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Epidemiology, Prevention and Management of Ventriculoperitoneal Shunt Infections in Children

Julia Prusseit[a] Matthias Simon[b] Christian von der Brelie[b] Axel Heep[a]
Ernst Molitor[c] Sebastian Völz[d] Arne Simon[a]

[a]Children's Hospital Medical Center, [b]Neurosurgery and [c]Institute for Medical Microbiology, Immunology and Parasitology, University of Bonn, Bonn, Germany; [d]Medicinkliniken, Norra Älvsborgs Länssjukhus, Trollhättan, Sverige

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Ventriculoperitoneal shunt · Hydrocephalus · Shunt infection

Abstract
The advent of ventriculoperitoneal shunts (VPS) represented a substantial progress in the neurosurgical management of hydrocephalus in children. VPS infection is the most frequently observed complication. VPS infection is related to substantial morbidity and mortality, and exerts a negative impact on the quality of life of patients. Considerable personnel and financial resources have been devoted to its diagnosis and treatment. This article reviews the current literature and includes suggestions for the prevention, diagnosis and management of VPS infections.

Background

Hydrocephalus is caused by either increased cerebrospinal fluid (CSF) production, impaired liquor absorption, an obstruction of the flow of CSF within the ventricular system (noncommunicating hydrocephalus) or a combination of these factors.

Acquired hydrocephalus can occur secondarily to intraventricular hemorrhage (IVH), meningitis and tumors of the central nervous system. The congenital form is frequently found in patients with Arnold-Chiari malformation, congenital cysts and aqueduct stenosis, or other kinds of malformation [1–4].

Improvements in neonatal intensive care have reduced the mortality rates of infants with an extremely low birth weight (<1,000 g), which run a significantly higher risk of IVH [5]. Up to 2% of these preterm infants eventually develop a posthemorrhagic hydrocephalus and require ventricular shunt therapy [6].

The advent of ventriculoperitoneal shunts (VPS) represented a major progress in the treatment of hydrocephalus. With regard to the ventriculoatrial shunt approach, the draining of liquor into the peritoneal cavity proved to have significant benefits and soon became the standard therapy [7].

In most cases, the shunt device consists of a proximal catheter, a reservoir, a valve to regulate pressure and flow, and a distal catheter. There are 2 general approaches a neurosurgeon can take when it comes to placing the

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PD Dr. Arne Simon
Children's Hospital Medical Center, University of Bonn
Adenauerallee 119
DE–53113 Bonn (Germany)
Tel. +49 2282 8733 254, Fax +49 2282 8733 301, E-Mail asimon@ukb.uni-bonn.de

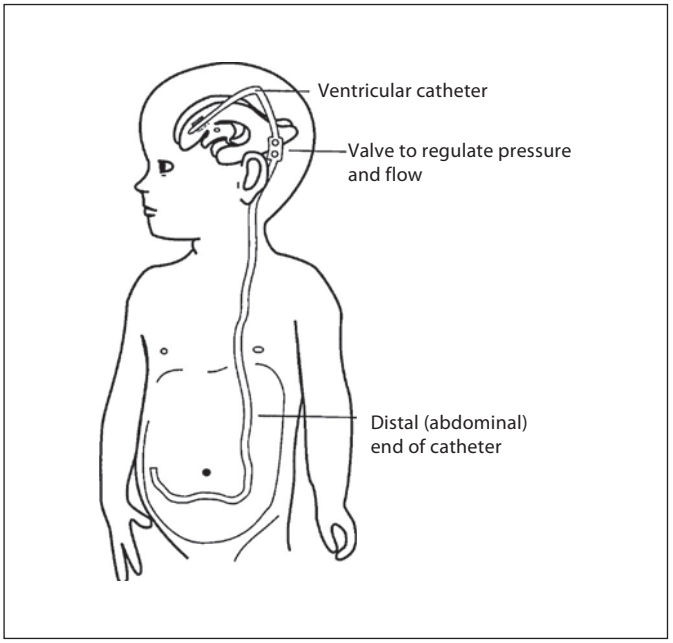

Fig. 1. VPS system.

