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Clinical infections in neurosurgical oncology: An overview

Tomaz Velnar, Nina Kocivnik, Roman Bosnjak

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Abstract

Central nervous system (CNS) infections are urgent conditions with high morbidity and mortality. Bacteria, viruses, parasites or fungi can cause them. Intracranial infections after craniotomies are an important complication of treatment, especially in oncological patients that are already immunologically compromised due to the disease and treatment. The consequence of CNS infections in oncological patients includes longer treatment with antibiotics, additional surgical procedures, higher treatment costs and poorer treatment outcomes. Additionally, the management of primary pathology may be prolonged or postponed as a result of the active infection. By introducing new and improved protocols, tightening controls on their implementation, constantly educating the entire team involved in patient treatment and educating both patients and relatives, the incidence of infections can be reduced effectively.

Key Words: Infection; Central nervous system; Neurosurgery; Oncology

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Core Tip: Various agents, including bacteria, viruses, parasites and fungi, can cause infections of the central nervous system. As urgent conditions with high morbidity and mortality, they need to be recognised promptly and treated aggressively. By introducing improved defence and treatment protocols, tightening controls on their implementation, constantly educating the entire team involved in patient care and educating patients and relatives, the incidence of infections can be reduced significantly.

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INTRODUCTION

The employment of new technological achievements and the number of invasive procedures in medicine are rising[1]. The advent of new technological possibilities has enabled the progress of better microscopy, visualisation, and development of neuroendoscopic and neuronavigational techniques and instruments. Surgical procedures, especially in neurosurgical oncology, are, therefore, becoming less invasive for patients[1,2]. They provide the opportunity to treat an increasing number of neurosurgical pathologies that can now be accessed with minimal potential morbidity, faster, easier, less invasive, more frequent, and with less tissue damage, contributing to better treatment outcomes[3-5]. The type of neurosurgical procedure depends on many factors, such as the location and size of the tumour, its vascularity and composition, the diversity of tumours (solitary, multiple metastases, or involvement of many lobes), accessibility, eloquent areas of the brain, the clinical condition and wishes of the patient, and the surgical equipment[6].

When considering brain surgery, it is essential to recognise that the primary goals of surgery vary depending on the pathology[7]. These include relieving the increased intracranial pressure for various reasons, treating the vascular pathology or haemorrhage, evacuating the hematoma, reducing the tumour as safely as possible, obtaining tissue for histologic diagnosis, and repairing the head injury[6-8]. Despite these advances in treatment, infections after oncological operations in neurosurgery are one of the drawbacks that can hamper recovery and lead to increased morbidity and mortality, especially when not treated promptly and correctly.

Central nervous system (CNS) infections are emergencies with high mortality and disability due to diverse and serious neurological sequelae[9]. The causative agents can be very different: Bacteria, viruses, parasites or fungi (Table 1). How the infection progresses depends on many factors, the two most important of which are the virulence of the causative agent and the host's immune system. Intracranial infections affect a variety of anatomical structures, ranging from the meninges (meningitis), brain tissue (encephalitis) and bone (osteomyelitis). The infection can be localised or diffuse, and in terms of time it can be acute or chronic. Infections are identified by clinical features, laboratory findings and diagnostic imaging. Treatment can be conservative or surgical[9-12].

CNS infections have certain characteristics that distinguish them from infections of other organs (Table 2). This is why these infections have distinct courses, clinical pictures and treatment modalities. These features of the CNS include: (1) A blood-brain barrier that is selectively permeable to chemotherapeutic agents (antibiotics); (2) The uniformity of the subarachnoid space, which allows a continuous spread of the infection through the cerebrospinal fluid; (3) Circulatory disturbances with increased intracranial pressure, leading to ischaemia from venous and arterial infarctions; and (4) Cerebral oedema resulting from infection causes an increase in intracranial pressure, which leads to brain damage, as the intracranial space is limited by the cranial bones and therefore its volume cannot change [11,12].

CNS infections can also occur as a consequence of neurosurgical procedures and are among the standard risks. After surgery, the average risk of intracranial infection is 6.1% [13-17]. Despite all countermeasures, they remain a serious problem. Infections with antibiotic-resistant microorganisms are also frequently encountered in clinical practice and are becoming an important entity. The consequence of CNS infections in oncological patients includes longer treatment with antibiotics, additional surgical procedures, higher treatment costs and poorer treatment outcomes. We briefly review the basic characteristics of cranial and spinal infections in neurosurgical oncology that occur as a result of surgical interventions.

CRANIAL INFECTIONS

Brain pyogenic abscess

Brain abscess is a localised infection of brain tissue that starts as a circumscribed area of inflammation-cerebritis with a necrotic core and leads to a localised purulent collection surrounded by a fibrovascular capsule[18]. It usually arises at the border between the grey and white matter of the brain. It is a rare infection, usually between the ages of 30 and 40 years, and in children between the ages of 4 and 7 years [11,19]. The causative organisms are most often pyogenic bacteria, rarely fungi or parasites. The most common causes of brain abscess are: (1) Purulent sinusitis and oral infections lead to abscess formation in the frontal lobes; (2) Otitis media and mastoiditis cause inflammation in the temporal lobe and

Table 1 A general overview of the central nervous system infections

Cranial infections	Spinal infections	Other infections
Brain abscess	Epidural abscess	Viral meningoencephalitis
Meningitis	Subdural empyema	Parasitic infections
Subdural empyema	Myelitis	Fungal infections
Epidural abscess	Spondylitis	Prion diseases
Shunt infection	Discitis	Wound infections
Osteitis		

Table 2 Specific factors affecting the course of central nervous system infections

Factor	Effect
Blood-brain barrier	Selective permeability to chemotherapeutic agents (affecting the infection course)
Uniformity of the subarachnoid space	Allows continuous spread of infection through the cerebrospinal fluid
Circulatory disturbances	Ischaemia from venous and arterial infarctions
Increased intracranial pressure	Vessel compression and thrombosis
Cerebral oedema	Leads to increase in intracranial pressure, potentiating brain damage

cerebellum (inflammation may be accompanied by sinus thrombosis, which aggravates cerebellar oedema); (3) After penetrating trauma to the brain and after neurosurgical procedures; and (4) Haematogenous (from pulmonary abscesses, bronchiectasis, bacterial endocarditis, pulmonary arteriovenous fistula, cyanotic heart disease, osteitis, skin infections, after dental, pelvic and abdominal surgery). In 20% to 40% of patients, the primary site of infection cannot be found, and this type of abscess is called a cryptogenic abscess. It occurs in 0.17% to 0.3% of cases after neurosurgical operations [18-20].

