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REVIEW

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Nosocomial ventriculitis and meningitis in neurocritical care patients

Abstract *Background* External ventricular drainage (EVD) is frequently necessary in neurological and neurosurgical intensive care patients. A major complication of this procedure is an EVD-related venticulitis or meningitis. The purpose of this review is (1) to address the magnitude of the problem in the neurocritical care patient population, (2) to discuss the difficulties in providing an appropriate and timely diagnosis of this disease entity and (3) to propose an algorithm for both rapid diagnosis and appropriate therapy. *Methods* A MEDLINE literature search was carried out for studies from January 1990 through March 2008 reporting on ventriculostomy, EVD-related central nervous system infections, in particular ventriculitis and meningitis. *Results* EVD-related ventriculitis is a serious nosocomial complication in the neurocritical care setting where EVD catheters are frequently used for the management of elevated ICP secondary to acute hydrocephalus primarily caused by subarachnoid and intraventricular hemorrhage or traumatic brain injury. Infection rate is high with reported incidences in the range of 5 % up to more than 20 %. Predisposing factors for infection are non-adherence to rigid insertion and maintenance protocols, leakage of cerebrospinal fluid (CSF), catheter irrigation and the frequency of EVD manipulation. Diagnosis is frequently impaired either by the presence of systemic inflammation due to the primary disease or because the hemorrhagic CSF itself may cause an inflammatory reaction. Furthermore, the most common pathogens involved in EVD-related infections, i. e., staphylococci, initially provoke only a mild inflammatory response in the CSF and therefore patients rarely present with clear-cut clinical signs indicating severe central nervous system infection, in particular, ventriculitis. *Conclusion* Nosocomial EVD-related ventriculitis is a significant cause of morbidity and mortality in critically ill neurological patients. Rapid diagnosis and prompt initiation of appropriate antimicrobial therapy is needed. A stepwise algorithm for the management of EVD-related ventriculitis is proposed.

Key words central nervous system infection · external ventricular drainage · meningitis · neurological critical care · ventriculitis

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Abbreviations

CRP	C-reactive protein
CSF	cerebrospinal fluid
EVD	external ventricular drainage
ICP	intracranial pressure
IVH	intraventricular hemorrhage
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSE	methicillin-resistant *Staphylococcus epidermidis*
PCT	procalcitonin
SAH	subarachnoid hemorrhage

Introduction

Nosocomial infections of the central nervous system are a serious complication of neurosurgical procedures (e.g., craniotomy, placement of invasive neuromonitoring techniques, EVD catheters or CSF shunts), penetrating head injury and systemic infections. This review focuses on nosocomial infections in patients with external ventriculostomy, also called EVDs. Infectious complications in patients suffering from traumatic brain injury or systemic infections with subsequent involvement of the nervous system are reviewed elsewhere.

Temporary external ventricular drainage is a commonly used procedure in neurological and neurosurgical intensive care patients because EVD catheters provide a reliable means of monitoring intracranial pressure (ICP) and controlling elevated ICP secondary to acute occlusive hydrocephalus. A major complication of external CSF drainage is bacterial colonization of the catheter and subsequent retrograde infection resulting in ventriculomeningitis, encephalitis, brain abscess, subdural empyema or even sepsis. Table 1 gives an overview of relevant EVD-related infectious complications in the order of likelihood of occurrence. Though infection of skin and soft tissues at the site of EVD insertion is the most frequent infectious complication, one has to bear in mind that nosocomial meningitis or ventriculitis represent possible life-threatening conditions which may lead to a permanent adverse outcome of neurocritical care patients. Other, non-infectious complications of external ventriculostomy comprise hemorrhage at the site of insertion, intraventricular hemorrhage, overdrainage leading to subdural hematoma, hygroma or the so-called slit ventricle syndrome and malfunction due to obstruction of the catheter.

