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Infections of the Central Nervous System

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Abstract

Central nervous system infections are among the most devastating infections in the world. Pathogens may enter the central nervous system as a result of dissemination from the upper respiratory tract or other primary site via blood and then crossing the blood-brain barrier. Pathogens present in health care facilities are not an exception. In addition, the neurosurgical procedures performed there are an additional way of entering the central nervous system. Moreover, nosocomial infections are characterized by very high morbidity and mortality, therefore their early diagnosis and treatment is important.

The aim of the study is to review the current knowledge and guidelines on the most common healthcare-associated infections of the central nervous system, their diagnosis and treatment.

Information searches were carried out in online databases, scientific and educational editions.

The most common healthcare-associated infection of the central nervous system is meningitis, followed by a subdural empyema and a brain abscess. The greatest risk factor is neurosurgery. In all of the most common infections of the central nervous system listed, rapid implementation of empiric antibiotic therapy is essential. Further antibiotic therapy depends on the identified etiological factor. As a rule, surgical treatment is required for subdural empyema and brain abscesses.

Healthcare-related central nervous system infections remain a significant problem. Due to the risk posed by them to the patient's health, prophylaxis, prompt diagnosis and treatment are essential.

Keywords: CNS, infections, diagnosis, management

Introduction

The skull, spine, and meninges form three protective barriers of the central nervous system. The blood-brain barrier is part of the meninges. It is a term describing the unique properties of blood vessels that supply the central nervous system with, among other things, nutrients and oxygen. These properties include tight junctions between endothelial cells, lack of fenestrations, low levels of transcytosis, specialized transmembrane transporters, lower expression of leukocyte adhesion molecules, and a denser glycocalyx compared to peripheral blood vessels. Their effect is limited transcellular and paracellular movement of solutes, permeability through the barrier only for specific nutrients such as glucose, lactate, amino acids, and fatty acids, reduced leukocyte penetration into the central nervous system, and prevention of the transport of larger molecules through the barrier (Profaci et al. 2020; Le Guennec et al. 2020). These properties not only strictly regulate transport but also prevent pathogens, blood cells, and neurotoxic plasma components from entering the central nervous system (Sweeney et al. 2019). Central nervous system infections are among the most devastating infections in the world (Le Govic et al. 2022). They can be caused by infectious and non-infectious agents. Non-infectious causes include tumors, autoimmune diseases, and drug reactions. Infectious causes include bacteria, viruses, fungi, and parasites (Hersi et al. 2022; Massacar et al. 2018; Bokhari and Mesfin 2022; De Andres Crespo et al. 2020). Central nervous system infections include meningitis, encephalitis, and brain abscesses (Sadigh-Eteghad et al. 2022; Giovane et al. 2018). Meningitis is an inflammation of the connective tissue membranes surrounding the brain and spinal cord (Hersi et al. 2022). Encephalitis is a rare, severe condition of neurological dysfunction caused by inflammation of the brain parenchyma (Messacar et al. 2018). A brain abscess, on the other hand, is a focal accumulation of pus with an overlying membrane in the brain parenchyma (Bokhari and Mesfin 2022; De Andres Crespo et al. 2020). Pathogens can enter the central nervous system in various ways. Bacteria can infect the central nervous system by spreading from the upper respiratory tract or another primary site via the bloodstream and then crossing the blood-brain barrier through: transcellular migration (binding to brain microvascular endothelial cells and then being transported by endocytosis), paracellular migration (moving between brain microvascular endothelial cells by disrupting tight and adherens junctions), or Trojan horse mechanism (infecting phagocytes that have the ability to cross the blood-brain barrier paracellularly). Viruses can multiply in the upper respiratory tract and gastrointestinal endothelial cells, from where they can enter the blood, reach the blood-brain barrier, and cross it using the mechanisms also used by bacteria, described above. Additionally, they can enter the central nervous system by non-hematogenous routes, including retrograde transport via peripheral nerve axons and the epithelium and olfactory neurons of the nose. Fungal infections of the central nervous system are usually opportunistic infections resulting from nervous system injury (Le Govic et al. 2022). These routes of infection can be utilized by pathogens present in healthcare facilities (Monegro et al. 2022). Additionally, neurosurgical procedures performed in these facilities provide an additional entry route for all the pathogens listed above into the central nervous system (Le Govic et al. 2022; Karvouniaris et al. 2022).