Table 1. Infection rates and incidence of VPS infections

Author	Year	Patients/ operations	Time period years	Shunt infections, n	Infection rate, %	Incidence %
Odio et al. [20]	1984	297/516	7	59	11.0	19.0
Dallacasa et al. [3]	1995	81/191	12	14	7.8	17.2
Ronan et al. [21]	1995	?/900	10	41	4.5	NA
Rotim et al. [2]	1997	201/382	4.5	36	9.4	17.9
Mancao et al. [19]	1998	145/268	6	29	10.8	20
Baird et al. [46]	1999	?/957	10	94	8.7	NA
Davis et al. [17]	1999	1,193/2,325	10	74	3.0	6
Bruinsma et al. [121]	2000	70/?	7	21	NA	30
Lan et al. [59]	2003	129/?	4.5	10	NA	7.7
Braga et al. [122]	2009	46/98	2	8	19.5	NA
Lima et al. [123]	2007	587/?	NA	16	27.6	NA

NA = Data not available.

proximal catheter. The first, referred to as the posterior approach, is when the proximal catheter is inserted into the lateral ventricle through a small skin incision at the back of the head and a drilled hole in the skull. In the other approach, referred to as the frontal approach, it is inserted through an opening made at the top of the head, just in front of one of the cranial sutures. The distal catheter is then placed subcutaneously and directed towards the peritoneal cavity (fig. 1). The valve does only allow a unidirectional flow; both flow- and pressure-controlled valves are available. The valve opening pressure may be adjusted externally. Hitherto, no particular valve form has proved to be superior to the others for the initial treatment of pediatric hydrocephalus [8, 9].

An infection of the VPS is the most serious complication of ventricular shunt therapy for hydrocephalus. It causes the highest morbidity and mortality, and results in high follow-up costs to health care systems [1].

Epidemiology and Risk Factors

The incidence of VPS infections[1] and the infection rate[2] vary from study to study. There are reported incidence rates of up to 39%; in recent studies, the incidence ranges from 5 to 10% [10–13]. The infection rates range from 3 to 20% [3, 14–22]. Table 1 shows the incidence and infection rates as documented in the literature. The data illustrate that the infection rates are significantly higher than in those documented for surgically implanted intravascular subcutaneous catheter systems [7, 23]. Confirmed risk factors for VPS infections are:

- Low gestational age and preterm birth
- Age at shunt placement (higher risk at younger age)
- Etiology of hydrocephalus (increased risk after IVH, infectious etiology, or children with malignant disease, chemotherapy-associated immunosuppression or long-term application of steroids above the Cushing threshold[3])
- Postoperative CSF leaks caused by impaired wound healing and wound dehiscence
- Number of manual contacts between the neurosurgeon and the shunt system
- Duration of surgical procedure and experience of the surgeon measured by cumulative operative volume
- Single glove use versus intraoperative double gloving strategy.

Several studies documented a significantly higher risk of infection for preterm infants [18]. This association may be explained by the poorly developed humoral and cellular immune system, the immaturity of the skin barrier

[1] Number of observed VPS infections related to all implanted VPS (in percent) during a defined surveillance period.
[2] Proportion of all VPS patients (in percent) who experience a VPS infection during a complete follow-up including secondary events after removal of the first device for any reason.
[3] >0.2 mg/kg/day prednisone equivalent for >4 weeks.

Table 2. Spectrum of pathogens causing VPS infection (%)

	CoNS	*S. aureus*	*Entero-coccus*	Gram-negative	Other
Odio et al. [20]	44	27	2	19	8
Enger et al. [124]	78	11	–	–	11
Ronan et al. [21]	17	30	2	24	5
Kontny et al. [4]	57	4	36	7	14
Mancao et al. [19]	48	24	–	10	7
McGirt et al. [25]	53	26	4	9	4

and the high density of colonizing bacteria on the skin of preterm infants treated in neonatal intensive care units [16, 24]. The infection rate is influenced not only by preterm birth, but also by the age at shunt placement [2–4]. Infants <6 months old run an increased risk [3]; 63% of the children with VPS infection were preterm infants, 29% neonates (≤4 weeks old) and 20% infants (5 weeks to 12 months old). Only 4.6% (1–7 years of age) and 1.6% (8–14 years of age) of the infections were observed in older children ($p < 0.01$) [2]. For each year that the patient was younger, a 4% increase in the risk of shunt infection was observed [25].

In contrast to these observations, other groups did not confirm a significant correlation between gestational age and VPS infection rate [17, 26].

While Dallacasa et al. [3] detected an increased infection rate in patients with VPS and hydrocephalus as a consequence of IVH or meningitis [3], other groups could not confirm this association [17, 18]. In order to gain time, a temporary Rickham reservoir may be implanted. Malresorptive hydrocephalus secondary to IVH shows a self-limiting course in many of the affected children and, eventually, does not demand shunt therapy in all cases. In neonates with meningomyelocele, an early surgical closure within the first 48 h after birth significantly decreases the risk of VPS infection [27, 28].