Epidemiology

According to recent literature the incidence of EVD-related infections ranges from 2 % to 27 % [1, 5, 6, 11, 38, 41] and a recent meta-analysis of 23 studies reported a cumulative rate of positive CSF cultures of 8.8 % per patient or 8.1 % per EVD [20]. In many neurocritical intensive care units prophylactic exchange of EVDs is a common practice with the aim of preventing CSF infection [12]. However, taking the reported case incidence of approximately 8 % per inserted catheter into account, elective revision itself might be causatively associated with an increased infection rate in the individual patient. Indeed, when analyzing the literature, there is little evidence to support the practice of prophylactic catheter exchange at a predefined interval [19]. Although it has been claimed that the majority of EVD-related infections occurs within the first 10 to 14 days after insertion, recent studies by our group [17] and others also identified a later peak of infection after 2 weeks, especially in patients requiring prolonged catheterization due to pronounced intracranial disease, e.g., severe traumatic brain injury or complicated subarachnoid hemorrhage. A possible explanation for the timing of the incidence of infection within the first 10 days is simply because of the rarity of prolonged EVD duration in the majority of studies [19, 20]. Several factors have been identified to increase the risk of EVD-related ventriculomeningitis [11, 20]. Relevant risk factors are duration of catherization, frequency of EVD manipulation (e.g., CSF sampling, irrigation), intraventricular hemorrhage and insertion technique (Table 2). A number of studies directly addressing the duration of catheterization found a significantly increased risk for device-related infection in patients with catheters in place for more than 5 days or longer with a peak at days 9 to 11 and a markedly decreased risk thereafter, despite a population that continued to be at risk [11, 12, 20, 22, 25, 39]. Concerning catheter manipulation, irrigation has consistently been associated with increased CSF infection rates. For example, Aucoin and coworkers reported a relative risk increase of approximately 6 % in patients in whom EVDs were flushed with an antibiotic solution as compared with those in whom no flush was used [2]. In contrast, drainage system leaks and disconnections have rarely been associated with increased infection rates despite the seemingly obvious risk of infection that they pose [20, 22].

Table 1 Possible infectious complications of EVD in the order of likelihood of occurrence

1. Skin and soft tissue infections (SSTI)
2. Ventriculitis/meningitis
3. Cerebritis/brain abscess
4. Subdural empyema
5. Osteomyelitis
6. Sepsis
7. Endocarditis
8. Intra-abdominal abscess formation

Table 2 Risk factors for EVD-related ventriculomeningitis [11]

EVD duration > 11 days
Frequency of CSF sampling
Intraventricular hemorrhage
Surgical technique (subcutaneously tunneled EVD, Rickham reservoir with percutaneous CSF drainage)

Microbiology

The etiologic agents most frequently identified in nosocomial ventriculomeningitis are listed in Table 3 [6, 20]. The variability in microbiological profiles between centers may be influenced by differences in antibiotic usage. Overall, gram-positive cocci consistent with skin flora such as *Staphylococcus epidermidis* and *Staphylococcus aureus* are the most common pathogens involved in EVD-related ventriculomeningitis. These organisms account for more than two-thirds of nosocomial CSF infections. Importantly, inflammation of meninges and ventricular ependyma may be less pronounced when caused by staphylococci. The presence of such a "low grade" infection illustrates the challenges of diagnosing ventriculomeningitis and explains the need for additional diagnostic means since prompt initiation of appropriate antimicrobial therapy is associated with improved outcome and reduction in length of stay at the ICU and hospital [13–15, 21].

The most common isolated gram-negative species are enterobacteriaceae and *Pseudomonas*, cases of *Acinetobacter* have also been reported. Nosocomial CSF infections caused by fungi are rare, although the frequency of *Candida* ventriculitis has increased in recent years. Risk factors for fungal EVD-related infections are broad-spectrum antimicrobial therapy and compromised immune status.

