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

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

[1]Department of Pediatrics, University of Washington/Seattle Children's Hospital, Seattle, Washington, United States

[2]Center for Clinical and Translational Research, Seattle Children's Research Institute, Seattle, Washington, United States

[3]Division of Infectious Diseases, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

[4]Division of Pediatric Neurosurgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

[5]Department of Microbiology, University of Washington, Seattle, Washington, United States

[6]Center for Infection and Prematurity Research, Seattle Children's Research Institute, Seattle, Washington, United States

This medical progress report will outline the epidemiology and healthcare utilization associated with cerebrospinal fluid (CFS) 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 will 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 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) Infection develops in 5% to 15% of all CSF shunts.(5, 6)

Corresponding Author Contact Information: Tamara D. Simon, MD, MSPH, Associate Professor, University of Washington Department of Pediatrics, Division of Hospital Medicine, Mailing Address: Seattle Children's Research Institute Building 1, M/S C9S-9, 1900 Ninth Avenue, Seattle, WA 98101, Tamara.Simon@seattlechildrens.org, Phone: (206) 884-1136; Fax: (206) 884-1405.

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The volume of pediatric surgeries related to CSF shunts is considerable in the United States, accounting for nearly 20,000 hospital admissions each year, of which approximately 4,500 are for initial CSF shunt placement, 10,000 for CSF shunt revision, and 3,200 for other CSF shunt surgeries.(7) Infections of CSF shunts account for over 2,000 hospital admissions each year and are associated with extensive 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 $46,000-$62,000 per admission).(7)

The true incidence of shunt infection is difficult to calculate, in part due to a 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 (CDC/NHSN), concerns post-operative (surgical site) infection, and does not attempt to address shunt infection specifically.(8) Other definitions, such as that put forth by the Hydrocephalus Clinical Research Network (HCRN),(9) focus solely on CSF shunts and the various ways infections are diagnosed.

The HCRN consensus definition for CSF shunt infection is: (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 for children with ventriculoatrial shunts, (d) 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.

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% to 8% of cases of malfunction.(11) Shunt malfunction, which leads to 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 most often are 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 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 to 72 hours, it is recommended that anaerobic cultures should 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 was 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 -i.e. proximal, meaning the portion of the shunt extending from the intracranial ventricle to valve, versus distal, meaning the portion of the shunt from the valve to the cavity into which CSF drains. Signs and symptoms of *proximal* shunt infection are less frequent than for 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 usually are a complication 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 are equivocal. One example is the use of prophylactic antibiotics intravenously (IV) during shunt surgeries. Until the mid-1990s, equal numbers of studies demonstrated benefit (13, 25–30) and no benefit.(5, 31–37) Two meta-analyses subsequently demonstrated benefit,(26, 27) and in 1999 prophylactic IV antibiotics were recommended as standard care in the U.S.(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 a 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 will be 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 infections include a

recent shunt insertion or revision, premature birth, young age, neuroendoscope use during shunt insertion, and prior shunt infection.(10, 44–48) Insertion of a shunt after a previous shunt infection is associated with a four-fold increase in the risk of shunt infection. To build on prior work using procedure-specific cohorts, we have 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.(49) (Figure 1) Our multicenter observational studies using HCRN registry and administrative data have identified only three patient factors consistently associated with development of first CSF shunt infection: young age, intervening shunt revision surgeries, and the number of shunt revisions.(48–51) History of a single revision surgery is associated with a 3- to 4-fold higher risk of infection, whereas history of two 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, 48–50)

Infection Prevention Quality Improvement Efforts

Substantial efforts have been taken to prevent CSF shunt infections in recent years that have led to reduction but not elimination of infections.(52, 53) Quality improvement methodology has been shown to prevent surgical site infection (SSI), including neurosurgical shunt infection. Much of the focus has been on standardizing intraoperative practice, which has shown success in HCRN and other cohorts.(9, 54)

Perhaps the largest effort to prevent pediatric shunt infection comes from Solutions for Patient Safety (SPS), a CMS-funded health engagement network of over 100 pediatric hospitals in North America.(55) 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% SSI reduction in a set of procedures within 10 months of implementation of a bundle to which adherence was high (>96%), with reduction of neurosurgical shunt infections from 3.2 to 2.3 per 100 procedures during the same time period.(56) Our subsequent work at a single institution showed that standardization of pre-operative activities such as bathing, *S. aureus* screening, and consistent communication with neurosurgical patients also reduced all post-operative infection, including shunt infections, significantly. (57)

