Management of infections associated with neurosurgical implanted devices

Anna Conen, Christoph A. Fux, Peter Vajkoczy & Andrej Trampuz

To cite this article: Anna Conen, Christoph A. Fux, Peter Vajkoczy & Andrej Trampuz (2016): Management of infections associated with neurosurgical implanted devices, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2017.1267563

To link to this article: http://dx.doi.org/10.1080/14787210.2017.1267563
Management of infections associated with neurosurgical implanted devices

Anna Conen1, Christoph A. Fux1, Peter Vajkoczy2 and Andrej Trampuz3

1Clinic of Infectious Diseases and Hospital Hygiene, Department of Internal Medicine, Kantonsspital Aarau, Aarau, Switzerland; 2Department of Neurosurgery, Charité - Universitätsmedizin Berlin, Berlin, Germany; 3Center for Musculoskeletal Surgery, Charité - Universitätsmedizin Berlin, Berlin, Germany

ABSTRACT

Introduction: Neurosurgical devices are increasingly used. With it, neurosurgical device-related infections gain relevance. As biofilms are involved in implant-associated infections the diagnosis and treatment is challenging and requires specific anti-biofilm concepts and management algorithms.

Areas covered: The literature concerning the management of neurosurgical device-associated infections is scarce and heterogeneous treatment concepts are discussed, but no standardized diagnostic and treatment procedures exist. Therefore, we emphasize extrapolating management strategies predominantly from orthopedic device-associated infections, where the concept is better established and clinically validated. This review covers infections associated with craniotomy fixation devices, cranioplasties, external ventricular and lumbar drainages, internal shunts and neurostimulators.

Expert commentary: Sonication of the removed implants significantly improves microbiological diagnosis. A combined surgical and antimicrobial management is crucial for successful treatment: appropriate surgical intervention is combined with prolonged anti-biofilm therapy of usually 12 weeks. In selected patients, new treatment algorithms enable cure of neurosurgical device-associated infections without implant removal or with a one-stage implant exchange, considerably improving the quality of patient lives.

1. Introduction

The use of implants to treat age-related disease conditions gains increasing interest in the context of the demographical evolution, not only in orthopedic patients with prosthetic joint replacement but also in neurology and neurosurgery [1]. In the United States, an estimated 450,000 neurosurgical implants are inserted annually, about 3–15% of which become infected [1]. Numbers of implanted and infected neurosurgical devices will increase; therefore, the need for an effective diagnostic and treatment management in neurosurgical implant-associated infections is emphasized [2,3]. The most commonly used neurosurgical implants are fixation devices for craniotomy or cranioplasty, synthetic cranioplastics, internal shunt systems, external ventricular and lumbar drainages, and neurostimulators.

With older age, not only cerebrovascular diseases increase, but also neoplasms with consecutive brain metastases. Decompressive craniectomies and craniotomies for diagnostic and therapeutic purposes are performed. Theretofore, the removed piece of skull is replaced and fixed with titanium fixation devices. Alternatively, a titanium or synthetic cranioplasty is used instead. In case of a chronic hydrocephalus, a permanent drainage of cerebrospinal fluid (CSF) may be necessary. This can be achieved by an internalized shunt system, draining the CSF into the right atrium (ventriculoperitoneal [VP] shunts) or – more commonly – into the peritoneal space (ventriculoperitoneal [VP] shunts). In case of an acute rise of intracranial pressure which compromises CSF circulation, for example, after intracerebral bleeding, intercurrent percutaneous CSF drainage can be achieved by an external ventricular drainage (EVD) or external lumbar drainage (ELD). Deep brain stimulators are one of the newest treatment modalities in the management of Parkinson’s disease and other movement disorders, whereas spinal cord stimulators are increasingly used to treat chronic refractory pain syndromes mostly due to degenerative spine diseases.

As biofilms are involved in implant-associated infections, the diagnosis and treatment is difficult. With newer diagnostic methods such as sonication, the diagnostic yield can be improved [4]. For antimicrobial treatment, drug combinations with anti-biofilm agents have to be administered [5–8]. In addition, in device-associated infections involving the central nervous system (CNS), the individual CSF penetration levels of antimicrobial agents have to be considered. Implant-associated infections are associated with high morbidity, mortality, and health-care costs. Usually, they require additional surgical interventions, which are not trivial facing the fact that CNS is involved. In orthopedic patients, revision surgery of an infected prosthetic joint is three times more expensive than primary implantation [1,9,10]. For neurosurgical implants, excess costs can only be estimated but probably will be even higher.

The literature concerning the management of neurosurgical device-associated infections is scarce and heterogeneous
treatment concepts are discussed which often include a complete device removal. This can be very bothersome for the patient compromising quality of life. As no standardized diagnostic and treatment procedure exists, many concepts need to be extrapolated from other implant-associated infections.

The aim of this review is to resume the pathophysiological aspects of implant-associated infections and to discuss the current diagnostic and treatment challenges. The management strategy will mainly be extrapolated from orthopedic device-associated infections, where the concept is well established and clinically validated. This review will cover the most commonly used neurosurgical implants, including craniotomy fixation devices, cranioplasties, internal shunt systems, external ventricular and lumbar drainages, and neurostimulators.

2. Concept of biofilm and pathogenesis of infection of neurosurgical implants

Implants are highly susceptible to bacterial colonization. As few as 100 bacteria in contact with a device are enough to cause infection during or shortly after surgery [11,12]. Within a few minutes, bacteria adhere to the implant surface, multiply and embed themselves in a matrix consisting of extracellular polymeric substances (EPS). This three-dimensional community of bacteria attached to a surface and embedded in EPS is called biofilm [13]. The biofilm protects microorganisms from the host immune system and renders them tolerant to antimicrobial treatments, because microorganisms are in a stationary growth phase with a slow replication rate [13]. Many antibiotics, including betalactams or vancomycin, exclusively kill replicating bacteria. Therefore, they have no activity against biofilms in vivo despite being fully active in vitro. In addition, the granulocyte function is disturbed in the peri-implant region, called frustrated phagocytosis [11].

The vast majority of neurosurgical implants becomes infected by exogenous colonization with bacteria of the skin or mucosal flora. The colonization occurs in the preoperative stage trough skin defects or open wounds, intraoperatively through contamination of the implant, or postoperatively during wound healing, particularly in case of a persistent wound drainage [11,12,14]. Rarely, and almost exclusively VA shunts, neurosurgical implants become infected through hematogenous seeding from a distant site of infection. Due to the endovascular placement of VA shunts, hematogenous infection any time after implantation during bacteremia is possible. This is in contrast to prosthetic joints, which are hematogenously infected in about 30% of cases [15].