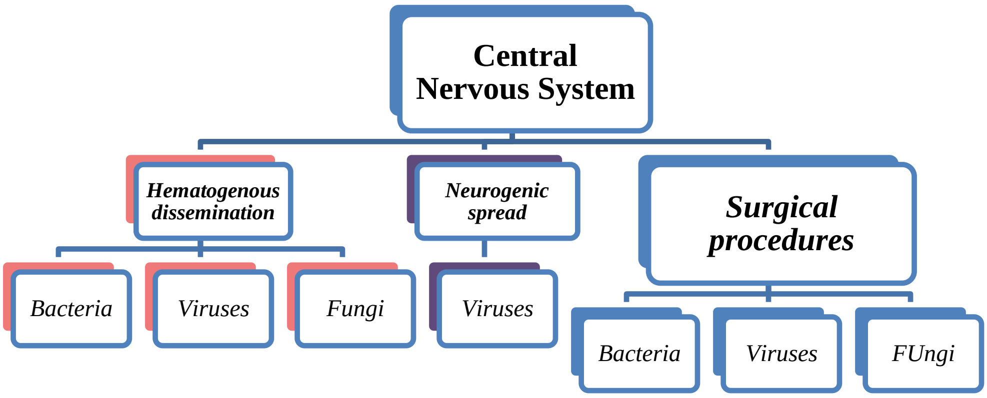

Fig. 1. Pathways of pathogen entry into the central nervous system in healthcare facilities

Nosocomial infections are characterized by very high morbidity and mortality. In addition to the risk of death, they prolong hospital stays, increase treatment costs, and pose a threat of permanent health damage; therefore, their early diagnosis and treatment are important (Monegro et al. 2022; Cai et al. 2020).

Aim of the Study

The aim of the study is to review the current knowledge and guidelines on the most common healthcare-associated infections of the central nervous system, their diagnosis, and treatment

Materials and Methods

Information searches were carried out in online databases, scientific, and educational editions, including PubMed, Elsevier, Research Gate, Web of Science, Springer, Scopus.

Epidemiology

The most common healthcare-associated infection of the central nervous system is meningitis, followed by subdural empyema and brain abscess (Martin et al. 2018; Kurtz et al. 2021). The greatest risk factor is neurosurgery. The risk of infection varies depending on the type of procedure, duration, location, entry route into the sinuses, postoperative cerebrospinal fluid leakage, and wound and implant infection. The risk of infection is higher during skull procedures, especially when part of the skull is removed and stored for a long time, such as in craniectomy. Craniectomy carries the highest risk of central nervous system infections among all neurosurgical procedures, with an infection risk ranging from 1% to 24.4%. The second place is taken by ventriculostomy, with an infection risk from 2% to 22%, due to the potential colonization of the device by microbes during placement, handling, and maintenance. Craniotomy ranks third, with an infection risk from 0.3% to 12%, associated with placing the removed skull fragment back in place during the same procedure, unlike in craniectomy (Martin et al. 2018). Additionally, the risk of infection increases with longer hospitalization (Bischoff et al. 2020).

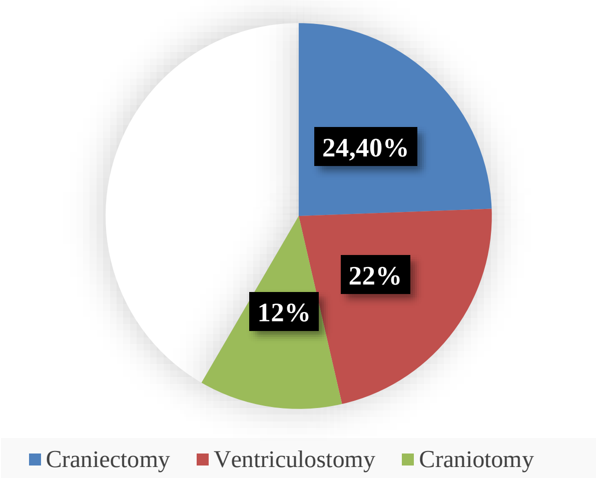

Fig. 2. Highest risk of central nervous system infection in neurosurgical procedures

Meningitis

Meningitis is a serious postoperative complication. Its incidence is estimated to range from <1% to 25% (Coelho et al. 2021; Adapa et al. 2021). Postoperative meningitis has the highest mortality rate among all surgical site infections resulting from neurosurgical procedures (Adapa et al. 2021; Srinivas et al. 2011). It can occur in bacterial or aseptic form. In the first case, the wound is infected with bacteria, most commonly Staphylococcus.

The aseptic form, on the other hand, is characterized by sterile cerebrospinal fluid cultures. The incidence of bacterial meningitis has decreased due to vaccinations, resulting in viruses becoming the most common cause of meningitis in many regions of the world. Among them, enteroviruses are the leading cause of this condition in countries such as Poland, Germany, Canada, the Czech Republic, Israel, Qatar, Tunisia, Kuwait, the United Kingdom, China, Denmark, and South Africa. The most vulnerable to infection are men and children, and the incidence decreases with age (Peer et al. 2019; Cantu and Das 2021; Mathew et al. 2021; Kohil et al. 2021; Davis 2018).