The formation of a brain abscess occurs in four stages: (1) Early and late cerebritis (first to the third day and fourth to 10th day after infection); (2) Early capsular abscess (10th to 13th day); and (3) Late capsular abscess (after 14 days).

Aetiology: The causative agents of brain abscesses include bacteria, fungi, protozoa and helminthes (Table 3). The most common bacterial pathogens of brain abscesses are *Staphylococcus aureus*, *Streptococcus milleri* and *Streptococcus viridans*, as these colonise the nasal and oral pharynx. *Pseudomonas spp.* can occur in brain abscesses due to otitis media or otitis externa. The most common organisms found in abscesses associated with brain lesions are *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Enterobacteriaceae*. *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa* and *Propionibacterium acnes* are most commonly found in abscesses associated with neurosurgical procedures [21-24]. Brain abscess after neurosurgical procedures or penetrating trauma is usually caused by *Staphylococcus aureus*, streptococci and enterobacteria and clostridia [25].

Fungal brain abscesses may also develop in immunocompromised patients and may be caused by *Candida*, *Cryptococcus*, *Aspergillus*, *Rhizopus arrhizus*, *Coccidioides*, *Blastomyces dermatitidis* and *Histoplasma capsulatum* [22,23].

Protozoa that can cause brain abscesses are *Toxoplasma gondii*, *Trypanosoma cruzi*, *Entamoeba histolytica*, *Naegleria fowleri* and *Acanthamoeba* [23].

Helminths are also among the causative agents of brain abscesses. The most common pathogens are *Taenia solium*, *Schistosoma spp.* and *Paragonimus* [22,23].

Clinical signs: Clinically, infection is manifested by signs of increased intracranial pressure (headache, nausea, vomiting, disturbed consciousness), fever, focal neurological signs and seizures [19].

Diagnostics: The most commonly used diagnostic methods include head imaging with computed tomography (CT) without and with contrast (contrast stains the hyperemic capsule nicely) and magnetic resonance imaging (MRI). Laboratory tests are often non-specific [10].

To diagnose brain abscesses, a CT scan with contrast is essential. The accuracy of the diagnosis of pathology using CT of the brain depends on the degree of abscess formation. Although less sensitive than MR imaging, it is easier to perform. It allows early detection, precise localisation, determination of the number and size of the abscess [24,26].

Table 3 Most common causative agents for brain abscess

Bacteria	Protozoa	Fungi	Helminthes
<i>Staphylococcus aureus</i>	Histoplasma capsulatum	Candida	Taenia solium
<i>Staphylococcus epidermidis</i>	Trypanosoma cruzi	Aspergillus	Schistosoma spp.
<i>Streptococcus milleri</i>	Entamoeba histolytica	Cryptococcus	Paragonimus
<i>Streptococcus viridans</i>	Naegleria fowleri	Rhizopus arrhizus	
<i>Pseudomonas spp.</i>	Acanthamoeba	Coccidioides	
Enterobacteriaceae		Blastomyces dermatitidis	
<i>Propionibacterium acnes</i>		Histoplasma capsulatum	
<i>Clostridium spp.</i>			

MRI is often considered as the first diagnostic approach in the diagnosis of brain abscesses due to its better sensitivity and specificity. Compared with CT imaging, it has a better ability to detect cerebritis, a stronger contrast between the cerebral oedema and the brain, better visualisation of the brainstem and earlier detection of satellite lesions[21,26]. Single or multiple lesions with ring contrast enhancement, with internal necrotic restriction on diffusion weighted images (DWI) are often observed in pyogenic abscess[27,28].

Laboratory tests are often non-specific[10]. Cerebrospinal fluid analysis and erythrocyte sedimentation rate are routinely performed to diagnose brain abscesses. Serological tests to measure C-reactive protein levels and blood tests to check leucocyte levels may also be performed. Blood cultures (at least two) should be taken before starting antibiotic treatment. Brain abscesses are characterised by increased erythrocyte sedimentation rate, high serum C-reactive protein levels and leucocytosis[21,26].

Treatment: Treatment is conducted with broad-spectrum antibiotics that penetrate the blood brain barrier and cover Gram-negative, Gram-positive bacteria and anaerobes. After neurosurgical intervention, depending on the expected nosocomial pathogens, vancomycin is prescribed for experimental treatment, together with 3rd or 4th generation cephalosporins, and later, if there is an isolated pathogen, according to the results of the antibiogram[25]. Treatment is given for 6 to 8 wk with intravenous doses, and continued orally for 2 to 6 mo. When conservative treatment is unsuccessful, surgical treatment is indicated, which may include neuronavigation or stereotactic needle biopsy, puncture and aspiration for large abscesses, or craniotomy. The latter may be used for encapsulated abscesses, foreign bodies, multilocular abscesses. Additional treatment is also important, including anti-oedema and anti-epileptic therapy. The mortality rate was 40%-60% before the use of CT but is now around 10%. 45% have permanent neurological damage[29-31].

Meningitis

Meningitis is defined as an inflammation of the meninges due to infection, usually of bacterial aetiology, but may also be viral or parasitic. After neurosurgical procedures, meningitis is rare and occurs in 1% to 2%[10]. After neurosurgery, meningitis is usually caused by *S. aureus*, coagulase-negative staphylococci, and aerobic Gram-negative bacilli including *Pseudomonas aeruginosa*[32].

Course of infection: Meningitis, which is a complication of neurosurgery, is rare. It occurs most frequently 7 to 14 days after surgery. Other causes include head trauma and congenital causes such as myeloceles, open dermal tracts. Clinical features include fever, headache, nausea, vomiting, and may also include disturbances of consciousness and signs of raised intraluminal pressure, stiff occiput, opisthotonus[20].

