

Active Cerebrospinal Fluid Exchange System for Treatment of Pyogenic Ventriculitis

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BACKGROUND: Despite recent advances in antibiotic treatment, pyogenic ventricular brain infections are still associated with adverse clinical outcome in 80% of affected patients and mortality rates approaching 60%. The limitation of antibiotic penetration into the cerebrospinal fluid (CSF) challenges the treatment. Intrathecal treatment remains an option for adjunctive therapy to intravenous (iv) antibiotics when the iv therapy fails to sterilize the CSF. Current treatment options do not allow for changing the CSF composition without adversely affecting intracranial pressure (ICP) and power of hydrogen (pH).

OBJECTIVE: To investigate if CSF composition exchange has impact on ventriculitis patients.

METHODS: We report 2 cases with pyogenic ventriculitis treated with a new intracranial active fluid exchange system that consists of a dual-lumen catheter to facilitate irrigation and drainage coupled with an intelligent digital pump.

RESULTS: This new technique allowed us to change the composition of CSF to an antibiotic-consisted fluid. This resulted in the ability to directly modify the concentration of the targeted antibiotics in the CSF, while simultaneously removing bacterial mass without harming brain tissue and controlling ICP and pH.

CONCLUSION: Our reported experience shows that drainage of purulent fluid caused by healthcare-associated ventriculitis or meningitis is now possible without harming brain tissue and ICP while also changing the composition of CSF to an antibiotic-consisted fluid. Actively removing pus and altering CSF in this manner had an impact on infection treatment and antibiotic penetration. Further cases are needed to confirm that our treatment algorithm is correctly tailored to assist clinicians in reliably treating this catastrophic condition.

KEY WORDS: Abscess, CSF, EVD, Meningitis, Ventriculitis

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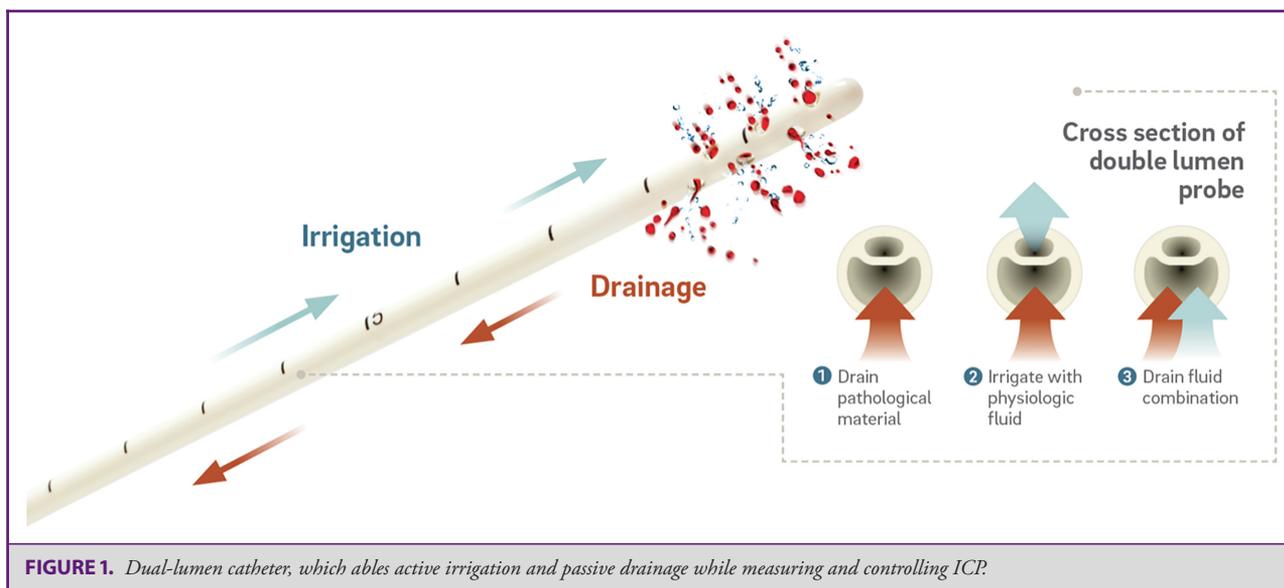
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Bacterial meningitis of the ventricular system or ventriculitis remain serious complications after neurosurgical procedures. The majority of these healthcare-associated infections evolves from complications related to external ventricular drainage (EVD) or shunts.¹ In rarer situations, these infections develop from a rupture of a brain abscess into the ventricles. When such an abscess does rupture into the ventricular system,

