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Central Nervous System Device Infections

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Abstract Nosocomial meningitis can occur in association with central nervous system (CNS) devices such as cerebrospinal shunts or drains, intrathecal pumps, and deep brain stimulators and carry substantial morbidity and mortality. Diagnosing and treating these infections may be challenging to physicians as cerebrospinal fluid cultures may be negative due to previous antibiotic therapy and cerebrospinal abnormalities may be secondary to the primary neurosurgical issue that prompted the placement of the CNS device (e.g., "chemical meningitis" due to intracranial hemorrhage). Besides antibiotic therapy given intravenously and sometimes intrathecally, removal of the device with repeat cultures prior to re-implantation is key in achieving successful outcomes.

Keywords Cerebrospinal fluid shunt or drains · Intrathecal pumps · Deep brain stimulators · Nosocomial meningitis

Introduction

Nosocomial meningitis can occur with a device infection (e.g., cerebrospinal fluid (CSF) shunts or drains, intrathecal pumps, deep brain stimulator), after a procedure (e.g., craniotomy, spinal anesthesia, lumbar puncture) or after head trauma with a CSF leak [1•]. The epidemiology of bacterial meningitis in the USA has shifted with the implementation of the conjugate vaccines [2, 3••]. The annual rates in the USA in 2010 of two community-acquired meningeal pathogens (*Neisseria meningitides* and *Haemophilus influenzae* type b) are now lower than the rates of the two most common nosocomial pathogens (e.g., Staphylococcus, Gram-negative bacteria) [3••]. In this review, we will focus on the diagnosis and management of nosocomial meningitis that occur in association with the most common device infections.

This article is part of the Topical Collection on *Central Nervous System Infections*

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Epidemiology

The most common central nervous system (CNS) device-related infections are due to CSF shunts or drains. Cerebrospinal fluid shunts and drains are catheters that are placed in the therapy of hydrocephalus or in conditions associated with intracranial pressure. CSF shunts are permanent catheters with a proximal end installed in the cerebral ventricle or in the lumbar subarachnoid space with the distal ending in the peritoneal or pleural space or in the atrium [4]. The incidence of infection of a CSF shunt varies widely (2.2–41 %) with the most important recognized risk factors being prematurity, intraventricular hemorrhage, previous shunt infection or revision, neurosurgeon's experience, perforated surgical gloves, use a neuroendoscope, longer duration of the procedure, and shaving of skin [5•]. CSF drains are temporary catheters with the proximal end in the cerebral ventricle or in the lumbar subarachnoid space (lumbar drain). External ventricular drains are most useful for temporary management in patients with elevated intracranial pressure secondary to acute hydrocephalus caused by intracranial hemorrhage, neoplasms obstructing the CSF circulation, or trauma. The distal end of the catheter is connected to a collecting system, which has a drip chamber, ports for measuring intracranial pressure, sampling and injection ports (used to obtain CSF and inject

medications), and a collection bag [4]. Drains are usually placed via one incision, and then tunneled a distance subcutaneously before exiting through the skin. In patients with external ventricular drains, the incidence of ventriculitis has ranged from 0 to 22 %. A recent meta-analysis of 35 studies of 752 ventriculostomy-associated infections reported an incidence rate of ventriculitis of 11.4 per 1000 catheter days (95 % CI 9.3 to 13.5) [6].

Intrathecal infusion pumps are implanted to treat intractable spasticity with baclofen or to treat intractable pain with opiates [7–10]. The catheter is inserted intrathecally in the lumbar region with the pump being placed either subcutaneously or below the fascia in the abdomen. The incidence of infection varies from 3.6 % in pumps placed underneath the fascia up to 20 % in those pumps placed subcutaneously [7]. The majority of the infectious complications are surgical wound infections with a minority of patients developing nosocomial meningitis [7–10].

Deep brain stimulators are used to treat Parkinson's disease, intractable seizures, essential tremor, dystonia, and obsessive-compulsive disorder [11, 12]. The stimulator has a generator that is placed in the infra-articular area with a connector and an intracranial lead [11]. All three components of the stimulator may become infected with an incidence rate that varies from 0 to 15 %. Two recent studies show an incidence rate of infectious complications to be 5–6 % with approximately 50 % of them developing in the first 30 days after implantation [11, 12]. The most common organisms causing infections are staphylococci with the majority of patients requiring partial or complete removal of the device.