A postoperative CSF leak significantly increases the risk of an early postoperative infection. In addition, a higher incidence of infections has been observed in case of a development of liquor accumulation along the subcutaneous shunt track. CSF leaks are likely to be the entranceway for bacteria colonizing the skin in the wound area [18]. Thus, postoperative CSF leaks have to be treated immediately with local antiseptics, closed by means of extra sutures and covered with a sterile dressing.

Risk factors, which may be subject to modification, include the surgeon's experience, the duration of the surgical procedure, the degree of manipulation of the VPS during the operation and an intraoperative double versus a single gloving strategy [29, 30]. In a retrospective multicenter study, Cochrane and Kestle [31] showed an association between the surgeon's experience and the infection rate.

In addition to that, Kulkarni et al. [18] stated that frequent contact between shunt and the neurosurgeon's gloves increased the risk of infection (hazard ratio = 1.07; 95% CI = 1.11–1.74; $p = 0.009$). Invisible material defects of up to 20% of all surgical gloves probably account for this [18]. Wearing 2 layers of gloves and the avoidance of unnecessary contact with the implantable shunt material may reduce the risk [29, 32].

Bacterial Pathogens

Most VPS infections are caused by Gram-positive opportunistic pathogens colonizing the skin of the patient [4, 19–21, 25, 33]. Coagulase-negative staphylococci (CoNS) have been detected in 17–78% of the cases (table 2), and *Staphylococcus epidermidis* accounts for 47–64% of all Gram-positive VPS infections [34]. *Staphylococcus aureus* was detected in 4–30% of all cases (table 2).

Departments with an early postoperative *S. aureus* infection rate of >15% should consider the possibility of an outbreak, genotype the isolates and scrutinize the concept of hospital hygiene and infection prevention [35].

CoNS often form an extracellular matrix built of glycoproteins that facilitate their adhesion to fibrin-coated devices and the forming of a tenacious biofilm [36–38]. The masses of bacteria that are encased in this biofilm are protected from both the immune system and antimicrobials which can hardly penetrate the biofilm.

Therapy resistance against glycopeptide antibiotics has been observed in VPS infections due to *S. epidermidis* but also *Staphylococcus lugdunensis* and *Staphylococcus haemolyticus*. Therefore, the attending microbiological laboratory should display species identifications and its determination of the in vitro minimal inhibitory concentrations.

Gram-negative bacteria were detected in 7–24% of all VPS infections [39]. In most cases, common nosocomial Gram-negative pathogens have been involved, such as Enterobacteriaceae and nonfermenters (e.g. *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*). The detection of Gram-negative bacteria may be related to an intraperitoneal inflamma-

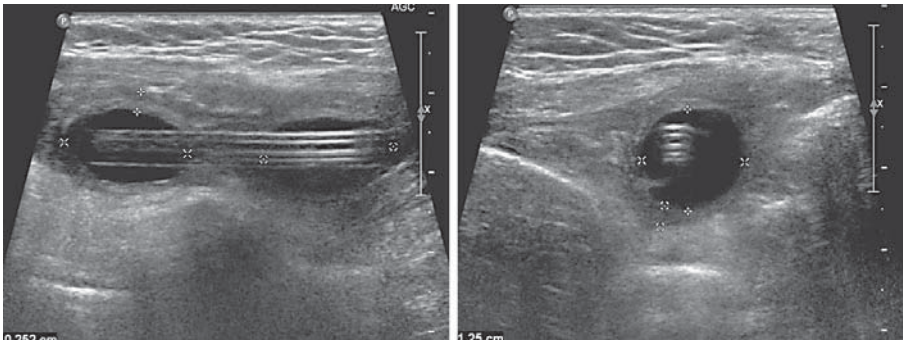

Fig. 2. Pseudocysts around the intraperitoneal VPS catheter.

tion or to a hematogenous spread from another focus. Asymptomatic perforations of the bowel wall by the distal tip of the catheter have been reported. Pseudocysts (fig. 2) may develop secondarily from VPS infections or a malposition of the distal catheter tip [40, 41]. Children treated in a pediatric intensive care facility run an increased risk of being colonized with Gram-negative bacteria on the skin and mucosa. Intraoperative contamination should be considered a possible cause of early postoperative VPS infection [39].

