Cerebrospinal Fluid Shunt Infections

Tamara D. Simon, MD, MSPH[a,b,*], Joshua K. Schaffzin, MD, PhD[c], Stacey Podkovik, DO[d], Paul Hodor, PhD[e]

KEYWORDS

• Cerebrospinal fluid • Shunt • Infection • Prevention • Treatment

KEY POINTS

- Cerebrospinal fluid (CSF) shunt infections are a particularly challenging clinical problem. Despite aggressive treatment of 2 surgeries and prolonged intravenous antibiotics, reinfection rates range from 20% to 25%.
- Staphylococcal species, especially coagulase-negative *Staphylococcus* and *Staphylococcus aureus,* account for almost two-thirds of all shunt infections.
- There is no standard clinical definition of a shunt infection, although a positive CSF culture in a patient with any type of shunt is generally accepted as sufficient evidence for surgical intervention and antimicrobial treatment.
- Management strategies are recommended in the 2017 Infectious Diseases Society of America guidelines.
- While prevention efforts have reduced infection rates, dilemmas in optimizing treatment remain. Ongoing research to further elucidate the mechanisms of shunt infection may also result in substantial advancements in care.

Cerebrospinal fluid (CSF) shunts are the predominant mode of therapy for children with hydrocephalus. Common causes of hydrocephalus in children include intraventricular hemorrhage, myelomeningocele, central nervous system (CNS) tumors, aqueductal stenosis, communicating hydrocephalus, head injury, and infections. The shunt apparatus diverts CSF away from the ventricles, preventing increases in intracranial pressure that may lead to neurologic sequelae. The typical CSF shunt has a proximal portion that enters the CSF space, an intermediate reservoir that lies outside the skull but underneath the skin, and a distal portion that terminates in either the peritoneal

[a] Division of Hospital Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA; [b] Department of Pediatrics, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; [c] Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; [d] Department of Neurological Surgery, Riverside University Health Sciences Medical Center, Riverside, CA, USA; [e] Aurynia, LLC, Seattle, Washington, USA
* Corresponding author. Children's Hospital Los Angeles, 4650 Sunset Boulevard, MS 94, Los Angeles, CA 90027.
E-mail address: tsimon@chla.usc.edu

Infect Dis Clin N Am 38 (2024) 757–775
https://doi.org/10.1016/j.idc.2024.07.008 **id.theclinics.com**

(ventriculoperitoneal [VP] shunt), vascular (ventriculoatrial [VA] shunt), or pleural space (ventriculopleural shunt).

CSF shunt placement has been the mainstay of hydrocephalus treatment of over 60 years.[1] CSF shunts allow children with congenital hydrocephalus to survive infancy and allow children with acquired hydrocephalus to avoid further brain injury. Despite their benefits, CSF shunts can cause new and chronic surgical and medical problems. Mechanical malfunction is frequent, and 60% of shunts require surgical revision within 4 years.[2–4] With each subsequent surgery, the risk of CSF shunt infection increases.[5–7]

CSF shunt infections are a particularly challenging clinical problem. Bacterial[8–11] (and occasionally fungal[12]) pathogens are responsible, and it is believed that in most instances, organisms are introduced onto the shunt at the time of surgery. Infections usually occur within 6 months of previous shunt surgery.[5] Because these pathogens adhere to the shunt itself, treatment requires a minimum of 2 surgeries to remove and replace the infected CSF shunt, and prolonged intravenous antibiotic (or antifungal) administration between the 2 surgeries.[13–15] Despite this aggressive treatment, reinfection rates range from 20% to 25%.[13,14,16] Furthermore, CSF shunt infection negatively impacts neurocognitive outcomes[17] and quality of life.[18] Finally, the infection can result in death.[17,19–23] CSF shunt infections are associated with substantial morbidity.

EPIDEMIOLOGY

The volume of pediatric CSF shunt surgeries is substantial in the United States, accounting for approximately 20,000 hospital admissions each year, of which about 4,500 are for initial CSF shunt placement and about 10,000 for CSF shunt revision.[24] CSF shunt surgeries are associated with the second highest condition-specific unadjusted 30 day readmission rate at children's hospitals, at 18.1%. Of CSF shunt surgery readmissions, 72% result in repeat CSF shunt surgery.[25] Infections account for over 2,000 hospital admissions each year and are associated with substantial resource utilization, including approximately 55,000 hospital days (mean of 14.2–15.1 days per admission) and up to $250 million in charges (mean of $46–62,000 per admission).[24] CSF shunt infections are associated with substantial resource utilization and costs.

Infection develops in 5% to 15% of all CSF shunts at some point in the life of the shunt.[26,27] The use of different definitions across studies makes it challenging to determine the true incidence of CSF shunt infections. The most common definition, put forth by the Centers for Disease Control and Prevention and the National Healthcare Safety Network, addresses postoperative (surgical site) infection and does not attempt to address shunt infection specifically.[28] Other definitions, such as that put forth by the Hydrocephalus Clinical Research Network (HCRN),[29] focus solely on CSF shunts and the various ways infections are diagnosed.

