Infectious intracranial complications in the neuro-ICU patient population
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Introduction
Infectious complications in the neuro-ICU patient population presenting as meningoencephalitis, ventriculitis, subdural or epidural empyema are frequently associated with invasive procedures such as craniotomy or intracranial device placement, for example, for intracranial pressure (ICP) monitoring or diversion of the cerebrospinal fluid (CSF) from an obstructed ventricular system [1,2]. Hence, the majority of these infections must be considered nosocomial, that is, hospital-acquired. Recently, the term nosocomial has been suggested to be replaced by healthcare-associated, a concept which is highly useful for the categorization of infections in the non-ICU setting, but seems to be less applicable in the neuro-ICU patient population [3]. Due to the severity of the underlying neurological illness such as aneurysmal subarachnoid hemorrhage or severe traumatic brain injury, neurocritical care patients often require the full range of ICU measures including mechanical ventilation, intravascular catheters, and so on. Therefore, these patients are also at high risk for infections arising at distant foci (e.g., endocarditis, bloodstream infections, pneumonia, urinary tract infections) [4,5]. Noteworthy, a neuro-ICU patient suffering from sepsis originating from an extracranial focus is at risk for sepsis-related neurological complications like septic encephalopathy [6,7] or critical illness neuromyopathy [8]. In addition, infectious complications may arise from more ‘exogenous’ sources such as transmission of pathogens from ICU personnel or the ICU environment. Poor hand hygiene has been demonstrated to be one of the most important causes of healthcare-associated infections [9]. This review concentrates on those intracranial infections that are related to invasive procedures, since these infections have been described as a distinct entity [10,11].

Purpose of review
To provide an overview of infectious intracranial complications secondary to invasive procedures or trauma in the neuro-ICU patient population. Nosocomial infections of the central nervous system are a serious complication contributing to morbidity, prolonged length of stay in the ICU and/or hospital, and mortality of neurocritical care patients.

Recent findings
Any type of neurosurgical interventions, specifically ventriculostomy/external ventricular drainage, constitutes a major risk factor for infectious intracranial complications. Other predisposing factors are comorbidities with immunocompromised state and the presence of a distant focus of infection. The emergence of multiresistant pathogens adds to the complexity of the management of infectious intracranial complications. In recent years, several antimicrobial agents suitable for the treatment of nosocomial central nervous system infections have been extensively studied with respect to pharmacodynamics and pharmacokinetics in serum and cerebrospinal fluid.

Summary
Despite recent advances in prevention and treatment, the management of nosocomial intracranial infections still poses a challenge to the neuro-ICU specialist and must consider timely diagnosis and prompt initiation of appropriate antibiotic therapy. This review focuses on the definition, epidemiology, clinical features, and therapeutic approach to this distinct complication of neurocritical care.

Keywords
antibiotics, intracranial infection, neuro-ICU patient, nosocomial meningitis
for Disease Control and Prevention (CDC/NHSN) has updated the surveillance definition of healthcare-associated infection and published criteria for various types of infections in the acute care setting [12\(^\text{a}\)]. There are three specific types of central nervous system (CNS) infections:

1. Intracranial infection:
   - (a) abscess
   - (b) subdural or epidural infection
   - (c) encephalitis
2. Meningitis or ventriculitis
3. Spinal abscess without meningitis.

As per the CDC/NHSN definition of CNS infection, intracranial infection must meet at least one of the following criteria [12\(^\text{a}\)]:

1. Patient has organisms cultured from brain tissue or dura.
2. Patient has an abscess or evidence of intracranial infection seen during a surgical operation or on histopathologic examination.
3. Patient has at least two of the following signs or symptoms with no other recognized cause: headache, dizziness, fever (>38°C), localizing neurologic signs, changing level of consciousness, or confusion, and at least one of the following:
   - (a) organisms seen on microscopic examination of brain or abscess tissue obtained by needle aspiration or by biopsy during a surgical operation or autopsy,
   - (b) positive antigen test on blood or urine,
   - (c) radiographic evidence of infection, and
   - (d) diagnostic single antibody titer (IgM) or four-fold increase in paired sera (IgG) for pathogen; and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