3. Risk factors for neurosurgical implant-associated infections

There are many perioperative risk factors known to be associated with neurosurgical device-associated infections, which are principally the same as for other surgical site infections. The predominant risk factors for post-craniotomy infections are the presence of EVD with an odds ratio (OR) of 7.2 (95% confidence interval [CI] 2.9–18.1), the administration of preoperative chemotherapy with an OR of 5.2 (95% CI 2.3–11.6), and the presence of a postoperative CSF leakage with an OR of 3.5 (95% CI 1.4–8.5) [16–18]. Other risk factors are not only contaminated wound classes, including contamination class 2 with an OR of 3.2 (95% CI 1.2–8.1) and contamination class 3 with an OR of 8.0 (95% CI 2.6–24.5), morbid obesity (OR 3.1, 95% CI 1.4–6.8), and emergency operations (OR 3.0, 95% CI 1.1–8.1), but also chronic steroid use, prior hospitalization for longer than 1 day and prolonged duration of surgery [16–19].

For shunts, risk factors for infection are previous shunt infection (relative risk (RR) 3.8, 95% CI 2.4–6.1), postoperative CSF leakage (hazard ratio 19.2, 95% CI 7.0–52.9), the use of a neuroendoscope (RR 1.6, 95% CI 1.0–2.5), but also advanced age, shunt revision for dysfunction, longer duration of shunt surgery, and the experience of the neurosurgeon [20–22]. For EVD, risk factors for infection are intraventricular and subarachnoid hemorrhage, cranial fracture with CSF leakage, duration of catheterization, and EVD irrigation [23–25]. For ELD, the following risk factors for infection have recently been described: duration of catheterization longer than 4 days (OR 6.1, 95% CI 1.8–20.4), drainage site leakage (OR 13.6, 95% CI 4.1–45.7), and length of hospitalization (for the duration of 16–20 days, OR 3.5 (95% CI 1.5–8.1) and for the duration ≥21 days, OR 5.8 (95% CI 2.1–16.2)) [26].

4. Classification of neurosurgical implant-associated infections

The classification of neurosurgical device-associated infections is extrapolated from other implant-associated infections [14,15,27]. The classification is essential for the determination of the management strategy, as discussed in the Section 6.

Early or acute infections occur within 4 weeks after device implantation (Table 1). Clinical presentation usually is acute with fever and local signs of inflammation, including local warmth, erythema, swelling, tenderness, and wound drainage. In early device-associated infections, an ‘immature’ biofilm is present and therefore eradication of infection with implant retention is successful if rigorous surgical debridement is followed by a 12-week anti-biofilm therapy. Delayed and late infections occur after 4 weeks of device implantation (delayed within 1 year and late after 1 year of implantation). The clinical presentation is low grade with persistent wound drainage or fistula. A ‘mature’ biofilm is present and eradication of infection with implant retention is very unlikely. Therefore, implant removal or exchange in a one-stage or two-stage procedure is necessary, followed again by a 12-week anti-biofilm therapy if an implant is in place. The concept of ‘immature’ and ‘mature’ biofilm is based on in vitro observations [6], experimental in vivo models [6–8,28], and clinical studies [5,29,30] but has also recently been reviewed by Bjarnsholt et al. [31].

EVD and ELD are exceptions to this classification, since they are temporary implants, which are in place for only a few days to weeks. In case of infection, they usually can be exchanged or even removed without replacement. Because of their temporary placement, no anti-biofilm therapy is needed and should be discarded, as resistant strains may emerge and compromise treatment of potential later infections of permanent implants, including shunt systems.
5. Sonication in the diagnosis of neurosurgical implant-associated infections

To optimize diagnosis in biofilm-associated infections, sonication of removed implant components and prolonged incubation of cultures is recommended [4]. By sonication, microorganisms are released from the implant surface and can qualitatively and quantitatively be detected from the detached biofilm in the sonication fluid. Compared to tissue cultures, sensitivity of sonication fluid is significantly higher with 80–90% compared to 60%. In particular, sensitivity is higher in case of antimicrobial pretreatment (75% with sonication vs. 45% without sonication) [4]. The specificity is high with 99%, which allows distinction of contamination and infection, especially if skin flora is cultured.

Sonication was initially evaluated in prosthetic joints, but seems to be useful for other implants as well, including osteosyntheses, cranioplasties, and catheter tips of EVD and shunt systems [32–34]. The sensitivity for detecting osteosynthesis-associated infections was 90.4% for sonication fluid and 56.8% for peri-implant tissue cultures (p < 0.05), for polymicrobial infections, it was 20.8% and 8.0%, respectively (p < 0.001) [32]. In a case report, successful sonication and pathogen identification in a low-grade cranioplasty-associated infection were demonstrated, detecting coagulase-negative staphylococci and Prevotella spp. Both pathogens were missed in tissue cultures [33]. Sonication of EVD (14 patients) and VP shunts (13 patients) was performed in 27 patients [34]. Sonication of EVD tips was significantly more likely to detect bacterial growth (9 of 14 cases, 64%) than cultures of aspirated ventricular CSF (2 of 14 cases, 14%; p < 0.05). This is explained by the fact that microorganisms grow on the implant surface as biofilm and are not detectable as planktonic bacteria in the CSF. In five patients with a positive sonication culture of the EVD tip but a negative CSF culture, results were interpreted as contamination: one patient became afebrile after EVD removal, two developed meningitis a few days after EVD removal, and two remained asymptomatic. In the VP shunt group, there was no significant difference between positive culture results of CSF and sonication fluid of VP shunts, possibly due to low patient numbers: bacterial growth was detected in 62% (8 of 13 cases) of sonicated VP shunts and 45% (5 of 11 cases, CSF not cultured in 2 cases) of the corresponding intraoperative CSF samples.

It is important to note that in case of EVD removal for sonication, the cutaneous exit site should be disinfected and air-dried before the catheter is pulled out. The ventricular catheter tip then is aseptically cut and placed in a sterile tube. Otherwise, skin flora of the EVD catheter exit site will be cultured, which has no diagnostic importance.

6. General treatment concept of neurosurgical implant-associated infections

In this section, the general treatment concepts of implant-associated infections are discussed (Figure 1). The specific treatment concepts for the individual neurosurgical implants are described in the Section 7. These recommendations are valid for permanent implants only, that is, fixation devices for craniotomy, cranioplasty, internal shunt systems, and neurostimulators. EVD and ELD are intercurrent implants and usually completely removed in case of infection. Therefore, treatment is shorter and without anti-biofilm antibiotics.

Successful treatment requires an interdisciplinary management and includes a combination of appropriate surgery and anti-biofilm therapy, which should include bactericidal antimicrobial drugs [15,27]. Surgery is necessary to remove necrotic tissue and to reduce bacterial load, that is, to mechanically clean the implant in acute infections or exchange the implant if symptom duration is longer than the proposed 4 weeks. The postoperative soft tissue coverage of the implant is a prerequisite for success; otherwise, the implant is at risk for consecutive superinfection with selected microorganisms of the skin flora.

The implant management strategy depends on two factors, namely the antimicrobial susceptibility pattern of the causing pathogen (susceptibility vs. non-susceptibility to anti-biofilm treatment) and the symptom duration (acute infections with symptom duration of less than 4 weeks vs. delayed or late infections with longer symptom duration). Without anti-biofilm therapy and in case of a long symptom duration, which is associated with a ‘mature’ biofilm, eradication of infection without implant removal or exchange, respectively, is unlikely.

