# Cerebrospinal Fluid Shunt Infection: Emerging Paradigms in Pathogenesis that Affect Prevention and Treatment

Tamara D. Simon, MD, MSPH[1,2], Joshua K. Schaffzin, MD, PhD[3], Charles B. Stevenson, MD[4], Kathryn Willebrand[5], Matthew Parsek, PhD[5], and Lucas R. Hoffman, MD, PhD[1,2,5,6]

In this medical progress report, we outline the epidemiology and healthcare utilization associated with cerebrospinal fluid (CSF) shunt-associated infections in the US, the clinical features of CSF shunt infection, and our evolving understanding of the prevention and treatment of CSF shunt infection. We describe an emerging paradigm in CSF shunt infection under active investigation.

## Epidemiology of CSF Shunt Infections

CSF shunt placement has been the mainstay of treatment for hydrocephalus for more than 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] Infection develops in 5%-15% of all CSF shunts.[5,6]

The volume of pediatric surgeries related to CSF shunts in the US is considerable, accounting for nearly 20 000 hospital admissions each year, of which approximately 4500 are for initial CSF shunt placement, 10 000 are for CSF shunt revision, and 3200 for other CSF shunt surgeries.[7] Infections of CSF shunts account for more than 2000 hospital admissions each year and are associated with extensive resource utilization, including approximately 55 000 hospital days (mean, 14.2-15.1 days per admission) and up to $250 million in charges (mean, $46 000-$62 000 per admission).[7]

Calculating the true incidence of shunt infection is difficult, owing in part to the lack of a standard definition for surveillance. The most common definition, put forth by the Centers for Disease Control and Prevention's National Healthcare Safety Network, concerns postoperative (surgical site) infection and does not attempt to address shunt infection specifically.[8] Other definitions, such as that promulgated by the Hydrocephalus Clinical Research Network (HCRN),[9] focus solely on CSF shunts and the various ways in which infections are diagnosed. The HCRN consensus definition for CSF shunt infection includes (a) microbiological determination of bacteria present in a culture or Gram stain of CSF, wound swab, and/or pseudocyst fluid; or (b) shunt erosion (visible hardware); or (c) abdominal pseudocyst (without positive culture); or (d) for children with ventriculoatrial shunts, presence of bacteria in a blood culture. The HCRN definition has not been widely adopted as a surveillance definition, presumably because the data needed to apply the HCRN definition are not routinely collected by infection prevention programs, and this definition has been tested only in pediatric patients. Nonetheless, common features of definitions of shunt infection include the recovery of microorganisms from the CSF of children with shunts.

| | |
|---|---|
| CSF | Cerebrospinal fluid |
| HCRN | Hydrocephalus Clinical Research Network |
| IV | Intravenous |
| PIA | Exopolysaccharide intercellular adhesin |
| SPS | Solutions for Patient Safety |

## Clinical Features of CSF Shunt Infections

The clinical features of CSF shunt infection depend on the mechanism of infection, the causative pathogen, and the type of shunt. The most common clinical symptoms are fever, headache, nausea, and lethargy.[5,10] Shunt infection is identified as the etiology of shunt malfunction in 3%-8% of cases of malfunction.[11] Shunt malfunction, which leads to the development of symptoms consistent with shunt failure, typically yields culture-negative CSF and is attributed to either apparatus obstruction or disconnection.

According to current, commonly held criteria, diagnosis of CSF shunt infection generally relies on the recovery of a microorganism from conventional culture of CSF.[9,12] The pathogens identified in CSF shunt infections are most often bacteria,[12-16] with fungi a distant second,[17] and it is believed that organisms are introduced onto the shunt apparatus at the time of surgery. Staphylococcal species, especially coagulase-negative *Staphylococcus* and *Staphylococcus aureus,* account for almost two-thirds of all shunt infections.[10,18] The most common infecting organism recovered from conventional aerobic cultures of CSF is *Staphylococcus epidermidis*.[19-21] *Cutibacterium acnes* (formerly *Propionibacterium acnes*[22]) has been isolated

From the [1]Department of Pediatrics, University of Washington/Seattle Children's Hospital; [2]Center for Clinical and Translational Research, Seattle Children's Research Institute, Seattle, WA; [3]Division of Infectious Diseases, Department of Pediatrics; [4]Division of Pediatric Neurosurgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [5]Department of Microbiology, University of Washington; and [6]Center for Infection and Prematurity Research, Seattle Children's Research Institute, Seattle, WA

T.S., M.P., and L.H. were supported by the National Institute of Neurological Disorders and Stroke (Grant R01 NS095979). The study funders played no role in study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the manuscript for publication. The contents are solely the responsibility of the authors and do not necessarily represent the official view of the funding sponsors. The authors declare no conflicts of interest.


https://doi.org10.1016/j.jpeds.2018.11.026

more often in recent series of ventriculoperitoneal shunt infections; this bacterium generally causes low-grade, indolent infections with few overt signs or symptoms.[23]

Although most bacteria causing shunt infections produce visible growth in broth or on agar within 48-72 hours, it is recommended that anaerobic cultures be ordered and monitored for growth for up to 10 days, because fastidious organisms such as *C acnes* grow relatively slowly.[24] Despite prolonged incubation, CSF cultures may yield no bacteria despite clinical symptoms of infection, particularly if the patient had been pretreated with antibiotics. In such instances, diagnosis typically is made using clinical judgment, close observation, and repeated CSF samples for Gram stain and culture.