the infection begins to colonize and becomes systemic. This subsequent bacterial growth occurs after cerebrospinal fluid (CSF) is first generated in the ventricular system and then becomes dispersed throughout the brain and spine. Despite advances in antibiotic therapy, these infections are still associated with adverse clinical outcomes approaching 80%² and mortality rates of 60%.³ Intrathecal and intravenous (iv) antibiotics remain the current treatments of choice.⁴ However, administration of these antibiotics and their ability to cross the blood-brain barrier in order to achieve therapeutic levels within the brain's ventricular system remains limited.

ABBREVIATIONS: EVD, external ventricular drainage; iv, intravenous; pH, power of hydrogen



Objective

Current treatment options do not allow for changing the CSF composition without adversely affecting intracranial pressure (ICP) and power of hydrogen (pH). We used automatic fluids exchange device to exchange CSF and control ICP to reduce infection composition and penetrate antibiotics to all part of the ventricular system.

METHODS

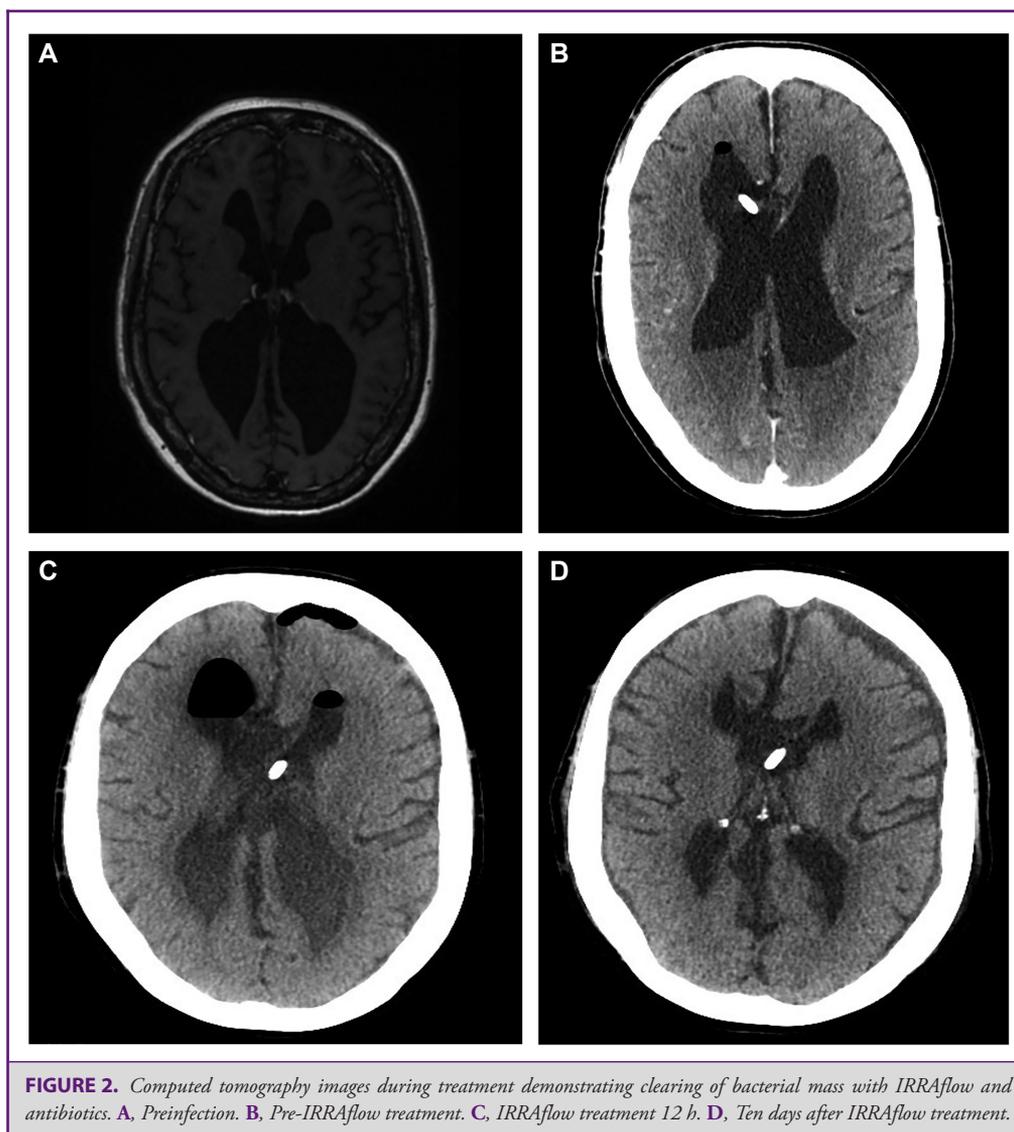
In our knowledge, this is the first report where automatic fluid exchange device, IRRFlow (IRRAS, Stockholm, Sweden), was utilized to enable in Situ treatment of 2 ventriculitis patients who were not responding to conventional antibiotic therapy. IRRFlow actively exchanges fluid by using a digital pump that automatically delivers a bolus of fluid through the catheter's irrigation lumen, see Figure 1. This irrigation bolus ensures that the catheter's tip remains free from solid particulate that can commonly occlude drainage with an EVD, and it also helps to dilute other solid particulate that may have formed in the ventricles. Then, the catheter's second lumen is dedicated to draining this diluted material, while simultaneously monitoring and controlling the patient's ICP. The treatment was based on World Medical Association Declaration of Helsinki, article 37, "In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available." The patient's family were consulted for experimental treatment and approval from national authority were obtained. Patient consent was not needed for life saving procedure.