Anti-biofilm therapy includes rifampin combinations against staphylococci and Propionibacterium spp. as well as fluoroquinolones against gram-negative bacilli (Tables 2 and 3). Antimicrobial treatment combinations with bactericidal activity generally are
preferred. If the infected compartment includes the CNS, sufficient CSF penetration of the antimicrobial agents is a prerequisite for success [35]. In addition, higher drug doses are recommended for CNS infections. Rifampin acts bactericidal also in the stationary growth phase of staphylococci and has a good CSF penetration (achieving 56% of plasma levels in CSF). Because of a rapid emergence of resistance in case of monotherapy, rifampin must always be combined with another antimicrobial agent with a good CSF penetration, for example, cotrimoxazole (i.e. trimethoprim/sulfamethoxazole; CSF penetration 40–50% of plasma levels), levofloxacin (30–50% of plasma levels), moxifloxacin (>50% of plasma levels) or doxycycline (26% of plasma levels). Treatment failure due to acquired rifampin resistance has been observed in shunt infections with coagulase-negative staphylococci treated with intravenous vancomycin and rifampin. This can be explained by insufficient CSF penetration of vancomycin resulting in rifampin monotherapy in the CNS [14]. In addition, rifampin should not be used in case of persistent wound drainage because of the risk of consecutive superinfection with selected rifampin-resistant microorganisms of the skin flora [36]. For gram-negative bacilli, ciprofloxacin is the only anti-biofilm therapy and has a CSF penetration of about 26% of plasma levels [5,35,37,38].

If the microorganism is known and susceptible to anti-biofilm therapy, then surgery includes implant debridement and retention in early infections (i.e. symptom duration up to 4 weeks), or a one- or two-stage implant exchange with a short (i.e. 2 weeks) implant-free interval at any time of infection. In all these cases, surgery is followed by a 12-week anti-biofilm therapy. The implant-free interval may be prolonged in case of severe soft tissue damage that does not allow adequate postoperative wound closure.

If the microorganism is not susceptible to anti-biofilm therapy, cure is possible only with implant removal and reinsertion usually after 6 weeks of postoperative antibiotic treatment, when the infection is eradicated. In shunt-associated infections, the implant-free interval can be shortened from 6 to 1 week (in case of coagulase-negative staphylococci or Propionibacterium acnes), 2 weeks (Staphylococcus aureus, Streptococcus spp., Enterococcus spp., and culture-negative infections), or 3 weeks (gram-negative bacilli), because CNS infections (i.e. meningitis) without implant are usually cleared after a shorter treatment duration. Alternatively, if implant removal is not possible, long-term antimicrobial suppression therapy can be discussed.

Agents for long-term antimicrobial suppression therapy are cotrimoxazole and doxycycline in case CNS is involved, and additionally clindamycin, if CNS is not involved. The following microorganisms are considered difficult to treat, as no anti-biofilm treatment is available: rifampin-resistant staphylococci, quinolone-resistant gram-negative bacilli, Enterococcus spp., and Candida spp.

7. Specific infections

7.1. Post-craniotomy and cranioplasty-associated infections

Craniotomy refers to the surgical removal of a section of the skull, the so-called bone flap, to access the intracranial

![Image of treatment algorithm](image-url)
Table 2. Antimicrobial treatment of neurosurgical device-associated infections according to the causing microorganism, CNS not involved.a

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Intravenous treatment, daily dose (2 weeks)</th>
<th>Oral treatment, daily dose (10 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em> or coagulase-negative staphylococci, <em>methicillin susceptible</em></td>
<td>Flucloxacillin 4 × 2 g IV OR Cefazolin 3 × 2 g IV&lt;sup&gt;a&lt;/sup&gt; OR Vancomycin 2 × 15 mg/kg body weight IV&lt;sup&gt;b&lt;/sup&gt; PLUS in all regimens Rifampin 2 × 450 mg PO&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Levofloxacin 2 × 500 mg PO OR Cotrimoxazole 3 × 960 mg PO&lt;sup&gt;d&lt;/sup&gt; OR Doxycycline 2 × 100 mg PO OR Fusidic acid 3 × 500 mg PO PLUS in all regimens Rifampin 2 × 450 mg PO&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>S. aureus</em> or coagulase-negative staphylococci, <em>methicillin resistant</em></td>
<td>Vancomycin 2 × 15 mg/kg body weight IV&lt;sup&gt;e&lt;/sup&gt; OR Daptomycin 1 × 8 mg/kg body weight IV PLUS in all regimens Rifampin 2 × 450 mg PO&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Levofloxacin 2 × 500 mg PO OR Cotrimoxazole 3 × 960 mg PO&lt;sup&gt;d&lt;/sup&gt; OR Doxycycline 2 × 100 mg PO OR Fusidic acid 3 × 500 mg PO PLUS in all regimens Rifampin 2 × 450 mg PO&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>Penicillin 4 × 5 Mio U IV OR Ceftriaxone 1 × 2 g IV&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Amoxicillin 3 × 750–1000 mg PO</td>
</tr>
<tr>
<td><em>Enterococcus species&lt;sup&gt;a&lt;/sup&gt;, penicillin susceptible</em></td>
<td>Amoxicillin 4 × 2 g IV PLUS Gentamicin 1 × 3 mg/kg body weight IV&lt;sup&gt;n&lt;/sup&gt; OR Amoxicillin 4 × 2 g IV PLUS Ceftriaxone 2 × 2 g IV PLUS consider for both regimens Fosfomycin 3 × 5 g IV</td>
<td>Amoxicillin 3 × 1000 mg PO</td>
</tr>
<tr>
<td><em>Enterococcus species&lt;sup&gt;a&lt;/sup&gt;, penicillin resistant</em></td>
<td>Vancomycin 2 × 15 mg/kg body weight IV&lt;sup&gt;e&lt;/sup&gt; OR Daptomycin 1 × 10 mg/kg body weight IV PLUS consider for both regimens Fosfomycin 3 × 5 g IV PLUS for both regimens Gentamicin 1 × 3 mg/kg body weight IV&lt;sup&gt;n&lt;/sup&gt;</td>
<td>Linezolid 2 × 600 mg PO</td>
</tr>
<tr>
<td><em>Propionibacterium acnes</em></td>
<td>Penicillin 4 × 5 Mio U IV OR Ceftriaxone 1 × 2 g IV&lt;sup&gt;f&lt;/sup&gt; PLUS in all regimens Rifampin 2 × 450 mg PO&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Levofloxacin 2 × 500 mg PO PLUS Rifampin 2 × 450 mg PO&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>Amoxicillin/Clavulanate 3 × 2.2 g IV OR Ceftriaxone 1 × 2 g IV&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Ciprofloxacin 2 × 750 mg PO</td>
</tr>
<tr>
<td>Non-fermenters (e.g. <em>Pseudomonas aeruginosa</em>), quinolone-susceptible</td>
<td>Cefepime 3 × 2 g IV&lt;sup&gt;i&lt;/sup&gt; OR Cefadizime 3 × 2 g IV&lt;sup&gt;i&lt;/sup&gt; OR Piperacillin/Tazobactam 3 × 4.5 g IV&lt;sup&gt;i&lt;/sup&gt; OR Meropenem 3 × 2 g IV&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Ciprofloxacin 2 × 750 mg PO</td>
</tr>
<tr>
<td>Culture-negative infection</td>
<td>Amoxicillin/Clavulanate 3 × 2.2 g IV PLUS Rifampin 2 × 450 mg PO&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Levofloxacin 2 × 500 mg PO PLUS Rifampin 2 × 450 mg PO&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Adapted from Zimmerli et al. [15] and Kleber et al. [27].