Diagnosis

The diagnosis of a CNS device infection may be challenging to clinicians as they can have different clinical presentations. A patient with a cerebrospinal fluid (CSF) shunt may present with fever, headache, nausea or vomiting, altered level of consciousness, pain and/or redness over the shunt tubing, localized signs of infection at the distal site of the shunt (e.g., peritonitis or pleuritis), and bacteremia in a patient with a ventriculoatrial shunt or with shunt malfunction [1•, 4, 5•, 6]. Intrathecal infusion pumps and deep brain stimulators may also present with signs of surgical wound infections [7–12]. In January 2015, the Centers for Diseases Control and Prevention (CDC) revised its reporting definition of nosocomial meningitis or ventriculitis; see Table 1 [13]. This definition has some limitations as some CSF and neurological abnormalities may be influenced by the primary neurosurgical issue (e.g., "chemical meningitis" associated with intraventricular hemorrhage), CSF Gram stains and cultures may be negative especially in the setting of previous antibiotic exposure, and some fastidious pathogens such as *Propionibacterium acnes* may take up to 10 days to grow or require special media. Furthermore, this definition does not include patients with ventriculoperitoneal or ventriculopleural shunts that present with abdominal pain or pleuritis symptoms, respectively.

Table 1 Centers for Disease Control and Prevention definition of health care associated ventriculitis or meningitis 2015 [13] [adapted from the CDC website on meningitis]

Meningitis or ventriculitis must meet at least one of the following criteria:

1. Patient has organisms identified from cerebrospinal fluid (CSF) by a culture or non-culture-based microbiologic testing method, which is performed for purposes of clinical diagnosis or treatment (e.g., not Active Surveillance Culture/Testing (ASC/AST)).
2. Patient has at least two of the following:
   - Fever (>38.0 °C) or headache[a]
   - Meningeal sign (S)[b]
   - Cranial nerve sign (S)[b]

And at least one of the following:

1. Increased white cells, elevated protein, and decreased glucose in CSF
2. Organisms seen on Gram stain of CSF
3. Organisms identified from blood by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (e.g., not ASC/AST)
4. Diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism

[a] In patients ≤1 year of age instead of headache assess for hypothermia (<36C), apnea, bradycardia, or irritability

[b] With no other recognized cause

A recent large study of 215 adults and children with health care-associated meningitis and ventriculitis using the updated 2015 CDC definition demonstrated that approximately 50 % of patients are treated with antibiotics before the lumbar puncture and also 50 % had negative CSF cultures with only 20 % having a positive Gram stain [14•]. In attempt to improve the diagnosis of nosocomial meningitis in patients with negative CSF Gram stain and cultures, studies have evaluated a cell index, an increasing CSF cell count, CSF lactate level, CSF procalcitonin, and polymerase chain reaction (PCR) [15–18, 19•]. The cell index is a ratio of CSF WBC/RBC to the serum WBC/RBC that was tested in 13 patients with ventriculostomies; 7 of them developed infections associated with an increasing cell index [15]. An increasing CSF WBC compared to the initial CSF when the drain was initially placed was the most reliable parameter in routine CSF studies in a study of 48 patients with ventricular drain infections [16]. Both the cell index and the increasing CSF WBC determinations require repeated manipulation of the ventricular device to access CSF that could further increase the risk of acquiring an infection [15, 16]. A CSF lactate level >4 has been proposed in nosocomial meningitis to differentiate bacterial meningitis from aseptic meningitis. In a recent study of 79 patients with suspected nosocomial meningitis, an elevated lactate had a high sensitivity (97 %) and specificity (78 %) and was better

than CSF glucose, protein, and neutrophilic pleocytosis in identifying patients with proven bacterial meningitis [17]. Limitations of using the CSF lactate levels as the sole criterion to identify patients with nosocomial meningitis include the high proportion of antibiotic exposure before the CSF analysis rendering bacterial cultures negative, the wide range of values in patients with proven health care-associated meningitis (1–22.8 mmol/L) and that only ~50 % of patients actually get a CSF lactate drawn [14•]. A procalcitonin either alone (≥0.075 ng mL) or in combination with a lactate (≥3.45 mmol/L) has also been used to differentiate bacterial from aseptic meningitis [18]. Lastly, broad-range PCR is an exciting tool that has detected pathogens in patients with negative CSF Gram stains and cultures but data is currently limited in nosocomial meningitis [19•].