Signs and symptoms of shunt infections are sometimes considered in relation to the location involved, that is, proximal (the portion of the shunt extending from the intracranial ventricle to valve) vs distal (the portion of the shunt from the valve to the cavity into which CSF drains). Signs and symptoms are less frequent in proximal shunt infection compared with distal infection and usually include external signs of local soft tissue inflammation, such as focal swelling, pain, erythema, and purulent drainage from around the scalp incision site. Such surface shunt infections are usually complications of surgery, due to direct inoculation of bacteria at the insertion site during shunt placement.

Signs and symptoms of distal shunt infection depend on the location of the distal shunt tip and whether the internal lumen or the external surface is infected. Intraluminal infection of a ventriculoatrial shunt can result in bacteremia and systemic signs of toxicity, although septic shock is uncommon. Intraluminal infection of a ventriculoperitoneal shunt usually produces signs of peritonitis. Infection related to the external surface manifests with signs of local soft tissue inflammation along the shunt tubing tract.

## Prevention of CSF Shunt Infections

### Our Understanding of the Prevention of CSF Shunt Infection Is Evolving

Studies related to the prevention of CSF shunt infections have been hampered by small sample sizes, and most have been performed retrospectively at single centers, limiting conclusions and generalizability. Results across studies often have been equivocal. One example is the use of prophylactic antibiotics intravenously (IV) during shunt surgeries. Until the mid-1990s, equal numbers of studies demonstrated a benefit[13,25-30] and no benefit.[5,31-37] Two meta-analyses subsequently demonstrated a benefit,[26,27] and in 1999 prophylactic IV antibiotics were recommended as standard care in the US.[38-40] Nonetheless, questions about the efficacy of intraoperative prophylactic IV antibiotics persist.[41] A 2012 National Institutes of Health-sponsored conference to assess research priorities in hydrocephalus highlighted the need for refinement of neurosurgical shunting procedures to improve survival and reduce infection rates.[42] Well-designed multicenter studies that can adjust analyses for variation between patient populations and centers and that provide adequate power are needed to advance our understanding of effective infection prevention techniques.

### Research on CSF Shunt Infection Prevention

Most infections become clinically apparent within 6 months of previous surgery.[6,43] We and others have shown that relatively few patient, medical, or surgical risk factors are associated with CSF shunt infection. Factors associated with CSF shunt infection include recent shunt insertion or revision, premature birth, young age, neuroendoscope use during shunt insertion, and previous shunt infection.[10,44-48] Insertion of a shunt after a previous shunt infection is associated with a 4-fold increased risk of shunt infection.

To build on previous work using procedure-specific cohorts, we assembled several cohorts of children undergoing initial CSF shunt placement to better understand the relative contribution of both patient and procedural factors to infection risk[47] (**Figure 1**). Our multicenter observational studies using HCRN registry and administrative data identified only 3 patient factors consistently associated with development of first CSF shunt infection: young age, intervening shunt revision surgery, and the number of shunt revisions.[47-50] A history of a single revision surgery is associated with a 3- to 4-fold greater risk of infection, whereas a history of 2 or more revision surgeries is associated with a 6- to 13-fold higher risk of infection.[47,48] The failure to identify additional patient, medical, or surgical risk factors for first infection is surprising and underscores the need for additional research.[44,47-49]

### Infection Prevention Quality Improvement Efforts

In recent years, substantial efforts have been taken to prevent CSF shunt infections that have led to a reduction, but not elimination, of infections.[51,52] Quality improvement methodology has been shown to prevent surgical site infections, including neurosurgical shunt infections. Much of the focus has been on standardizing intraoperative practice, which has shown success in the HCRN and other cohorts.[9,53]

Perhaps the largest effort to prevent pediatric shunt infection comes from Solutions for Patient Safety (SPS), a Centers for Medicare & Medicaid Services-funded health engagement network of more than 100 pediatric hospitals in North America.[54] Starting as an 8-hospital collaborative in Ohio, SPS has achieved measurable reduction of patient harm through partnerships to improve patient safety. SPS reported a 21% reduction in surgical site infections in a set of procedures within 10 months of implementation of a bundle to which adherence was high (>96%), with a reduction in neurosurgical shunt infections from 3.2 to 2.3 per 100 procedures during the same time period.[55] Our subsequent work at a single institution showed that standardization of preoperative activities such as bathing, *S aureus* screening, and consistent communication with neurosurgical patients also reduced all postoperative infections, including shunt infections, significantly.[56]

Although SPS has focused on simple bundles for a variety of surgeries, the HCRN has focused on more extensive shunt infection prevention bundles that have included the restriction of operating room traffic, use of hair clipping, preparation

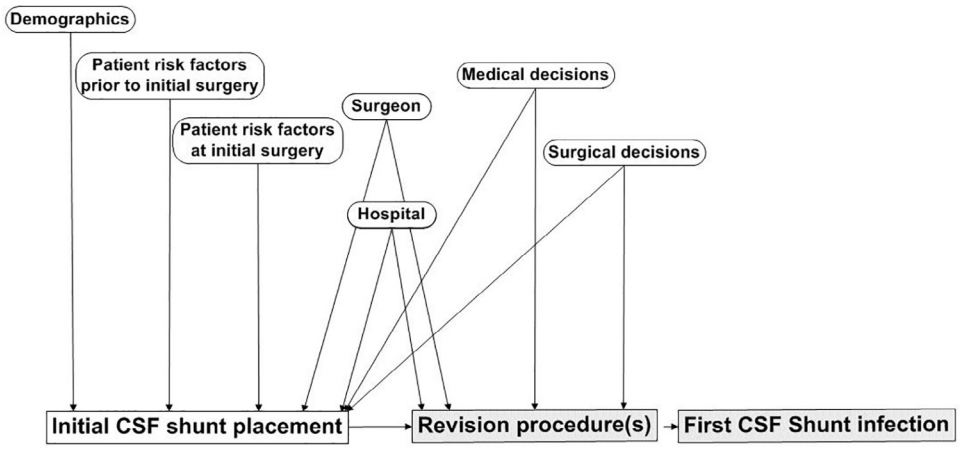


**Figure 1.** A framework for understanding patient and procedural risk factors for development of a first CSF shunt infection. Shaded boxes indicate possible surgeries. CSF infection can occur without an interval revision procedure.