CNS: Central nervous system; IV: intravenous; PO: oral.

<sup>a</sup>Including post-craniotomy and cranioplasty-associated infections, neurostimulator-associated infections without brain lead infection.

<sup>b</sup>In case of a non-type I allergic reaction to penicillin use intravenous cefazolin, in case of a type I allergic reaction to penicillin use intravenous vancomycin.

<sup>c</sup>Start rifampin as soon as all drainage sites are removed and wounds are dry.

<sup>d</sup>One cotrimoxazole double-strength tablet (960 mg) contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

<sup>e</sup>Goal: Vancomycin trough level 15–20 mg/l, measure at least twice weekly; start rifampin only if trough level is in the therapeutic range.

<sup>f</sup>In case of a non-type I allergic reaction to penicillin use intravenous ceftriaxone.

<sup>i</sup>Measure aminoglycoside trough levels and creatinine to monitor for toxicity at least twice weekly.

<sup>n</sup>Measure vancomycin trough levels to monitor for toxicity at least twice weekly.

Infections usually manifest early at median of 1.5 months (range, 4 days - 5 years) after craniotomy. The most common causing pathogens are not only *S. aureus* and coagulase-negative staphylococci but also gram-negative bacilli [40,41]. In 50 patients included in a study by Dashti et al., the predominant symptoms were...
Table 3. Antimicrobial treatment of neurosurgical device-associated infections according to the causing microorganism, CNS involved.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Intravenous treatment, daily dose (2 weeks)</th>
<th>Oral treatment, daily dose (10 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus or coagulase-negative staphylococci, methicillin susceptible</strong></td>
<td>Penicillin 4 × 5 Mio U IV OR Meropenem 3 × 2 g IV&lt;sup&gt;b&lt;/sup&gt; OR Vancomycin 2 × 15 mg/kg body weight IV&lt;sup&gt;a,c&lt;/sup&gt; PLUS in all regimens Rifampin 2 × 600 mg PO&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Ceftriaxone 2 × 2 g IV PLUS Vancomycin 2 × 15 mg/kg body weight IV&lt;sup&gt;b&lt;/sup&gt; PLUS Rifampin 2 × 600 mg PO&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>S. aureus or coagulase-negative staphylococci, methicillin resistant</strong></td>
<td>Vancomycin 2 × 15 mg/kg body weight IV&lt;sup&gt;c&lt;/sup&gt; PLUS Rifampin 2 × 600 mg PO&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus species</strong></td>
<td>Penicillin 4 × 5 Mio U IV OR Ceftiraxone 2 × 2 g IV&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Enterococcus species&lt;sup&gt;a&lt;/sup&gt;, penicillin susceptible</strong></td>
<td>Amoxicillin 6 × 2 g IV PLUS Fosfomycin 3 × 5-8 g IV PLUS Consider gentamicin 1 × 3 mg/kg body weight IV&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Enterococcus species&lt;sup&gt;a&lt;/sup&gt;, penicillin resistant</strong></td>
<td>Vancomycin 2 × 15 mg/kg body weight IV&lt;sup&gt;c&lt;/sup&gt; PLUS Fosfomycin 3 × 5-8 g IV PLUS Consider gentamicin 1 × 3 mg/kg body weight IV&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Propionibacterium acnes</strong></td>
<td>Penicillin 4 × 5 Mio U IV OR Ceftiraxone 2 × 2 g IV&lt;sup&gt;e&lt;/sup&gt; PLUS in all regimens</td>
<td></td>
</tr>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td>Rifampin 2 × 600 mg PO&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Non-fermenters (e.g. Pseudomonas aeruginosa), quinolone-susceptible</strong></td>
<td>Ceftazidime 3 × 2 g IV&lt;sup&gt;i&lt;/sup&gt; OR Meropenem 3 × 2 g IV&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Culture-negative infection</strong></td>
<td>Ceftriaxone 2 × 2 g IV PLUS</td>
<td></td>
</tr>
</tbody>
</table>
cranioplasty material (autologous vs. allogeneic) nor of the time point of cranioplasty (early within 3 months vs. late more than 3 months after craniectomy) with infection [47]. Limitations of this review are the inclusion of predominantly retrospective studies with the inherent risk of recall and observer bias, the lack of uniform definitions of infection and complication, and the variability of follow-up time. But recently, an association between infection and a time interval of more than 2 weeks until cranioplasty was described in an observational cohort of 754 cranioplasties [41]. Therefore, not only for cosmetic reasons and brain protection, but also because of a potentially lower infection risk, timely cranioplasty should be considered.

In both, post-craniotomy and cranioplasty-associated infections, the distinction between superficial and deep wound infections is not possible because the superficial and deep compartments are in contiguity after surgery. Therefore, all infections should be considered as deep and bone flap-/cranioplasty-associated. Surgical revision with debridement of necrotic tissue and evacuation of pus is necessary, as is debridement or exchange of the implant, depending on the duration of infection and the susceptibility pattern of the microorganism (Figure 1). The current clinical practice in post-craniotomy and cranioplasty-associated infections is the removal of the bone flap or implant and delayed cranioplasty after weeks to months, once the infection is cleared. Newer concepts inspired by the orthopedic literature include debridement and retention of the infected bone flap or cranioplasty in acute infections or immediate (one-stage) cranioplasty at any time of infection if soft tissues are preserved. Alternatively, a two-stage exchange of the implant with only a short (i.e. 2 weeks) implant-free interval is possible. Both strategies include a 12-week anti-biofilm therapy postoperatively (Table 2). These newer concepts may lead to better cosmetic results and brain protection.

7.2. VP and VA shunt-associated infections

Neurosurgical shunt systems are permanent implants used in the presence of chronic communicating hydrocephalus as a result of intracerebral hemorrhage or infection, in case of an obstructive hydrocephalus secondary to tumors or congenital malformations, or in case of a normal pressure hydrocephalus in elderly people [2,14,48,49]. Normal pressure hydrocephalus increases with age with a pooled prevalence of 1.3% in subjects older than 65 years of age [2]. Two different shunt systems are used for CSF drainage either into the peritoneal cavity – the VP shunt – or into the right atrium – the VA shunt. The infection rate is about the same for both systems (5–15% for VP and 2.5–12% for VA shunts), but VA shunts require significantly more revisions due to dysfunction (49.7% in VA vs. 33.8% in VP shunts, p < 0.001) [50,51]. In addition, complications in VA shunts are more severe and include myocardial injury, cardiac arrhythmias, distal disconnection, and intra-atrial migration, intra-cardiac thrombi with subsequent pulmonary embolism or endocarditis with consecutive septic embolism. Difficult revisions may explain the higher mortality in VA shunts reported in older studies [51–53]. Nowadays, VP shunts are generally preferred because of the lower complication rate. However, in patients with previous abdominal surgery, a history of peritonitis, morbid obesity, and previous VP shunt failure, VA shunts are chosen. In these patients, not only the perioperative complication risk in abdominal surgery is increased, but also CSF resorption is impaired because of peritoneal fibrosis and adhesions due to previous surgery and infections, which leads to dysfunction of the abdominal shunt part.