Infection versus contamination and catheter colonization

Efforts must be made to identify clinically relevant CSF infections and suspected or confirmed ventriculomeningitis must be differentiated from contamination and catheter colonization. Though there is some variability in the definitions in the literature, most researchers adhere to the criteria proposed by Lozier and coworkers to identify CSF infections in patients with EVD [20]. According to these authors contamination constitutes an isolated positive CSF culture in the absence of abnormal CSF findings. EVD catheter colonization is defined by multiple positive CSF cultures with expected CSF profiles and lack of clinical signs other than fever. Abnormal CSF findings, especially advancing CSF pleocytosis in the absence of positive cultures characterizes suspected EVD-related infection, whereas definite nosocomial ventriculomeningitis is defined by a positive CSF culture accompanied by abnormal CSF findings or appropriate clinical signs and symptoms (Table 4).

Table 3 Microbiology of EVD-related ventriculomeningitis

Staphylococcus epidermidis	70 %
Staphylococcus aureus	10 %
Others (including gram negative bacteria and fungi)	< 20 %
– Gram negative rods (Klebsiella spp., E. coli, Pseudomonas spp.)	15 %
– Anaerobes	rare
– Candida spp.	very rare

Diagnosis

It is evident that the timely diagnosis of EVD-related ventriculomeningitis is a relevant outcome factor for neurocritical care patients requiring external ventriculostomy. As outlined above, a catheter-related ventriculomeningitis can be assumed definite when all the criteria listed in Table 4 are fulfilled [20, 34]. However, one has to bear in mind that in the typical neurocritical care patient population clinical parameters indicative for central nervous system infection frequently cannot be assessed appropriately because such signs may be a manifestation of the underlying disease, e. g., intracranial hemorrhage or severe traumatic brain injury. Fever may also be from other, extracerebral sources of infection. Neurocritical care patients are usually subjected to various complications of intensive care treatment (e. g., pneumonia) and regularly present with systemic inflammatory response syndrome, multiorgan dysfunction or even failure [8]. Systemic inflammation leads to increased levels of C-reactive protein, procalcitonin, lactate and to a high white blood cell count [27]. Acute-phase parameters have been examined for their usefulness in diagnosing ventriculomeningitis, including C-reactive protein (CRP) and serum procalcitonin (PCT). Whereas in patients not fulfilling the sepsis criteria serum procalcitonin has been demonstrated to add to the diagnostic precision in bacterial ventriculitis [4], monitoring of these parameters is not helpful for the differential diagnosis of ventriculitis in intensive care patients as they do not allow discrimination between systemic or local inflammation in this patient population [24]. In addition, CSF analysis – in most instances the

Table 4 Diagnostic clues for EVD-related ventriculomeningitis

Laboratory parameters
– Reduced CSF glucose
– Increased CSF protein
– CSF pleocytosis
– Positive CSF culture or Gram's stain
Clinical signs
– Fever
– Meningism
– Reduced level of consciousness
– Photophobia, phonophobia

cornerstone of diagnosis of central nervous system infections – might not prove useful in identifying ventriculitis because spillage of blood into CSF provokes an invasion of leukocytes to clear the intraventricular blood by phagocytosis leading to a so-called aseptic inflammation [37]. Indeed, a number of studies investigating the value of CSF laboratory parameters that are regularly used to diagnose CSF infection, such as CSF leukocyte count, CSF protein, increased CSF lactate and a decreased CSF glucose/serum ratio, conclude that no single parameter can reliably predict or exclude EVD-related infection [4, 24, 27, 34].