of the surgical site, formal hand scrub, and double gloving.[9] Although the intrathecal instillation of broad-spectrum antibiotics into shunts upon placement had been reported in the literature,[34,36,57,58] this practice was used rarely until recently. However, in 2007, the HCRN implemented a peri-operative infection prevention protocol that included one-time instillation of 2 intrathecal antibiotics (ie, vancomycin and gentamicin) for all CSF shunt surgeries (totaling 1571 surgeries).[9] The HCRN reported both a reduction in the overall network infection rate from 8.8% before implementation of the protocol to 5.7% after implementation of the protocol ($P = .0028$; absolute risk reduction, 3.15%; relative risk reduction, 36%), and reductions in per-procedure infection rates at 3 of 4 participating centers in 2011.[9] In the face of emerging evidence favoring the utility of antibiotic-impregnated catheters in preventing CSF shunt infections, in January 2012 the HCRN discontinued the routine use of intrathecal antibiotics and initiated the use of antibiotic (clindamycin plus rifampin)-impregnated shunt tubing in its shunt infection prevention protocol. Among 1935 procedures performed at 8 centers between January 1, 2012, and September 30, 2013, the overall network 6-month infection rate was 6.5% before implementation and 6.0% after implementation. Overall protocol compliance was 77%. The HCRN concluded that the change in the protocol from instillation of antibiotic through the shunt to use of antibiotic-impregnated shunt tubing did not significantly reduce the rate of shunt infection, and that use of either procedure reduced shunt infection compared with use of neither procedure.[53] The current HCRN protocol permits optional use of either technique.

## Management of CSF Shunt Infection

Management of CSF shunt infections is challenging. Because microorganisms adhere to the shunt itself, treatment of infection requires both surgical and medical management. Surgical management usually includes a minimum of 2 surgeries for removal and subsequent replacement of the infected shunt,[12,15,19-21,59,60] bridged by insertion of an external ventricular drain at the time of shunt removal.[20,52,61-65] The duration of IV antimicrobial therapy often is based on the organism recovered and duration of positive cultures, with definitive drug choice based on the susceptibilities of the recovered organism, its known bactericidal activity, and penetration of the blood-brain barrier. CSF shunt replacement generally does not occur until the CSF is culture-negative and treatment is complete, usually at 10-14 days. The Infectious Diseases Society of America published management guidelines in 2017.[24] Despite aggressive management, reinfection rates range from 20% to 25%.[19-21] Furthermore, CSF shunt infection negatively impacts neurocognitive outcomes[66] and quality of life.[67] In some cases, infection can result in death.[29,31,59,66,68,69]

## Investigation of Roles of Microbial Diversity and Biofilms

Increasing evidence suggests that CSF shunt infections are often polymicrobial, with most organisms not cultivatable,[70,71] and that biofilms play an important role in in CSF shunt infections.[72-74] Until recently, the presence of bacteria during disease traditionally was determined by the growth of bacteria in conventional culture.[75,76] Using culture-independent molecular approaches, the microbiota on and in human tissues, in both health and disease, has been shown to be more complex than can be detected by culture.[75,77,78] Sterility of CSF in the presence and absence of shunts in healthy individuals is difficult to confirm given current technological limitations in the study of low-abundance microbiota.

In a study of 8 patients with CSF shunt infection and uninfected controls using quantitative polymerase chain reaction (qPCR) and high-throughput sequencing, we identified small amounts of bacterial and fungal DNA of both cultivatable and noncultivatable species in the CSF of all patients with CSF shunt infection but in no control CSF.[71] A

