CASE SERIES

INTRAVENTRICULAR ANTIMICROBIAL THERAPY IN CHILDREN WITH MULTI-DRUG RESISTANT VENTRICULITIS: A TERTIARY HOSPITAL EXPERIENCE AND LITERATURE REVIEW

Francesca Mae T. Pantig, MD*
Anna Lisa T. Ong-Lim, MD*

*Section of Infectious and Tropical Diseases in Pediatrics (INTROP), Department of Pediatrics, UP-Philippine General Hospital

Correspondence: Dr. Francesca Mae T. Pantig
Email: francesca.pantig@gmail.com

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

BACKGROUND: Intraventricular antimicrobial therapy (IVT), defined as the direct installation of antimicrobial agents into the lateral ventricles has been utilized as the last therapeutic option for the treatment of multidrug-resistant ventriculitis. The aim of this case series is to report our institution's experience with IVT in pediatric patients with ventriculitis.

MATERIAL AND METHODS: Retrospective chart review was done. The demographic data, cerebrospinal fluid (CSF) culture isolates, treatment regimens, and clinical outcomes of these patients were collected and described.

RESULTS: Between 2016 to 2018, seven (7) pediatric patients diagnosed with ventriculitis caused by multidrug-resistant organisms underwent intraventricular antimicrobial therapy in combination with intravenous therapy. The median age was 1 year (range 1 month to 17 years old, mean: 4.4 years). Fifty-seven (57) percent of the patients were females. The isolated pathogens were *Acinetobacter baumannii* MDRO (n = 3), *Klebsiella pneumoniae* MDRO (n = 2), Methicillin-resistant *Staphylococcus aureus* (n = 1), and Methicillin-resistant *Staphylococcus epidermidis* (n = 2). One patient had mixed isolates on CSF culture (*Acinetobacter baumannii* and MRSE). The antimicrobial agents for IVT used were colistin (n = 4), vancomycin (n = 2), and gentamicin (n = 1). The mean time to initiation of intraventricular therapy from the diagnosis of ventriculitis was 19 days. The mean duration of IVT therapy was 15 days. The survival rate was 57%.

CONCLUSION: Ventriculitis caused by drug-resistant organisms is an emerging concern. Optimal therapy is not yet established and experience with IVT is limited. This series showed that there were no adverse effects related to IVT thus it may be considered an option for MDRO ventriculitis. Gram negative organisms are more common causes of ventriculitis in our institution.

KEYWORDS: *intraventricular IVT, ventriculitis, multidrug-resistant organism MDRO*

INTRODUCTION

Healthcare-associated ventriculitis is a type of deep incisional surgical site infection (SSI) from neurosurgery associated with significant mortality and long-term neurologic sequelae, prolonged hospital stay, and high burden of cost. [1,2]

Identified risk factors for healthcare-associated ventriculitis include presence of an external ventricular drain (EVD), duration of EVD placement exceeding 5 days, frequency of EVD manipulation for CSF sampling, drain irrigation, presence of intraventricular or subarachnoid hemorrhage, presence of cranial fracture with CSF leak, craniotomy, perioperative steroid use, and poor surgical technique.[4,5,6] In pediatric neurosurgical patients, the presence of a CSF shunt has particularly been identified as a risk factor for the development of SSI. In addition, other non-shunt-related neurosurgical procedures have also been identified, including myelomeningocoele closure, spine surgery/laminectomy, tumor excision, and epilepsy surgery. Other risk factors identified include female sex, development of pneumonia in the post-operative period, cerebral palsy, use of immunosuppressants, and emergency surgery. [1]

Gram-positive bacteria from skin flora, such as methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci, account for almost 80% of the etiology of healthcare-associated ventriculitis. [7] However, multidrug-resistant gram-negative bacteria are increasingly becoming more prevalent, with *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and carbapenemase-producing Enterobacteriaceae being reported in literature as the most common pathogens. These organisms are associated with a higher morbidity and mortality especially in children due to limited treatment options.[2,8,9] Ventriculitis caused by fungi have been reported but generally account for only a small fraction of cases.[10]

Treatment of drug-resistant ventriculitis poses a challenge since choices of antimicrobial therapy are limited and response to standard intravenous antimicrobial therapy is generally poor.[11] For intravenous therapy to be effective, antimicrobial agents must be able to achieve and sustain adequate CSF concentrations. Ironically, ventriculitis is associated with less meningeal inflammation compared to meningitis, which can result in reduced antimicrobial penetration into the focus of infection. [12 13]