Aetiology: Bacterial meningitis occurs when a bacterium infects the body and the infection spreads to the meninges[33]. The most common bacterial agents of meningitis are *Streptococcus pneumoniae*, Group B *Streptococcus*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Listeria monocytogenes* and *Escherichia coli*[34]. However, some bacteria are more likely to affect certain age groups. The most common causative agents of bacterial meningitis in neonates are *Streptococcus pneumoniae*, *Listeria monocytogenes* and *Escherichia coli*. In infants and young children, meningitis is most often caused by infection with *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, Group B *Streptococcus* or *Mycobacterium tuberculosis*. In teenagers and young adults, meningitis is caused by *Neisseria meningitidis* and *Streptococcus pneumoniae*. Older adults develop meningitis due to infection with Group B *Streptococcus*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Neisseria meningitidis* or *Haemophilus influenzae*[35]. In people with recent surgery or trauma, the most common causative agent of brain abscess is *Staphylococcus aureus*[36].

Fungal meningitis occurs as a result of a fungal infection spreading to the meninges. An individual becomes infected with fungi by inhaling spores from the environment. The most common causative agents of fungal meningitis are *Cryptococcus neoformans*, *Coccidioides immitis*, *Aspergillus*, *Candida* and *Mucormycosis*[35,36].

Viral meningitis occurs when a virus enters the body and spreads to the meninges[33]. Viruses that cause meningitis in humans include enteroviruses, mumps, Epstein-Barr virus, herpes simplex virus, varicella-zoster virus, measles virus, influenza virus and arboviruses (Table 4)[36].

Diagnosics: Diagnostic investigations include CT, MRI, laboratory tests and lumbar puncture. Imaging tests such as CT and MRI are performed when lumbar puncture is unsafe.

CT is performed before lumbar puncture, to evaluate if there is no contraindication (as tonsillar herniation) to the procedure. MRI offers a superior image. The fluid attenuated inversion recovery (FLAIR) weighted images with contrast application are more sensitive and specific than T1 phase with contrast application (gadolinium is used as a contrast agent) and the FLAIR sequence is used for spotting the leptomeningeal enhancement, which is encountered in meningeal inflammation[37].

Blood tests may also be done to diagnose meningitis, where high leucocyte levels indicate a severe infection such as meningitis. Procalcitonin levels help to determine whether meningitis is due to a viral or bacterial infection, where high levels indicate a bacterial infection. A blood culture, which tests the blood for certain organisms, can also be taken to help guide treatment. Cerebrospinal fluid analysis may also be performed to identify the causative agent of meningitis. The most reliable way to diagnose meningitis is by lumbar puncture, in which cerebrospinal fluid is taken from the lower back using a long, thin needle. In meningitis, low levels of glucose and elevated levels of leucocytes and proteins are present in the cerebrospinal fluid, which is characteristic for bacterial meningitis. In viral meningitis, on the other hand, the glucose levels are within the normal range[33,34,38].

Treatment: For treatment of the bacterial infection, antibiotics are used. These are introduced after lumbar puncture, first empirically and then targeted according to the isolated pathogen and its susceptibility. For the experimental setting, vancomycin is usually prescribed in combination with ceftazidime, cefepime or meropenem[32]. The disease can be fatal or have serious complications and sequelae, including disability or disturbances in the circulation of the lymph fluid (hydrocephalus)[20,39]. For viral meningitis, intravenous acyclovir is most commonly used. Other antiviral agents (oral valaciclovir and concomitant intravenous aciclovir administration) for the treatment of herpes simplex encephalitis have also been tested[40,41].

Epidural abscess

This is an inflammation of the CNS with collection of pus in the epidural space and may also occur as a result of neurosurgical procedures. The most common pathogens of epidural abscess after neurosurgery are *S. aureus* and Gram-negative bacilli[30].

Course of infection: The clinical picture is less dramatic here, as pus accumulation and abscess spread is limited by the adherence of the dura to the bone. Clinical signs are manifested by increased intraluminal pressure, fever, headache, focal neurological signs. They are similar to meningitis and brain abscess. The most common causative agents are streptococci (usually anaerobic forms such as peptostreptococcus) and other anaerobes (*Propionibacterium* (*Cutibacterium*) *acnes*) but may also include gram-negative bacilli or fungi. When the infection is a complication of a surgical procedure, staphylococci, mainly *S. aureus*, and gram-negative bacteria are the most common causative agents[36,38].

Diagnosics: Diagnostic methods are similar to other infections. They include imaging (CT, MRI), laboratory tests and lumbar puncture. MRI is the first method of choice due to its highest diagnostic accuracy, particularly on DWI, as epidural abscess demonstrates restriction. It has a sensitivity of 90% to 95% and a specificity of more than 90%. In the event of inconclusive findings, the whole investigation should be repeated. CT imaging with intravenous contrast is used when MRI cannot be performed. It allows us to visualise the fluid in the epidural space, but it is possible to miss abscesses that would be clearly visible on MRI[42]. When an epidural abscess is suspected, a complete blood count (CBC) is also performed. Laboratory findings consistent with a diagnosis of an epidural abscess include leucocytosis, thrombocytopenia, elevated C-reactive protein (CRP) and increased erythrocyte sedimentation rate[42-44]. A lumbar puncture for the diagnosis of epidural abscess is rare due to its non-specificity and the risk it poses[44].

Treatment: Treatment includes surgical drainage of the abscess and antibiotic therapy depending on the causative organism[10,30]. For the experimental treatment of epidural abscess after neurosurgery, vancomycin is used in combination with third generation cephalosporins (ceftriaxone) or with another antimicrobial drug with antistaphylococcal activity (meropenem, rifampicin, nafcillin, or fosfomycin). For the treatment of streptococcal, haemophilus, and anaerobic infections, the most appropriate agents are third generation cephalosporins, vancomycin and metronidazole. Treatment can then be modified according to the antibiogram. We also use linezolid and daptomycin. For the experimental treatment of epidural abscess after neurosurgery, we use vancomycin in combination with ceftazidime, cefepime or

Table 4 Most common causative agents for meningitis

Bacteria	Viruses	Fungi
<i>Streptococcus pneumoniae</i>	Herpes simplex virus	Cryptococcus neoformans
<i>Listeria monocytogenes</i>	Epstein-Barr virus	Coccidioides immitis
<i>Escherichia coli</i>	Mumps	Aspergillus
<i>Neisseria meningitidis</i>	Enteroviruses	Candida
<i>Haemophilus influenzae</i>	Varicella-zoster virus	Mucormycosis
Group B <i>Streptococcus</i>	Measles	
<i>Mycobacterium tuberculosis</i>	Influenza	
<i>Staphylococcus aureus</i>	Arboviruses	

meropenem[45]. Antibiotic therapy usually lasts from 4 to 6 wk, and up to 8 wk if the bone is involved [10,30,46].