Anaerobic bacteria, in particular *Propionibacterium acnes*, were also detected as causative agents [42, 43]. These infections were mostly early postoperative events that presented as soft-tissue and bone infections [44].

Classic causative agents for pyogenic meningitis at child's age (group B *Streptococcus, Streptococcus pneumoniae* and *Neisseria meningitidis*) accounted for only 5% of the reported VPS infections.

VPS infections caused by *Candida* spp. have rarely been reported, and merely in premature neonates and highly immunocompromised patients [45]. Despite the consensus that most causative agents for VPS infections arise from the patient's own microbial flora, current published studies report an association between causative agent and isolated organisms by perioperative swab samples in only 20% of all cases. Several authors detected a contamination of the surgical instruments and covering used in the operation theater, which should therefore be considered to be a potential additional source of VPS infection.

Latency Period between Surgery and Infection

The time period between surgery and first occurrence of VPS infection as documented in the current literature ranges from 15 days to 12 months after shunt placement; 80% of the infections occur within the first 3 months, 90% within the first 6 months. Several studies have revealed that infections due to Gram-positive bacteria (CoNS, *S. aureus*) mostly start within the first 8 weeks after surgery. Therefore, it can be assumed that most VPS infections are caused by intraoperative or early postoperative contamination with a subsequent colonization of the shunt with bacteria belonging to the skin flora [11, 46]. Secondary infectious events due to Gram-negative bacteria and *Candida* spp. tend to occur later in the clinical course.

Symptoms

The symptoms of VPS infection are often fastidious and nonspecific. Fever (orally or rectally measured temperature of >38.5°C) and malfunction of the VPS are the leading signs. In every patient with VPS and fever, an infection of the VPS has to be ruled out [11]. Fever was observed in 42–87% (mean: 77%) of all VPS infections, which permits the conclusion that afebrile patients may suffer from VPS infection as well [47]. Every malfunction of the VPS may be a sign of infection. Further clinical signs are headache, vomiting, lethargy to the point of unconsciousness. Neonates and infants may present with a marked increase in head circumference. Vomiting without fever is often a sign of VPS malfunction [22, 33]. Seizures in patients with hydrocephalus are common (patients with 1 or more event: 6–59%). Patients with epilepsy quite frequently present shunt malfunction and VPS infection in combination with seizures [48, 49].

Patients with infections related to the intra-abdominally placed distal end of the catheter present with abdominal pain, food intolerance and clinical signs of peritonitis. The spontaneous draining of an infected pseudocyst into the peritoneal cavity frequently causes acute peritonitis [7, 50–53]. In the same manner, intra-abdom-

Table 3. Clinical symptoms in patients with VPS infection (%)

	Kontny et al. [4] (n = 28)	Mancao et al. [19] (n = 29)	Odio et al. [20] (n = 59)	Ronan et al. [21] (n = 49)	Turgut et al. [1] (n = 35)
Fever	96	62	87	72	77
Shunt malfunction	50	0	0	36	54[1]
Local tenderness	25	69[2]	81	27	–
Vomiting	0	–	39	24	69
Meningism	21	–	0	20	20
Cellulitis	0	24	19	15	11
Abdominal pain	36	17	22	15	0
Lethargy	0	0	0	12	0

[1] Included headache and cerebral seizures.
[2] Included vomiting, local tenderness and meningism.

inal infections and surgical interventions such as the implantation of a percutaneous endoscopic gastrostomy can cause VPS infection [50, 54, 55].

Infections along the subcutaneous course of the catheter present with local redness, swelling, heat, induration and liquor accumulation along the shunt track. Table 3 shows the distribution of the symptoms as documented in 5 representative studies.

The great variability and missing specificity of the symptoms do not permit a tentative clinical diagnosis. Shunt infections (and shunt malfunction) are neurosurgical emergencies that require immediate and appropriate treatment. In case of a suspected shunt infection, complementary diagnostic measures must instantly be undertaken.

Diagnostic Panel

The diagnosis of VPS infection is based on liquor pleocytosis and corresponding clinical symptoms (fever, VPS malfunction, newly emerged neurological or abdominal symptoms) [20]. Diagnosis can be difficult and demands clinical experience. In sporadic cases of infection with unknown focus in children with VPS, catheter removal is performed only on suspicion of a VPS infection. An increased liquor cell count (pleocytosis; >15/μl; in neonates: >32/μl) is an important diagnostic parameter. The liquor cell count is dependent on a multitude of factors. To define a generally accepted cell count that clearly indicates infection is therefore not possible. Not all patients with VPS infection caused by CoNS display a pleocytosis [33]. An increased liquor cell count may also be observed in VPS patients without infection.