Most infections occur within 6 months of initial shunt placement.[27,30] Factors associated with CSF shunt infections include a recent shunt insertion or revision, premature birth, young age, neuroendoscope use during shunt insertion, and prior shunt infection.[5–7,31–33] Insertion of a shunt after a previous shunt infection is associated with a 4 fold increase in the risk of shunt infection. A single revision surgery is associated with a 3 to 4 fold higher risk of infection, and 2 or more revision surgeries are associated with a 6 to 13 fold higher risk of infection.[6,7]

MICROBIOLOGY

The etiologic agents associated with CSF shunt infections are shown in **Box 1**.[8] Staphylococcal species, especially coagulase-negative *Staphylococcus* (CoNS) and

Staphylococcus aureus, account for almost two-thirds of all shunt infections.[33,34] The remaining infections are produced by a wide variety of organisms. *Cutibacterium acnes* is a less common etiologic agent that generally causes low-grade, indolent infections.[35,36] *C acnes* infection may be more likely to be detected with use of anaerobic culture media and prolonged (up to 10 or more days) incubation times, as recommended by the Infectious Diseases Society of America (IDSA).[17] *Candida* species, while a rare cause of CSF shunt infection, should be considered in premature infants and other immunocompromised patients as well as in those patients receiving parenteral nutrition or prolonged corticosteroid therapy.[12] Pathogens identified in previous shunt infections may be detected in subsequent infections.

Four mechanisms of shunt infection have been postulated[36]:

1. *Local inoculation of bacteria at the time of surgery*: This is the most common mechanism of infection, and usually manifests within several weeks of the operation.
2. *Bacterial entry through breakdown of skin overlying the shunt or insertion of a needle into the shunt reservoir to sample CSF*: Bacterial entry following breakdown of skin overlying the shunt may occur if the incision fails to properly heal or if the patient disrupts the healing process by scratching the open wound. This scenario is more likely to yield gram-positive bacteria. Pressure from the shunt (thin infant skin or repeatedly operated upon skin) internally or externally (immobility in infants or in neurologically impaired children) can cause ulceration and direct access for bacteria to the shunt. Accessing the shunt by needle puncture can introduce colonizing skin bacteria into the shunt system should a breach in sterile technique occur.
3. *Hematogenous shunt inoculation (for VA shunts)*: Children with shunts in their vascular system (eg, VA shunts) are continually at risk of infection from bacteremia with retrograde spread to the ventricles.
4. *Retrograde infection from the distal end of the shunt (for VP and ventriculopleural shunts)*: Retrograde infection from the distal end of a VP shunt as a consequence of viscus (eg, bowel, gallbladder) perforation or bacterial translocation to the peritoneum may lead to distal catheter contamination. Additionally, a proteinaceous CSF-filled pseudocyst can develop at the distal shunt tip. Gram-negative bacteria are most commonly isolated when the distal VP catheter is involved.

Box 1
Microbiology of cerebrospinal fluid shunt infections

Common
- Coagulase-negative *Staphylococci*
- *Staphylococcus aureus*
- Enteric gram-negative bacilli[a]

Less common
- *Cutibacterium acnes*
- Viridans group *Streptococci*

Rare
- Other streptococci[b]
- *Enterococcus* spp.
- *Candida* spp.
- *Corynebacterium* spp.

[a]Usually *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, and *Proteus* species.

[b]Usually group B Streptococcus, *Streptococcus pyogenes*, or *Streptococcus pneumoniae*.

CLINICAL CARE OF CEREBROSPINAL FLUID SHUNT INFECTION

History and Physical Examination

The patient with a ventricular shunt requires a review of the symptoms and signs associated with increased intracranial pressure and CNS infection. The most common clinical symptoms of shunt infection are fever, headache, nausea, and lethargy (**Box 2**).[26,33] Historic information obtained from patients or their caregivers should include timing and indications for shunt placement, postoperative course, and history of shunt malfunction and/or infection. Asking what signs and symptoms were present at previous malfunction or infection events is often helpful since patients may present with similar signs and symptoms subsequently (**Table 1**).

Physical examination should include palpation of the skull and scalp, as well as the length of the subcutaneous shunt tubing, including burr hole(s) and all incision sites on the skull, neck, chest, and abdomen with inspection for signs of fluid accumulation or soft tissue infection such as erythema and tenderness to palpation. Attention should be directed toward swelling and fluctuance, which may represent CSF or a purulent fluid collection. In infants, the physical examination should include a measurement of head circumference and assessment of size and softness of the anterior fontanelle.

A complete neurologic examination should be performed, including cranial nerve assessment and fundoscopy to detect papilledema and optic atrophy that suggest elevated intracranial pressure. The neck should be palpated to detect cervical and posterior auricular adenopathy, which may occur with infections of the scalp or shunt insertion site.

Signs of meningitis such as meningismus and photophobia are less common because infected CSF from the ventricles may not communicate with CSF in the subarachnoid space. Children with infections caused by indolent organisms such as *C acnes* or CoNS may have an insidious course with few overt symptoms.