Subdural empyema

This type of infection is characterised by a collection of pus in the subdural space. It is a rare infection but may occur in 2% to 14% after neurosurgical operations[12,47,48].

Characteristics of the infection: It most commonly occurs between the ages of 15 and 30 years, is 95% supratentorial, and comprises 15% to 20% of localised intra-lobar infections[49]. Causes include neurosurgical and otological procedures and head trauma, in addition to paranasal sinusitis, middle ear infection, haematogenous carriage from lung abscesses, local inflammatory areas of the head and neck, and bacterial meningitis. The most common causative agents are group A streptococci, staphylococci, gram-negative aerobes, anaerobic streptococci. After neurosurgery, staphylococci and Gram-negative aerobic bacilli are the most common, possibly including *C. acnes*, especially if artificial material has been used[45].

The clinical picture here is dramatic and serious, as the infection is very dangerous: Increased intraluminal pressure, fever, meningeal loops, focal neurological deficits, seizures. As subdural empyema is an emergency condition, surgical drainage *via* borehole or craniotomy and antibiotic therapy are required, first empirically, then depending on the antibiogram result. The mortality rate is 20%. The most common complications are neurological impairment (epilepsy, paresis), which occurs in as many as 50%[12,47,49].

Diagnostics: Diagnostic methods include imaging (CT, MR), laboratory tests and lumbar puncture. DWI shows restriction in the purulent material. A CT scan with contrast is most commonly used to diagnose subdural empyema, as it allows a quick assessment. On the image, the subdural empyema appears as a thin, hypodense area overlying the cerebral hemisphere with linear enhancement of the medial surface. Depending on the size of the subdural empyema, an associated mass effect with displacement of the medial structures may be observed. The problem is the possibility of a false negative result, which is often due to early symptomatology with no obvious signs of change. Therefore, MRI with intravenous gadolinium enhancement and DWI are used as the gold standard for the diagnosis of subdural empyema. This is an investigation with a sensitivity of 93%, which, unlike CT imaging, shows more morphological details. The subdural empyema is seen as a crescentic area of hypointensity[50-52].

Laboratory analyses are non-specific and often only add evidence to the presumptive diagnosis. In the presence of subdural empyema, leucocytosis, increased erythrocyte sedimentation rate and elevated C-reactive protein levels are seen on blood smears. Blood cultures may also be taken, but the chance of confirming the diagnosis in this case is poor. It is therefore recommended that intraoperative sampling and culture should be performed in all operations. These allow us to obtain pathogenic information, but they also have a high chance of false negative results[52].

Lumbar puncture is an invasive procedure and is not recommended as it can cause herniation and neurological deterioration. If the procedure is performed, the resulting puncture is Gram-stained, and a culture is prepared from the specimen. This gives an indication of the number of cells that are indicative of inflammation[52,53].

Treatment: As subdural empyema is an emergency condition, surgical drainage *via* a borehole or craniotomy and antibiotic therapy are required, preferably after sample collection for microbiological investigations, first empirically (the choice of antibiotics include vancomycin, meropenem, metronidazole, ceftriaxone) and then according to the antibiogram result[54]. Meropenem alone can also be used as a first line antibiotic as it covers both Gram positive and Gram negative and anaerobic bacteria. For the empirical treatment of epidural abscess after neurosurgery, vancomycin with ceftazidime,

cefepime or meropenem is prescribed[45]. Mortality is around 20%[11,47,49].

Drainage system infections

Drainage system infections include infections of the external and internal drains that drain fluid from the ventricular system[55].

Characteristics of infections: Complications of drainage systems are common in clinical practice. The most dangerous period for infection of the external and internal drains is limited to the time of surgery. It increases with the length of the operation and may persist even later, in the postoperative period during the wound healing phases of the first nine months after surgery. The risk of infection is slightly lower here, up to 4%[11,55].

Bacteria can attach to the artificial material of the drains and form a biofilm that is resistant to antibiotic treatment. The main complication of drainage is ventriculitis and meningitis, in addition to potential infection of the surgical wound and the part of the body where the end of the drainage tube is passed. There are internal ventricular drains (IVDs) and external ventricular drains (EVDs). The latter are also frequently used in the treatment of intracranial haemorrhage with the aim of lowering intracranial pressure. The procedure is often performed in intensive care units or in the emergency room at the patient's bedside. As a consequence, the percentage of infection is high, ranging up to 20%. Factors that increase the risk of infection are leakage of fluid through the wound, flushing of the catheter and the frequency of ventricular punctures (insertion of the EVD) in the same patient. Diagnosis is often complicated by the presence of a primary infection or disease or because haemorrhagic fluid itself may trigger an inflammatory reaction similar to ventriculitis. The incidence of infection is lower with internal drains, at less than 10%[11,56].

The most dangerous period for infection of external and internal drains is limited to the time of surgery. It increases with the length of the operation and may persist even later, in the postoperative period during the wound healing phases of the first nine months after surgery. The risk of infection is slightly lower here, up to 4%[56].

Infection is most often due to colonisation of the drainage system by the usual non-pathogenic skin flora at the time of surgery. The characteristics of the material from which the drainage system is made may increase the risk of infection, as well as the timing of the surgical procedure. Staphylococci are the most common pathogens in 75% and Gram-negative bacilli in the remainder. Symptoms include meningitis, fever (in 26%), headache, nausea, vomiting, disturbed consciousness, and may also include signs of sepsis. Poor drainage (26%), abdominal pain at the wound in the case of ventriculoperitoneal drainage (19%) and additional symptoms and signs due to disturbances in the flow of fluid are usually associated[9,11,29,39,57].

Diagnostics: When drainage system infection is suspected, CSF is collected for bacteriological, biochemical and cytological investigations. In the case of EVD, the sample is taken directly from the drainage system, whereas in the case of internal drainage, it is taken by percutaneous puncture of the drainage valve (or lumbar puncture). The laboratory indicator is an elevated leucocyte count in the fluid and isolation of the microorganism. Haemoculture results are also important (positive in 90% of infected ventriculoatrial drains and in 20% of infections of other drains). Laboratory blood results are generally non-specific[10].