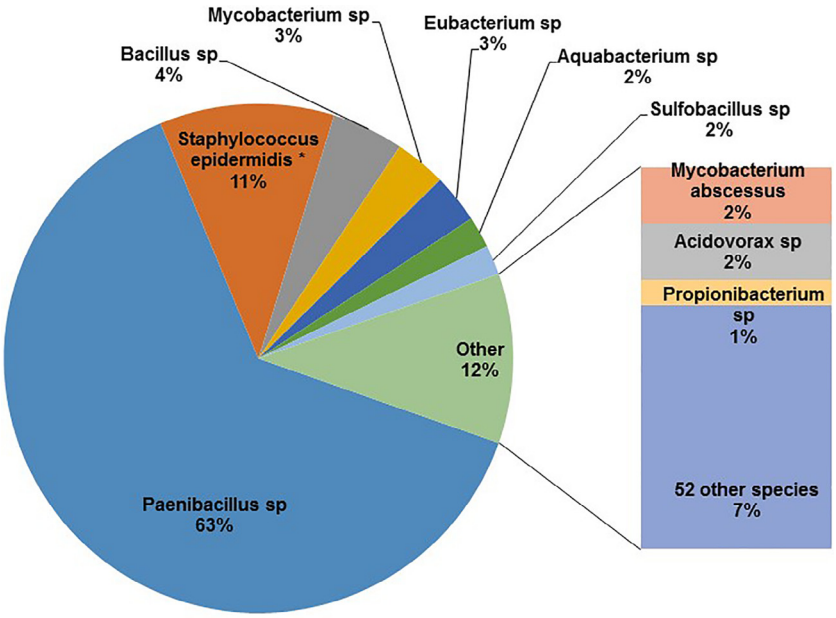


**Figure 2.** Microbiota in the CSF of a child with CSF shunt infection. Shown are bacterial taxa identified by 16S bacterial tag-encoded FLX-titanium amplicon pyrosequencing (bTEFAP) at the time of an initial CSF sample, presented as the proportion of all sequence detections in the sample representing bacteria for which detection comprised ≥1% of the total. The sole bacterium identified in conventional culture (*S epidermidis*) is designated with an asterisk. Negative controls of donated CSF that underwent concurrent DNA extraction revealed no detection by bTEFAP analysis (data not shown).

representative example of the variety of bacterial DNA obtained from a child with *S epidermidis* culture-positive CSF shunt infection is shown in **Figure 2**. Surprisingly, the predominant organism detected by this analysis, a *Paenibacillus* species, was markedly more abundant compared with the isolated *S epidermidis*.

Emerging evidence suggests that the microbes that cause CSF shunt infections live in complex, adherent assemblages of microbes encased in an extracellular matrix,[79] known as biofilms, associated with the shunt catheter surface.[72-74] Biofilms are thought to be responsible for numerous persistent and chronic infections[77,80] and are increasingly understood to play a role in other medical device infections.[81,82] Biofilm-dwelling bacteria grown in vitro are tolerant to antimicrobial activity,[83] a characteristic common among CSF infections. Currently, conventional culture techniques are designed to detect rapid-growing, liquid-suspended clonal populations of individual microbial species[75] and might not detect slow-growing organisms residing in surface-adherent biofilms.[79]

Using bacterial PCR-based quantitation, we reported that bacterial DNA was detectable only early in the course of infection, if at all, in most samples of CSF from shunt infections,[70] lending support to the concept that bacteria predominantly occupy shunt-adherent biofilms.

Various chronic,[77,80] device-associated,[81,82] biofilm-associated infections are known to be highly resistant to clearance by the immune system, with decreased phagocytosis.[84,85] Biofilm structure, immunomodulation, and extracellular molecules produced by biofilm-forming bacteria likely contribute to increased fitness in the presence of immune cells. Leukocytes are observed to penetrate biofilms, but phagocytosis and bactericidal activity is diminished compared with activity against planktonic bacteria. In addition, decreased cytokine activity has been measured in response to biofilm-grown *S epidermidis* compared with planktonic *S epidermidis*.[86]

For *S epidermidis*, the exopolysaccharide intercellular adhesin (PIA) also may contribute to immune evasion. PIA is secreted by biofilm-producing cells and is believed to mediate adherence to surfaces and other organisms participating in the biofilm.[87] *S epidermidis* PIA knockout mutants (*ica*-) grown in biofilm were observed to be more susceptible to phagocytosis than wild-type biofilm *S epidermidis* and also more susceptible to killing by antimicrobial peptides.[84] In another study, *ica*- mutants were observed to be more susceptible to complement killing than wild-type *S epidermidis*.[85]

Other antimicrobial resistance factors in biofilm infections have been identified, including slow growth of organisms, glycocalyx production, high density, and adherence to surfaces.[88] Biofilm matrix production has been shown to inhibit the penetrance of oxacillin, cefotaxime, and vancomycin, but not amikacin and ciprofloxacin, into the deeper layers of the biofilm.[89] The slow rate of growth and anaerobic growth of microbes in biofilm communities also likely contribute to antibiotic resistance. *Pseudomonas aeruginosa* grown in anaerobic conditions is associated with decreased susceptibility to tobramycin and ciprofloxacin, likely due to slow growth rate, because most antibiotics act on actively dividing cells. However, when nitrate is added to the anaerobically grown cells, growth rate increases but resistance to tobramycin and ciprofloxacin increases,[90] suggesting that slow growth rate is not the sole factor

contributing to antibiotic resistance. It is possible that an abundance of nutrients up-regulates the expression of antimicrobial resistance genes. More investigation is needed to clarify these issues.

The presence of biofilms on CSF shunts,[72-74] the detection of noncultivatable organisms and biofilms in recalcitrant infections,[75,77,78,80] as well as other medical device-associated infections[81,82] have been reported previously. Biofilm infections in the CSF pose a special challenge because of limited achievable antibiotic concentrations in the CSF. Although treatment of meningitis may be enhanced by a more permissive blood-brain barrier, shunt infection and ventriculitis might not generate significant meningeal inflammation. Few of the agents effective for bloodstream or tissue infection, such as $\beta$-lactam agents, carbapenems, and aminoglycosides, cross efficiently into the CSF. Fluoroquinolones demonstrate better CSF penetration, but typically are avoided in younger patients. Likewise, linezolid can achieve relatively high CSF levels, but its bacteriostatic properties make it less desirable as first-line therapy. Higher doses of drugs such as $\beta$-lactams and aminoglycosides can be given to drive CSF penetration, but this is often limited by systemic toxicity.[91] In addition, higher concentrations of antibiotics are not singularly effective against biofilm infections. Thus, it is recommended that antibiotic therapy be coupled with removal of the contaminated device. Meticulous care during shunt insertion to prevent procedure-associated infection and more research into nonsurgical treatment of biofilm and shunt infections are needed.