To address these concerns, non-conventional methods of treatment are now being utilized more frequently and IVT is one modality being used by physicians. It is necessary in patients with CSF shunt or drain infections that are difficult to eradicate with intravenous (IV) antimicrobial therapy alone, and is often utilized as the last therapeutic option for the treatment of multidrug-resistant and extensively drug-resistant organisms.[14] This route of administration bypasses the blood–CSF barrier, with controlled delivery of the antimicrobial agent to the site of infection. Intraventricular antimicrobials have the theoretical advantage of achieving high CSF concentrations without high systemic blood concentrations, hence lower potential systemic toxicities.[5] IVT antibiotic therapy can be delivered through Ommaya reservoir placement, ventriculostomies, or via direct ventricular puncture.[15,16] No standardized protocol for the treatment of CNS infection with intraventricular antibiotics has been established to date.[15]

This case series aims to describe our institutional experience with IVT in children diagnosed with ventriculitis caused by multidrug-resistant organisms, and to review literature on the use of IVT in children, duration of treatment, and adverse effects.

MATERIALS AND METHODS

This was a retrospective case series done at the Philippine General Hospital that included all pediatric patients below 19 years old diagnosed with multidrug-resistant ventriculitis who received IVT between 2016-2018. These patients were treated via IVT with an antimicrobial agent with

documented susceptibility, combined with intravenous antibiotic therapy. Cases that fulfilled the inclusion criteria were identified through a review of patient censuses. Electronic and hard copies of individual patient records were reviewed.

Cases were included based on a diagnosis of ventriculitis according to the following criteria: 1) positive CSF culture results, 2) CSF parameters consistent with ventriculitis, 3) clinical manifestations consistent with ventriculitis, and 4) a decision of the physician to treat as such.

The following data were obtained from patient records: demographic data; presence of underlying neurologic condition or congenital anomaly; results of CSF culture; treatment regimen and duration of IVT treatment. Outcomes were described as: cured, treatment completed, relapse and died. The time to initiation of IVT from the time of diagnosis of ventriculitis was also collected.

DEFINITION OF TERMS

Intraventricular antibiotic therapy (IVT) is defined as the direct installation of antimicrobial agents into the lateral ventricles.[5]

The 2018 CDC/NHSN surveillance definition of healthcare-associated meningitis/ventriculitis[3] must meet at least one of the following criteria:

1) organism(s) identified from cerebrospinal fluid (CSF) by culture or non-culture based microbiologic testing method

2) at least two clinical signs (fever > 38°C or headache, meningeal signs, or cranial nerve signs), and at least one of the following: increased white cells, elevated protein, and decreased glucose in CSF; organisms seen on gram stain of CSF; organisms identified from blood by a culture or non-culture based microbiologic testing method; or a diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for the organism.

For patients ≤ 1 year of age, clinical signs include fever > 38°C or hypothermia < 36°C, apnea, bradycardia, or irritability; meningeal signs; or cranial nerve signs.

Outcome definition as follows:

1) cured- negative CSF cultures, normalization of abnormal CSF parameters, resolution of clinical signs and symptoms, and completion of the intended duration of therapy

2) treatment completed- negative CSF cultures with resolution of signs and symptoms after completion of the intended duration of therapy, but without normalization of CSF parameters

3) relapsed- isolation of the same organism in the CSF or recurrence of abnormal CSF parameters with clinical symptoms, within 3 weeks of completing therapy for the initial episode[17];

4) died- death during the course of treatment, with or without documentation of resolution of infection.

RESULTS

Table 1. Demographic, clinical and treatment data of patients with multidrug-resistant ventriculitis