Treatment: Due to the formation of biofilm on the drainage system, the infection cannot be cured with antibiotics alone. The drainage must be removed and, if necessary, a temporary EVD should be placed. If the patient is tolerant, a short period without drainage while receiving intravenous antibiotic therapy is preferable. EVD cures haemato- or hydrocephalus but exposes the patient to the risk of infection. Once the infection is completely cured, usually after at least two sterile fluid samples and a fluid protein level below 1 g/L, a new internal drain is placed, with which the risk of re-infection is higher than it was during the surgical procedure when the drain was first inserted[56-59].

Infections of the skull bone - osteitis

Osteitis is a bacterial infection of the skull bone[60].

Characteristics of the infection: The most common causes of this type of infection are trauma and neurosurgical procedures, or inflammatory foci in the soft tissues nearby. Infection may involve the base (cause of sinus and middle ear inflammation) or the cranial barrel. These are usually long-standing, slow-moving infections with complications including meningitis, epidural and subdural abscess and venous sinus thrombosis. Immunosuppression, diabetes, irradiation, dialysis, intravenous drug users and implants after neurosurgery or foreign bodies are predisposing factors for these infections. Again, *S. aureus*, *Escherichia coli* (mostly in children) and Gram-negative bacilli are the most common pathogens, while in surgical practice *S. aureus* and skin flora are the most common pathogens[11,39,60].

Diagnostics: Diagnosis is made by MR, CT, X-ray, scintigraphy, laboratory tests and bone biopsy for microbiological (preferably two samples) and histological examination and by clinical examination in

addition to imaging[10]. Imaging tests are usually performed to make an early diagnosis and to determine the location and extent of the infection. X-ray imaging allows us to see bone damage, but the damage will only be visible if the osteitis has been present for a long time (for several weeks). Due to the low sensitivity and specificity, more detailed imaging examinations are needed to make a diagnosis. MR imaging is used to assess the location and extent of the infection and also shows very detailed images of the bone and soft tissues. It is also a more sensitive examination for determining the extent of disease. CT imaging is usually performed when MR imaging cannot be performed. CT can be used without enhancement or with contrast. It is an examination that is sensitive to bone erosion or skeletal remodelling and demineralisation. Contrast-enhanced CT can show soft tissue swelling and enhancement, obliteration of normal fat pads, involvement of the foramina of the skull base and vascular complications. In scintigraphic imaging, a radionuclide that emits radiation is injected intravenously and detected by gamma cameras. It allows the assessment of abnormal bone metabolism, which in osteitis manifests as increased uptake of the radionuclide. Three radionuclide tests are most common in the diagnosis of osteitis: Triphasic, gallium and leucocyte imaging[61-64].

Laboratory investigations in osteitis show elevated leucocyte counts, increased erythrocyte sedimentation rates and elevated C-reactive protein levels. Blood tests are non-specific - they cannot confirm or reject suspected osteitis. They are only performed as a test to help guide the doctor for further investigations. If the disease is due to an infection, the tests can show the type of microbe in the blood[61,63,64].

Bone biopsy helps to identify the microbial infectious agent, but sometimes cannot be performed. If microbiological isolation is successful, this test can also confirm the diagnosis[62,63]. In some cases, the biopsy may also need to be repeated. A repeat biopsy is necessary if the first culture is negative or to exclude malignant disease in patients in whom the disease persists despite appropriate antibiotic treatment. In the case of a fungal agent, this is demonstrated by silver staining of histological sections [61].

On clinical examination, the doctor palpates the area around the affected bone to determine the presence of tenderness, swelling or warmth. On the basis of the clinical examination, he/she then orders a combination of tests to diagnose osteitis[63].

Treatment: Treatment is surgical, either by removal of the bone lobe or of the diseased part of the bone, and the surgical debridement should be as thorough as possible. Antibiotics, which are usually prescribed according to the isolated causative organism, are indispensable and the treatment is lengthy and may last from 8 to 20 wk[60].

Dexamethasone therapy in malignant tumours has been shown to be a risk factor for postoperative wound infections and osteomyelitis[65,66]. On average, infections occurred in one or two months after the procedure. The most frequently isolated bacteria include *P. acnes*, *S. aureus* and *S. epidermidis*. All such cases require reoperation, longer antibiotic therapy and consequently longer hospitalisations, delayed primary tumour treatment and increased treatment costs. In view of the more superficial infections accompanied by wound dehiscence, it is necessary to strengthen the implementation of asepsis measures, to pay more attention to postoperative wound care, to the cleanliness of the surrounding area, and also to properly instruct patients and relatives on the care of the surgical wound [65-67].

SPINAL INFECTIONS

Spinal epidural abscess

A spinal epidural abscess is an infection in the spine with pus accumulation in the epidural space[30].

Characteristics of the infection: A spinal epidural abscess is twice as common as a cerebral abscess. It can also occur as a complication of surgery, where the risk of epidural abscess formation is up to 1.5% [60]. Other risk factors include spinal trauma and disease, systemic complications in the context of sepsis, and spread from distant inflammatory foci. Patients with associated diseases, diabetes mellitus, HIV and alcoholics are also more prone to these infections. Direct infection is present in 30% due to trauma and invasive treatment, and in 50% it occurs haematogenously. The causative agents are bacteria (*S. aureus* in 60%, *S. epidermidis*, Gram-negative bacilli, mycobacteria), rarely fungi and parasites. The cervical spine is rarely affected, with infection most commonly located in the thoracic (65%) and lumbar spine (35%). Clinical symptomatology is manifested by severe post-surgical pain and systemic loops of infection, possibly with radicular pain and neurological signs under the affected part (paraparesis, tetraparesis, sensory and sphincter disturbances). The diagnostic triad is particularly characteristic: Pain (75%), fever (50%) and neurological disturbances (30%). These are due to spinal cord injury during infection caused by pressure, inflammation and thrombosis of blood vessels, ischaemia and release of microbial toxins and inflammatory mediators[30,68,69].