Pleocytosis subsequent to infection during the first 14 days after complex neurosurgical intervention cannot be discriminated from pleocytosis secondary to the trauma of the intervention. In this scenario, clinical presentation is critical. McClinton et al. [33] detected an increased average liquor cell count in patients with VPS infection compared to the levels of those with VPS malfunction (2,197 ± 4,510/μl vs. 49 ± 169/μl; $p < 0.001$). The CSF neutrophil count was increased in patients with infection (>10%) [33].

Liquor pleocytosis (WBC >100/μl and >10% granulocytes) in patients with VPS and fever showed a sensitivity of 82%, a specificity of 99%, a positive predictive value of 93% and, in case of <10% granulocytes, a negative predictive value of 95% [33].

Several studies used liquor eosinophilia (>5%) as a diagnostic marker for an infection. It has been assumed that staphylococci trigger the activation of eosinophils and their migration into CSF. Another possible cause of liquor eosinophilia is intolerance to or allergy against shunt material, the shunt system's antimicrobial impregnation or residuals of ethylene dioxide subsequent to sterilization [56–58].

Increased protein levels (>45 mg/dl; in neonates: >90 mg/dl) and a decreased liquor glucose concentration (liquor/serum ratio: ≤0.4; in mature neonates: ≤0.6) may indicate an infection; however, normal glucose and protein concentrations do not rule out infection [11, 12, 59]. In a severe infection of the central nervous system, especially as a result of neurosurgical treatment, increased liquor lactate levels are common (>4 mmol/l).

The interpretation of systemic laboratory parameters of inflammation such as C-reactive protein [60, 61], interleukin-6 and -8 [62–64], and procalcitonin [65] in regard to VPS infection remains an unresolved issue. Negative C-reactive protein values do not rule out a VPS infection.

Liquor cultures prior to empirical antimicrobial treatment are mandatory in order to allow a specific pharmacological therapy during the course of the treatment. On reasonable suspicion of a VPS infection, the results of microbiological liquor diagnostics must not be awaited to start antibiotic therapy. CSF should be acquired for cultural diagnostics by tapping the shunt system's subcutaneous liquor reservoir, which is in direct contact with the ventricular system [21]. In case of disturbed liquor drainage or noncommunicating ventricles, liquor that has been drawn from a lumbar tap may remain sterile despite confirmed ventriculitis [7, 66].

Ideally, liquor acquired under aseptic conditions should immediately be transported without cooling to a microbiological laboratory. After centrifugation of the sample, the sediment is Gram-stained and cultivated both in a fluid medium and on agar disks.

An inoculation of liquor into blood culture bottles (for example during night or weekend duty) is possible but may lead to a 24-hour delay in the cultivation of single colonies, the identification of the infectious agent and in vitro sensitivity testing.

Both the native CSF and the inoculated blood culture bottles should be stored at least at room temperature (ideally at 35°C) and should be transported to a microbiological laboratory as soon as possible.

The detection of a causative agent is successful in only 50% of the cases. The detection of *S. epidermidis* can be impaired by biofilms and the occurrence of so-called small colony variants [67].

Vanaclocha et al. [68] collected data of 54 cases of VPS infection. Only 9% showed positive liquor cultures, whereas the detection of the infectious agent by cultivating explanted shunt material showed a colonization in 59% of all cases.

A liquor culture may remain negative if the patient has undergone previous antimicrobial treatment or if the acquisition or inoculation of the liquor sample is not sufficient. No more than 20% of all VPS infections are accompanied by positive blood cultures [12], a finding that might be based on the fact that there is no direct drainage of liquor into the bloodstream in VPS. Prior to antimicrobial treatment, both liquor and blood cultures should be collected. An immediate cultivation of the explanted shunt catheter often leads to the detection of the responsible pathogen [68].

Routine imaging techniques in case of suspected VPS infection include cranial CT and cranial ultrasound (in neonates) in order to evaluate ventricle width, and native X-ray in case of scheduled shunt removal. Abdominal ultrasound and abdominal MRI or CT may be of importance in the emergency diagnostics of infectious and mechanical intra-abdomial complications (such as pseudocysts) (fig. 2).

Nonpharmacological Prevention

The safest method for preventing shunt infection is to not implant a shunt system at all. Advancement in neuroendoscopy and particularly in the field of endoscopic third ventriculostomy present an important alternative to VPS implantation; success rates for endoscopic third ventriculostomy range between 65 and 75% [15].