Viral and bacterial meningitis are characterized by slight differences in physical and subjective examination (Cantu and Das 2021; Kohil et al. 2021). The diagnostic challenge is that in both forms, laboratory tests may show an increase in leukocytes and a decrease in glucose levels in the cerebrospinal fluid. Therefore, the only sure difference between bacterial and aseptic forms is the isolation of bacterial cultures in patients with bacterial meningitis (Hussein et al. 2017).

Currently, meningitis is further complicated by increasing rates of infections caused by multidrug-resistant Gram-negative bacteria, particularly Acinetobacter baumannii, which is the main pathogen in some neurosurgical units (Hussein et al. 2017; Karvouniaris et al. 2022).

Diagnosis of Meningitis

Typical symptoms of meningitis include fever, headache, neck stiffness, and altered mental status. According to studies, at least two of these symptoms will occur in 95% of patients; therefore, the occurrence of any of these symptoms should prompt a physician to consider the possibility of meningitis. A patient suspected of having this condition should undergo a lumbar puncture, and the obtained cerebrospinal fluid should be sent for Gram staining, culture, and total cell count (Cantu and Das 2021; Young and Thomas 2018; Runde et al. 2022; Rekomendacje postępowania w zakażeniach bakteryjnych ośrodkowego układu nerwowego 2011; Griffiths et al. 2018).

Treatment of Meningitis

If it is necessary to wait for the identification of the cause of the meningitis, it is recommended to implement empirical therapy as soon as possible. Delaying the administration of antibiotics by 3 to 6 hours is associated with an increased risk of patient death. Recommendations for empirical therapy vary by country or region. North American recommendations suggest administering dexamethasone with ceftriaxone and vancomycin to all patients. Recommendations from Australia, the United Kingdom, and Europe suggest administering dexamethasone with ceftriaxone, while vancomycin is only recommended for patients with an increased likelihood of pneumococcal meningitis or epidemiological risk factors for Streptococcus pneumoniae infection. In Poland, empirical therapy for patients from

3 months to 5 years of age recommends cefotaxime or ceftriaxone with vancomycin, while dexamethasone is not recommended based on clinical symptoms alone and is advised only when pneumococcal etiology is suspected. Further treatment depends on the identified pathogen Young and Thomas 2018; Runde et al. 2022; Rekomendacje postępowania w zakażeniach bakteryjnych ośrodkowego układu nerwowego 2011; Griffiths et al. 2018).

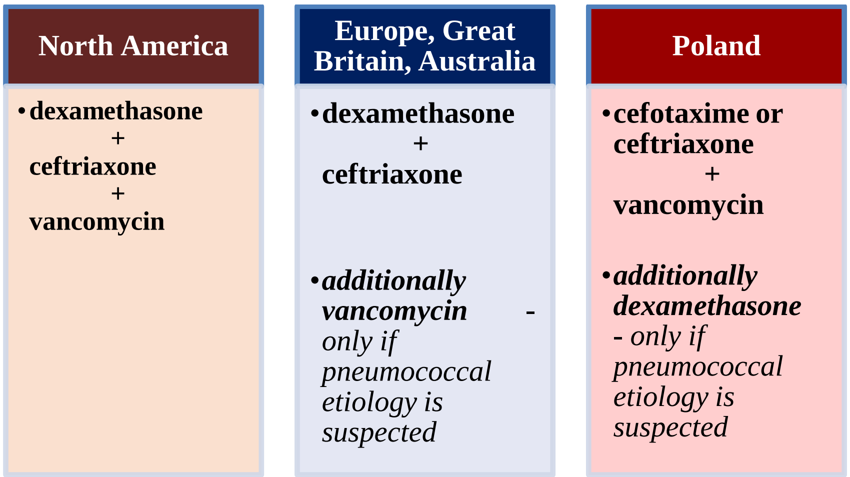

Fig. 3. Differences in empirical therapy recommendations for empiric therapy in suspected meningitis around the world

Subdural Empyema

Intracranial subdural empyema is a collection of pus located in the subdural space between the dura mater and the arachnoid mater (Fernández-de Thomas and De Jesus 2022; Nour and Shumbash 2020). Subdural empyema occurs relatively rarely (Nour and Shumbash 2020; Dedeciusová et al. 2018). In healthcare facilities, the causes of empyema may include surgical procedures on the skull and improper treatment of ear and sinus infections (Fernández-de Thomas and De Jesus 2022; Greenlee 2003).

Diagnosis of Subdural Empyema

Subdural empyema should be considered in patients with diagnosed sinusitis or ear infection who develop skull pain, headache, and fever. It should also be considered in patients after drainage of a subdural hematoma who develop new neurological deficits, fever, and seizures. Laboratory tests can provide additional evidence for diagnosis. Magnetic resonance imaging or computed tomography should be ordered in patients to confirm the diagnosis (Fernández-de Thomas and De Jesus 2022; Nour and Shumbash 2020; Greenlee 2003; Yoon et al.). Lumbar puncture is not indicated as it can cause mass effect and endanger patients with increased intracranial pressure and empyema (Fernández-de Thomas and De Jesus 2022).