The clinical features of CSF shunt infection depend on the mechanism of infection, the causative pathogen, and the type of shunt. Shunt infection may occur with or without shunt malfunction. Signs and symptoms of *proximal* shunt infection are often those of shunt malfunction (ie, increased intracranial pressure or failure to drain properly). Shunt infection is confirmed as the cause for shunt malfunction in 3% to 8% of cases, although the true portion could be higher.[37] Proximal shunt infection may

Box 2
Clinical features associated with cerebrospinal fluid shunt infection

Systemic signs of infection
- Fever
- Headache
- Malaise
- Nausea
- Vomiting
- Irritability
- Lethargy or altered mental status
- Seizures
- Meningismus
- Paresis

Focal signs of infection
- Pain at distal site (ie, peritoneum) or wound
- Purulent drainage from wound site
- Inflammation (erythema, warmth, swelling) along subcutaneous course of the shunt

Table 1
Pertinent history and physical examination

Important Medical and Surgical History	
Indications for insertion	
Dates of insertion and revision(s)	
Medications and allergies	
History of prior shunt malfunction: symptoms, cause, and correction	
History of prior shunt infections: symptoms, organisms, and therapy	
Important Elements of the Physical Examination	
Head, Eye, Ear, Nose, Throat	Head circumference in infants Characteristics of fontanelles and position of sutures in infants Burr holes: size, number, location, and features (soft, tense, tender) Scalp infections
Neurologic	Papilledema, optic atrophy Pupil size and reactivity, extraocular motor function Mental status: alertness, orientation
Neck	Tenderness Meningismus Adenopathy
Abdomen	Tenderness Ascites Masses
Skin	Surgical incision site(s) Catheter length and connections: fluid collections or inflammation
Catheter	Position of reservoir, valve, distal catheter

present with external signs of local soft tissue inflammation such as focal swelling, pain, erythema, and purulent drainage from the incision site. Skin breakdown can lead to exposure of shunt material, which is considered a surface shunt infection.

Signs and symptoms of *distal* shunt infection depend on the location of the shunt tip and whether the internal lumen or the external surface is infected. Intraluminal infection of a VA shunt can result in bacteremia and systemic signs of toxicity, including fever, chills, and tachycardia. Rarely, compression of the reservoir or catheter track of an infected VA shunt can lead to intermittent bacteremia accompanied by fever and chills; this phenomenon has been referred to as the "shampoo clue" by some authors since some cases of VA shunt infection were suspected after inadvertent manipulation of the catheter track during hair washing caused fever and rigors.[38] Severe sepsis or septic shock is uncommon.

Intraluminal infection of a VP shunt usually produces signs of focal infection. Sepsis and shock can be seen if peritonitis occurs, although in such cases the shunt is infected incidentally. Abdominal pseudocysts develop as a consequence of clinical or subclinical infections that cause an inflammatory reaction around the catheter tip (**Fig. 1**). Pseudocysts complicate VP shunt placement in 0.7% to 4.5% of cases; usually as a late complication, occurring greater than 12 months after initial shunt placement.[39–41] The pseudocysts may grow quite large since the CSF encased within the pseudocyst cannot be resorbed by the peritoneal cavity although infected pseudocysts tend to be smaller, presumably because they cause symptoms earlier than noninfected pseudocysts. Among patients with abdominal pseudocysts, the abdominal symptoms

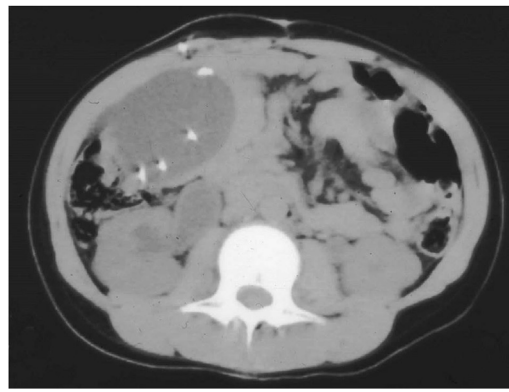

Fig. 1. Computed tomography of the abdomen reveals that the distal portion of the ventriculo-peritoneal catheter (the bright white area) is encased in a collection of cerebrospinal fluid in the peritoneal space.

typically precede CNS complaints such as lethargy, headache, and visual disturbances for several days or weeks.

If a VA shunt infection goes untreated for extended periods, deposition of antibody–antigen complexes in the renal glomeruli can occur and is termed "shunt nephritis." Shunt nephritis occurs in 5% to 15% of VA shunt infections and can be difficult to distinguish from other immunologic sequelae such as those due to bacterial endocarditis.

Differential Diagnosis

The differential diagnosis should focus on distinguishing shunt-related complications from other causes of headache, nausea, or altered mental status with fever. In addition to shunt-related infection, other acute infectious causes of headache include meningoencephalitis, brain abscess, sinusitis, orbital disease, and cranial neuralgias (eg, herpes zoster). Other causes include stroke, subarachnoid hemorrhage, hypoglycemia, hypertension, idiopathic intracranial hypertension, collagen vascular disease, and migraine headaches.