In a retrospective analysis including 78 adult patients with neurosurgical shunt systems, shunt infection was mainly acquired intraoperatively through shunt contamination (72%) or early postoperatively (27%) through skin wounds (proximal and distal shunt part) and perforated gut (distal shunt part in VP shunts) [14]. For VA shunts, hematogenous seeding from a distant site of infection is possible, as found in one patient. The predominant microorganisms involved in shunt infections are coagulase-negative staphylococci (37%), S. aureus (18%), P. acnes (9%), and polymicrobial infections (15%) including gram-negative bacilli [14]. In early infections, mainly microorganisms of the skin flora are found, that is, coagulase-negative staphylococci, S. aureus, and P. acnes, whereas in delayed and late infections, mainly polymicrobial infections due to wound dehiscence and gut perforation of the distal VP shunt part.

Shunt infections can present with few or no clinical signs and symptoms [14]. Chronic low-grade shunt infection often results in shunt dysfunction manifesting as hydrocephalus (e.g. headache, vomiting, and seizures). Of 78 patients, only 78% had fever, 64% neurological signs or symptoms, and 49% local signs of infection. Nevertheless, symptom duration before infection diagnosis was usually short with a median of 5 days (range, 0–21 days). The clinical presentation depends on which shunt part is infected. Proximal shunt infections manifest with signs of ventriculitis, meningitis, or shunt dysfunction. Distal shunt infections in VP shunts manifest with signs of peritonitis, pseudoappendicitis, or intraabdominal pseudocysts detected by sonography or computed tomography scan. In VA shunt infections, fever, signs of right sided endocarditis and shunt nephritis are typically present [14,48,49,54]. Chronic VA shunt infections by coagulase-negative staphylococci or P. acnes may persist for weeks or months before endocarditis and immune complex-mediated shunt nephritis occur. These severe late complications of a chronic low-grade VA shunt infection were recently presented in a case report [54]. A 26-year-old woman with congenital hydrocephalus and a VA shunt in place since 14 years complained of fever and myalgia. Blood and CSF investigations as well as echocardiography were without pathologies at the initial visit; the patient was then lost to follow-up. Four years later, she presented with end-stage renal disease requiring hemodialysis. A kidney biopsy revealed immune complex-mediated glomerulonephritis and echocardiography right-sided endocarditis. P. acnes was cultured in CSF collected from the shunt system. The shunt was explanted, a third ventriculocisternostomy performed and the patient treated with 4 weeks of intravenous penicillin and at a later stage a kidney transplant. The diagnostic yield of different CSF collection sites was studied in a retrospective analysis, comparing CSF from ventricular, lumbar, or shunt valve puncture [14]. Overall, CSF leukocyte count was elevated in only 80%. Leukocyte counts were
significantly higher in lumbar and shunt valve puncture with median 573 and 484 cells/µl compared to ventricular CSF with median 8.5 cells/µl (p < 0.001 and p = 0.016, respectively). This possibly reflects differences in inflammation and CSF flow in patients with hydrocephalus. Alternatively, it could be explained by the fact that lumbar and shunt valve punctures were performed in patients with more advanced shunt infections. CSF cultures were positive in 66% overall, with the highest positivity rate in CSF from shunt valve puncture (91%), compared to ventricular (70%) and lumbar (45%) CSF, respectively. The high microbial density close to the biofilms at the site of infection might explain these results, which was also supported by a relatively high positivity rate of shunt tip cultures with 78% (when the study was performed, no sonication was available; it can be expected that with sonication, the shunt tip positivity rate would have been even higher). However, differences in the rate of antimicrobial pretreatment might play a role as well. Blood cultures are particularly important in VA shunt infections with positivity rates of at least 83%, explained by the endovascular position of the implant, whereas in VP shunt infections, the diagnostic yield is low with a positivity rate of only 11% [14].

No standardized treatment algorithm for shunt infections exists. The only randomized trial of 50 patients was published in 1981, comparing cure rates of 3 different treatment strategies: shunt removal, one-stage shunt exchange, and shunt retention [55]. Patients were treated with 2 weeks of intraventricular combined with 3 weeks of systemic antimicrobial therapy. No anti-biofilm therapy with rifampin was used. Cure rates were 95% with shunt removal, 88% with one-stage shunt exchange, and only 36% if no revision surgery was performed. The predominant pathogens involved in this study were coagulase-negative staphylococci in 62%.

In a retrospective observational study of 78 patients, 81% were treated with a combined surgical and antimicrobial therapy and 19% with an antibiotic treatment only [14]. The overall cure rate was 96%, being 98% in the combined and 87% in the conservative treatment group. The combination treatment group included shunt removal without replacement (47%) and a one- (10%) or two-stage shunt exchange with or without an intermittent EVD (23%). Overall, only two patients had an infection relapse, one in the combined and one in the antimicrobial alone treatment group. Both relapses were caused by coagulase-negative staphylococci with newly acquired rifampin resistance. Both patients initially received a vancomycin and rifampin treatment combination. It was speculated that insufficient CSF vancomycin levels due to the low CSF penetration rate of vancomycin resulted in a functional rifampin monotherapy in CSF with the emergence of resistance. In addition, insufficient vancomycin trough levels could have contributed to the failure; however, these were not measured in this retrospective study. Based on these results, it is recommended to treat such patients if possible with the combination of ceftriaxone and rifampin, because of a much better CSF penetration of ceftriaxone compared to vancomycin; alternatively, an initial high-dose single vancomycin treatment for a few days may reduce the bacterial load before switching to the oral combination. Overall, these data show that both retention and immediate shunt replacement are efficient. In Table 3, treatment recommendations are summarized. In contrast to post-craniotomy and cranioplasty-associated infections, CSF penetration of the antimicrobial treatment is a prerequisite for success in shunt-associated infections. Furthermore, in VA shunt infections, longer intravenous treatment durations may be mandatory in case of a secondary infective endocarditis [39].