As per the CDC/NHSN definition of meningitis or ventriculitis, at least one of the following criteria must be met [12\(^\text{a}\)]:

1. Patient has organisms cultured from CSF.
2. Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38°C), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability and at least one of the following:
   - (a) increased white cells, elevated protein, and/or decreased glucose in CSF,
   - (b) organisms seen on Gram’s stain of CSF,
   - (c) organisms cultured from blood,
   - (d) positive antigen test of CSF, blood, or urine, and
   - (e) diagnostic single antibody titer (IgM) or four-fold increase in paired sera (IgG) for pathogen; and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

In addition to these major types, other intracranial infections may arise in the neuro-ICU patient population such as septic thrombosis of cerebral sinus and/or veins [13].

### Infection versus contamination and catheter colonization

Infections that require immediate therapeutic attention must be differentiated from contamination and catheter colonization. According to the criteria proposed by Lozier et al. [14] contamination constitutes an isolated positive CSF culture in the absence of abnormal CSF findings. Catheter colonization is defined by at least two positive CSF cultures with expected CSF profiles and lack of clinical signs. Pathological CSF findings in the absence of positive cultures characterizes a suspected device-related infection, whereas definite nosocomial meningitis or ventriculitis is defined by positive CSF culture accompanied by abnormal CSF findings or appropriate clinical signs and symptoms. In addition, ‘aseptic’ inflammation resulting from tissue response to tissue injury or stimulation by noninfectious agents such as blood breakdown products or chemicals should be distinguished from infection [15,16].

### Epidemiology, pathogenesis, and microbiology

The true prevalence of healthcare-associated intracranial infectious complications is difficult to estimate because epidemiological data are limited. Most reports refer to postneurosurgical (e.g., craniotomy and ventriculostomy) infectious complications [15,17\(^\text{a}\),18,19]. In contrast, only few studies on the epidemiology of infections secondary to traumatic brain injury are available [20].

Important risk factors for nosocomial intracranial infections are a history of neurosurgery, CSF leakage or recent head trauma, presence of cranial or extracranial infectious foci such as otitis, sinusitis or pneumonia and, potentially, an immunocompromised state [11,15,21]. The incidence of ventriculostomy-related infections ranges from 2 to 27% [1,11,14,17\(^\text{a}\)]. A recent meta-analysis of 23 retrospective studies reported a cumulative rate of positive CSF cultures of 8.8% per patient and 8.1% per external ventricular drainage (EVD) [14]. It has been claimed that the majority of EVD-related infections occurs within the first week after insertion, but recent studies identified a later peak of infection even after 2 weeks, particularly in patients with prolonged EVD placement due to severe intracranial disease [1,22]. As infection may be acquired by introduction of bacteria following insertion of a new
catheter, routine exchange of catheters might be actually harmful by possibly increasing the rates of infection [23]. Other relevant risk factors for EVD-related intracranial infection are frequency of CSF sampling, intraventricular hemorrhage, surgical technique, and presence of other distant infections [14,18,24]. Approximately, 1.5% of patients suffer from postcraniotomy nosocomial meningitis as a serious complication [18].

The incidence of bacterial meningitis after moderate or severe traumatic brain injury has been estimated to range between 1 and 2% with CSF leakage as the major risk factor and fracture of the basal skull increasing the risk up to 25% [20]. Recently, Weisfelt et al. [11] evaluated the characteristics of nosocomial meningitis in a prospective cohort study. Underlying conditions such as a history of neurosurgery or CSF leakage were present in 94% of the episodes, 28% of the patients had more than one risk factor. Any kind of neurosurgical intervention accounted for 64% of the infections, whereas an immunocompromised state was present in 28% of the cohort, and distant focus of infection was identified in 18%.

Staphylococci have been incriminated to be the most important and most frequent causative agents (up to 80%), whereas Gram-negative bacilli account for 10–15%. Anaerobes and fungi, primarily Candida species are rarely identified [14,25].