Shunt infection may be difficult to distinguish from other common febrile illnesses such as gastroenteritis (vomiting) or viral respiratory infection. Ruling out alternative causes such as viruses can help avoid missing a true shunt infection and an unnecessary shunt revision that will increase the risk of downstream morbidity.

Diagnosis

There is no standard clinical definition of a shunt infection, although a positive CSF culture in a patient with any type of shunt, and/or a positive blood culture in a patient with a VA shunt, is generally accepted as sufficient evidence for surgical intervention and antimicrobial treatment. In the absence of either result, other less reliable clinical parameters can be applied, including clinical signs or symptoms (see **Table 1**). Ultimately, the decision to intervene relies on the clinical suspicion of the care team, often involving discussion between the neurosurgeon and pediatrician and/or internist.

Cerebrospinal fluid studies

CSF collected from the shunt system should be sent for cell count, glucose, protein, Gram stain, and aerobic and anaerobic bacterial culture (**Box 3**).[42,43] A CSF fungal

Box 3
Diagnostic tests for patients with a cerebrospinal fluid shunt and suspected infection

Step 1: Detect shunt malfunction
1. Shunt series (radiographs of skull, neck, chest, and abdomen) to assess for disconnection or malposition
2. Computed tomography or MRI to evaluate ventricular size or other changes that suggest elevated intracranial pressure
3. Consider abdominal ultrasound (VP shunt) looking for pseudocyst and free fluid (small amount expected)

Step 2: Detect infection
1. Shunt "tap" (at the discretion of the neurosurgeon)
   - Gram stain
   - Aerobic and anaerobic culture
   - Cell count and differential
   - Glucose, protein
2. Blood cultures (especially with VA shunt)
3. If VA shunt nephritis suspected: urinalysis, serum C3 and C4 complement

culture should also be performed in premature infants, in children with other immunocompromising conditions, and in children with a history of fungal CNS or shunt infection.[12] CSF parameters are less reliable for diagnosis than those for meningitis. CSF pleocytosis alone is not diagnostic of infection. Mild-to-moderate pleocytosis (20–500 white blood cells/mm^3) also occurs as a consequence of postsurgical or foreign body (ie, shunt)-associated inflammation. Normal CSF parameters (including CSF white blood cell count) have been reported in 17% to 35% of children with VP shunt infections.[8,30,42] A mild CSF pleocytosis, low CSF glucose level (hypoglycorrhacchia), and elevated CSF protein may be present in cases of ventricular involvement.[8,30,42] Infections caused by indolent organisms such as *C acnes* may fail to induce a vigorous inflammatory response. White blood cell differentials, particularly CSF eosinophilia (>8% of total CSF white blood cell count), have poor specificity for shunt infection. CSF eosinophilia can be associated with CSF extravasation and blood in the CSF in the absence of infection.[44]

Ideally, fluid from the reservoir should be obtained by percutaneous aspiration under sterile conditions. Shunt CSF sampling should be performed by a neurosurgeon or a clinician with experience in performing this procedure. The potential complications of draining CSF directly from the shunt include bleeding at the puncture site, CSF leakage, mechanical damage to the valve, and introduction of infection. In addition, draining CSF too rapidly may cause intraventricular or subdural bleeding and damage to ventricular or cortical tissue. Bacteria are identified by Gram stain of CSF obtained from the reservoir in up to 80% of cases though the likelihood of a positive Gram stain (ie, bacteria are observed) depends on the causative organism. *S aureus* and aerobic gram-negative rods such as *Escherichia coli* typically have positive Gram stain results, while *C acnes*, CoNS, and viridans group streptococci are positive in less than 40% of cases.[8] Therefore, a negative Gram stain (ie, no bacteria identified) does not exclude the diagnosis of shunt infection. Although most bacteria causing shunt infections grow within 48 to 72 hours, anaerobic cultures should be held for up to 10 days since fastidious organisms such as *C acnes* may take longer to grow. Contamination and true infection cannot be readily differentiated when indolent bacteria are identified by culture in the context of normal CSF parameters. In such cases, infection should be strongly considered and shunt aspiration repeated; a positive culture with the same bacteria usually indicates true infection. If an infected patient is pretreated with antimicrobials, CSF cultures

may show no growth despite prolonged incubation. In such instances, clinical judgment and close observation along with repeat CSF cultures may be helpful.

Lumbar puncture tends to be less helpful to diagnose a shunt infection. Children requiring a CSF shunt often have impaired CSF flow and ventricular fluid may have little or no communication with the lumbar spinal fluid. Thus, CSF obtained by lumbar puncture may appear reassuring despite the presence of a shunt infection or ventriculitis. Nonetheless, isolation of bacteria from CSF obtained by lumbar puncture suggests CSF shunt infection in the appropriate context.