An algorithm for the management of shunt infections is proposed in Figure 2. If a shunt infection is suspected, CSF should preferably be collected from shunt valve puncture. In case of pathological CSF results (i.e. CSF leukocyte count >5 × 10^6 cells/µl, with predominantly granulocytes, CSF lactate levels >1.9 mmol/l, and total protein levels >0.45 g/l as well as a decreased glucose CSF/blood ratio <0.5), empiric treatment should cover the predominant pathogens with intravenous vancomycin (2 × 15 mg/kg body weight daily) plus an intravenous cephalosporin (ceftriaxone 2 × 2 g or cefepime 3 × 2 g or ceftazidime 3 × 2 g daily according to local surveillance data). If there is acute infection, absence of ventriculitis, abscess, shunt dysfunction, skin erosion, or gut perforation and if the microorganism is known to be susceptible to anti-biofilm therapy, the implant can be retained or immediately exchanged. Thereafter, the patient should be treated for 12 weeks with a CSF-penetrating anti-biofilm therapy. In all other cases, the shunt should be explanted and reinsered once the infection is cleared – in case of coagulase-negative staphylococci or P. acnes usually after 5–7 days, in case of S. aureus, Streptococcus spp., Enterococcus spp., and culture-negative infections after 14 days, and in case of gram-negative bacilli after 21 days. Eventually an intercurrent EVD/ELD needs to be inserted. If CSF culture is still positive at the time of shunt reimplantation, a 12-week anti-biofilm therapy is recommended with the new implant in situ. If CSF culture is negative at the time of shunt reimplantation, a 4-week anti-biofilm therapy should strongly be discussed, in particular if an intercurrent EVD/ELD was in place, making persistent infection on the EVD/ELD more likely. With this strategy, any remaining viable microorganism should be eradicated.

7.3. External ventricular and lumbar drainages

In contrast to the other neurosurgical implants mentioned in this review, which are permanent, EVD and ELD are temporary implants. They are used to treat acute hydrocephalus, for example, after intracranial or subarachnoid bleeding, acute meningitis, or head trauma. In Table 4, the differences between internalized shunts and EVD/ELD, respectively, are contrasted. The fact that 44% of patients with an external CSF drainage require a permanent shunt at a later time point represents a challenge in case of an ongoing EVD- or ELD-associated infection [56].

The overall infection risk of external CSF drainages lies between 10% and 15% [23,24,26,57,58]. EVD and ELD indwelling times have been found to be associated with the infection risk: the latter is increasing over the first 10 days with a peak after 7–11 days, and markedly lower thereafter. This is contra-
intuitive, as one would expect the infection risk to be linear as shown for central venous catheters [23,24,26,59]. Changes in risk profiles over time may explain part of the results, which are not free from confounding, especially in the continuously smaller patient population at risk. In a study of 48 patients with an EVD, the median indwelling time was 7 days (range, 1–39 days) and the infection occurred at median of 6 days (range, 1–17 days) [56]. Interestingly, 23% of patients with an EVD-associated infection only presented within 10 days after EVD removal, what implies that one must be aware of EVD-

Table 4. Comparison of infections associated with ventriculoperitoneal and ventriculoatrial shunts and external ventricular and lumbar drainages, respectively.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Ventriculoperitoneal and ventriculoatrial shunt</th>
<th>External ventricular and lumbar drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection risk</td>
<td>5–15%</td>
<td>10–15% (increases with duration of catheterization)</td>
</tr>
<tr>
<td>Risk factors for infection</td>
<td>Serial revisions</td>
<td>Catheter irrigation</td>
</tr>
<tr>
<td></td>
<td>Postoperative CSF leakage</td>
<td>Duration of catheterization</td>
</tr>
<tr>
<td></td>
<td>Previous infection</td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Prolonged duration of surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal infections*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infections with secondary bacteremia*</td>
<td></td>
</tr>
<tr>
<td>Infection acquisition</td>
<td>Intraoperative</td>
<td>Contiguous</td>
</tr>
<tr>
<td></td>
<td>Contiguous (skin wound, perforated gut *)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematogenous*</td>
<td></td>
</tr>
<tr>
<td>At the end</td>
<td>Shunt dysfunction, hydrocephalus</td>
<td>Up to 44% require an internal shunt</td>
</tr>
</tbody>
</table>

CSF: Cerebrospinal fluid.
*Ventriculoperitoneal shunts.
#Ventriculoatrial shunts.

Figure 2. Proposed management algorithm for shunt-associated infections. Adapted from Conen et al. [14].
Abbreviations: CSF: Cerebrospinal fluid; EVD: external ventricular drainage; ELD: external lumbar drainage; IV: intravenous.
* Pathological CSF results: CSF leukocyte count >5x10^6 cells/µl, with predominantly granulocytes, CSF lactate >1.9 mmol/l, CSF total protein >0.45 g/l, glucose CSF/blood ratio <0.5
# Blood cultures especially in ventriculo-atrial shunt infections recommended
§ For low-virulent microorganisms, including coagulase-negative staphylococci and P. acnes, re-implantation after 5–7 days; for S. aureus, Streptococcus spp., Enterococcus spp. and culture-negative infections 14 days; for Enterobacteriaceae and P. aeruginosa 21 days.
associated meningitis also in patients in whom EVD has been removed. This has also been shown by Jost et al. in the sonication study of EVD catheter tips [34]. In five patients with positive EVD sonication cultures, the respective CSF culture results were negative or interpreted as contamination. Two of these five patients developed overt meningitis a few days after EVD removal. We strongly believe that sonication improves early recognition of EVD-related infections. Patients whose removed EVD tips are densely colonized may be considered at high risk for developing meningitis and merit close clinical follow-up.

Low-virulent microorganisms cause most of the infections associated with external CSF drainages. Culture results are positive in about 77%. Coagulase-negative staphylococci are the predominant microorganisms found in 63%, P. acnes in 15% and polymicrobial infections in 21% [56]. Nearly all EVD-associated infections are acquired through external contamination because of repetitive manipulations on the system (e.g., regular CSF collection for diagnostic purposes) and/or via EVD colonization with skin and environmental flora. Microorganisms contiguously spread along the drainage tube to the internal EVD system and the CSF.

In the context of a suspected EVD- or ELD-associated infection, the interpretation of clinical signs and symptoms and CSF results is difficult. The primary medical condition leading to the EVD/ELD placement itself, for example, intracerebral bleeding or infection, may cause identical pathological clinical (fever and alterations in Glasgow Coma Scale) and CSF findings. Nevertheless, patients with an external CSF drainage-associated infection usually present with signs of ventriculitis and meningitis (headache, neck stiffness, increase in CSF leukocyte count, and lactate level, which has been found to be a valuable test to identify patients with bacterial meningitis after neurosurgery) or exit site infection [56,60]. In a retrospective study of 48 patients, clinical signs and symptoms as well as CSF results at the time of EVD placement and at the time of EVD infection were compared [56]. In case of an EVD-associated infection, fever (79% vs. 15% at EVD insertion, p < 0.001), headache, vomiting, and neck stiffness (31% vs. 6% at EVD insertion, p = 0.003) were the predominant signs and symptoms [56]. Furthermore, there was a significantly higher CSF leukocyte count at the time of infection diagnosis compared to EVD insertion (175 compared to 46 cells/µl, p = 0.021). Some authors suggest the calculation of the cell index, which is the ratio between leukocyte and erythrocyte counts in CSF compared to blood [61]. This index is based on the hypothesis that intraventricular hemorrhage dilutes the CSF with blood. On the other hand, additional leukocytes invade the CSF to clear the blood. Therefore, leukocyte level in the CSF is variable and it is not possible to define an absolute cutoff indicative of infection. However, a continuous increase of the cell index is highly indicative of infection. This management would imply daily CSF sampling with again a lower CSF leukocyte count at the time of infection diagnosis compared to EVD insertion (175 compared to 46 cells/µl, p = 0.021).