The general recommendations for the prevention of nosocomial infections have to be applied to any contact with patients with VPS as well.

Hands must be disinfected before and after each patient contact [69]. Manipulation in the area of the operation wound should be minimized and may only be accepted under aseptic conditions. Patients and parents have to be informed about the possibility of infection and typical clinical symptoms [70].

If possible, the time of surgical intervention should be carefully deliberated, considering that the postoperative infection risk decreases with a child's age. Especially in regard to preterm infants and neonates, the temporary implantation of a Rickham reservoir should be considered.

A thorough repeated skin disinfection of the operation field with an approved antiseptic, with due consideration of the necessary residence time, and sterile coverings around the operation field are required [71]. Hair in the immediate area of the operation field is not to be shaved but cut by means of sterile scissors [70, 71]. Intraoperative manipulation of material and skin should be kept to an absolute minimum [18, 72, 73].

A study of Thompson et al. [74] turned the attention to a possible bacterial colonization of the shunt system during the early phase of wound healing. Hitherto, there have been no controlled studies investigating the frequency of postoperative wound dressing changes and the repeated application of antiseptics in the area of the primarily closed wound. In either case, the accurate application of hygiene standards in wound dressing changes (hand disinfection and no-touch technique in direct contact with the sterile wound dressing material) is recommended to avoid an infection of the wound [71]. A postoperative liquor fistula has to be diagnosed at an early stage and immediately treated with a suture [18].

Perioperative Antibacterial Prophylaxis

The available data on the effect of perioperative antibacterial prophylaxis are incomplete, but published studies reveal a high potential for improving the standard workflow [75, 76]. As in the therapy for meningeal infection, the eligible antibiotics should act in a bactericidal manner and have the capacity to penetrate the blood-brain barrier in sufficient amounts. Perioperative antibiotics should always be applied 30–60 min prior to an operation [77].

Even the commonly used single-shot prophylaxis (operation duration: <4 h; >2.5 times the elimination half-life of the antibiotic substance applied) may foster the selection of resistant pathogens [78].

A recently published survey concerned with the routine of single-shot prophylaxis in 45 neurosurgical centers [79] showed that each center uses preoperative antibacterial prophylaxis. The introduction of perioperative antibiotic prophylaxis has helped to decrease the incidence of VPS infections [11, 33, 80]. A current Cochrane report documented a decreased VPS infection risk with antibiotic prophylaxis (odds ratio: 0.52; 95% CI: 0.36–0.74) [32].

It is reasonable to administer a second-generation cephalosporin (for example cefuroxime 50 mg/kg) or ampicillin/sulbactam (50 mg/kg) 30–60 min before skin incision. Repeated administration is only necessary if the duration of surgery exceeds 4 h. A further extension of the prophylactic administration period is not supported by reliable evidence. Clindamycin has been used as an alternative substance in patients with penicillin allergy [79]. With the exception of data on cerebral toxoplasmosis in patients with HIV infection, there is only very limited information on the capability of clindamycin to penetrate the blood-brain barrier. Nevertheless, clindamycin shows good penetration into soft tissue and bone [81, 82]. A prophylactic intraoperative, intraventricular application of gentamicin or vancomycin has been recommended by some experts as an adjuvant measure [83].

The choice of antibiotic regime as preoperative prophylaxis may be influenced by the colonization of a patient with resistant bacterial pathogens. In these cases, consultation of a microbiologist or a specialist for pediatric infectious diseases might be necessary. Single-shot prophylaxis with a glycopeptide in children colonized by methicillin-resistant *S. epidermidis* (MRSE) or *S. aureus* (MRSA) is not recommended and may have severe side effects [84]. The concentration of vancomycin in CSF after a single intravenous dose is commonly below the minimal inhibitory concentration of the corresponding pathogens [85]. Prior to any elective surgical intervention in children with MRSA colonization, a decolonization attempt should be made with mupirocin nasal ointment, octenidine or polyhexanide washing solutions, and – in case of gastrointestinal colonization [86] – with oral administration of co-trimoxazole and rifampicin (in vitro sensitivity?) [87, 88].