Diagnostics: Diagnosis is made by clinical signs, MRI, CT and sometimes myelography, although the latter is not recommended because of its invasive nature and the possibility of contamination of the

subarachnoid space. In patients with persistent symptoms who have a diagnostically inconclusive MR scan, a repeat scan in two to three weeks should be considered. MRI should include DWI in the protocol. Laboratory findings are often non-specific[10,68]. Leukocytosis is present in 60% to 80% of patients with spinal epidural abscesses. Serum CRP and erythrocyte sedimentation rates are more sensitive and are elevated. Haemocultures are positive in approximately half of the patients. When an epidural abscess is suspected, an image-guided biopsy should be performed to confirm the diagnosis and plan antibiotic therapy. In patients with suspected epidural abscess, lumbar puncture should be avoided because of the risk of spreading the infection to the subarachnoid space[68].

Treatment: Treatment consists of spinal cord decompression with laminectomy and pus removal, i.e. decompression of the neural structures, followed by at least six weeks of antibiotic therapy according to the sensitivity of the pathogen isolated from intraoperatively collected samples[30,69].

Spinal subdural empyema

This is an inflammation and collection of pus in the spinal subdural space. It is a rare infection that most commonly arises from the spread of infection from the epidural space, distant foci or iatrogenically (after surgical procedures). It is caused by staphylococci, streptococci and gram-negative bacilli. Clinical signs are manifested by fever, localised spinal pain and neurological manifestations. Treatment for neurological disorders includes urgent decompression and antibiotic trapping depending on the isolated causative agents[69,70].

Discitis

Is an infection of the nucleus pulposus of the intervertebral disc with a secondary infection of the terminal disc and vertebral body[71].

Characteristics of the infection: May arise from an inflammatory focus or iatrogenically (one to four weeks after surgical procedures, most commonly after discectomy). Risk factors for infection include immunosuppression, obesity, active infection in other parts of the body, and age. The causative agent is most commonly *S. aureus*. Clinical signs include localised pain that is worse during movement. Less commonly, it is radicular pain. The problems are accompanied by paravertebral muscle tension and fever[71,72].

Diagnostics: In addition to clinical signs, MR and CT imaging are used for diagnosis. The use of contrast stains the inflamed disc tissue nicely. MRI is one of the most sensitive and specific imaging modalities for assessment of the lumbar spine. It offers information not only about the intervertebral discs, but also about the vertebral bodies and the structures in the spinal canal, including the meninges, spinal cord, conus, cauda equina and the nerve roots. MRI is the most suitable imaging modality for evaluating spinal discitis and also osteomyelitis. Characteristic is an abnormal signal within the inflamed intervertebral disc in addition to the bone marrow oedema and endplate irregularity in the adjacent vertebrae. Post-contrast MRI may precisely define the degree of the intervertebral disc involvement and the extension of the inflammation into the adjacent vertebral bodies, paraspinal structures and along the spinal canal. The imaging will also provide information about the extension of the inflammation and purulent discharge into epidural and intradural space, as well as the leptomeningeal involvement[73,74].

On X-ray imaging, air inclusions in the disc or bone resorption in the terminal discs may be visible. Tissue biopsy (ultrasound- or CT-guided disc puncture) is very important to obtain the mass and target antibiotic therapy[10,71,72].

Treatment: Treatment is with antibiotics (intravenously for one to two months, then orally for one to two months) and immobilisation (in 90%). Surgical intervention is rarely necessary, especially when the removal of inflamed tissue is required[69,71].

Viral infections of the CNS

Viral infections of the CNS are caused by viruses that invade the host and infect its brain and spinal cord[75].

Characteristics of the infection: Viruses are a common cause of CNS infections, and the expression of viral diseases is influenced by the immune response of the infected host and by factors of the causative agent (neuroinvasiveness, neurotropism and neurovirulence). Viruses cause neurological disease in different ways. They can cause it directly by infecting or damaging neuronal cells or indirectly by stimulating host immune responses that alter the function of the host's cells[75,76]. Most viral infections of the CNS begin with the entry and replication of the virus in cells near the respiratory or gastrointestinal tract. Viruses then spread to the CNS haematogenous and enter the brain *via* the choroid plexus or through the vascular epithelium[75].

The clinical manifestation of infection also depends on the type of virus infecting the CNS host, the anatomical location of the infection and the speed of infection. Meningitis is the most common virally

induced neurological disorder and occurs as a consequence of infection of the meninges. It presents with malaise, headache, vomiting, and neck or back pain. Meningitis may be caused by enteroviruses, herpes simplex virus, Epstein-Barr virus, cytomegalovirus and HIV. In addition to meningitis, viral infectious agents of the CNS often cause encephalitis, which results from infection of the brain parenchyma. This causes signs of brain dysfunction such as seizures, focal neurological dysfunction and coma, in addition to headache, fever and vomiting. Encephalitis may be caused by La Crosse virus, measles virus, Epstein-Barr virus, *etc*[75,77,78].

Aetiology: The most common causative agents of CNS infections are enteroviruses such as enterovirus 70, enterovirus 71, poliovirus, coxsackievirus, echovirus and parechovirus. They are followed by arboviruses, among which La Crosse virus and West Nile virus, Japanese encephalitis virus and Zika virus are the most common. Herpes viruses are also common agents, including herpes simplex virus and Varicella-Zoster virus, Epstein-Barr virus and cytomegalovirus. Paramyxoviruses can also cause CNS infections, the most common of which are the measles virus and mumps. Influenza virus, adenoviruses, parvovirus B19 and lymphocytic choriomeningitis virus are also reported to cause CNS infections[76,77,79].

Diagnostics: CNS viral infections are diagnosed by imaging tests such as CT and MRI. Lumbar puncture, polymerase chain reaction (PCR), serological tests and brain biopsy may also be performed. The first step in the diagnosis of a possible CNS infection is brain imaging. This can exclude changes such as tumours, oedema or hydrocephalus. This is crucial as these conditions can cause brain herniation during a lumbar puncture[75,76].

MRI is the preferred investigation for detecting early lesions as it has a higher sensitivity than CT. The next step is a lumbar puncture, in which the cerebrospinal fluid is analysed. In the case of viral encephalitis or meningitis, the cerebrospinal fluid has an elevated lymphocyte count, mildly elevated protein content and normal or slightly reduced glucose content[75]. Cerebrospinal fluid profiles differ in other virally induced neurological disorders. Major advances in the diagnosis of viral CNS infections have been made through the development of PCR, which amplifies viral nucleic acids from cerebrospinal fluid. Due to its high sensitivity and specificity, this has become the preferred method for the diagnosis of viral CNS infections. Serological tests detect antibodies in serum. This principle is used in the diagnosis of West Nile virus infections. Brain biopsies are rarely performed when the benefits outweigh the risks. It is performed in the case of a serious neurological disorder for which a diagnosis is necessary for therapeutic or prognostic reasons but cannot be identified by imaging or cerebrospinal fluid analysis [75,76,78].