Patient	Age (yr)	Sex	CSF culture	Diagnosis	CNS device	IV antibiotics	IVT antibiotics	Duration of IVT (days)	Elapsed period before IVT (days)	IVT access	Outcome and Length of Hospital Stay
1	0.7	M	Methicillin-resistant *Stapylococcus aureus*	Congenital hydrocephalus secondary to aqueductal stenosis s/p ventriculoperitoneal shunt insertion	VPS	Vancomycin	Vancomycin 10 mg daily	23	33	External ventricular drain	Treatment completed (Discharged after 83 days)
2	1.0	F	Methicillin-resistant *Stapylococcus epidermidis*	Hydranencephaly s/p ventriculoperitoneal shunt insertion	VPS	Vancomycin	Vancomycin 10 mg daily	10	25	Ommaya reservoir	Treatment completed (Discharged after 147 days)
3	0.08	F	*Acinetobacter baumannii* MDRO	Chiari II malformation with ruptured lumbosacral meningocoele s/p lumbosacral meningocoele repair	None	Colistin, Ampicillin-Sulbactam	Colistin 125,000 IU daily	14	27	Ommaya reservoir	Relapsed (Discharged after 107 days, relapse of infection 1 week post-discharge, died)
4	7.0	F	*Acinetobacter baumannii* MDRO	Medulloblastoma s/p ventriculoperitoneal shunt insertion, gross excision of tumor	VPS	Colistin, Ampicillin-Sulbactam	Colistin 125,000 IU daily	10	11	External ventricular drain	Died (Intracranial bleed)
5	17.0	M	*Klebsiella pneumoniae* MDRO	Mixed germ cell tumor, s/p right frontal ventriculoperitoneal shunt insertion Intracranial hemorrhage secondary to tumor bleed, s/p shunt removal, left frontal tube ventriculostomy	VPS	Colistin, Meropenem	Colistin 125,000 IU daily	6*	1	External ventricular drain	Home per request (27 days)
6	0.33	F	Methicillin-resistant *Stapylococcus epidermidis*, *Acinetobacter baumannii*	Chiari II malformation, s/p lumbosacral meningocoele repair, ventriculoperitoneal shunt insertion	VPS	Vancomycin , Meropenem	Gentamicin 8mg daily	10	26	External ventricular drain	Cured (Discharged after 59 days)
7	5.0	M	*Klebsiella pneumoniae* MDRO	Medulloblastoma, s/p suboccipital craniectomy, excision of tumor, C1 laminectomy, ventriculoperitoneal shunt insertion	VPS	Colistin, Meropenem	Colistin 125,000 IU daily	30	10	External ventricular drain	Cured (Discharged after 126 days)

* treatment duration not completed

From 2016 to 2018, seven (7) pediatric patients diagnosed with ventriculitis caused by multidrug-resistant organisms had intraventricular antimicrobial therapy in combination with intravenous therapy (see table 1). The median age of patients who received combination intraventricular and intravenous therapy was 1 year (range 1 month to 17 years old, mean 4.4 years).

Fifty-seven (57) percent of the patients were females.

Four (4) patients underwent surgery for repair of a congenital CNS anomaly (1 case of congenital hydrocephalus, 1 case of hydranencephaly, and 2 cases of Chiari II malformation with lumbosacral meningocoele),

while 3 patients had surgery due to a CNS tumor (2 cases of medulloblastoma and 1 case of mixed germ cell tumor). Six of the 7 patients had shunt-related infections, while 1 patient developed infection related to lumbosacral meningocoele repair.

The isolated pathogens were *Acinetobacter baumannii* MDRO (n = 3), *Klebsiella pneumoniae* MDRO (n = 2), Methicillin-resistant *Staphylococcus aureus* (n = 1), and Methicillin-resistant *Staphylococcus epidermidis* (n = 2). One patient had mixed isolates on CSF culture (*Acinetobacter baumannii* and MRSE). Gram-negative bacteria accounted for 71% of all infections, while gram positive bacteria accounted for 43% of infections.

The antimicrobial agents used for IVT were colistin (n = 4), vancomycin (n = 2), and gentamicin (n = 1). In addition to IVT, IV antibiotics were given concurrently to all patients. In six of the seven patients, the same antibiotic was given intraventricularly and intravenously (see table 1.) The mean duration of IVT was 15 days (range of 6 to 30 days). The decision to start IVT was made on a case to case basis since there are no definite criteria to start IVT. But most of them were started due to the presence of MDRO in the CSF or repeated CSF culture positive results. The mean time to initiation of IVT from the diagnosis of ventriculitis was 19 days (range of 1 to 33 days). Twenty eight percent were cured (n = 2), and another 28% completed treatment and were discharged stable despite the presence of abnormal CSF parameters. One patient had an infection relapse and eventually expired while one patient died during treatment due to intracranial hemorrhage giving a 28% mortality rate for this case series. One patient went home against medical advise; sterilization of CSF was not documented in this patient. The overall survival rate was 57%.