Because the results of the CSF leukocytes count may be confounded by intraventricular hemorrhage, the "cell index" was introduced as a new parameter for the diagnosis of EVD-related ventriculomeningitis [31]. Calculation of this "cell index" (Fig. 1) is based on the hypothesis that intraventricular hemorrhage simply leads to dilution of CSF with blood. Therefore, the corpuscular blood elements, i. e. erythrocytes and leukocytes, should be distributed in the CSF in a similar proportion as in the peripheral blood. Any change in the CSF leukocyte count may be theoretically detected by a calculation relating the white cell count to red cell count ratio in the CSF to the corresponding ratio in peripheral blood. Ideally, in patients with intraventricular blood and no evidence of ventricular or systemic inflammation the "cell index" is supposed to be 1. Because clearance of intraventricular blood by immigrating white blood cells is a physiological process the level of the "cell index" is subjected to fluctuations. For this reason it is not possible to determine an absolute cut-off value for proven infection. However, a significant increase of this index is highly indicative of EVD-related ventriculitis in patients with hemorrhagic CSF. Pfausler and coworkers demonstrated in a series of neurocritical care patients with intraventricular hemorrhage requiring EVD that calculation of the "cell index" on a daily basis allows the timely diagnosis and hence initiation of antimicrobial therapy of catheter-related ventriculomeningitis [31]. In this study the increase of "cell index" usually preceded the diagnostic capacity by conventional means on average by 3 days (Fig. 2).

$$\text{Cell index} = \frac{WBC_{CSF}\,[mm^3] \div RBC_{CSF}\,[mm^3]}{WBC_{blood}\,[mm^3] \div RBC_{blood}\,[mm^3]}$$

Fig. 1 Calculation of the cell index [31] in patients with hemorrhagic CSF

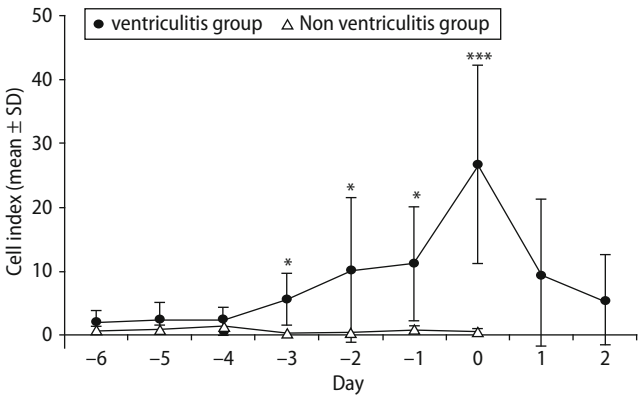

Fig. 2 Time course of mean cell index (± SD) of patients with EVD-related ventriculitis (filled circles) compared to patients without EVD-related ventriculitis (triangles). A statistically significant rise in the cell index preceded the diagnostic capacity by conventional means (i. e., positive CSF culture on day "0") on average by 3 days (adapted from [31] with permission)

Therapy

Several studies have demonstrated that delayed or inappropriate antimicrobial therapy is associated with increased mortality and morbidity for numerous infectious diseases. A prospective clinical investigation addressing the occurrence of initially delayed appropriate antibiotic treatment for ventilator-associated pneumonia found that delaying treatment with an appropriate antibiotic regimen for more than 24 hours is associated with adverse clinical outcome (69.7 % versus 28.4 %) [15]. Concerning adequacy of the prescribed antimicrobial treatment Ibrahim and coworkers demonstrated in a prospective cohort study that the hospital mortality rate of patients with a bloodstream infection receiving inadequate antimicrobial treatment was statistically higher than the hospital mortality rate of patients receiving appropriate antimicrobial therapy (61.9 % versus 28.4 %). Moreover, the same authors identified potential risk factors for the administration of inadequate antimicrobial treatment including prior antibiotic therapy during the same hospitalization, longer duration of indwelling catheterization and infection caused by *Candida* species. Additionally, they found that bloodstream infections caused by antibiotic-resistant pathogens were associated with the greatest rates of inadequate antimicrobial treatment [14]. These findings are consistent with those of studies of community-acquired and nosocomial infections of the central nervous system where early antimicrobial therapy and appropriate selection of antibiotics can prevent adverse neurological sequelae [8, 19, 21]. Therefore, the therapeutic approach to EVD-related ventriculomeningitis needs to consider the most likely pathogens involved, nature of the underlying disease and patient factors such as age, co-morbidity and immune status. The antiinfectives selected must penetrate the blood-brain and blood-CSF barriers, respectively. Infection of the ventricular lining enhances the ability of antimicrobial agents to diffuse into CSF. However, as mentioned above, the inflammatory response may be less pronounced in ventriculomeningitis [32].