Case 1

A 58-yr-old female had had an atrial shunt placed in childhood because of congenital meningomyelocele and Arnold-Chiari syndrome. Before this hospital admission, the patient was receiving disability pension but was able to carry out usual daily activities. The patient suffered from high fever and after laboratory examination in primary healthcare was admitted to the hospital because of *Staphylococcus aureus* sepsis, thrombovegetation of the heart, and shunt infection. Pathogen was identified 3 d after admission. Given this, antibiotic therapy with cloxacillin 12 g/day intravenously was started. Upon evaluation, a bacterial vegetation was found to be attached to the atrial catheter of the shunt, and the shunt was removed surgically (ventricular catheter and valve) and endoscopically (atrial catheter). Because of long-term shunt dependency, an EVD was inserted. For 4 d, the ventriculostomy remained closed without any clinical or imaging data indicating worsening hydrocephalus, and the EVD was removed with the patient discharged to the infectious disease department for continued treatment of sepsis.

The patient's clinical condition subsequently declined over the course of the next week and leakage of CSF through the EVD insertion site was observed. Therefore, the patient was readmitted to the department of neurosurgery for a new ventriculostomy. During follow-up imaging, a bacterial mass was found to be growing in the ventricles, and upon evaluation of CSF samples (li-leukocytes 5760 E6, li-lactate 19.65 mmol/l, gram-negative bacteria on the stain, later showed to be a *Citrobacter*-strain), the infection was deemed to be a fulminant ventriculitis.

The patient deteriorated rapidly over the next 12 h, she had an epileptic seizure, remained postictally confused, and electroencephalogram demonstrated status epilepticus. She was intubated and antiepileptic medication escalated with levetiracetam, lacosamide, and valproate. Burst-suppression anesthesia with propofol was continued for 24 h, until the situation resolved. Antibiotic treatment was changed first to ceftazidime, then shortly to meropenem (this had to be stopped because of interaction with valproate), and then to cefotaxime. Concurrently with meropenem, intrathecal gentamycin 9 mg/day bolus was started.