## Areas for Further Study

Using recent advances in molecular and microscopic microbiology, careful characterization of the CSF microbiota over time may lead to a better understanding of the qualitative and quantitative changes in the microbial community that contribute to patient morbidity. The practical implications of a diverse CSF microbiota in hydrocephalus remain unclear. One possibility is that if a CSF microbiota is present before infection, CSF shunt revision surgeries may disrupt the local environment either by introducing new organisms or permitting further growth of extant organisms, thus increasing infection risk. One theoretical infection prevention approach worthy of study might be to reduce bacterial load at the time of CSF shunt revision by a short perioperative course of broad-spectrum antibiotics.

Various related clinical questions arise if the plastic surface of a shunt acts as a nucleation site for microbial biofilm formation. Preventing infection may require surgical approaches that disrupt biofilms. Potentially the use of a different shunt tract at the time of CSF shunt revision could reduce infection risk because biofilm may be left behind in the tract following shunt removal.

The implications of CSF microbiota and/or biofilm formation also may impact how we approach treatment of CSF shunt infections. Might there be a role for identification of noncultivatable species to better define treatment? How does the establishment of biofilm lead to overgrowth (ie, infection) of a predominant organism? Are biofilms polymicrobial-integrated communities or do they consist of single species aggregates dispersed across the shunt surface? Might shunts be epithelialized, like vascular conduits? If so, does epithelialization increase or decrease the risk of infection? Does culture-negative shunt malfunction reflect infection of the shunt tubing by a biofilm, with resulting occlusion? Does the passive nature of CSF flow through the catheter influence biofilm formation? Do the tissues surrounding the shunt become colonized or infected with these microbiota, either during the infection itself or during shunt surgeries, serving as a nidus for reinfection?

Can certain antimicrobial agents better target biofilms? Does different hardware and/or surgical approaches affect microbial load and hence microbiota/biofilm formation? What impact does antibiotic-impregnated catheter tubing have on biofilm microbiota and/or biofilm antimicrobial resistance? What other factors contribute to biofilm antimicrobial resistance? And finally, is there a better approach to the surveillance of shunts given this microbial hypothesis?

Knowledge of the involvement of a microbiota and polymicrobial biofilm in the pathogenesis of CSF shunt infections represents a paradigm shift in this field. Given the high disease burden and the inadequacies of current pathophysiological models, diagnostic modalities, and treatments in the prevention and cure of these infections, this conceptual shift provides a promising way forward to improving the care of children with hydrocephalus. ■

Submitted for publication Jun 18, 2018; last revision received Nov 9, 2018; accepted Nov 13, 2018

Reprint requests: Tamara D. Simon, MD, MSPH, University of Washington, Department of Pediatrics, Division of Hospital Medicine, Seattle Children's Research Institute, Building 1, M/S C9S-9, 1900 Ninth Ave, Seattle, WA 98101. E-mail: tamara.simon@seattlechildrens.org

## Data Statement

Data sharing statement available at www.jpeds.com.

## References

1. Kestle JR. Pediatric hydrocephalus: current management. Neurol Clin 2003;21:883-95, vii.
2. Browd SR, Ragel BT, Gottfried ON, Kestle JR. Failure of cerebrospinal fluid shunts: part I: obstruction and mechanical failure. Pediatr Neurol 2006;34:83-92.
3. Browd SR, Gottfried ON, Ragel BT, Kestle JR. Failure of cerebrospinal fluid shunts: part II: overdrainage, loculation, and abdominal complications. Pediatr Neurol 2006;34:171-6.
4. Kestle J, Drake J, Milner R, Sainte-Rose C, Cinalli G, Boop F, et al. Long-term follow-up data from the Shunt Design Trial. Pediatr Neurosurg 2000;33:230-6.
5. Kontny U, Höfling B, Gutjahr P, Voth D, Schwarz M, Schmitt HJ. CSF shunt infections in children. Infection 1993;21:89-92.
6. Mancao M, Miller C, Cochrane B, Hoff C, Sauter K, Weber E. Cerebrospinal fluid shunt infections in infants and children in Mobile, Alabama. Acta Paediatr 1998;87:667-70.