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 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, 58, 59) 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 two intrathecal antibiotics (i.e. vancomycin and gentamicin) for all CSF shunt surgeries (totaling 1,571 surgeries).(9) The HCRN reported both a reduction in the overall Network infection rate from 8.8% prior to the protocol to 5.7% while using the protocol ($p = 0.0028$, absolute risk reduction 3.15%, relative risk reduction 36%), and reductions in per-

procedure infection rates at three of four 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 1,935 procedures performed at 8 centers between January 1, 2012, and September 30, 2013, the overall Network 6-month infection rate before and after implementation were 6.5% and 6.0%, respectively. Overall protocol compliance was 77%. The HCRN concluded that the change in the protocol from instillation of antibiotic through the shunt to antibiotic impregnated shunt tubing did not significantly reduce shunt infection, and that use of either procedure reduced shunt infection compared with use of neither.(54) 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 two surgeries for removal and subsequent replacement of the infected shunt,(12, 15, 19–21, 60, 61) bridged by insertion of an external ventricular drain at the time of shunt removal. (20, 53, 62–66) The length of IV antimicrobial therapy often is based on the organism recovered and duration of positive cultures, with definitive drug choice based upon 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 to 14 days. The Infectious Diseases Society of America (IDSA) recently published guidelines on their management in 2017.(24) Despite aggressive management, re-infection rates range from 20% to 25%.(19–21) Furthermore, CSF shunt infection negatively impacts neurocognitive outcomes (67) and quality of life.(68) In some cases, infection can result in death. (29, 31, 60, 67, 69, 70)

Investigation of Roles of Microbial Diversity and Biofilms

Increasing evidence suggests that CSF shunt infections often are polymicrobial, with most organisms not cultivatable, (71, 72) and that biofilms play an important role in in CSF shunt infection. (73–75) Until recently, the presence of bacteria during disease traditionally was determined by growth of bacteria in conventional culture. (76, 77) By use of culture-independent molecular approaches, the microbiota on and in human tissues, in both health and disease, in shown to more complex than is detectable by culture.(76, 79, 80) 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 eight cases of CSF shunt infection and uninfected controls using quantitative PCR (qPCR) and high-throughput sequencing, we identified small amounts of bacterial and fungal DNA of both cultivatable and non-cultivatable species in CSF of all with CSF shunt infection and in no control CSF.(72) A representative example of the variety of bacterial DNA obtained from a child with *Staphylococcus epidermidis* culture-positive CSF shunt

infection is shown in Figure 2. Surprisingly, the predominant organism detected by this analysis, a *Paenibacillus* sp., was markedly more abundant than was 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 (81), known as biofilms, associated with the shunt catheter surface.(73–75) Biofilms are thought to be responsible for many persistent and chronic infections,(79, 82) and are increasingly understood to play a role in other medical device infections.(83, 84) Biofilm-dwelling bacteria grown *in vitro* are tolerant to antimicrobial activity,(85) a characteristic common among CSF infections. Currently, conventional culture techniques are designed to detect rapidly-growing, liquid-suspended clonal populations of individual microbial species,(76) and may not detect slow-growing organisms residing in surface-adherent biofilms.(81)

Using bacterial PCR-based quantitation, we reported that bacterial DNA was only detectable early in the course of infection, if at all, in most samples of CSF from shunt infections,(71) strengthening the concept that bacteria predominantly occupy shunt-adherent biofilms.

A variety of chronic (79, 82), device-associated (83, 84), biofilm associated infections are observed to be highly resistant to clearance by the immune system, with decreased phagocytosis.(86, 87) 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 decreased compared with activity against planktonic bacteria. Additionally, decreased cytokine activity has been measured in response to biofilm-grown compared with planktonic *S. epidermidis.* (88)

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.(89) *S. epidermidis* PIA knockout mutants (*ica*-) grown in biofilm were observed to be more susceptible to phagocytosis than wild-type biofilm *S. epidermidis* and were also more susceptible to killing by antimicrobial peptides.(86) In another study, *ica*- mutants were observed to be more susceptible to complement killing than wild-type *S. epidermidis.(*87*)*

Other antimicrobial resistance factors in biofilm infections have been identified: slow growth of organisms, glycocalyx production, high density, and adherence to surfaces.(90) Biofilm matrix production has been shown to inhibit the penetrance of oxacillin, cefotaxime, and vancomycin into the deeper layers of the biofilm, but not amikacin and ciprofloxacin.(91) Slow rate of growth and anaerobic growth of microbes in biofilm communities also likely add to antibiotic resistance. *P. 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(92), suggesting that, slow growth rate is not the only factor contributing to antibiotic resistance. It is possible that an abundance of nutrients upregulates

the expression of antimicrobial resistance genes. More experimentation is needed to clarify these issues.