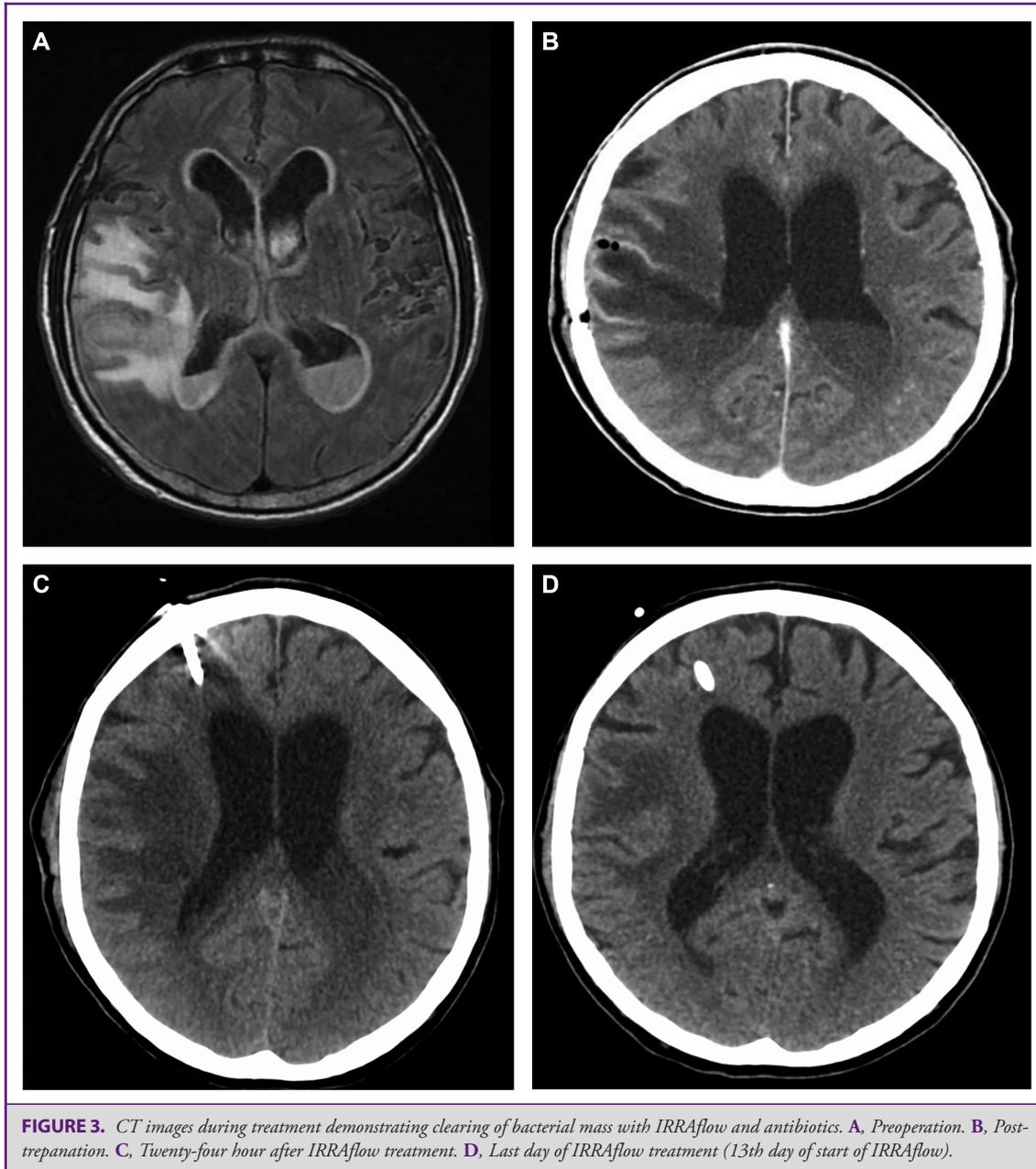


Despite the expansion of targeted antibiotic treatment, the patient's clinical status deteriorated further, the response to pain was extension, and infection symptoms increased. Given the grave situation, the treatment options were evaluated in a multidisciplinary meeting. It was determined that the major cause of the patient's poor condition was the bacterial growth in the ventricular system preventing the antibiotics to have the desired effect (Figure 2).