DISCUSSION

We report seven pediatric patients diagnosed with post-operative multidrug-resistant ventriculitis treated with intraventricular antimicrobial therapy (IVT). IVT is increasingly becoming a therapeutic option in the management of multidrug-resistant ventriculitis poorly responsive to standard intravenous therapy. For an antimicrobial to work on CNS infections, it must achieve adequate CNS levels. This occurs via passage through the blood-brain barrier (BBB), which depends on the antimicrobial agent's physicochemical properties, including molecular weight, plasma protein-binding affinity, degree of ionization, and lipophilicity. Apart from these antimicrobial agent properties, another important consideration in the passage of antimicrobial agents through the BBB is the presence of meningeal inflammation. CSF penetration is improved via two mechanisms: 1) inflammatory mediators break down the BBB and increase permeability; and 2) the presence of meningitis causes a decrease in CSF production and outflow rates, leading to an increased CNS concentration and duration of time the antimicrobial agent remains in the CSF. Across the BBB, antimicrobial agents are transported via passive drug entry, facilitated diffusion, or active transport. Efflux pumps that actively transport antimicrobials out of the CNS also cause lower CSF concentrations; however, meningeal inflammation inhibits the activity of the efflux pumps, leading to higher CSF concentrations.

Efficacy and safety of intraventricular route of antibiotic administration have not been demonstrated in controlled trials, and antimicrobial agents are not approved by the US Food and Drug Administration for intraventricular administration, due to insufficient evidence to recommend their general use.[5] Despite the lack of sufficient evidence and standard protocol for IVT, the use of IVT in children has been reported in recent literature.[16,17,18,19,20,21,22]

The safety and efficacy of IVT antimicrobial therapy has been under constant debate. A Cochrane review on the use of intraventricular antibiotics for bacterial meningitis in neonates and older infants concluded that IVT with gentamicin in combination with IV antibiotics resulted in a three-fold increased risk for mortality, and the duration of

CSF culture positivity did not differ significantly compared to standard treatment with IV antibiotics alone. The poor outcomes in these patients were attributed to an increased endotoxin and interleukin-1 concentrations in the CSF of infants treated with IVT gentamicin, leading to further increase in inflammation.[23] In our series, only one patient received IVT gentamicin, a 4-month old female with Chiari II malformation who underwent lumbosacral meningocoele repair and ventriculoperitoneal shunt insertion, then developed ventriculitis with mixed isolates on CSF culture (Methicillin-resistant *Staphylococcus epidermidis* and *Acinetobacter baumannii*). This patient underwent shunt removal and was treated with 10 days of IVT gentamicin in combination with IV meropenem (duration of 23 days) and vancomycin (duration of 29 days). CSF studies post-treatment showed negative CSF culture and normal CSF parameters, hence patient underwent VPS reinsertion and was discharged improved with no adverse events noted during the entire duration of treatment. In contrast, one study reported focal seizures that lasted for more than one hour in a patient given IVT gentamicin (at a dose of 2mg/kg/dose) via EVD. The study did not provide the age of this patient, but only mentioned that their subjects were children ages 1 month to 16 years (mean ± SD: 23 ± 4 months). The seizures were controlled with IV phenobarbital maintained throughout the duration of IVT; treatment was discontinued for 24 hours and then restarted at a lower dose of 1mg/kg/dose with no recurrence of seizure episodes thereafter.[16]

Although the Cochrane review was specific for the use of IVT gentamicin particularly in neonates (69% of the studied population), other studies have reported the successful use of various antimicrobial agents for IVT in the neonatal population. One case report detailed the successful treatment of neonatal multidrug-resistant *Acinetobacter baumannii* ventriculitis in an 18-day old preterm infant (delivered at 34 weeks) using IVT polymyxin B.[24] In our series, the youngest patient was a newborn female diagnosed with Chiari II malformation with ruptured lumbosacral meningocoele who underwent meningocoele repair on the 5th day of life. The patient developed multidrug-resistant *Acinetobacter baumannii* ventriculitis on the 8th day of life, sensitive only to colistin. This neonate was initially treated with IV colistin and ampicillin-sulbactam, but persistence of the same organism on two succeeding CSF cultures warranted the addition of IVT colistin. This patient was treated with a total of 14 days of IVT colistin and 27 days of IV colistin and ampicillin-sulbactam that resulted in sterilization of the CSF. She was discharged improved, but was readmitted 1-week post-discharge due to purulent discharge at the shunt site. She was managed as a case of surgical site infection, treated with meropenem and vancomycin, but eventually expired due to septic shock from health-care associated sepsis. CSF parameters were abnormal but CSF culture was negative.