The presence of biofilms on CSF shunts(73–75), the detection of non-cultivatable organisms and biofilms in recalcitrant infections (76, 79, 80, 82), as well as other medical device-associated infections (83, 84) 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 may not generate significant meningeal inflammation. Few of the agents effective for bloodstream or tissue infection, such as β-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 β-lactams and aminoglycosides can be given to drive CSF penetration, but often are limited by systemic toxicity.(93) Additionally, 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 non-surgical 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 currently are 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 peri-operative courses of broad spectrum antibiotics.

A variety of 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 may also impact how we approach treatment of CSF shunt infections. Might there be a role for identification of non-cultivatable species to better define treatment? How does the establishment of biofilm lead to overgrowth (i.e. infection) of a predominant organism? Are biofilm polymicrobial integrated communities or do they consist of single species aggregates dispersed across the shunt surface? Might shunts be epithelialized (as are 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 re-infection?

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 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 burden of disease and the inadequacies of current pathophysiologic 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.

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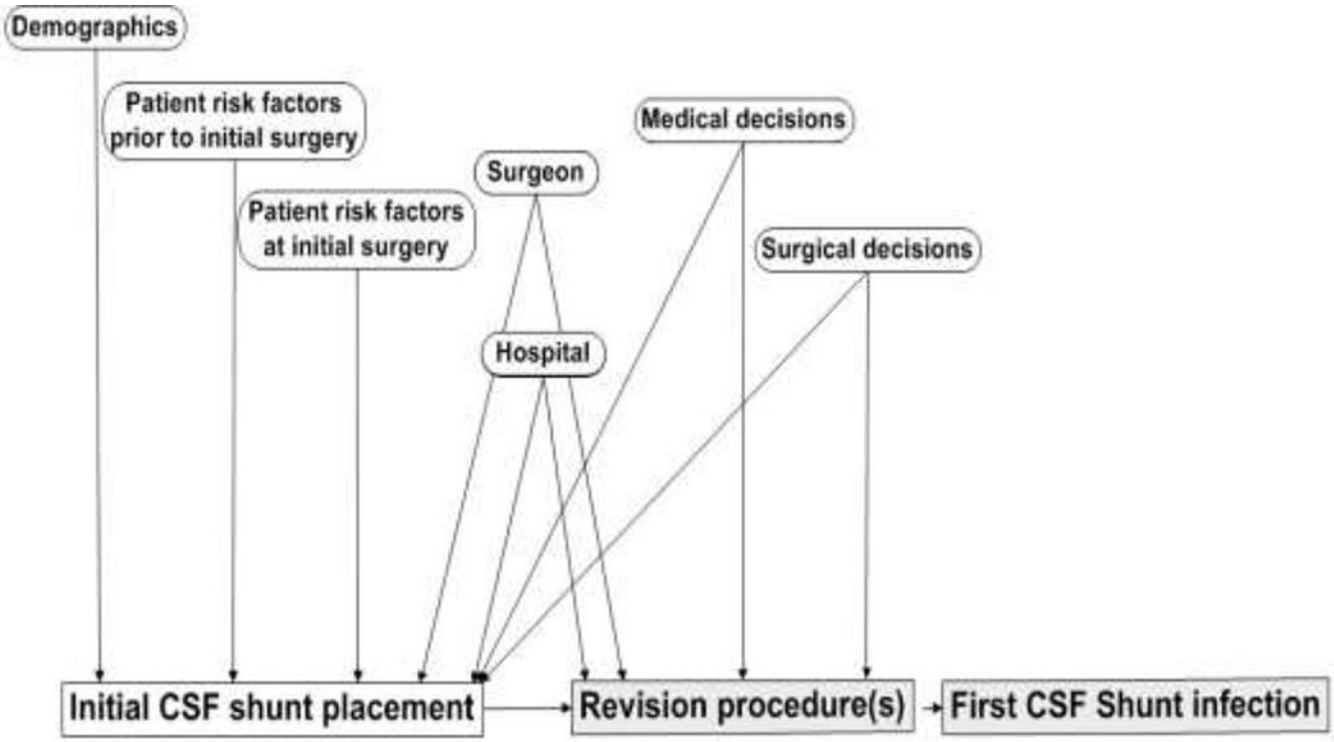

Figure 1.