Other laboratory studies

Blood should be routinely obtained for culture from patients evaluated for suspected shunt infection. While a negative peripheral blood culture does not rule out a shunt infection, a positive blood culture often influences the choice of antimicrobial therapy. Among patients with confirmed VP shunt infection, blood cultures are positive in 20% to 30% of cases.[8,30] Peripheral cultures are more likely to be positive in patients with VA shunt infection, where blood cultures are positive in 90% of cases.[31,33]

Neuroimaging

Imaging studies, including radiographs of the skull, neck, chest, and abdomen (the "shunt series") and imaging to assess ventricle size (computed tomography [CT] or MRI of the head), should be performed as part of the routine evaluation of a child with a suspected CSF shunt malfunction or infection. Specific abnormalities that can be visualized on the shunt series include disconnection of the distal catheter, retraction of the distal catheter tip, and discontinuity near the proximal shunt bulb. Routine performance of shunt series has a low overall yield but on rare occasions detects abnormalities that are missed by CT.[45] Both CT and MRI of the head will detect increased ventricular size; this finding may reflect either increased intracranial pressure or hydrocephalous ex vacuo, a condition where the increased ventricle size reflects shrinkage of brain parenchyma rather than an increase in the intracranial pressure. Given the number of abnormalities that may be visible on CT scan, it is critical to review previous imaging to determine to what extent the current findings reflect an evolving process versus the patient's baseline. CT may not be sensitive enough to detect subtle size changes in patients who have undergone multiple shunt revisions because overtime the ventricular walls become less compliant, and intracranial pressure could increase without significant ventricular enlargement. Similarly, some patients are sensitive to small changes in intracranial pressure, referred to as shunt dependence. Such patients may become symptomatic without radiographic evidence of change in ventricular size.

Ventriculitis and meningitis can be visualized on CT and MRI as enhancement of the ventricular ependymal lining or cerebral cortical sulci.[46] In rare cases, subdural empyema or brain abscess may be the first indication of shunt infection. Radiologic imaging of other areas should be considered depending on the location of the distal catheter tip. CT or ultrasound of the abdomen may identify abdominal peritoneal pseudocysts at the distal portion of a VP shunt (see **Fig. 1**). Some free fluid in the peritoneal cavity is normal but larger amounts should raise concern for infection. Similarly, chest radiography can detect unexpectedly large pleural effusions associated with ventriculopleural shunt infection.

Management

A child with a ventricular shunt infection should be managed in consultation with neurosurgical and infectious diseases specialists. Treatment with intravenous antibiotics

with shunt removal and delayed replacement is considered optimal management compared to intravenous antibiotics without shunt removal; intravenous and intraventricular antibiotics without shunt removal; or intravenous antibiotics with shunt removal and immediate replacement.[34,47] All components of the infected shunt are removed and a temporary external ventricular drain (EVD) placed to maintain normal intracranial pressure, facilitate resolution of ventriculitis, and permit continued monitoring of CSF parameters. EVDs should remain until the CSF is sterile.[30,34,47–49]

In cases of distal shunt infection, some neurosurgeons prefer to remove only the most distal portion of the shunt and to attach the more proximal portion to an EVD system. This strategy maintains CSF flow and still offers the ability to perform frequent ventricular fluid sampling without subjecting the patient to a more extensive surgical procedure. However, early infection of the proximal portion of the shunt may be obscured by antibiotic treatment with symptoms manifesting after discontinuation of therapy and reinsertion of the distal portion of the shunt. In general, if any portion of the shunt is thought to be infected, the entire shunt should be removed.[36]

Treatment

Until an organism is isolated, patients should be treated with empiric antibiotic therapy that covers the range of potentially causative pathogens.[49] Backbone therapy consists of a cephalosporin with good CSF penetration such as ceftriaxone, cefotaxime, or cefepime. Ceftazidime can be considered in patients with a history of *Pseudomonas*, or meropenem in those with a history of extended-spectrum beta-lactamase organisms. Vancomycin can be added for ill-appearing patients and those with a history of methicillin-resistant *S aureus* (MRSA). Linezolid has been used successfully in adults and children for CNS infections including shunt infections.[50,51] However, prolonged therapy has been associated with reversible bone marrow suppression and irreversible peripheral neuropathy.[52,53] Linezolid is therefore considered a second-line agent, reserved typically for targeted situations where a beta-lactam or vancomycin cannot be used safely.[17] Daptomycin and clindamycin have relatively poor CNS penetration and should not be used as empiric therapy.

Situations that may warrant additional measures include cases of delayed ventricular fluid sterilization (>3 days) and cases where the patient cannot safely undergo EVD removal and shunt placement. First, intraventricular antibiotic administration should be considered. No antibiotic has been approved by the Food and Drug Administration for intraventricular use, and insufficient evidence exists to recommend routine use for pediatric CSF shunt infections. Furthermore, intraventricular antibiotics should be avoided in neonates; in one trial, patients receiving both intraventricular gentamicin and intravenous antibiotics had a 3 fold increased risk of death compared with those receiving intravenous antibiotics alone.[54,55] Commonly used intraventricular antibiotics include vancomycin, gentamicin, tobramycin, and amikacin.[56–58] Polymyxin B and colistin have also been administered directly into the ventricles to treat ventricular infections caused by gram-negative bacteria resistant to many commonly used antibiotics.[59–62] Penicillin and cephalosporins should *not* be instilled directly into the ventricles since intraventricular administration of these antibiotics has been associated with increased neurotoxicity, including seizures.