An algorithm for suspected EVD- and ELD-associated infections is proposed in Figure 3 and antimicrobial management strategies are presented in Table 5. Optimal CSF penetration of the antimicrobial drugs is critical, as is the fact that for intercurrent implants, no rifampin as anti-biofilm therapy must be used. In a febrile patient with an EVD/ELD in place, CSF analysis is recommended,
Table 5: Antimicrobial treatment in external ventricular- and lumbar drainage-associated infections according to the causing microorganism, CNS involved.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Intravenous treatment, daily dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> or coagulase-negative</td>
<td>Flucloxacillin 6 × 2 g IV</td>
</tr>
<tr>
<td>staphylococci, <em>methicillin susceptible</em></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Meropenem 3 × 2 g IV(^b)</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Vancomycin 2 × 15 mg/kg body weight IV(^b,c)</td>
</tr>
<tr>
<td><em>S. aureus</em> or coagulase-negative staphylococci,</td>
<td>Vancomycin 2 × 15 mg/kg body weight IV(^c)</td>
</tr>
<tr>
<td><em>methicillin resistant</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus</em> species</td>
<td>Penicillin 4 × 5 Mio U IV</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone 2 × 2 g IV(^d)</td>
</tr>
<tr>
<td><em>Enterococcus species, penicillin susceptible</em></td>
<td>Aminocillin 6 × 2 g IV PLUS</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus species, penicillin resistant</em></td>
<td>Consider gentamicin 1 × 3 mg/kg body weight IV(^e)</td>
</tr>
<tr>
<td></td>
<td>Vancomycin 2 × 15 mg/kg body weight IV(^f) PLUS</td>
</tr>
<tr>
<td><em>Propionibacterium acnes</em></td>
<td>Consider gentamicin 1 × 3 mg/kg body weight IV(^g)</td>
</tr>
<tr>
<td></td>
<td>Penicillin 4 × 5 Mio U IV OR</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone 2 × 2 g IV(^d)</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>Ceftriaxone 2 × 2 g IV</td>
</tr>
<tr>
<td>*Non-fermenters (e.g. <em>Pseudomonas aeruginosa</em>)</td>
<td>Ceftazidime 3 × 2 g IV(^f)</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Meropenem 3 × 2 g IV(^f)</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime 2 × 2 g IV PLUS</td>
</tr>
<tr>
<td><em>Culture-negative infection</em></td>
<td>Vancomycin 2 × 15 mg/kg body weight IV(^c)</td>
</tr>
</tbody>
</table>

**: Intravenous; CNS: central nervous system.

*Treatment duration dependent on the microorganism: coagulase-negative staphylococci and *P. acnes* 5–7 days; *S. aureus, Streptococcus spp., Enterococcus spp., and culture-negative infections* 14 days; *Enterobacteriaceae and P. aeruginosa* 21 days.

\(^{b}\)In case of a type I or non-type I allergic reaction to penicillin use intravenous vancomycin or intravenous meropenem, meropenem has better CSF penetration than vancomycin and is therefore preferred over vancomycin.

\(^{c}\)Goal: vancomycin trough level 15–20 mg/l, measure at least twice weekly.

\(^{d}\)In case of a non-type I allergic reaction to penicillin use intravenous ceftriaxone.

\(^{e}\)Measure aminoglycoside trough levels and creatinine to monitor for toxicity at least twice weekly.

\(^{f}\)If the patient does not respond to systemic therapy or if highly resistant microorganisms are present [62]. Replacement of the EVD/ELD should be considered in infections with *S. aureus, gram-negative bacilli,* or *Candida spp.* or in case of an inadequate response to therapy. Treatment duration is usually 7 days in case of coagulase-negative staphylococci and *P. acnes,* 14 days in case of *S. aureus, Streptococcus spp., Enterococcus spp., and culture-negative infections,* and 21 days in case of gram-negative bacilli.

Daily CSF sampling and prophylactic EVD/ELD exchange are not recommended, as every EVD/ELD manipulation increases the risk for infection [59,63,64]. As EVD/ELD are intercurrent implants, rifampin-containing treatment regimens are strongly discouraged. Rifampin is the only antibiotic therapy to curatively treat permanent implant-associated infections with staphylococci or *Propionibacterium* spp. Every systemic antimicrobial therapy changes the skin microbiome. With rifampin therapy, rifampin-resistant microorganisms emerge on the skin increasing the risk of a rifampin-resistant infection of the possibly ensuing permanent shunt, which then would not be curatively treatable [36]. For the same reason, we strongly discourage the use of rifampin-coated EVD/ELD [65]. With the use of rifampin-coated EVD/ELD, pathogens are exposed to rifampin monotherapy in CSF and rifampin-resistant microorganisms (mainly coagulase-negative staphylococci) emerge.

7.4. Neurostimulator-associated infections (deep brain and spinal cord stimulators)

Neurostimulators include spinal cord stimulators to treat chronic refractory pain, and deep brain stimulators to treat movement disorders, especially Parkinson’s disease and dystonia, but refractory pain as well. Parkinson’s disease is one of the most common neurological disorders with about 4.1 million patients worldwide. Studies estimate that until 2030, the
number of patients suffering from Parkinson's disease will have doubled and the use of deep brain stimulators probably with it [3]. Both stimulators consist of an impulse generator, which is implanted subcutaneously in the abdominal wall for spinal cord stimulators and in the chest wall for deep brain stimulators. The generator is connected via wires to the leads that are placed in the spinal epidural space for spinal cord stimulators and in the brain for deep brain stimulators.

The majority of infections occur early within 1 month after implantation. For spinal cord stimulators, the infection rate is about 5% (range, 2.5–14%) with 38% manifesting as early implant-associated infections [10,66–68]. For deep brain stimulators, the infection rate is about 5.6% (range, 0–15%) with 52% manifesting as early infections [69–71]. The wide ranges in infection rates result from a lack of a standardized definition of infection and different follow-up times in the studies. For both implants, the most common causative pathogens are S. aureus, coagulase-negative staphylococci, and P. acnes. In spinal cord stimulator-associated infections, also *Pseudomonas aeruginosa* has been described in a significant proportion.

More than 50% of neurostimulator-associated infections present with a pocket infection at the impulse generator implantation site, manifesting with local signs of inflammation, including local warmth, erythema, swelling, tenderness, and wound drainage. Less common are wire or wire extender infections and lead infections with consecutive spinal epidural or brain abscesses [66,69].