We decided to employ article 37 of the Helsinki Declaration and explore all possible treatment options. The patient's family members were consulted, and the decision was made to experimentally treat the ventriculitis with the active fluid exchange system. The IRRAflow dual lumen catheter was introduced, and the system's irrigation and drainage exchange was started with NaCl 0.9% 180 ml/hour. Special attention was paid to ensure that the system's hourly input did not exceed the output rate, and the system's high

ICP alarm was set at 20 mmHg to control prevention of over irrigation.

The active fluid exchange system is currently indicated to irrigate only using neutral physiological fluids, such as saline or Ringer's lactate or acetate. We theorized that, by combining the irrigation fluid with antibiotic, the active fluid exchange would help combat the bacterial mass by increasing penetration of the intrathecal antibiotic. So, for 3 wk, the patient received intrathecal gentamycin 9 mg as a daily bolus, the irrigation continued for 11 d using 21 L of saline with gentamycin 3 mg/l added during the days 5 to 8 of the irrigation. The serum concentration of gentamycin was checked and was found to be below detection limit. As mentioned, the systemic antibiotic therapy was managed with cefepime against *S. aureus* sepsis and citrobacter-ventriculitis. The patient was rotated every 4 h to facilitate antibiotic penetration throughout the ventricular system and to help draining the pus.



During the treatment period, for clinical reasons, the IRRAflow system was turned off for 3 d. Computed tomography (CT) scans showed that the bacterial mass was again enlarging, and the patient's clinical condition deteriorated, and the treatment with fluid exchange was resumed with decrease in the bacterial growth in the ventricles. Sequential CSF samples demonstrated clearing of the CSF. Figure 2 demonstrates how utilizing active fluid exchange system with antibiotic-irrigation was able to clear the bacterial mass over an 11-d treatment period.

Infection and inflammation response caused the CSF protein content to remain very high, and it was deemed that a shunt would not remain functioning. During third ventricle fenestration attempt, it was observed

that ventricles had multiple adhesions and fibrosis. A third attempt at endoscopic third ventriculostomy (ETV) 3 mo after starting the ventriculitis therapy finally succeeded. The patient was discharged to rehabilitation after 37 d of therapy, she lives in a nursing home and is able to communicate. During 2.5 yr follow-up, there were no new central nervous system infection.

Case 2

A 64-yr-old male who had been living independently was admitted to a local hospital showing neurological symptoms of neglect and right-sided clumsiness. The patient suffered from diabetes mellitus and

TABLE 1. Lesson Learned From 2 Pyogenic Ventriculitis Cases Treated With CSF Exchange Device

Lesson 1	Immediately starting treatment by directly introducing an antibiotic solution and initiating CSF exchange allowed us to effectively remove the bacterial mass from the ventricles.
Lesson 2	High-dose cortisone was subsequently needed to decrease inflammatory responses of ventricular system and fibrosis of brain parenchyma.
Lesson 3	Rotation of the patient every 4 h helped facilitate antibiotic penetration throughout the ventricular system and drainage of pus.
Lesson 4	Antiepileptic medication was required as the aggressive infection induced status epilepticus.
Lesson 5	The patient remained shunt dependent after treatment and resolution of ventriculitis due to the associated inflammatory response of the ventricular system.

hypertension and had a history of alcohol abuse but had been sober for 9 yr. Initial imaging showed a cerebral abscess that had burst into the ventricular system (Figure 3). The patient was admitted to the Department of Neurosurgery at the University Hospital, and the abscess was evacuated via trepanation. Empirical antibiotic therapy was started with iv ceftriaxone and metronidazole, and after a standard EVD was inserted, intrathecal vancomycin therapy (10 mg bolus/day) was combined to the antibiotic regimen. When the pathogen was identified 2 d after evacuation of abscess as *Streptococcus anginosus*, ceftriaxone was changed to benzylpenicillin (24 million U/day), and metronidazole and it-vancomycin therapy continuing as before.