Six of the 7 patients developed device-related infection after surgery (infected ventriculoperitoneal shunts), while 1 patient had a non-device-related infection related to repair of a lumbosacral meningocoele. All patients with shunt-related infections underwent shunt removal and placement of an external ventricular drain that served as their access for IVT. The patient with non-device-related infection underwent Ommaya reservoir insertion that served as the IVT access.

In our series, gram negative organisms accounted for the majority of culture isolates (71%), compared to gram positive organisms (43%). One patient had mixed isolates on CSF culture, consisting of one gram negative and one-gram positive organism. Our results contrast that of various reports in literature where gram positive organisms prevail as the leading cause of ventriculitis. In the systematic review of 8 studies involving 86 patients with neurosurgical ventricular shunt infections by Drew et al., 46 patients had gram positive infections, 43 patients had gram negative infections. Mixed infections (gram positive and gram negative) were

described for four patients in the review, and one patient had a fungal infection. Of the 86 patients in that systematic review, 16 children were classified as refractory cases with multidrug-resistant organisms, defined as those who received second-line antimicrobial therapy following failed initial therapy. In these 16 children, there were 15 episodes of gram-positive organisms (majority of which are coagulase negative Staphylococcus species), and only 3 episodes of multidrug-resistant gram-negative organisms. It was not specified in the systematic review whether these refractory cases received IVT as part of their treatment regimen.[2] In another report by Arnell et al. of 34 episodes of CSF shunt infections in 30 children treated with systemic and intraventricular antibiotic therapy, gram positive organisms accounted for 29 episodes, while gram negative organisms accounted for only 5 episodes, with some patients having more than 1 infection.[19] The findings in this case series of gram negative organisms being more commonly isolated than gram positive in ventriculitis is important so that clinicians should include gram negative coverage when starting an empiric therapy.

Resistance rates of causative organisms identified in our series have been increasing or have remained high over recent years. The most recent national antimicrobial resistance surveillance data show that the cumulative MRSA rate is at 57%. For *Acinetobacter baumannii*, 42% of isolates tested against the full panel of antibiotics had a multidrug-resistant profile with combined resistance to aminoglycosides, carbapenems, fluoroquinolones, and sulbactam; only 23% of these isolates remained pan-susceptible. *Klebsiella pneumoniae* isolates have also been found to be more commonly resistant to multiple classes of antimicrobials, with up to 11% of isolates showing resistance to at least 2 or more classes of antimicrobials, such as penicillins (including beta-lactam and beta-lactamase inhibitor combinations), cephalosporins, aminoglycosides, carbapenems, fluoroquinolones, and trimethoprim-sulfamethoxazole.[25]

Dosages of antibiotic agents used for IVT may vary depending on the size or volume of ventricles, and on the volume of EVD output. The Infectious Diseases Society of America (IDSA) published the recommended dosages of common antimicrobial agents used for IVT, determined empirically based on the ability of the agent to achieve adequate CSF concentrations.[5] In our series, all dosages followed the IDSA recommendations. The IDSA also recommends CSF therapeutic drug monitoring to ensure that adequate CSF concentrations of antimicrobial agents are obtained. However, this was not done for any of the patients in this series due to limited resources.

To date, there is no existing consensus on the duration of IVT for drug-resistant ventriculitis. The shortest duration reported in literature is 1 day of IVT gentamicin in an adult with gram-negative ventriculitis, while the longest duration reported is 6 months of IVT levofloxacin and amikacin in a 25-year old male with multidrug-resistant *Mycobacterium tuberculosis* meningitis.[26,27] One retrospective report on treatment of shunt infections in children proposed an aggressive protocol where IVT is initiated at the onset of treatment upon removal of the infected shunt, and discontinued once the patient showed no further signs of infection and CSF culture is negative. The duration of IVT in this report was 6.2 ± 1.7 days, with no reported relapse in the long term follow up period (7.7 ± 3.6 years). This report concluded that shunt infections can be successfully treated with IVT without prolonged IV antibiotic courses and extended hospital stay.[16] In our series, the longest duration is 30 days of IVT colistin in a patient treated for *Klebsiella pneumoniae* MDRO ventriculitis and sepsis, who was cured and discharged stable with no relapse of infection on serial follow up.

Adverse events of IVT commonly reported in literature include chemical meningitis/ ventriculitis, seizures, and hearing loss.[28] In this case series, there were no reported episodes of seizures during the course of treatment of all patients. Hearing loss post-treatment was not assessed for these patients.

