	3	2	Survived
25	52/F	Hydrocephalus	Endoscopic third ventriculostomy	EF	Vancomycin	4	11	III	Sterile	4	4	Endoscopic third ventriculostomy	8	2	1	Survived
26	55/M	Intraventricular	External ventricular	PA	Gentamicin,	2	13	II	Sterile	4	3	Ventriculoperito-neal	23	1	1	Survived

		hemorrhage	drainage		Amicacin							shunt				
27	49/M	Hydrocephalus	External ventricular drainage	SE, EF	Vancomycin	4	11	III	Sterile	5	4	Ventriculoperito-neal shunt	17	3	3	Survived
28	51/M	Hydrocephalus	Endoscopic third ventriculostomy	PA, KP	Gentamicin, Amicacin	4	12	II	Sterile	4	3	Ventriculoperito-neal shunt	30	2	1	Survived
29	35/M	Intraventricular hemorrhage	External ventricular drainage	SA,SE	Vancomycin	5	10	III	Sterile	5	4	Ventriculoperito-neal shunt	7	3	3	Survived
30	50/F	Hydrocephalus	Ventriculoperit-oneal shunt	SE	Vancomycin	4	11	IV	Sterile	4	4	Endoscopic third ventriculostomy	27	3	2	Survived
31	31/M	Head injury	Open surgery	EF	Gentamicin, Amicacin	4	9	IV	Sterile	6	6	Endoscopic third ventriculostomy	—	—	—	Died
32	49/M	Head injury	Open surgery	SA,SE	Vancomycin	4	11	III	Sterile	4	3	Ventriculoperito-neal shunt	15	3	2	Survived

M: Male; F: female; SE: *Staphylococcus epidermidis*; SA: *Staphylococcus aureus*; EF: *Enterococcus faecium*; PA: *Pseudomonas aeruginosa*; KP: *Klebsiella pneumoniae*; EC: *Enterobacter cloacae.*

Additional Table 2 Relation between neuroendoscopic classification of cerebral ventricular infection and the number of neuroendoscopic surgeries

	1th NES	2th NES	3th NES	Total
GI	3	0	0	3
GII	0	13	0	13
GIII	0	10	0	10
GIV	0	3	3	6
Total	3	26	3	32

Additional Table 3 Linear regression analysis results of Additional Table 2

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	*t*	Sig.
	(Constant)	1.092	0.167		6.549	0.000
	GI-IV	0.350	0.061	0.725	5.757	0.000

[a]Dependent variable: neuroendoscopic surgery