Fourteen hours after admission to the neurosurgical ICU, the patient lost consciousness and had to be intubated. Because of the rapid deterioration in the clinical condition and the large bacterial mass filling the ventricular system, the university hospital multidisciplinary team, with the recent experience from the previously described patient case, suggested immediate treatment with the active fluid exchange system. The patient's family members were consulted, and the decision was made to treat the ventriculitis experimentally with IRRAflow system under Article 37 of the Helsinki Declaration. The traditional EVD was exchanged for a dual-lumen catheter, and active fluid exchange treatment was initiated. A 10 mg bolus of intrathecal vancomycin was administered daily with irrigation stopped for 1 h to achieve high antibiotic concentration in the CSF. For the rest of the day, ventricles were irrigated with warm (37°C) sodium chloride 0.9% solution to which 50 mg/l vancomycin had been added. We used the system's maximum irrigation rate of 180 ml/hour which means 4.1 L of sodium chloride solution and 207 mg of vancomycin flushing the ventricular system and subarachnoid space daily. The serum vancomycin concentration was measured twice during the treatment but was below the detection limit. During the treatment period, a total of 42 L antibiotic solution was used. As in the first case, the patient was rotated every 4 h to drain the bacterial debris that tends to sediment in the posterior horns of the lateral ventricles if patients are kept supine.

During the first days of treatment, the patient was increasingly hyperventilating with pH going as high as 7.64 and PaCO₂ as low as 2.5 kPa. We theorized that the low pH of the sodium chloride and vancomycin combination (pH 6.8) was making the CSF acidic. Therefore, we changed the irrigation fluid from sodium chloride 0.9% to Ringer's acetate to which vancomycin was added as before (50 mg/l). Hyperventilation was alleviated, and the pH of the CSF returned to normal approximately 12 h after exchanging the irrigation fluid.

Based on our experience from the first case, we understood that ventriculitis would cause inflammatory reaction and fibrosis of the CSF system, therefore we proactively started cortisone therapy (dexamethasone 3 mg thrice a day for the first 2 wk). The steroid therapy was continued for 2 mo. Prophylactic anticonvulsants were also used.

The patient's radiological condition cleared in 2 d, and on the fifth day of the treatment with active fluid exchange, the clinical condition also improved and the patient regained consciousness. On the seventh day, the patient was extubated. Figure 3 demonstrates how the administration of intrathecal antibiotics with the active fluid exchange system was able to clear the bacterial mass over a 19-d treatment period.

Intravenous therapy with benzylpenicillin and metronidazole was given for 3 wk, and then iv ceftriaxone continued for 3 more weeks. For the first 2 wk of the therapy, the intrathecal vancomycin boluses and irrigation were combined to iv medication. The patient needed a permanent CSF diversion because of postinfection hydrocephalus and received a ventriculoperitoneal shunt a week after discontinuation of antibiotic therapy. Three months after the start of therapy, the patient was living independently at home. During 2 yr and 3 mo follow-up, there were no new central nervous system infection.

RESULTS

Previously, for ventriculitis cases, EVDs had to be monitored for possible occlusions and replaced or flushed manually, when necessary. In the management of meningitis, previous studies have demonstrate that unsuspected ventriculitis may be a source of persistent infection and therapeutic failure.^{5,6} Further gram-negative bacteria, may be resistant to standard antibiotics.⁷ Due to the potential for fatal neurological damage to occur, early treatment of gram-negative bacillary meningitis is crucial.⁸

DISCUSSION

We showed that it is possible to safely exchange CSF to actively deliver medication without significant ICP changes, potentially decreasing the mortality and morbidity of ventriculitis, in 2 demonstrated cases. To our knowledge, these are the first 2 reported cases in which the automatic pump system

was utilized to treat ventriculitis via controlled, automated active fluid exchange in the ventricular system percutaneously through a single twist-drill hole. Based on the experience learned from these initial experimental treatments, our team learned several lessons (Table 1).

CONCLUSION

Our reported experience shows that drainage of purulent fluid caused by healthcare-associated ventriculitis or meningitis is now possible. Neither patient suffered apparent brain tissue injury or ICP control difficulties without harming brain tissue and ICP while also changing the composition of CSF to an antibiotic-consisted fluid. Actively removing pus and altering CSF in this manner had an impact on infection treatment and antibiotic penetration. Further cases are needed to confirm that our treatment algorithm is correctly tailored to assist clinicians in reliably treating this catastrophic condition. Safety and effectiveness of the procedure remain to be demonstrated.

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Disclosures

Dr Rezai Jahromi became consultant and stock share and warranty holder of the company IRRAS after treating the reported patients.

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