7. Simon TD, Riva-Cambrin J, Srivastava R, Bratton SL, Dean JM, Kestle JR. Hospital care for children with hydrocephalus in the United States: utilization, charges, comorbidities, and deaths. J Neurosurg Pediatr 2008;1:131-7.
8. Centers for Disease Control and Prevention. Surgical site infection (SSI) event. In: National Healthcare Safety Network patient safety component manual. 2016; p. 9-14.
9. Kestle JR, Riva-Cambrin J, Wellons JC 3rd, Kulkarni AV, Whitehead WE, Walker ML, et al. A standardized protocol to reduce cerebrospinal fluid shunt infection: the Hydrocephalus Clinical Research Network Quality Improvement Initiative. J Neurosurg Pediatr 2011;8:22-9.
10. Morris A, Low DE. Nosocomial bacterial meningitis, including central nervous system shunt infections. Infect Dis Clin North Am 1999;13:735-50.
11. Kim TY, Stewart G, Voth M, Moynihan JA, Brown L. Signs and symptoms of cerebrospinal fluid shunt malfunction in the pediatric emergency department. Pediatr Emerg Care 2006;22:28-34.
12. Fan-Havard P, Nahata MC. Treatment and prevention of infections of cerebrospinal fluid shunts. Clin Pharm 1987;6:866-80.
13. Odio C, McCracken GH Jr, Nelson JD. CSF shunt infections in pediatrics. A seven-year experience. Am J Dis Child 1984;138:1103-8.
14. Nelson JD. Cerebrospinal fluid shunt infections. Pediatr Infect Dis 1984;3(3 Suppl):S30-2.
15. Sells CJ, Shurtleff DB, Loeser JD. Gram-negative cerebrospinal fluid shunt-associated infections. Pediatrics 1977;59:614-8.
16. Jamjoom A, al-Abedeen Jamjoom Z, al-Hedaithy S, Jamali A, Naim-Ur-Rahman, Malabarey T. Ventriculitis and hydrocephalus caused by *Candida albicans* successfully treated by antimycotic therapy and cerebrospinal fluid shunting. Br J Neurosurg 1992;6:501-4.
17. Chiou CC, Wong TT, Lin HH, Hwang B, Tang RB, Wu KG, et al. Fungal infection of ventriculoperitoneal shunts in children. Clin Infect Dis 1994;19:1049-53.
18. Yogev R. Cerebrospinal fluid shunt infections: a personal view. Pediatr Infect Dis 1985;4:113-8.
19. Kestle JR, Garton HJ, Whitehead WE, Drake JM, Kulkarni AV, Cochrane DD, et al. Management of shunt infections: a multicenter pilot study. J Neurosurg 2006;105(3 Suppl):177-81.
20. Kulkarni AV, Rabin D, Lamberti-Pasculli M, Drake JM. Repeat cerebrospinal fluid shunt infection in children. Pediatr Neurosurg 2001;35:66-71.
21. Tuan TJ, Thorell EA, Hamblett NM, Kestle JR, Rosenfeld M, Simon TD. Treatment and microbiology of repeated cerebrospinal fluid shunt infections in children. Pediatr Infect Dis J 2011;30:731-5.
22. Scholz CF, Kilian M. The natural history of cutaneous propionibacteria, and reclassification of selected species within the genus *Propionibacterium* to the proposed novel genera *Acidipropionibacterium* gen. nov., *Cutibacterium* gen. nov., and *Pseudopropionibacterium* gen. nov. Int J Syst Evol Microbiol 2016;66:4422-32.
23. Thompson TP, Albright AL. *Propionibacterium* [correction of *Proprionibacterium*] *acnes* infections of cerebrospinal fluid shunts. Childs Nerv Syst 1998;14:378-80.
24. Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Michael Scheld W, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Clin Infect Dis 2017. doi:10.1093/cid/ciw861. [Epub ahead of print].
25. Kestle JR, Hoffman HJ, Soloniuk D, Humphreys RP, Drake JM, Hendrick EB. A concerted effort to prevent shunt infection. Childs Nerv Syst 1993;9:163-5.
26. Langley JM, LeBlanc JC, Drake J, Milner R. Efficacy of antimicrobial prophylaxis in placement of cerebrospinal fluid shunts: meta-analysis. Clin Infect Dis 1993;17:98-103.
27. Haines SJ, Walters BC. Antibiotic prophylaxis for cerebrospinal fluid shunts: a metanalysis. Neurosurgery 1994;34:87-92.
28. Savitz MH, Katz SS. Prevention of primary wound infection in neurosurgical patients: a 10-year study. Neurosurgery 1986;18:685-8.
29. Schoenbaum SC, Gardner P, Shillito J. Infections of cerebrospinal fluid shunts: epidemiology, clinical manifestations, and therapy. J Infect Dis 1975;131:543-52.