Unfortunately, therapy of nosocomial CSF infections has not yet been standardized. Given the frequent implication of staphylococci in EVD-related ventriculomeningitis initial therapy with an antistaphylococcal agent with good CSF penetration such as rifampicin or fosfomycin and a cephalosporin may be considered as first-line therapy for this infection. If staphylococci indeed are isolated and the organism is methicillin susceptible, therapy can be changed to flucloxacillin. Importantly, based on local resistance patterns, substitution with the glycopeptide antibiotic vancomycin is highly recommended where multidrug-resistant gram-positive nosocomial pathogens (especially MRSA or MRSE) are suspected. Penetration of intravenously administered vancomycin into CSF is poor, even in the presence of meningeal inflammation [32]. To overcome this pharmacokinetic drawback direct instillation of antimicrobial agents into the ventricles has been used. Daily vancomycin dosages have ranged from 5 to 20 mg. Although not standardized, this approach is occasionally necessary in patients with nosocomial EVD-related ventriculitis that is difficult to eradicate. Other agents have been successfully utilized in the treatment of nosocomial staphylococcal ventriculitis and meningitis, as fosfomycin [33], linezolid [3, 23, 28, 29] and most recently daptomycin [7]. Importantly however, the latter agents should be reserved for CSF infections with mulidrug-resistant gram-positive bacteria. Because intensive care patients are also at risk for infections with resistant gram-negative organisms, such as *Pseudomonas* and *Acinetobacter* species, initial empirical therapy should include a cephalosporin with antipseudomonal activity or a carbapenem until culture results provide information to optimize therapy [43]. When administering carbapenems, meropenem is the agent of choice in patients with infections of the nervous system [18], since the combination of imipenem plus cilastatin has been associated with neurotoxicity, especially seizures [40]. In cases of fulminant gram-negative ventriculitis, intraventricular aminoglycosides also have been administered [35]. Prolonged therapy with broad-spectrum antibiotics may be complicated by fungal superinfection, primarily with *Candida* species. For the treatment of fungal infections of the central nervous system the new triazole antifungal voriconazole, besides the polyene amphotericin B, is regarded as a promising option for susceptible infections, whereas the use of echinocandines (e. g., caspofungin) is still discussed controversially (Table 5) [43].

A switch to the appropriate antimicrobial agent tailored to the causative pathogen must be made as soon as microbiologic data from culture are available. In the case of persistent CSF infection despite appropriate antimicrobial therapy removal of the device may be an important adjunctive measure.

Table 5 Treatment options in case of suspected infection with Candida spp. (especially following therapy with broad spectrum antibacterial agents)

Amphotericin B (intravenous or intraventricular application)
Fluconazole
Voriconazole
Caspofungin (?)
Anidulafungin (?)

Algorithm for the management of suspected EVD-related ventriculitis

Nosocomial ventriculitis should be considered when a patient with an EVD presents with signs and symptoms of infection, such as fever together with abnormal CSF findings, i. e., increase in the "cell index" or advancing CSF pleocytosis, progressively declining CSF glucose with a decreased CSF glucose/serum glucose ratio [20]. The management of EVD-related ventriculitis involves decisions related to catheter exchange, the type and route of administration (intravenous versus intrathecal) of antimicrobial therapy, based on the type of suspected organism and its resistance pattern, and the duration of antimicrobial therapy. However, recommendations on the duration of antimicrobial therapy have not been rigorously studied. In most cases treatment is continued for 10 to 14 days, although some experts have recommended shorter durations (i. e., 5 to 7 days) if repeated CSF cultures are negative. In any case, careful follow-up to ensure infection control is critical.