Management

Empirical management of suspected CNS device-associated infection includes imaging and empiric antibiotic therapy for the most common pathogens [1•, 4]. Cranial imaging is indicated in suspected CSF shunt infections to assess the presence of hydrocephalus, hemorrhage, and suppurative intracranial infections or to assess shunt malfunction [4]. In patients with ventriculoperitoneal (VP) shunts with abdominal pain, a computed tomography (CT) of the abdomen may detect CSF loculations at the distal shunt. The empirical antimicrobial therapy for a CNS device infection should include vancomycin and a beta-lactam with anti-pseudomonal activity (e.g., cefepime or meropenem) (see Table 2) [1•, 4, 5•, 6]. In patients with vancomycin allergy or intolerance, linezolid, ceftaroline, daptomycin, or trimethoprim-sulfamethoxazole could be utilized and in patients with severe beta lactam allergies, aztreonam or ciprofloxacin may be used [1•, 20, 21]. Once susceptibilities are obtained, antibiotic therapy should be modified accordingly and continued for a total of 10–14 days [1•, 4, 22]. In suspected CNS device infections due to Candida, liposomal amphotericin B with or without 5-flucytosine should be used initially [23].

Removal of the infected CSF shunt, external ventricular drain, intrathecal infusion pump, or deep brain stimulator with re-implantation of the device once repeat negative CSF cultures have been documented is key in the successful treatment of these infections [1•, 4, 5•, 6, 8–12]. In CSF shunt infections, lack of removal of the shunt is associated with a successful outcome only in 35 % of patients with high mortality, immediate shunt removal and reinsertion in 65–75 %, and shunt removal with a delayed reimplementation in more than 85 % [5•]. The high failure rate seen with shunt retention is thought to be due to the production of biofilms by the bacteria that protect them from antimicrobial therapy and host immune defense [4, 5•].

In patients that are not responding clinically or microbiologically to intravenous antibiotic therapy, intraventricular antimicrobial therapy should be considered [1•, 4, 5•, 24••, 25]. There are no clinical trial data evaluating the efficacy of intraventricular therapy but observational studies have shown promising results especially in a subset of patients with nosocomial meningitis such as those caused by multi-drug-resistant *Acinetobacter baumanii*. In a review of 83 episodes of *A. baumanni* ventriculitis and meningitis, a successful outcome was seen in 89 % of patients with the combination of intravenous and intrathecal polymyxin E with 11 % of patients developing reversible chemical meningitis [26]. The endpoints of intraventricular antibiotics administration should be a >10–20-fold ratio between the CSF trough concentration of the antibiotic and the minimum inhibiting concentration (MIC) of the organism, clinical improvement, and a negative CSF culture [4].

Outcomes

Patients with nosocomial meningitis have high rates of adverse clinical outcomes. Only two studies have evaluated prognostic factors on multivariable analyses. A study of 91 patients with nosocomial meningitis demonstrated a mortality rate of 16.5 %%; risk factors for death included lack of removal of the catheter and septic shock [27]. In the largest study to date evaluating prognosis in 215 adults and children, an adverse clinical outcome was observed in 77.7 % of patients as defined by the Glasgow outcome scale [14•]. Logistic regression analysis identified aged ≥45 years, abnormal neurological exam, and mechanical ventilation as independent risk factors for an adverse outcome. The main limitations of these studies are that the primary neurosurgical condition (e.g., intracranial hemorrhage, tumors, head trauma) could also contribute to the high rates of adverse clinical outcomes.