Treatment of Subdural Empyema

It is recommended to initiate broad-spectrum antibiotic therapy as soon as possible. Intracranial subdural empyema can contain multiple microorganisms; therefore, empirical therapy in case of unknown pathogen should be directed against: Staphylococcus aureus, Streptococci, anaerobes, and Gram-negative organisms. Empirical antibiotic therapy should include: nafcillin, oxacillin, or vancomycin; third-generation cephalosporin; metronidazole. Proper treatment of empyema typically involves both pharmacological and surgical therapy. Sole antibiotic therapy is rarely used but may be utilized in patients in good condition without significant neurological deficit, with a small amount of pus, and documented early response to antibiotic therapy. Surgical options include craniotomy and skull trepanation. Craniotomy generally results in better outcomes and fewer recurrences.

Trepanation can be used when the empyema is easily accessible, thin, and not divided by septa (Fernández-de Thomas and De Jesus 2022; Nour and Shumbash 2020; Dedeciusová et al. 2018; Greenlee 2003; Yoon et al.).

Brain Abscess

A brain abscess is the most common focal purulent infection of the brain. Rapid and accurate diagnosis at the earliest possible stage is crucial for its proper treatment. However, to this day, differentiating it from encephalitis and brain tumors poses a major diagnostic challenge due to the similarity in radiological, pathological, and clinical features (Bokhari and Mesfin 2022; Liu et al. 2018).

Diagnosis of Brain Abscess

Diagnosis of brain abscesses involves: computed tomography, magnetic resonance imaging, stereotactic computed tomography-guided aspiration, conventional spin-echo with contrast, diffusion tensor imaging, proton magnetic resonance spectroscopy. Lumbar puncture is rarely required and may be performed only after prior CT and MRI ruling out elevated intracranial pressure (Bokhari and Mesfin 2022; Liu et al. 2018).

Treatment of Brain Abscess

Therapy includes pharmacological and surgical treatment. The choice of surgical treatment depends on the surgeon's preferences and skills - available methods include: needle aspiration under ultrasound or computed tomography guidance using craniotomy, trepanation, or stereotactic procedure. Pharmacological treatment depends on the isolated microorganism from blood or cerebrospinal fluid (Liu et al. 2018). Currently, the most common cause of brain abscesses are Streptococci from the viridans group and Staphylococcus aureus; therefore, they should be the first target of empirical therapy when the pathogen has not yet been identified (Bokhari and Mesfin 2022; Lee et al. 2018).

Discussion

Healthcare-associated central nervous system infections remain a significant problem. Due to the significant threat they pose to patient health, prophylaxis, rapid diagnosis, and treatment are crucial (Monegro et al. 2022; Cai et al. 2020; Martin et al.). The frequency of postoperative central nervous system infections can be reduced by implementing appropriate air filtration systems in operating rooms and their regular maintenance (Chidambaram et al. 2018; Dong et al. 2020). Promising for improving the diagnosis of brain abscesses may be newly developed bacterial chemical exchange saturation transfer magnetic resonance imaging (bacCEST MRI) (Liu et al. 2018). Endoscopic expanded endonasal approach (EEA) may become an effective alternative in treating subdural empyema caused by sinusitis in children by eliminating some of the disadvantages of the standardly used craniotomy (Touchette et al. 2020).

Disclosure:

Author's contribution:

Conceptualization: Mateusz Dobosz, Klaudia Arciszewska, Aleksandra Bogoń; Methodology: Mateusz Dobosz, Jakub Buczkowski, Jakub Maciej Pieniążek; Software: Jakub Buczkowski, Aleksandra Padkowska; Check: Michał Paprocki, Anna Mataczyńska, Mateusz Dobosz; Formal analysis: Aleksandra Laskowska, Aleksandra Bogoń; Investigation: Mateusz Dobosz, Jakub Maciej Pieniążek; Resources: Klaudia Arciszewska, Aleksandra Bogoń, Michał Paprocki; Data curation: Klaudia Arciszewska, Anna Mataczyńska, Aleksandra Laskowska; Writing - rough preparation: Mateusz Dobosz, Klaudia Arciszewska, Aleksandra Padkowska; Writing - review and editing: Klaudia Arciszewska, Aleksandra Bogoń, Mateusz Dobosz; Visualization: Mateusz Dobosz, Aleksandra Bogoń, Klaudia Arciszewska; Supervision: Mateusz Dobosz, Klaudia Arciszewska; Project administration: Mateusz Dobosz, Jakub Buczkowski;

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