Most studies recommend device removal, antimicrobial treatment, and reimplantation once the infection is cured, usually 3 months later. However, removal of the leads, mainly in deep brain stimulators with lead placement in the brain, is associated with high morbidity. Therefore, the following management strategies are suggested, depending on the site of infection (epidural or brain abscess vs. pocket infection vs. lead extender or wire infection), the susceptibility pattern of the causing microorganism (susceptibility vs. non-susceptibility to anti-biofilm therapy), and the duration of infection (early infection within 4 weeks of implantation vs. delayed/late infections) (Table 6). Implant debridement and retention in acute infections or immediate or early reimplantation (i.e. within 2 weeks) at any stage of infection is possible if the microorganism is susceptible to anti-biofilm therapy and no brain or epidural abscess is present. In every scenario, the affected portion of the device needs surgical debridement and consecutive soft tissue coverage. In case of an epidural or brain abscess, abscess evacuation and complete device removal are needed. The following infection sites and management strategies can be discriminated preconditioned that no difficult to treat microorganisms are detected and an acute infection is present: in case of a pocket infection, the generator and the implantation site (due to the soft tissue condition) should be changed; wires and leads can be retained. If extracranial wires are infected, the wires and wire connectors should be changed; generator and leads can be retained. In case the device was removed, immediate or delayed reimplantation after 2–6 weeks is possible. In every scenario, surgical treatment is followed by a 12-week anti-biofilm therapy, except if a long implant-free interval (i.e. 6 weeks) is chosen, where no anti-biofilm treatment is necessary. In selected patients, a long-term antimicrobial suppression therapy can be discussed, if a difficult to treat microorganism was detected or a chronic infection is present and the device cannot be removed.

### 8. Conclusions

Neurosurgical device-associated infections gain relevance with the aging population and newer treatment options such as neurostimulators for pain and movement disorders. In analogy to every implant-associated infection, infected neurosurgical devices should be treated as biofilm infections. Microbiological diagnosis is significantly improved by sonication of the removed implants and prolonged incubation of cultures. An interdisciplinary management is of high importance, including surgical intervention and usually a 12-week anti-biofilm therapy. Different CSF penetration levels and higher drug doses should be respected in case CNS is

### Table 6. Recommendations for the management of neurostimulator-associated infections according to the site of infection.

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Management of the neurostimulator</th>
<th>Antimicrobial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pocket infection (no difficult to treat microorganisms detected)</td>
<td>Change generator (and implantation site because of soft tissue condition)</td>
<td>12 weeks anti-biofilm treatment</td>
</tr>
<tr>
<td>Extracranial wire infection (no difficult to treat microorganisms detected)</td>
<td>Change wires, lead extenders, or connector sites</td>
<td>12 weeks anti-biofilm treatment</td>
</tr>
<tr>
<td>Neurostimulator removed (no difficult to treat microorganisms detected)</td>
<td>Immediate reimplantation (one-stage exchange)</td>
<td>12 weeks anti-biofilm treatment</td>
</tr>
<tr>
<td>Pocket infection, extracranial wire infection (difficult to treat microorganisms detected)</td>
<td>Remove implant, reinset after a long implant-free interval (≥6 weeks)</td>
<td>12 weeks anti-biofilm treatment</td>
</tr>
</tbody>
</table>

*For microorganism-specific treatments without central nervous system involvement, see Table 2 and with central nervous system involvement Table 3, respectively.*

*Agents for long-term antimicrobial suppression therapy are cotrimoxazole and doxycycline in case central nervous system is involved, and additionally clindamycin, if central nervous system is not involved.*
involved. The adherence to treatment algorithms is necessary to achieve high treatment success. Moreover, it is important to note that there are efficient strategies to cure infections without implant removal or with a one-stage implant exchange.

9. Expert commentary

Neurosurgical device-associated infections are increasing, but validated diagnostic and treatment concepts are lacking. Most recommendations are therefore extrapolated from other device-associated infections. From this experience, we learned that combined surgical and antimicrobial management is crucial for successful treatment outcome.

The microbiological diagnosis is significantly improved by sonication of the removed implants and prolonged culture incubation. Regarding surgical treatment, cure without implant removal or with a one-stage implant exchange are new options, which considerably improve the quality of patient lives. Furthermore, in these less invasive surgical concepts, the antimicrobial treatment needs to be optimized and effective against microbial biofilms.

There are some critical points to be respected in the treatment of neurosurgical device-associated infections. First, there are differences in CSF penetration between antimicrobial drugs – some do, others do not reach therapeutic drug levels. For that reason, some drug combinations foreseen in orthopedic device-associated infections cannot be used for CNS infections. Also, higher drug doses are recommended to achieve therapeutic drug levels in CSF. Second, removal of the implant is often difficult or impossible in neurosurgical implants, as brain tissue may be involved and forced removal may result in severe complications such as intracerebral bleeding. Therefore, the management of neurosurgical device infections is even more challenging.

10. Five-year view

Future clinical studies should cover diagnostic aspects, mainly the routine implementation of sonication in neurosurgical device-associated infections to optimize microbiological diagnosis or alternative biomarkers such as neutrophil degranulation products to discriminate between infection and inflammation. Modern molecular tests, such as multiplex polymerase chain reaction, may improve the sensitivity for detection of infection, especially in patients receiving previous antibiotics. Rapid identification of the causative pathogen and its susceptibility can further improve the treatment outcome.

Furthermore, the proposed treatment algorithms should be validated in larger clinical studies involving sufficient patient numbers, as it has been demonstrated for orthopedic devices. Different antimicrobial treatment combinations should be compared in their efficiency to clear CNS infections with an indwelling device or eradicate biofilms from implant surface.

Finally, prophylaxis should be addressed. Newly designed neurosurgical implants with antimicrobial properties may improve treatment outcome of device-associated infections. These implants include anti-biofilm coatings (with antimicrobials, anti-adhesive properties), systems for local drug-delivery (such as resorbable hydrogels, or non-resorbable biomaterials impregnated with antibiotics), or other innovative approaches such as bacteriophage therapy, lytic enzymes, or targeting biofilm matrix or quorum-sensing. With improved infection prevention and treatment options, it is expected that more complex surgeries and implants can be used, which may open new ideas and treatment options in the field of neurosurgical implants.

Key issues

- Neurosurgical implants are increasingly used, which is paralleled by an increase in neurosurgical device-associated infections.
- The most commonly used neurosurgical implants are craniotomy fixation devices, cranioplasties, internal shunt systems, external ventricular and lumbar drainages and neurostimulators (i.e. spinal cord and deep brain stimulators).
- Every implant-associated infection is a biofilm infection and needs careful diagnostic and treatment management to achieve cure.
- No standardized diagnostic and treatment procedure exists; therefore, many concepts are extrapolated from experience with other implant-associated infections.
- Microbiological diagnosis is optimized by sonication of the removed implants and prolonged incubation of cultures, which allows cultivating microorganisms directly from the detached biofilm.
- Interdisciplinary management is of high importance, including surgical intervention and usually a 12-week anti-biofilm therapy.
- Different CSF penetration levels and higher drug doses should be respected in the treatment of neurosurgical device-associated infections.
- The adherence to treatment algorithms is necessary to achieve high treatment success.
- There are efficient strategies to cure infections without implant removal or with a one-stage implant exchange.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.


**This article describes the method of sonication for optimizing the diagnosis of biofilm-associated infections.**


**This article includes the largest adult patient population with shunt-associated infections and describes clinical, diagnostic, and treatment aspects.**


**This article comprehensively describes surgical and antimicrobial treatment strategies in implant-associated infections.**


**This article validates the treatment algorithm of implant debridement and retention in acute infections if anti-biofilm therapy is available.**


**This manuscript describes clinical and microbiological characteristics of craniotomy-associated infections.**

This article describes clinical and diagnostic findings of external ventricular drainage-associated infections compared to the time of drainage insertion.