Treatment: Treatment of CNS viral infections is tailored to the severity of the disease and the antiviral drugs available. As few virally induced neurological diseases can be cured with antiviral drugs, the first approach is to stabilise patients and treat any complications. Possible complications include seizures, increased intracranial pressure and difficulty breathing. Antiviral drugs aim to prevent the virus from replicating and to reduce or prevent virus-induced nerve cell damage. Drugs can treat herpes simplex virus encephalitis, Varicella-zoster virus encephalitis or myelitis, systemic HIV infections and congenital or invasive cytomegalovirus infections. Acyclovir is used to treat herpes simplex virus or Varicella-Zoster virus infections in the CNS. Intravenous immunoglobulin is used to treat enterovirus infections [76,78].

Viral meningoencephalitis

Viral meningoencephalitis is a condition referring to inflammation of the brain and meninges (meningitis), resulting from a viral infection[80].

Characteristics of the infection: Meningoencephalitis involves inflammation of the meninges (called meningitis) and inflammation of the brain (called encephalitis). Most meningoencephalitis is caused by viruses; in which case we are talking about viral meningoencephalitis[81,82]. The most common signs of infection include fever, sensitivity to light, headache, stiff neck, hallucinations, personality changes, thinking problems, fatigue, unconsciousness[81-83].

Aetiology: The most common viral agent of meningoencephalitis is herpes simplex. There are two types of herpes simplex virus (type 1 and type 2) that cause meningoencephalitis, but infection with herpes simplex virus type 1 is more common. Other viral agents include enteroviruses, Varicella-Zoster virus, measles virus, HIV, Japanese encephalitis virus, Epstein-Barr virus and mumps[80,83].

Diagnostics: If meningoencephalitis is suspected, a general and neurological examination, imaging tests including MRI and CT, electroencephalography, laboratory tests, cerebrospinal fluid culture and lumbar puncture are performed. A general and physical examination assesses motor and sensory impairment, coordination, balance and altered mental status. Of the imaging investigations, MRI is the investigation of choice. It allows us to have multifaceted imaging, better soft tissue contrast and high anatomical resolution. On T2 and FLAIR weighted images (WI), cortical and subcortical temporal lobe hyperintensity is a finding characteristic of herpes simplex encephalitis. Encephalitis can initially be unilateral, thereafter evolving to asymmetric bilateral involvement. Foci of cortical bleeding, areas of restricted

diffusion-on DWI and gyriform contrast enhancement can also be observed[84,85].

CT is usually used only as a screening test and is performed before a neurological examination or when MRI cannot be performed[81,82]. Echoencephalography measures brain waves through electrodes placed in the brain. It is a non-specific test, as its results rarely show specific features that would help in the differential diagnosis. Its main advantage is that it shows brain involvement at an early stage of the disease. Laboratory tests are non-specific. They include blood tests in which the peripheral blood count and cell morphology are examined. This distinguishes between viral and non-viral infections. In the case of a viral infection, there is an elevated level of lymphocytes in the blood and a normal erythrocyte sedimentation rate. A cerebrospinal fluid culture is done to try to identify the infectious agent microbiologically. A sample of cerebrospinal fluid should be collected for the investigation, incubated on a culture medium and then examined for the presence of specific infectious agents. A lumbar puncture involves the aspiration of a sample of cerebrospinal fluid with a needle. The sample is then examined for the presence of inflammatory cells, proteins and organisms[81,82,86].

Treatment: The main goals of treatment are to treat the symptoms and the cause of the inflammation. Treatment modalities vary depending on the type of causative agent and the severity of the condition. For the most common form of the disease, herpes meningoencephalitis, caused by the herpes simplex virus, treatment involves the intravenous administration of the drug acyclovir for up to 14 days. Other antiviral drugs used include vidarabine or famciclovir, but in the later stages of the infection, antiviral drugs are no longer as effective. Drugs to relieve the symptoms of meningoencephalitis, such as antispasmodics (dilatant and phenytoin), drugs to reduce pressure and swelling in the brain (corticosteroids and diuretics), and analgesics are also used[81,82].

Fungal infections

Fungi are ubiquitous. Their spores are most often present in the air or soil, which is why fungal infections most often start in the lungs or on the skin. Most spores that are inhaled, acquired on the skin or enter the body through a wound, cut or infection do not cause infections in humans at all or are not serious. Fungal infections are divided into primary or opportunistic infections. Depending on the extent of the infection, they are divided into localised, which can be superficial or invasive, and systemic[87]. Primary fungal infections develop whenever a person becomes infected with a specific fungus that is capable of causing infection. Primary infections include Histoplasmosis, Blastomycosis, Coccidioidomycosis and Paracoccidioidomycosis. Opportunistic infections, on the other hand, develop in people with a weakened immune system. The most common opportunistic infections are Aspergillosis, Candidiasis and Mucormycosis. Localised fungal infections affect only one part of the body (usually the nails, vagina or mouth) and occur in people with weakened or normal immune systems. Systemic fungal infections, on the other hand, usually develop when the immune balance is disturbed and affect several parts of the body (typically the lungs, eyes, liver and brain)[87,88]. The symptoms of fungal infections depend on the type of fungus causing the infection in the person and the site of the infection. Signs of infection most commonly appear on the skin, nails or mucous membranes, but can also occur in the lungs, brain, eye, intestines or sinuses[87].

Aetiology: The most common causative agents of fungal infections in humans are the yeast *Candida albicans*, and other environmental fungi such as *Histoplasma*, *Coccidioides*, *Blastomyces* and *Aspergillus*[87]. Different fungi cause different fungal infections. Surface fungal infections are most commonly caused by *Sporothrix*, *Fonsecaea pedrosoi*, *Cladophialophora bantiana*, *Pseudallescheria boydii* and others. *Histoplasma*, *Coccidioides*, *Blastomyces*, *etc.* are common causative agents of invasive fungal infections[87-90]. The fungi that are most frequently fatal are *Cryptococcus*, *Candida*, *Aspergillus* and *Pneumocystis*[89].