30. Blomstedt GC. Results of trimethoprim-sulfamethoxazole prophylaxis in ventriculostomy and shunting procedures. A double-blind randomized trial. J Neurosurg 1985;62:694-7.
31. George R, Leibrock L, Epstein M. Long-term analysis of cerebrospinal fluid shunt infections. A 25-year experience. J Neurosurg 1979;51:804-11.
32. Di Rocco C, Marchese E, Velardi F. A survey of the first complication of newly implanted CSF shunt devices for the treatment of nontumoral hydrocephalus. Cooperative survey of the 1991-1992 Education Committee of the ISPN. Childs Nerv Syst 1994;10:321-7.
33. Griebel R, Khan M, Tan L. CSF shunt complications: an analysis of contributory factors. Childs Nerv Syst 1985;1:77-80.
34. Shurtleff DB, Stuntz JT, Hayden PW. Experience with 1201 cerebrospinal fluid shunt procedures. Pediatr Neurosci 1985;12:49-57.
35. Rieder MJ, Frewen TC, Del Maestro RF, Coyle A, Lovell S. The effect of cephalothin prophylaxis on postoperative ventriculoperitoneal shunt infections. CMAJ 1987;136:935-8.
36. Quigley MR, Reigel DH, Kortyna R. Cerebrospinal fluid shunt infections. Report of 41 cases and a critical review of the literature. Pediatr Neurosci 1989;15:111-20.
37. Wang EE, Prober CG, Hendrick BE, Hoffman HJ, Humphreys RP. Prophylactic sulfamethoxazole and trimethoprim in ventriculoperitoneal shunt surgery. A double-blind, randomized, placebo-controlled trial. JAMA 1984;251:1174-7.
38. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control 1999;27:97-132; quiz 133-4; discussion 96.
39. Ratilal B, Costa J, Sampaio C. Antibiotic prophylaxis for surgical introduction of intracranial ventricular shunts. Cochrane Database Syst Rev 2006;3:CD005365.
40. Ratilal B, Costa J, Sampaio C. Antibiotic prophylaxis for surgical introduction of intracranial ventricular shunts: a systematic review. J Neurosurg Pediatr 2008;1:48-56.
41. Klimo P Jr, Van Poppel M, Thompson CJ, Baird LC, Duhaime AC, Flannery AM. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 6: preoperative antibiotics for shunt surgery in children with hydrocephalus: a systematic review and meta-analysis. J Neurosurg Pediatr 2014;14(Suppl):44-52.
42. McAllister JP 2nd, Williams MA, Walker ML, Kestle JR, Relkin NR, Anderson AM, et al. An update on research priorities in hydrocephalus: overview of the third National Institutes of Health-sponsored symposium "Opportunities for hydrocephalus research: pathways to better outcomes". J Neurosurg 2015;123:1427-38.
43. Ronan A, Hogg GG, Klug GL. Cerebrospinal fluid shunt infections in children. Pediatr Infect Dis J 1995;14:782-6.
44. McGirt MJ, Zaas A, Fuchs HE, George TM, Kaye K, Sexton DJ. Risk factors for pediatric ventriculoperitoneal shunt infection and predictors of infectious pathogens. Clin Infect Dis 2003;36:858-62.
45. Naradzay JF, Browne BJ, Rolnick MA, Doherty RJ. Cerebral ventricular shunts. J Emerg Med 1999;17:311-22.
46. Dallacasa P, Dappozzo A, Galassi E, Sandri F, Cocchi G, Masi M. Cerebrospinal fluid shunt infections in infants. Childs Nerv Syst 1995;11:643-8; discussion 649.
47. Simon TD, Butler J, Whitlock KB, Browd SR, Holubkov R, Kestle JR, et al. Risk factors for first cerebrospinal fluid shunt infection: findings from a multi-center prospective cohort study. J Pediatr 2014;164:1462-8.e2.
48. Simon TD, Whitlock KB, Riva-Cambrin J, Kestle JR, Rosenfeld M, Dean JM, et al. Revision surgeries are associated with significant increased risk of subsequent cerebrospinal fluid shunt infection. Pediatr Infect Dis J 2012;31:551-6.
49. Simon TD, Hall M, Riva-Cambrin J, Albert JE, Jeffries HE, Lafleur B, et al. Infection rates following initial cerebrospinal fluid shunt placement across pediatric hospitals in the United States. Clinical article. J Neurosurg Pediatr 2009;4:156-65.
50. Simon TD, Whitlock KB, Riva-Cambrin J, Kestle JR, Rosenfeld M, Dean JM, et al. Association of intraventricular hemorrhage secondary to