Second, rifampin has excellent CSF penetration and can work synergistically with an antistaphylococcal agent to treat biofilms. Rifampin can be administered orally or intravenously when the infection is caused by susceptible *Staphylococci*.[63,64] Rifampin should not be used alone without a second agent (eg, vancomycin for MRSA) because of the rapid development of resistance.

Third, neuroimaging should be performed to diagnose an intracranial abscess or empyema. MRI is preferred due to its higher sensitivity but contrast-enhanced CT is sufficient in many cases.

Finally, either the trough ventricular antibiotic concentration or the ventricular fluid bactericidal titer should be measured to assess the adequacy of antibiotic therapy. No standardized values exist but many experts agree that the trough antibiotic concentration should exceed the minimum inhibitory concentration of the organism by 10 to 20 fold; lower values indicate suboptimal ventricular fluid antibiotic concentrations. Bactericidal titer measurements may not be readily available since they are technically difficult and time-consuming to perform; if no turbidity is observed after 24 hours of incubation—reflecting failure of bacteria to grow—at a dilution of 1:8 or higher (ie, more dilute), then the ventricular antibiotic concentrations are probably sufficient.[34]

Management strategies recommended in the 2017 IDSA guidelines are summarized in **Fig. 2**.[36] Duration of antibiotic therapy varies depending on the causative organism, the time to CSF sterilization, the extent of CSF inflammation, and the patient's clinical response. However, few studies have rigorously analyzed the relationship between duration of therapy and clinical outcomes. Days of therapy typically are counted from the day of the first negative culture following shunt removal and EVD placement. The 2017 IDSA guidelines recommend 10 days of therapy for CoNS or *C acnes* infection with minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms or systemic features. CoNS or *C acnes* infection with low glucose or significant CSF

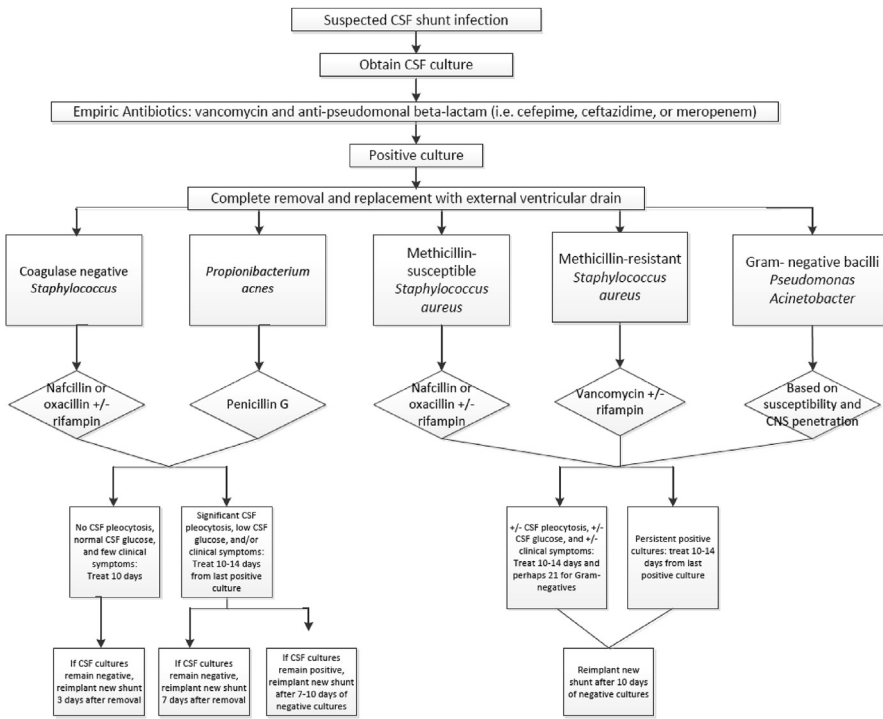

Fig. 2. Management strategies recommended in the 2017 Infectious Disease Society of America guidelines. (*Source:* From Pediatrics Infectious Diseases: Essentials for Practice, 2nd edition with permission).

pleocytosis or clinical or systemic features should be treated for 10 to 14 days from the first negative CSF culture prior to replacement of the shunt. A total of 10 to 14 days of antibiotics from the first negative CSF culture may be appropriate for *S aureus* and gram-negative bacilli with normal CSF parameters and few clinical symptoms, although some advocate for 21 days of treatment of a gram-negative bacillus.

Patients with a complicated course or suppurative complications such as brain abscess or intracranial empyema may require longer therapy.

Some have advocated for a trial off therapy before replacing the shunt, although the 2017 IDSA guidelines recommend against it. Similarly, the guidelines do not specify whether antimicrobial therapy should be continued following replacement and provide for shunt replacement prior to finishing treatment based on organism and duration of culture positivity.[36]

Course and Prognosis

The mortality associated with ventricular shunt infections is low. Potential morbidity includes new or more frequent seizures and worsening neurologic impairment. Infections caused by *S aureus* and *Candida* species have a substantially higher rate of recurrence despite adequate therapy than infections caused by other organisms.