Application of Antimicrobially Active Shunt Materials

Hitherto, there has been a number of studies including mostly adult populations that showed a statistically significant reduction in VPS infections by the use of antibiotically impregnated shunt catheters (AIS; rifampicin with or without minocycline or clindamycin) [32]. According to the above-mentioned Cochrane meta-analysis, the application of AIS reduces the risk of VPS infection (odds ratio: 0.21; 95% CI: 0.08–0.55) [89]. Pattavilakom et al. [32] performed 243 operations in 178 patients. The applied shunt catheters were impregnated with rifampicin and clindamycin. Compared to a historical control group (7 years; 36 infections in 551 VPS operations) there was a statistically significant reduction in VPS infections from 6.5 to 1.2% ($p = 0.0015$). The antimicrobial activity of the shunt catheter impregnation persisted up to 127 days [90]. Sciubba et al. [91] documented 211 pediatric patients with 353 shunt placement procedures: 208 (59%) of the VPS were placed with nonimpregnated catheters, 145 (41%) with AIS. Of all the patients with nonimpregnated catheters, 25 (12%) developed a VPS infection, whereas only 2 patients (1.4%) with AIS experienced shunt infection within the 6-month follow-up period ($p < 0.01$).

A multivariate analysis revealed that AIS were independently associated with a 2.4-fold decrease in the likelihood of shunt infection [91]. However, most of the published studies use either historical control groups [92] or refer to a rather small number of cases [15, 90]. Kan and Kestle [93] observed a lower infection rate for AIS in a pediatric patient group (5.0 vs. 8.8% in the control group), but the number of patients in this study (80 patients/group) was too small to confirm a significant benefit.

It has to be noted that several of the studies investigating the use of AIS showed very high infection rates in the control groups. One may speculate whether the positive effect of AIS might have been accomplished by other means of prevention as well [94].

Treatment

Infections with colonized synthetics coated with a tenacious biofilm cannot be effectively treated by routine administration of antibiotics. For this purpose, it would require local in vivo concentrations that are 100–1,000 times higher than the minimal inhibitory concentration of the corresponding pathogen [38].

In most cases, infected shunts are removed in time. If there is no liquor pleocytosis but intra-abdominal infection and, therefore, a risk of colonization of the distal end of the shunt catheter, the peritoneal end has to be externalized, and antimicrobial treatment is started [95]. Nevertheless, the removal of the whole VPS may be required during the course of a progressing infection. However, in case of superficial soft-tissue infection and lymphadenopathy, preliminary observation and conservative inpatient treatment may be attempted.

In case of imperative ventricle shunting, external ventricular drainage is performed subsequent to the removal of the VPS. Morissette et al. [96] recommend external ventricle draining, antimicrobial treatment up to 7 days after a new contralateral VPS implantation. Schreffler et al. [97] confirmed the benefits of this strategy. As soon as the CSF is sterile and inflammatory parameters are no longer detectable, the placement of a new VPS system may be undertaken [12, 95].

Complete recovery from a VPS infection may be assumed with a sterile CSF specimen after 72 h without antimicrobial treatment and the absence of clinical signs of infection.

Empirical Antimicrobial Treatment

According to the US American authors and the Infectious Diseases Society of America (IDSA) guidelines of 2004, empirical therapy for suspected VPS infection should be carried out with a glycopeptide, if necessary in combination with ceftazidime, cefepime or meropenem [12].

Relatively high rates of MRSA in US American neurosurgical units may explain these recommendations [98]. However, controlled prospective and randomized studies with a sufficient number of patients, comparing glycopeptides with other antibiotics, are hitherto not available.

The predominantly bacteriostatic effect of glycopeptides (vancomycin 60 mg/kg/day; teicoplanin 20 mg/kg/day; adapted dose recommendations for preterm infants and neonates; vancomycin trough level: 15–20 mg/l) correlates with the duration of time during which the concentration in the target area is above the minimal inhibitory concentration of the corresponding pathogen (goal: protracted phase with concentration of >10 times the minimal inhibitory concentration) [99–101]. Teicoplanin is neither nephrotoxic nor ototoxic and may be administered once daily as a 30-min infusion [102, 103]. In order to prevent the development of the life-threatening 'red man syndrome', vancomycin should be administered as a 1-hour infusion. Some isolates of *S. haemolyticus* show an intrinsic resistance to teicoplanin.

The attending microbiological laboratory should provide the clinicians with information on the minimal inhibitory concentration of the different antimicrobial therapy options in regard to the detected pathogen.

In contrast to the US American guidelines, the German Paul Ehrlich Society for Chemotherapy recommends ceftriaxone plus fosfomycin as an initial empirical treatment of secondary meningitis in children and adolescents, flucloxacillin plus fosfomycin in infections with Gram-positive bacteria, and ceftazidime or cefepime plus tobramycin in infections with Gram-negative bacteria. Glycopeptides, meropenem and rifampicin are listed as second-line options [104].