Chemical meningitis, the most commonly reported adverse event, poses a challenge for the physician to diagnose, as it is difficult to differentiate from progression of the ongoing infection or reinfection with a new pathogen due to multiple device manipulations. Forgacs et al. proposed specific clinical and CSF findings to distinguish chemical meningitis from a bacterial infection, and concluded that chemical meningitis can be differentiated from bacterial meningitis using their proposed criteria.[29] However, other authors have provided contradicting statements and have proposed to treat patients with clinical and laboratory features of post-operative meningitis as a bacterial infection, due to the high burden of morbidity and mortality from delays in initiation of therapy.[30] In this series, two patients demonstrated increasing CSF WBC counts and persistent low glucose concentrations but with sterile CSF cultures during the course of treatment. One patient was managed as a progressing infection, while another patient was diagnosed with a new-onset infection; antibiotics were shifted accordingly for both patients. None of the patients in this series were diagnosed to have chemical meningitis.

One patient in this case series showed a relapse in CNS infection after treatment. One patient, a 7-year old female diagnosed with medulloblastoma who underwent excision of tumor and VPS insertion, died of intracranial bleeding in the course of treatment for *Acinetobacter baumannii* MDRO ventriculitis with IVT colistin. The intracranial bleed was determined to have occurred as a complication of the underlying condition, and was not related to the treatment of the infection. The patient was on day 10 of IVT colistin at the time of demise; CSF cultures were already negative and other CSF parameters were improving. One patient, a 17-year old male diagnosed with mixed germ cell tumor with tumor bleed, underwent VPS insertion then developed *Klebsiella pneumoniae* MDRO ventriculitis. This patient was brought home per request of the family after 6 days of IVT colistin. Clinical improvement and resolution of infection were not documented in this patient, despite having the shortest time to initiation of IVT from the time of diagnosis of infection (1 day).

CONCLUSION

Ventriculitis caused by drug-resistant organisms is an emerging concern. Optimal therapy is not yet established and experience with IVT in this condition is limited, but IVT may be considered as a treatment option for ventriculitis caused by drug-resistant organisms. Well-designed, large-scale prospective studies are needed to determine the most effective IVT regimen, recognize adverse events, and monitor long-term patient outcomes.

REFERENCES

1. Sherrod BA, Arynchyna AA, Johnston JM, Rozzelle CJ, Blount JP, Oakes J, et al. Risk factors for surgical site infection following nonshunt pediatric neurosurgery: a review of 9296 procedures from a national database and comparison with a single-center experience. Journal of Neurosurgery: Pediatrics. 2017 April; 19(4). Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5450913/pdf/nihms860363.pdf DOI: 10.3171/2016.11.PEDS16454.
2. Drew RJ, Cole TS, Lee MK, Paulus S, Mallucci CL, Riordan A. Antimicrobial treatment options for neurosurgical ventricular shunt infections in children from 1993 to 2012: a systematic review. Child's Nervous System. 2013 December. Available from:https://www.ncbi.nlm.nih.gov/pubmed/24322604 DOI: 10.1007/s00381-013-2333-z.
3. CDC/NHSN. CDC/NHSN Surveillance definitions for specific types of infections. National Healthcare Safety Network (NHSN) Patient Safety Component Manual. 2018 January. Available from:https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf.
4. Humphreys H, Jenks PJ. Surveillance and management of ventriculitis following neurosurgery. Journal of Hospital Infection. 2015. Available from: https://www.journalofhospitalinfection.com/article/S0195-6701(15)00051-1/fulltext DOI: 10.1016/j.jhin.2014.12.019.
5. Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Scheld WM, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clinical

Infectious Diseases. 2017; 64(6): p. e34-e65. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5848239/pdf/ciw861.pdf DOI:10.1093/cid/ciw861.