Prevention

Prevention of CNS device infections is done by perioperative prophylactic antimicrobial therapy, implementation of a standardized protocol for inserting CSF shunts and drains and by using of antimicrobial-impregnated shunts or drains [28–31, 32••, 33–35]. A meta-analysis demonstrated that antimicrobial prophylaxis given before incision and continued for 24 h after placement of CSF shunts decreases postoperative infection (OR 0.51; 95 % CI 0.36–0.73) [33]. Adherence to protocols for insertion of CSF shunts has also shown to decrease infectious complications [28–31]. Four studies have shown a significant decrease in CSF shunt infection rates after the implementation of a protocol even though the compliance varied

Table 2 Intravenous and intraventricular dosing of the most commonly used antimicrobial agents in the treatment of central nervous system device infections

Antimicrobial agent	Intravenous (pediatric)	Intravenous (adult)	Intraventricular[a]
Amikacin	7.5 mg/kg q 8 h	5 mg/kg q 8 h	30 mg per day
Amphotericin B-lipid formulation	3–5 mg/kg q 24 h	3–5 mg/kg q 24 h	0.1–1 mg per day
Ampicillin	100 mg/kg q 6 h	2 g q 4 h	NR
Aztreonam	40 mg/kg q 8 h	2 g q 6 h or q 8 h	NR
Cefepime	50 mg/kg q 8 h	2 g q 8 h	NR
Ceftazidime	50 mg/kg q 8 h	2 g q 8 h	NR
Ceftriaxone	50 mg/kg q 12 h	2 g q 12 h	NR
Ciprofloxacin	10 mg/kg q 8 h	400 mg q 8 h or q 12 h	NR
Colistin	2.5 mg/kg q 12 h	2.5 mg/kg q 12 h	10 mg per day
Daptomycin	6–10 mg/kg q 12 h	6–10 mg/kg q 24 h	2–5 mg per day
Fluconazole	12 mg/kg q 24 h	400–800 mg q 24 h	NR
Gentamicin	2.5 mg/kg q 8 h	5 mg/kg q 24 h	1–8 mg per day
Meropenem	40 mg/kg q 8 h	2 g q 8 h	NR
Nafcillin	50 mg/kg q 4 h	2 g q 4 h	NR
Penicillin G	75,000 units/kg q 6 h	4 million units q 6 h	NR
Rifampin	20 mg/kg q 24 h	600 mg q 24 h	NR
Tobramycin	2.5 mg/kg q 8 h	5 mg/kg q 24 h	5–20 mg per day
Trimethoprim-sulfamethoxazole	5 mg/kg q6h or q 12 h	5 mg/kg q 6 h o q12h	NR
Vancomycin	15 mg/kg q6 h	15–20 mg/kg q 8 h or q 12 h	5–20 mg per day

Dosing with normal renal and hepatic function

NR not reported

[a] Dosing should be adjusted by obtain CSF trough concentration of the drug divided by the minimum inhibitory concentration (MIC) of the pathogen; a ratio of >10–20 is desired for maximal bactericidal activity

and errors were documented frequently [28–31]. Some of the components of the protocols included positioning the patient head away from the main door, hair clipping, removal of dirt and adhesive materials, applying chlorhexidine to the surgical field, scrubbing hands with iodine or chlorhexidine, using double gloves, antibiotic prophylaxis, injection of antibiotics into the shunt reservoir, minimizing of implant and skin edge manipulation, reducing traffic in the operating room, performing the procedure first in the morning, and avoiding CSF leaks. Antimicrobial-impregnated shunts and drains use either minocycline or clindamycin, combined with rifampin and can decrease nosocomial meningitis (RR 0.37; $P < 0.0001$) [34] and hospital costs [35]. Lastly, as the incidence of nosocomial meningitis increases with catheter duration, prompt removal of the ventricular drain is recommended when no longer needed [4, 5•, 31].

Conclusion

Despite effective preventative and effective treatment strategies, nosocomial meningitis due to CNS device infections continues to occur with significant neurological morbidity and mortality. The differentiation between true infection and chemical meningitis remains a challenge to physicians due to the high proportion of antibiotic use before CSF studies are done. Further studies should be done to delineate the diagnostic accuracy of a CSF lactate level, procalcitonin, and PCR in this syndrome.

Compliance with Ethical Standards

Conflict of Interest Dr Habun declares he has no conflicts of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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