Cefepime has shown good efficacy against both Gram-negative infections (with the exception of extended-spectrum β-lactamase-producing isolates) and Gram-positive infections (with the exception of MRSE, MRSA, *Enterococcus* spp. and *Listeria monocytogenes*) and has been approved for the treatment of meningitis in children [104–108]. Treatment with cefepime in combination with fosfomycin may be an effective option for the initial empirical treatment of VPS infections [expert opinion].

In case of suspected Gram-negative infection, for example after intestinal perforation or forming of an abdominal pseudocyst, antimicrobial therapy with piperacillin/tazobactam or meropenem should be considered [expert opinion]. It has to be noted that even VPS infections subsequent to an abdominal infection are often caused by Gram-positive pathogens. The adjuvant administration of rifampicin may be beneficial after the detection of an in-vitro-sensitive Gram-positive pathogen.

Rifampicin may not be administered as a monotherapy due to the risk of developing one-step resistance [12]. Rifampicin affects the hepatic metabolism of several other drugs and, before administration, the risk of drug interaction has to be considered.

Multiresistant Gram-negative bacteria often require therapy with meropenem or ciprofloxacin. Fluoroquinolones have been approved by the American Academy of Pediatrics as an option for severe infections caused by multidrug-resistant pathogens for which there is no safe and effective alternative [109].

In case of persistently positive CSF cultures, intrathecal administration of vancomycin and aminoglycosides may be considered [1, 11, 12, 110]. In case of CoNS infections with teicoplanin-sensitive pathogens, both systemic administration and additional intrathecal administration are options [111, 112]. Reports of the intrathecal

administration of tobramycin, amikacin, colistin and amphotericin B have been published as well [34]. In contrast to the internationally accepted standard (early shunt catheter removal) [47, 113], Brown et al. [110] recommended a conservative therapy approach in patients with well-functioning VPS and a confirmed CoNS infection (overall success rate: 84%). Their therapy algorithm included the mandatory intrathecal application of vancomycin, combined with a systemic administration of rifampicin. The cumulative level of scientific evidence for the intrathecal treatment approach in children is low. Neurotoxicity, allergic reactions and substance-induced inflammatory reactions are possible side effects. Particularly in neonates and preterm infants, potential benefits should be thoroughly balanced against possible short- and long-term adverse effects.

Preliminary data suggest a successful treatment of VPS infection caused by MRSE, MRSA or glycopeptide-resistant *Enterococcus faecium* with linezolid [109, 114–118]. The treatment with linezolid, however, should be restricted to infections with particular multiresistant Gram-positive pathogens; due to the risk of severe neurotoxic side effects, the administration period should be limited to 21 days.

In VPS infections caused by *Candida* spp., an immediate removal of the VPS and antifungal treatment with high-dose fluconazole and liposomal amphotericin B is mandatory [119].

Duration of Antimicrobial Treatment

After VPS removal, the antimicrobial treatment of the VPS infection should be extended to 7 days (CoNS) and 14–21 days (*S. aureus,* Gram-negative bacteria and *Candida* spp.) after the first negative CSF culture, respectively [12, 95]. There are no randomized studies available which prospectively investigate the duration of antibiotic treatment after shunt removal in case of an infection with *S. aureus*, Gram-negative pathogens or *Candida* spp. Therefore, it seems prudent to refer to common practice in analogy to the treatment of other device-associated infections [120].

Prospects

The incidence of VPS infections in most neurosurgical units is >5% [15]. Prevention, early detection and instant treatment reduce morbidity and (particularly in case of Gram-negative infections) mortality in patients suffering from this severe complication of shunt placement.

In recent years, the overall mortality has been >15%, but the percentage of patients with neurological residuals could be reduced to 10%, which was interpreted as a positive result concerning adjustments in empirical treatment. Preoperatively administered antibacterial prophylaxis [80] according to consensus guidelines and improvements in neurosurgical procedure have contributed to a lower incidence of VPS infection [11, 23, 33, 80]. Both aspects may be improved in regard to their clinical implementation, which may be facilitated by setting written local standards.

Prospective randomized studies are needed to confirm the positive results concerning the application of AIS systems, to increase the sensitivity and specificity of diagnostics and to evaluate the risks and benefits of the adjuvant intrathecal administration of antimicrobials.

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