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*.

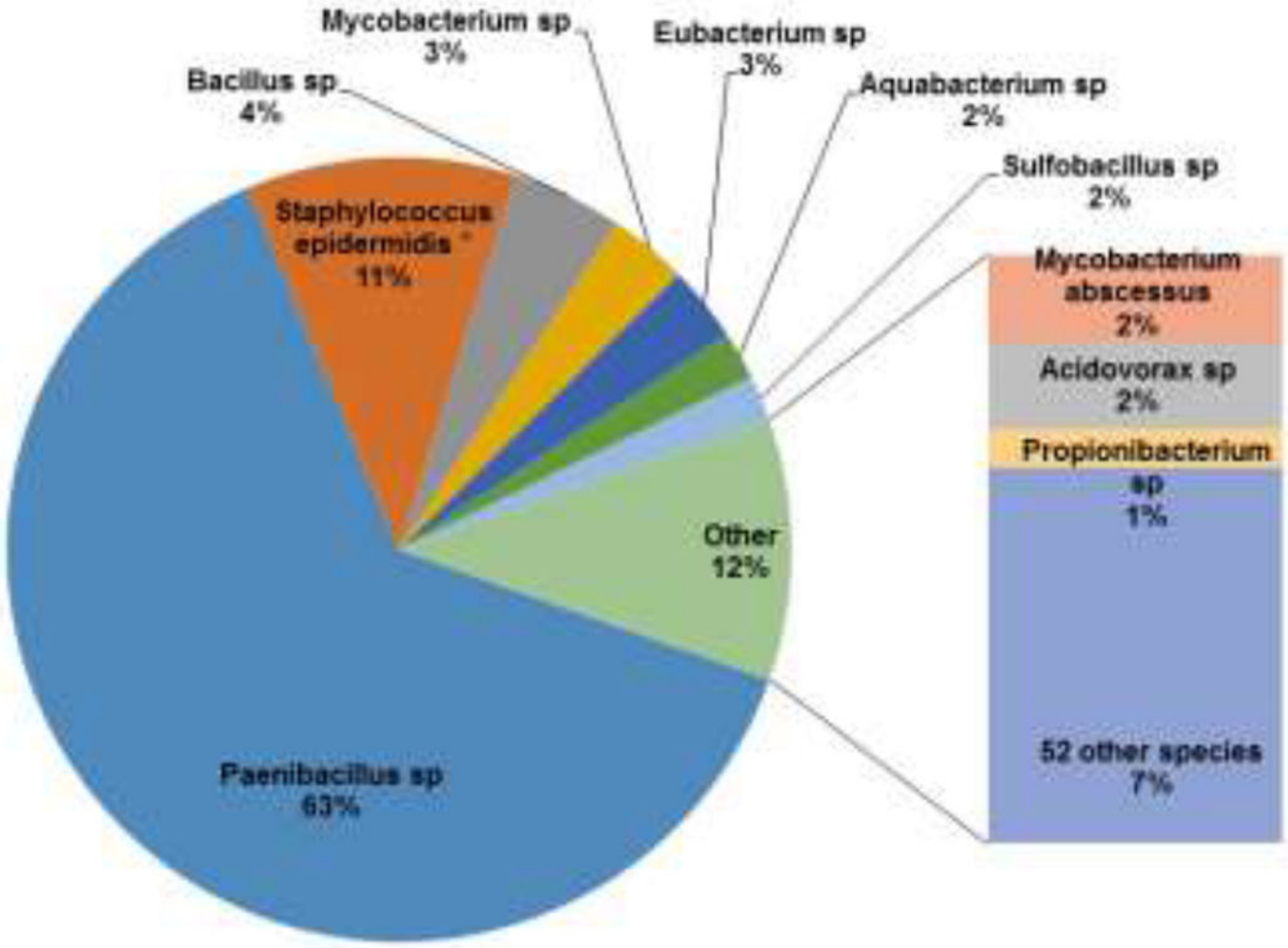

Figure 2.

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 a proportion of all sequence detections in the sample representing bacteria for which detection comprised 1% or more of the total. The sole bacterium that was 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).