Clinical features and diagnosis
Any suspected intracranial infection must prompt an immediate diagnostic workup and the initiation of empirical antimicrobial chemotherapy. Fever and deterioration in the level of consciousness or an increase in ICP in the comatose or sedated patient are important early indicators for the potential presence of intracranial infections. Neuroimaging and CSF analysis are the cornerstones in the diagnosis of CNS infections. It should be emphasized that performance of such examinations must not delay initiation of anti-infective therapy. In many cases, lumbar puncture may be contraindicated due to increased intracranial pressure. CSF recovery may be possible through ventricular catheters. Noteworthy, one has to bear in mind that analysis of ventricular CSF does not always allow the diagnosis of bacterial meningitis, as CSF circulation and thereby spread of the infection might be blocked with blood or expanding masses. The presence of a focal collection of pus (e.g., abscess, empyema) warrants immediate neurosurgical evacuation both to reduce ICP and to allow for microbiological analysis of the purulent collection. In addition, cultures from blood and other body fluids such as secretions from paranasal sinus must be obtained [1,11]. However, cultures may require prolonged incubation times and the result may be negative in patients with prior antibiotic therapy. Schade et al. [26] compared the results from Gram stains and CSF cultures and demonstrated that Gram staining had a very high specificity but an unacceptable low sensitivity (18%) in screening for device-related bacterial meningitis.

In every patient with a history of neurosurgery or head trauma, there must be a high level of suspicion for intracranial infectious complications in case of the development of systemic inflammatory response syndrome. On the contrary, clinical and biochemical parameters such as fever or increase in acute-phase proteins may also be a manifestation of the underlying neurological disease [27,28]. In addition, monitoring of inflammatory parameters does not allow discrimination between systemic or intracranial infection in the neuro-ICU patient population [29]. Studies investigating the value of CSF biochemical parameters such as CSF leukocyte count, CSF protein, increased CSF lactate, and decreased CSF/serum glucose ratio conclude that no single parameter can reliably predict or exclude nosocomial intracranial infection [2,17,30].

Further, CSF analysis might be of limited value in identifying intracranial infections due to aseptic inflammation in case of hemorrhagic CSF. In this setting, calculation of the so-called cell index (ratio of leukocytes and erythrocytes in CSF divided by the ratio of leukocytes and erythrocytes

<table>
<thead>
<tr>
<th>Table 1 Recommendations for empiric antimicrobial therapy for bacterial intracranial infections in adults according to risk factor</th>
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<tr>
<td>Risk factor</td>
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<td>-------------</td>
</tr>
<tr>
<td>Post craniotomy</td>
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<tr>
<td>Penetrating head injury</td>
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<tr>
<td>Basal skull fracture (early)</td>
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* Suggested daily dosing in adult patients with normal renal and/or hepatic function: vancomycin 15 mg/kg every 8 h to maintain a serum trough concentration of 15–20 mg/l; linezolid 600 mg every 12 h; meropenem 2 g every 8 h.

* Suggested daily dosing in adult patients with normal renal and/or hepatic function: cefotaxime 2 g every 4–6 h (antimicrobial coverage should be based on local antimicrobial susceptibility).

* Suggested daily dosing in adult patients with normal renal and/or hepatic function: cefepime 2 g every 4–6 h (antimicrobial coverage should be based on local antimicrobial susceptibility).
in peripheral blood) may confirm intracranial infection [31,32]. In a case series by Pfausler et al. [31], a significant increase in the cell index preceded the diagnostic capacity by conventional means on average by 3 days.

**Therapeutical considerations**

Delayed or inappropriate antimicrobial therapy is associated with increased morbidity and mortality for many cases of meningitis. In the absence of diagnostic testing, empiric therapy should be administered to cover likely pathogens. The management of suspected meningitis is shown in Figure 1.

**Figure 1 Flow diagram for the management of suspected nosocomial cerebrospinal fluid infection**

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**CRBSI**, catheter-related blood stream infection; **ESBL**, extended-spectrum beta-lactamase; **MRSA**, methicillin-resistant *Staphylococcus aureus*; **MRSE**, methicillin-resistant *Staphylococcus epidermidis*; **UTI**, urinary tract infection; **VAP**, ventilator associated pneumonia. Adapted from Beer et al. [1].