The approaches to the therapy of EVD-related ventriculitis in the published literature have included antimicrobial treatment with or without device removal [43]. According to our experience [3, 32, 33] the decision as to whether the catheter should be removed or retained largely depends on the causing organism. This view is supported by recommendations recently published in a topic-specific review on intravascular catheter-related infections [36]. Almost 80 % of catheter-related infections caused by coagulase-negative staphylococci can be treated with glycopeptide antibiotics without removal of the invasive device. If the EVD is to be retained, a longer duration of therapy (10 to 14 days rather than 5 to 7 days if the catheter is exchanged) has to be considered. Removal of the intravascular device in *Staphylococcus aureus* catheter-related bloodstream infections is associated with a more rapid response to therapy and a lower relapse rate. Whether this observation can be transferred to EVD-related infections requires further studies. In case of ventriculitis caused by gram-negative bacteria removal and reinsertion of the EVD together with a 1- to 2-week course of appropriate broad-spectrum antimicrobials is strongly recommended since it has been shown that catheter-related infections caused by gram-

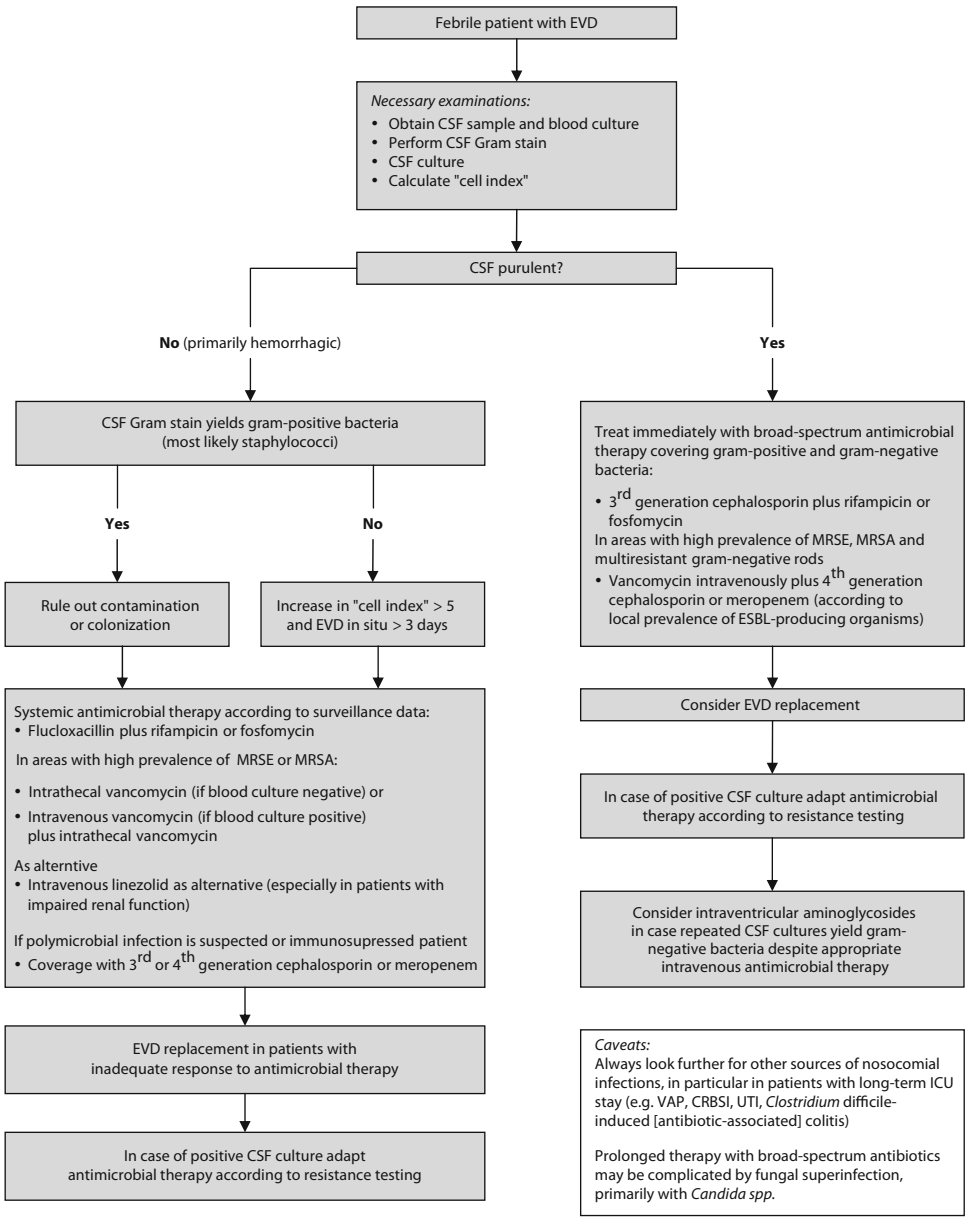

Fig. 3 Algorithm for the management of suspected EVD-related ventriculitis. Purulent CSF denotes > 300 polymorphonuclear cells/mm³, CSF glucose/serum glucose ratio < 0.4, CSF lactate > 2.1 mmol/l; *CRBSI* catheter-related bloodstream infection; *UTI* urinary tract infection; *VAP* ventilator-associated pneumonia

negative rods were associated with a high frequency of relapse if the catheter was retained [10]. In patients with fungal catheter-related infections device retention proved to be a significant factor for the persistence of the infection and was associated with higher mortality [30]. In compliance with data on nosocomial candidemia, duration of therapy for EVD-related ventriculitis caused by *Candida* should be 2 weeks from the last positive CSF culture [26]. The algorithm for the management of suspected EVD-related ventriculomeningitis is summarized in Fig. 3.