CURRENT RESEARCH ON PREVENTION AND TREATMENT

Numerous studies have evaluated various patient-level risk factors that contribute to shunt infections. Simon and colleagues[7] evaluated 102 children who developed a first-time shunt infection and identified the need for a shunt revision as one of the single largest risks for developing an infection. Many studies, in addition to the one above, have not found significant associations between any medical or surgical risk factors, aside from revision surgery and preceding infections.[5–7,65] A previous 2012 literature review found that surgical time under 30 minutes also was associated with lower infection risk.[66]

Multiple quality improvement initiatives have been trialed and published in an effort to reduce infection rates. The HCRN conducted 2 such prospective initiatives. In the first one, Kestle and colleagues evaluated the use of a one time injection of intrathecal antibiotics, consisting of vancomycin and gentamicin, during the time of shunt placement. Their results demonstrated that the HCRN network infection rate decreased from 8.8% to 5.7% between the years 2007 and 2009.[29] Subsequently, the HCRN implemented a new protocol that consisted of using antibiotic-impregnated catheters for shunt surgeries, which were coated in rifampin and clindamycin.[29] The 2016 Kestle and colleagues[67] study determined that patients who followed the created protocol with antibiotic-impregnated catheters had an infection rate of 5.0%.[67] Podkovik and colleagues[68] evaluated trends between 2007 through 2012 and found that trends of antibiotic-impregnated catheter usage increased starting in 2011 following the creation of the HCRN protocol. In 2019, the BASICS trial demonstrated that antibiotic-impregnated shunts were associated with a significant decrease in failure secondary to infection as compared to standard shunts; silver-impregnated catheters did not show similar results.[69]

Despite multiple initiatives by the HCRN, there had not been direct comparisons of the different infection prevention techniques. A 2015 meta-analysis by Konstantelias and colleagues[70] demonstrated that antibiotic-impregnated catheters were associated with a lower infection risk as compared to standard catheters; however, most of the data were collected based on efficacy studies of impregnated catheters. A 2024 Podkovik and colleagues retrospective analysis at 6 tertiary-care pediatric

institutions across the United States utilized propensity score modeling to assess the risk of infection between both intrathecal antibiotics and antibiotic-impregnated catheters as compared to standard prophylactic pre-operative intravenous antibiotic administration. The results demonstrated no statistically significant benefit of one technique over the other during low-risk surgeries (ie, initial shunt placements and shunt revisions); however, the study did have a slight trend toward lower infection risk with antibiotic-impregnated catheters but was underpowered to definitively detect differences.[71]

A limited evidence base exists for the management of CSF shunt infection.[1,72–75] The IDSA provided recommendations for both surgical and antibiotic decisions in the treatment of CSF shunt infection embedded within 2004 guidelines for the management of bacterial meningitis.[76] In March 2017, the IDSA published a set of guidelines for health care-associated ventriculitis and meningitis that expanded upon and provided more extensive recommendations for the treatment of CSF shunt infection than the 2004 guidelines.[36] Applying both the 2004 and 2017 IDSA guidelines in a cohort of first shunt infection cases from 2008 to 2012, we have observed high adherence to surgical recommendations; poor adherence to intravenous (IV) antibiotic duration recommendations, with overuse of IV antibiotics observed in the majority of cases; and no differences in reinfection rates among the few IV antibiotic duration-adherent shunt infections.[77,78]

CURRENT RESEARCH ON MECHANISM OF INFECTION

An implicit assumption of the mechanisms of infection described earlier is the sterility of CSF. This assumption has recently been called into question. Ghose and colleagues[79] searched for viruses in CSF using microscopy and high-throughput sequencing. They found a diversity of viruses present in CSF of healthy individuals, of which a large proportion were bacteriophages. In another study, Pandey and colleagues[80] directly investigated the presence of bacteria in CSF from children undergoing initial surgical intervention for CSF shunt placement. Their approach consisted in enhanced culture methods and identification of bacteria by mass spectrometry and sequencing. Although growth was detected in over 10% of CSF samples, the authors concluded that it likely represented false positives. While there is no definitive evidence for the presence of commensal bacteria in the CSF, the possibility of their existence, and thus a potential role in CSF shunt infection, should not be discounted.

That local inoculation of bacteria at the time of surgery is the primary mechanism for shunt infection and is substantiated by the identity of infecting microorganisms, which are mostly components of the natural skin flora (see **Box 1**). An additional argument is the observation that there is a strong association between risk of infection and a history of prior revision surgeries.[6,7] Infections occur at least 3 times more often when the patient had 1 prior revision surgery compared to no surgery. The infection likelihood increases with each additional prior surgery.

A testable hypothesis derived from the local inoculation mechanism is that microorganisms identified during infection should be present, and thus detectable, at the previous surgical event, whether initial shunt placement or revision. We have investigated a cohort of 13 patients, for which CSF was available both from an infection episode and from a previous surgery event (3 initial shunt placements and 10 shunt revisions). The presence and identity of bacteria at the previous surgery were assayed by culture, 16S ribosomal RNA (rRNA) high-throughput sequencing, and mass spectrometry. No bacteria were detected in any of the preinfection samples

(manuscript entitled "A search for bacteria identified from cerebrospinal fluid shunt infections in previous surgical events" under review).