prematurity with cerebrospinal fluid shunt surgery in the first year following initial shunt placement. J Neurosurg Pediatr 2012;9:54-63.
51. Flannery AM, Mazzola CA, Klimo P Jr, Duhaime AC, Baird LC, Tamber MS, et al. Foreword: pediatric hydrocephalus: systematic literature review and evidence-based guidelines. J Neurosurg Pediatr 2014;14(Suppl 1):1-2.
52. Williams MA, McAllister JP, Walker ML, Kranz DA, Bergsneider M, Del Bigio MR, et al. Priorities for hydrocephalus research: report from a National Institutes of Health-sponsored workshop. J Neurosurg 2007;107(5 Suppl):345-57.
53. Kestle JR, Holubkov R, Douglas Cochrane D, Kulkarni AV, Limbrick DD Jr, Luerssen TG, et al. A new Hydrocephalus Clinical Research Network protocol to reduce cerebrospinal fluid shunt infection. J Neurosurg Pediatr 2016;17:391-6.
54. Children's Hospital Solutions for Patient Safety. Available at: http://www.solutionsforpatientsafety.org/. Accessed December 1, 2018.
55. Schaffzin JK, Harte L, Marquette S, Zieker K, Wooton S, Walsh K, et al. Surgical site infection reduction by the solutions for patient safety hospital engagement network. Pediatrics 2015;136:e1353-60.
56. Schaffzin JK, Simon K, Connelly BL, Mangano FT. Standardizing preoperative preparation to reduce surgical site infections among pediatric neurosurgical patients. J Neurosurg Pediatr 2017;19:399-406.
57. Ragel BT, Browd SR, Schmidt RH. Surgical shunt infection: significant reduction when using intraventricular and systemic antibiotic agents. J Neurosurg 2006;105:242-7.
58. Lambert M, MacKinnon AE, Vaishnav A. Comparison of two methods of prophylaxis against CSF shunt infection. Z Kinderchir 1984;39(Suppl 2):109-10.
59. Walters BC, Hoffman HJ, Hendrick EB, Humphreys RP. Cerebrospinal fluid shunt infection. Influences on initial management and subsequent outcome. J Neurosurg 1984;60:1014-21.
60. Tamber MS, Klimo P Jr, Mazzola CA, Flannery AM. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 8: management of cerebrospinal fluid shunt infection. J Neurosurg Pediatr 2014;14(Suppl 1):60-71.
61. Kanev PM, Sheehan JM. Reflections on shunt infection. Pediatr Neurosurg 2003;39:285-90.
62. Gardner P, Leipzig T, Phillips P. Infections of central nervous system shunts. Med Clin North Am 1985;69:297-314.
63. Gardner P, Leipzig TJ, Sadigh M. Infections of mechanical cerebrospinal fluid shunts. Curr Clin Top Infect Dis 1988;9:185-214.
64. Morissette I, Gourdeau M, Francoeur J. CSF shunt infections: a fifteen-year experience with emphasis on management and outcome. Can J Neurol Sci 1993;20:118-22.
65. Venes JL. Infections of CSF shunt and intracranial pressure monitoring devices. Infect Dis Clin North Am 1989;3:289-99.
66. Vinchon M, Dhellemmes P. Cerebrospinal fluid shunt infection: risk factors and long-term follow-up. Childs Nerv Syst 2006;22:692-7.
67. Kulkarni AV, Cochrane DD, McNeely PD, Shams I. Medical, social, and economic factors associated with health-related quality of life in Canadian children with hydrocephalus. J Pediatr 2008;153:689-95.
68. Tuli S, Tuli J, Drake J, Spears J. Predictors of death in pediatric patients requiring cerebrospinal fluid shunts. J Neurosurg 2004;100(5 Suppl Pediatrics):442-6.
69. Renier D, Sainte-Rose C, Pierre-Kahn A, Hirsch JF. Prenatal hydrocephalus: outcome and prognosis. Childs Nerv Syst 1988;4:213-22.
70. Simon TD, Van Yserloo B, Nelson K, Gillespie D, Jensen R, McAllister JP 2nd, et al. Use of quantitative 16S rRNA PCR to determine bacterial load does not augment conventional cerebrospinal fluid (CSF) cultures among children undergoing treatment for CSF shunt infection. Diagn Microbiol Infect Dis 2014;78:188-95.
71. Simon TD, Pope CE, Browd SR, Ojemann JG, Riva-Cambrin J, Mayer-Hamblett N, et al. Evaluation of microbial bacterial and fungal diversity in cerebrospinal fluid shunt infection. PLoS One 2014;9:e83229.
72. Fux CA, Quigley M, Worel AM, Post C, Zimmerli S, Ehrlich G, et al. Biofilm-related infections of cerebrospinal fluid shunts. Clin Microbiol Infect 2006;12:331-7.
73. Guevara JA, Zúccaro G, Trevisan A, Denoya CD. Bacterial adhesion to cerebrospinal fluid shunts. J Neurosurg 1987;67:438-45.
74. Stoodley P, Braxton EE Jr, Nistico L, Hall-Stoodley L, Johnson S, Quigley M, et al. Direct demonstration of Staphylococcus biofilm in an external ventricular drain in a patient with a history of recurrent ventriculoperitoneal shunt failure. Pediatr Neurosurg 2010;46:127-32.
75. Rhoads DD, Wolcott RD, Sun Y, Dowd SE. Comparison of culture and molecular identification of bacteria in chronic wounds. Int J Mol Sci 2012;13:2535-50.
76. Falkow S. Molecular Koch's postulates applied to microbial pathogenicity. Rev Infect Dis 1988;10(Suppl 2):S274-6.
77. Han A, Zenilman JM, Melendez JH, Shirtliff ME, Agostinho A, James G, et al. The importance of a multifaceted approach to characterizing the microbial flora of chronic wounds. Wound Repair Regen 2011;19:532-41.
78. Seng P, Rolain JM, Fournier PE, La Scola B, Drancourt M, Raoult D. MALDI-TOF-mass spectrometry applications in clinical microbiology. Future Microbiol 2010;5:1733-54.
79. Rickard AH, Gilbert P, High NJ, Kolenbrander PE, Handley PS. Bacterial coaggregation: an integral process in the development of multi-species biofilms. Trends Microbiol 2003;11:94-100.
80. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science 1999;284:1318-22.
81. Vergidis P, Patel R. Novel approaches to the diagnosis, prevention, and treatment of medical device-associated infections. Infect Dis Clin North Am 2012;26:173-86.
82. Stenehjem E, Armstrong WS. Central nervous system device infections. Infect Dis Clin North Am 2012;26:89-110.
83. Bayston R, Ullas G, Ashraf W. Action of linezolid or vancomycin on biofilms in ventriculoperitoneal shunts in vitro. Antimicrob Agents Chemother 2012;56:2842-5.
84. Vuong C, Kocianova S, Voyich JM, Yao Y, Fischer ER, DeLeo FR, et al. A crucial role for exopolysaccharide modification in bacterial biofilm formation, immune evasion, and virulence. J Biol Chem 2004;279:54881-6.
85. Kristian SA, Birkenstock TA, Sauder U, Mack D, Götz F, Landmann R. Biofilm formation induces C3a release and protects *Staphylococcus epidermidis* from IgG and complement deposition and from neutrophil-dependent killing. J Infect Dis 2008;197:1028-35.
86. Leid JG, Shirtliff ME, Costerton JW, Stoodley P. Human leukocytes adhere to, penetrate, and respond to *Staphylococcus aureus* biofilms. Infect Immun 2002;70:6339-45.
87. Rupp ME, Fey PD, Heilmann C, Götz F. Characterization of the importance of *Staphylococcus epidermidis* autolysin and polysaccharide intercellular adhesin in the pathogenesis of intravascular catheter-associated infection in a rat model. J Infect Dis 2001;183:1038-42.
88. König C, Schwank S, Blaser J. Factors compromising antibiotic activity against biofilms of *Staphylococcus epidermidis*. Eur J Clin Microbiol Infect Dis 2001;20:20-6.
89. Singh R, Ray P, Das A, Sharma M. Penetration of antibiotics through *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms. J Antimicrob Chemother 2010;65:1955-8.
90. Borriello G, Werner E, Roe F, Kim AM, Ehrlich GD, Stewart PS. Oxygen limitation contributes to antibiotic tolerance of *Pseudomonas aeruginosa* in biofilms. Antimicrob Agents Chemother 2004;48:2659-64.
91. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev 2010;23:858-83.