Prevention

Because of potential pitfalls in diagnosis and subsequently delayed initiation of appropriate antimicrobial therapy adding to morbidity or mortality, prevention of EVD-related ventriculomeningitis is of paramount importance. Special emphasis should be placed on the avoidance of modifiable risk factors [16]. Available data suggest that prophylactic catheter exchange does not significantly reduce the incidence of EVD-related ventriculomeningitis [1, 19, 20]. The efficacy of prophylactic and periprocedural antibiotics in reducing nosocomial CSF infections is far outweighed by predisposing the pa-

tient to infections by more resistant pathogens with a higher mortality rate [20, 43]. More promising, antimicrobial-impregnated EVD-catheters which are capable of preventing bacterial colonization along the catheter surface have been shown to reduce the risk of device-related ventriculomeningitis [42]. However, induction of antimicrobial resistance posing major health-care problems is a significant concern. A relatively new option which might bypass this disadvantage represent indwelling catheters impregnated with silver nanoparticles [9]. Indeed, the efficacy of silver nanoparticles impregnated EVDs was evaluated in a prospective comparative pilot study. In this trial Lackner and coworkers demonstrated a significant reduction in CSF infection rates [17].

Summary

Neurocritical care patients requiring external ventriculostomy bear a considerable risk for developing device-related nosocomial infections. Despite recent advances in diagnosis and antimicrobial treatment, the management of patients with EVD-related ventriculomeningitis is challenging and must consider timely (earliest possible) diagnosis, prompt initiation of appropriate antibiotic therapy, continuous surveillance including systematic collection and analysis of data on the occurrence and microbiology of nosocomial (central nervous system) infections, and alertness to recognize new developments in this field.

Conflict of interest The authors declare no conflict of interest.

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