6. Beer R, Lackner P, Pfausler B, Schmutzhard E. Nosocomial ventriculitis and meningitis in neurocritical care patients. Journal of Neurology. 2008; 255. Available from:https://link.springer.com/article/10.1007%2Fs00415-008-0059-8 DOI: 10.1007/s00415-008-0059-8.
7. Chen K, Wu Y, Wang Q, Wang J, Li X, Zhao Z, et al. The methodology and pharmacokinetics study of intraventricular administration of vancomycin in patients with intracranial infections after craniotomy. Journal of Critical Care. 2015; 30. Available from:https://www.sciencedirect.com/science/article/pii/S0883944114004031?via%3Dihub DOI: 10.1016/j.jcrc.2014.09.020.
8. Bargiacchi O, Rossati A, Car P, Brustia D, Brondolo R, Rosa F, et al. Intrathecal/intraventricular colistin in external ventricular device-related infections by multi-drug resistant Gram negative bacteria: case reports and review. Infection. 2014 April. Available from:https://link.springer.com/article/10.1007%2Fs15010-014-0618-0 DOI: 10.1007/s15010-014-0618-0.
9. Karaiskos I, Galani L, Baziaka F, Katsouda E, Ioannidis I, Andreou A, et al. Successful treatment of extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis with intraventricular colistin after application of a loading dose: a case series. International Journal of Antimicrobial Agents. 2013 February; 41. Available from:https://www.ijaaonline.com/article/S0924-8579(13)00070-8/fulltext DOI:10.1016/j.ijantimicag.2013.02.010.
10. Stenehjem E, Armstrong WS. Central nervous system device infections. Infectious Disease Clinics of North America. 2012; 26: p. 89-110. Available from: https://www.sciencedirect.com/science/article/pii/S089155201100081X?via%3Dihub DOI:10.1016/j.idc.2011.09.006.
11. 1Patel JA, Pacheco SM, Postelnick M, Sutton S. Prolonged triple therapy for persistent multidrug-resistant Acinetobacter baumannii ventriculitis. American Society of Health-System Pharmacists. 2011 August; 68. Available from:http://www.ajhp.org/content/68/16/1527.long?sso-checked=true DOI: 10.2146/ajhp100234.
12. Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. Pediatric Drugs. 2013; 15. Available from:https://link.springer.com/article/10.1007%2Fs40272-013-0017-5 DOI: 10.1007/s40272-013-0017-5.
13. Kumta N, Roberts JA, Lipman J, Cotta MO. Antibiotic distribution into cerebrospinal fluid: Can dosing safely account for drug and disease factors in the treatment of ventriculostomy-associated infections? Clinical Pharmacokinetics. 2017. Available from: https://link.springer.com/article/10.1007%2Fs40262-017-0588-3 DOI: 10.1007/s40262-017-0588-3.
14. Karaiskos I, Galani L, Baziaka F, Giamarellou H. Intraventricular and intrathecal colistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis: a literature review. International Journal of Antimicrobial Agents. 2013. Available from: https://www.ijaaonline.com/article/S0924-8579(13)00054-X/fulltext DOI: 10.1016/j.ijantimicag.2013.02.006.
15. Mrowczynski OD, Langan ST, Rizk EB. Intra-cerebrospinal fluid antibiotics to treat central nervous system infections: A review and update. Clinical Neurology and Neurosurgery. 2018 May; 170: p. 140-158. Available from:https://www.sciencedirect.com/science/article/pii/S0303846718301896?via%3Dihub DOI: 10.1016/j.clineuro.2018.05.007.
16. James HE, Bradley JS. Aggressive management of shunt infection: Combined intravenous and intraventricular antibiotic therapy for twelve or less days. Pediatric Neurosurgery. 2008 January; 44: p. 104-111. Available from:https://www.karger.com/Article/Abstract/113111 DOI: 10.1159/000113111.
17. Cascio A, Mezzatesta ML, Odierna A, Di Bernardo F, Barberi G, Iaria C, et al. Extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacter cloacae ventriculitis successfully treated with intraventricular colistin. International Journal of Infectious Diseases. 2014; 20: p. 66-67. Available from:https://linkinghub.elsevier.com/retrieve/pii/S1201-9712(13)00375-5 DOI:10.1016/j.ijid.2013.11.012.
18. James HE, Bradley JS. Management of complicated shunt infections: a clinical report. Journal of Neurosurgery: Pediatrics. 2008; 1. Available from: https://thejns.org/pediatrics/view/journals/jneurosurg-pediatr/1/3/article p223.xml?rfr_dat=cr_pub=pubmed&rfr_id=ori:rid:crossref.org&url_ver=Z39.88-2003 DOI:10.3171/PED/2008/1/3/223.