A related hypothesis can be stated for the case of reinfection, that is, when a patient has 2 or more infection episodes and associated shunt replacement surgeries. An infecting organism may persist from one infection episode to the next, thus making it possible to detect it in the earlier episode. Whitlock and colleagues[80] analyzed 7 reinfection pairs from 6 patients for the presence of bacteria using 16S rRNA sequencing. In 6 of the 7 pairs, infecting organisms were detected at the end of the previous infection, even when the CSF sample was culture negative. However, this result was not statistically significant, and the possibility that sequential infections were independent could not be excluded.

Although high-throughput sequencing of 16S rRNA has proven useful for the detection of unculturable microorganisms in CSF,[81] its limits with respect to both specificity and sensitivity have been apparent when analyzing samples with low bacterial DNA content such as CSF. The method typically identifies bacteria at the genus level and in some cases at the family level only. Species and strain-specific differences are highly relevant when investigating persistence of a common microorganism across time but are undetectable by 16S rRNA analysis. Sensitivity of the method when applied to CSF was thoroughly analyzed by Pope and colleagues.[82] Even after optimizing DNA extraction and strategies to computationally remove contaminants, the method still underperformed detection of bacteria by culture.

It is therefore desirable to develop experimental methods with improved specificity and sensitivity. For example, whole genome sequencing of bacteria cultured from an infection episode could be used to develop strain-specific polymerase chain reaction probes. Such probes could be applied to CSF from previous surgeries, thus improving the limit of detection by orders of magnitude. Strain-specific genomic information can even be obtained from CSF directly, when microbiological cultures are not available. In a proof of concept study, Hodor and colleagues[83] obtained a high-quality draft genomic sequence of *Staphylococcus epidermidis* from CSF of an infection episode. Total DNA was extracted from CSF and analyzed by whole genome amplification followed by shotgun sequencing. About 20% (or 700,000) of reads were nonhuman and were assembled into a 2.4 Mbp draft genome, which allowed assignment to an MLST class and comparison with genomes of other *S epidermidis* strains.

In all 4 mechanisms of CSF shunt infection, it is likely that biofilms form on shunts, whose role in pathogenesis is a current area of investigation.[81] It is possible that certain microorganisms are mostly sessile, embedded in biofilms, and thus unlikely to be detectable in CSF, especially prior to a symptomatic infection. Novel techniques, for example, microscopic and molecular, will be needed to investigate the role of biofilms in infection and their response to treatment.

Additional experimental tools for investigating the in vivo pathogenesis of CSF shunt infections are animal models. While animal studies are often not directly translatable to humans, their power consists in the versatility, rigor, and scale at which they can be performed, as well as the expanded range of available experimental techniques. An animal model specific to CSF shunt infection was described by Snowden.[84] It consists of a catheter coated with bacterial biofilm implanted into the lateral ventricle of mice or rats. This model was used to characterize changes to cellular composition and protein biomarkers in CSF, which are induced by the presence of *S epidermidis*,[85] *C acnes*,[86] and *Pseudomonas aeruginosa.*[87] Such studies may help with the development of novel diagnostic tools, applicable especially when infection is accompanied by negative bacterial culture results.

FUTURE DIRECTIONS

CSF shunt infections are associated with substantial morbidity for individuals with hydrocephalus. While prevention efforts have reduced infection rates, dilemmas in optimizing treatment remain. Ongoing research to further elucidate the mechanisms of shunt infection may also result in substantial advancements in care.

SUMMARY

CSF shunt infections are a particularly challenging clinical problem. Despite aggressive treatment often consisting of 2 surgeries and prolonged intravenous antibiotics, reinfection rates range from 20% to 25%. CSF shunt infections are associated with substantial resource utilization and costs. Staphylococcal species, especially CoNS and *S aureus,* account for almost two-thirds of all shunt infections. Detailed management strategies are recommended in the 2017 IDSA guidelines. While prevention efforts have reduced infection rates, dilemmas in optimizing treatment remain. Ongoing research to further elucidate the mechanisms of shunt infection may also result in substantial advancements in care.

CLINICS CARE POINTS

- Staphylococcal species, especially CoNS and *S aureus*, account for almost two-thirds of all shunt infections.
- The patient with a ventricular shunt requires a review of the symptoms and signs associated with increased intracranial pressure and CNS infection.
- There is no standard clinical definition of a shunt infection, although a positive CSF culture in a patient with any type of shunt, and/or a positive blood culture in a patient with a VA shunt, is generally accepted as sufficient evidence for surgical intervention and antimicrobial treatment.
- Treatment with intravenous antibiotics with shunt removal and delayed replacement is considered optimal management. Detailed management strategies are recommended in the 2017 IDSA guidelines.

FUNDING

We are funded by the NIH/NINDS, grants R01 NS101029 and R01 NS095979.

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