Diagnostics: Diagnosis is based on physical examination of symptoms, microscopy, culture, serological tests, molecular diagnostics and, in some cases, imaging. The physical examination involves locating the infected site and taking a sample of skin, hair or nails for laboratory analysis to determine the type of viral infectious agent. For infections not present on the surface of the body, a sample of body fluids such as blood, vaginal secretions, sputum, and urine may be taken. Microscopy is one of the diagnostic tests that form the basis of the diagnosis of fungal infections. The sensitivity of microscopy depends on the type of causative organism and the source and quality of the sample. Culture is considered the gold standard for the diagnosis of fungal infections, as it allows us to identify the specific causative organism in the event of a positive result. Serological tests are used to detect the presence of antibodies and antigens. The use of serological tests for the diagnosis of fungal infections has many advantages, as the results can show a positive result even in the case of a negative culture, the cultivation of potentially dangerous fungi is avoided, and obtaining a sample for serological testing is a minimally invasive procedure[89,90]. Molecular diagnostics include diagnosis by PCR, real-time PCR and sequencing. PCR uses species-specific primers to amplify fungal DNA. The final reading of the results is done by electrophoresis of the PCR products stained with ethidium bromide. Real-time PCR is a more specific method compared to conventional PCR as it uses fluorescent dyes to increase specificity. This is achieved either by using non-specific dyes that bind to DNA or by using a specific fluorescently labelled probe directed

to the target sequence. Sequencing of fungal ribosomal targets is becoming an increasingly used diagnostic method as fungal ribosomes become more abundant, increasing the sensitivity of detection. Imaging tests are performed for the diagnosis of invasive infections of the tonsils. Respiratory infections are diagnosed by CT, neurological infections are diagnosed by MRI (DWI, spectroscopy and contrast are important to the correct diagnosis) and abdominal infections are diagnosed by CT or MRI[90-93].

Treatment: Fungal infections are treated with antifungal agents applied directly to the infected site, which can also be taken orally or intravenously if necessary[87,88].

Operative wound infections

Wound infection is a condition in which pathogenic organisms invade the vital tissue surrounding a wound, triggering an immune response in the host that leads to inflammation and tissue damage, and slows the healing process[94].

Characteristics of infection: Wound infection is defined by the US Centres for Disease Control and Prevention (CDC) as a surgical site infection (SSI), which is further subdivided into superficial incisional SSIs. This can be superficial or deep, and organic or spatial. Superficial incisional SSI involves only the skin and subcutaneous tissue in the incision area, deep incisional SSI involves the deep tissues, and organ/space SSI involves any organ or space that is not part of the incision but has been opened and manipulated during the operation. The most common SSI is superficial incisional SSI[95,96]. All surgical wounds are contaminated with microbes, but due to the host's innate mechanisms, infection often does not develop at all. If there is an increased concentration of bacteria that are part of the normal flora and a weakened immune response, an infection may develop at the wound site[96]. The clinical picture of infected wounds includes fever, reddened skin, oedema, pain and purulent discharge[97]. Risk factors that influence the susceptibility of a wound to infection are divided into endogenous factors related to patient characteristics and exogenous factors related to the surgical procedure. Endogenous risk factors include age, diabetes mellitus, obesity, malignancy, pre-existing diseases, malnutrition, smoking, *etc.* Exogenous risk factors include the length of the surgical procedure[95]. Complications in infected wounds may be local or systemic. The most common local complication is the arrest of wound healing, causing pain and discomfort. Systemic complications include cellulitis, osteomyelitis or septicæmia[97].

Aetiology: Wound infection is most commonly caused by bacteria from the host's normal flora on the skin, although it may also be caused by bacteria from other parts of the body and the external environment[94]. *Staphylococcus aureus* is a Gram-positive coccus and is the most common causative agent of wound infections. *Corynebacterium* spp. are also part of the normal human flora that commonly causes wound infections. *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichia coli* and *Streptococcus* spp. are also common causative agents of wound infections in humans[96,97].

Diagnostics: The diagnosis of wound infection is made by reviewing the clinical signs and symptoms reported by patients and by wound culture, laboratory tests and imaging. When an infection is suspected by visual inspection, a wound culture is performed, which is the golden standard in the diagnosis of wound infections. The culture is performed to confirm the initial diagnosis, identify the micro-organisms and determine the appropriate antibiotic treatment. Currently, there are three techniques for microbial identification: Swab culture, needle aspiration and tissue biopsy. In addition to wound culture techniques, laboratory markers such as C-reactive protein, procalcitonin, presepsin, microbial DNA and bacterial protease activity can be measured to diagnose wound infections[97]. C-reactive protein concentrations are elevated during acute infections. However, they are used only as a supportive measure and not for direct and final diagnosis. Procalcitonin and presepsin levels are also elevated during the infection course. The PCR or real-time PCR assays can detect the presence of microbial DNA, although these tests are not widely used due to their high cost and complexity of application. The measurement of bacterial protease activity allows us to understand the pathological behaviour of micro-organisms in the wound. Traditional imaging tests include CT and MRI and are often used to confirm the diagnosis. CT is helpful in the diagnosis of soft tissue infections and intra-abdominal abscesses as it is fast and widely available, allows multiplanar imaging and has a high spatial resolution. MRI is important in the diagnosis of soft tissues mainly because of its high spatial and contrast resolution. It also provides information on the extent of infection in both soft tissues and underlying bone[96,97].

Treatment: Antibiotics are most commonly used to treat wound infections, but sometimes surgery is also necessary. The identification of the infectious agent helps to determine which antibiotic is most optimal. The wound should also be cared for regularly, with consistent cleaning and changes of wound dressings. Sometimes surgery is needed to clean the necrotic tissue[97].

CONCLUSION

Despite all the measures that should be implemented in the management of the surgical patient, we can conclude from the literature that infections after oncological surgery of the CNS are still a significant problem. In addition, infections and colonisation with resistant strains are also occurring. Post-surgical intracranial infections prolong treatment, require pre-surgery, contribute to the poorer neurological outcome, increase the time to appropriate follow-up and rehabilitation and, finally, significantly increase the cost of care. It is therefore necessary to introduce protocols with measures to minimise the occurrence of infections at all stages of patient management and to ensure that they be executed consistently. Among imaging modalities, MRI is essential to acquire the correct and early diagnosis, particularly to detect the purulent material with the DWI sequence.

FOOTNOTES

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