19. Arnell K, Enblad P, Wester T, Sjolin J. Treatment of cerebrospinal fluid shunt infections in children using systemic and intraventricular antibiotic therapy in combination with externalization of the ventricular catheter: efficacy in 34 consecutively treated infections. Journal of Neurosurgery: Pediatrics. 2007; 107. Available from:https://thejns.org/pediatrics/view/journals/j-neurosurg-pediatr/107/3/article-p213.xml?rfr_dat=cr_pub=pubmed&rfr_id=ori:rid:crossref.org&url_ver=Z39.88-2003 DOI: 10.3171/PED-07/09/213.
20. Jaspan HB, Brothers AW, Campbell AJP, McGuire JK, Browd SR, Manley TJ, et al. Multidrug-resistant Enterococcus faecium meningitis in a toddler: Characterization of the organism and successful treatment with intraventricular daptomycin and intravenous tigecycline. Pediatric Infectious Disease Journal. 2010 April; 29(4): p. 379-381. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4778705/pdf/nihms759305.pdf DOI:10.1097/INF.0b013e3181c806d8.
21. Remes F, Tomáš R, Jindrák V, Vaniš V, Šetlík M. Intraventricular and lumbar intrathecal administration of antibiotics in postneurosurgical patients with meningitis and/or ventriculitis in a serious clinical state. Journal of Neurosurgery. 2013 August. Available from:https://thejns.org/view/journals/j-neurosurg/119/6/article-p1596.xml DOI:10.3171/2013.6.JNS122126.
22. Turgut M, Alabaz D, Kocabas E, Erman T, Alhan E, Aksaray N. Cerebrospinal fluid shunt infections in children. Pediatric Neurosurgery. 2005; 41: p. 131-136. Available from:https://www.karger.com/Article/Abstract/85869 DOI: 10.1159/000085869.
23. Shah SS, Ohlsson A, Shah VS. Intraventricular antibiotics for bacterial meningitis in neonates. Cochrane Database of Systematic Reviews. 2012;(7). Available from:https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004496.pub3/full DOI: 10.1002/14651858.CD004496.pub3.
24. Mehar V, Zade P, Joshi M, Rajput N, Bhatambar G. Neonatal ventriculitis with multi drug resistant Acinetobacter baumanii: A case report and review of literature. Pediatrics and Therapeutics. 2012; 2(5). Available from:https://www.omicsonline.org/neonatal-ventriculitis-with-multi-drug-resistant-acinetobactor-baumanii-a-case-report-and-review-of-literature-2161-0665.1000131.php?aid=7714 DOI: 10.4172/2161-0665.1000131.
25. Antimicrobial Resistance Surveillance Reference Laboratory, Department of Health Research Institute of Tropical Medicine. Antimicrobial Resistance Surveillance Program (ARSP) 2017 Data Summary Report. 2017. Available from:http://arsp.com.ph/wpcontent/uploads/2018/07/2017_annual_report_summary.pdf.
26. Tangden T, Enblad P, Ullberg M, Sjolin J. Neurosurgical gram-negative bacillary ventriculitis and meningitis: A retrospective study evaluating the efficacy of intraventricular gentamicin therapy in 31 consecutive cases. Clinical Infectious Diseases. 2011; 52(11): p. 1310-1316. Available from:https://academic.oup.com/cid/article/52/11/1310/408246 DOI: 10.1093/cid/cir197.
27. Berning SE, Cherry TA, Iseman MD. Novel treatment of meningitis caused by multidrug-resistant Mycobacterium tuberculosis with intrathecal Levofloxacin and Amikacin: Case report. Clinical Infectious Diseases. 2001; 32: p. 643–6. Available from:https://academic.oup.com/cid/article/32/4/643/466248 DOI: 10.1086/318698.
28. Wang JH, Lin PC, Chou CH, Ho CM, Lin KH, Tsai CT, et al. Intraventricular antimicrobial therapy in postneurosurgical Gram-negative bacillary meningitis or ventriculitis: A hospital-based retrospective study. Journal of Microbiology, Immunology and Infection. 2014; 47: p. 204-210. Available from:https://ejmii.com/retrieve/pii/S1684118212002046 DOI: 10.1016/j.jmii.2012.08.028.
29. Forgacs P, Geyer C, Freidberg S. Characterization of chemical meningitis after neurosurgery. Clinical Infectious Diseases. 2001; 32(2): p. 179-185. Available from:https://academic.oup.com/cid/article/32/2/179/319157 DOI: 10.1086/318471.
30. Brown E, de Louvois J, Bayston R, Lees P, Pople I. Distinguishing between chemical and bacterial meningitis in patients who have undergone neurosurgery [Letters to the editor]. Clinical Infectious Diseases. 2002; 34. Available from: https://academic.oup.com/cid/article-pdf/34/4/556/23993107/34-4-556.pdf.