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infectious diseases [2,33–35]. Risk factors for the administration of inadequate anti-infective therapy are preceding antibiotic therapy during the same hospitalization, longer duration of indwelling catheterization, and infections caused by multidrug resistant bacteria and infections by \textit{Candida} species [33]. Empirical antimicrobial therapy of nosocomial intracranial infections must consider the most likely pathogens involved, local resistance pattern, underlying disease, and patient factors such as age, comorbidities, and immune status (Table 1). The antibiotics selected must adequately penetrate the blood–brain and blood–CSF barriers. A flow diagram for the management of device-related nosocomial intracranial infections is presented in Fig. 1 [1]. As in the neuro-ICU patient population nosocomial intracranial infections can be caused by multidrug resistant Gram-positive and Gram-negative pathogens, initial empiric treatment with the glycopeptide antibiotic vancomycin in combination with a cephalosporin with antipseudomonal activity or a carbapenem is recommended until culture results provide information to adapt antimicrobial therapy according to resistance testing [1,2,32]. In patients with a contraindication for systemic vancomycin administration in whom a ventricular catheter is placed, vancomycin can be safely administered intrathecally [36,37**]. For patients with severe allergy to beta-lactam antibiotics, moxifloxacin might prove as an alternative. The efficacy of linezolid for the treatment of nosocomial Gram-positive ventriculitis meningitis has been demonstrated recently [38,39]. Nosocomial intracranial infections due to antibiotic resistant \textit{Acinetobacter} species is becoming an increasingly clinical entity. In these cases, combination therapy of systemic and intrathecally administered polymyxins plus removal of infected devices is recommended [40*].

Recommendations on the duration of antimicrobial therapy of infectious intracranial complications in the neuro-ICU population have not been studied rigorously. Mostly, treatment is continued for 10–14 days. If repeated CSF cultures are negative, some experts have suggested shorter durations [41]. However, it needs to be stressed that therapy of nosocomial intracranial infectious complications therapy must be individualized because some patients with preceding or concurrent anti-infective therapy may need appropriate empiric antimicrobial treatment despite negative microbiological testing.

Although the routine prophylactic exchange of noninfected indwelling devices is still discussed controversially, consensus exists on the timely removal of neurosurgical hardware infected with pathogens capable of biofilm formation [1]. Importantly, catheter removal requires concomitant antimicrobial therapy [2]. Recurrence of nosocomial infections is reported in 25% of cases [42]. Therefore, a high level of suspicion needs to be maintained after termination of antimicrobial therapy.

\section*{Prevention}

Because of difficulties in early diagnosis and subsequent delayed initiation of appropriate antimicrobial therapy, prevention of nosocomial intracranial infection is of paramount importance. Preventive measures include adequate surgical techniques and hygiene as well as the preventive administration of antibiotics in patients undergoing neurosurgery [43]. However, the benefit of prophylactic and peri procedural antibiotics may be outweighed by predisposing the patient to infections by more resistant pathogens with a higher mortality rate [14]. Recently, the insertion of antimicrobial-impregnated EVD catheters has been proposed to prevent bacterial colonization along the catheter surface, thereby reducing the risk of device-related ventriculomeningitis [44]. However, the possible induction of antimicrobial resistance, leading to major healthcare problems, is a significant concern. A relatively new option that may overcome this disadvantage is the introduction of ventriculostomy catheters impregnated with silver nanoparticles. A prospective pilot study and a retrospective analysis found reduced infection rates with the use of silver nanoparticles bearing EVD catheters [22,45*].

\section*{Conclusion}

The neuro-ICU patient population is at considerable risk for developing intracranial infectious complications contributing to morbidity and mortality. The emergence of multidrug resistant pathogens contributes to the complexity of the management of nosocomial infections of the CNS. Continuous surveillance including systematic collection and analysis of data on the occurrence and microbiology of this distinct infectious disease entity is required. Specific risk factors such as neurosurgical intervention or presence of a distant focus of infection must be assessed. Timely diagnosis and prompt initiation of appropriate antimicrobial chemotherapy is of utmost importance being associated with improved outcome.

\section*{References and recommended reading}

Papers of particular interest, published within the annual period of review, have been highlighted as: • of special interest •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 177).

This review gives an overview on the pathophysiology of this severe neurological complication of sepsis.


This contemporary retrospective analysis indicates that silver-bearing external ventricular drainage catheters may reduce the risk of device-related infections in neurosurgical patients.