If a patient suffers from neurological symptoms, lots of differential diagnoses have to be considered. The following article is organized according to the different pathogens: bacteria, viruses, protozoa and fungi. Learn and repeat everything from the approach from acute bacterial meningitis to virally-triggered CNS infections with HSV, ESME, VZV and CMV, and to opportunistic infections in immunodeficient patients. This way, no neurological question in the second state examination concerning infectious diseases of the CNS remains unclear!
Introduction

Meningitis is defined as infection and inflammation of the pachymeninges.

There are various causes of infections meningitis that can be grouped into:

- Bacterial meningitis: The most common cause of meningitis and it is a common disease in the developing world.
- Viral causes of CNS infections: They include herpes and varicella viruses. They can also lead to encephalitis.
- Parasitic causes are very rare due to high hygiene standards as they have been associated with immunosuppression.

The main reason for classification according to etiology is to:

- Differentiate the pathogen classes and thus plan on the therapeutic approach
- For classification purposes and easier diagnosis in future

In our part of the world, you will mostly encounter bacterial and viral causes of CNS infections. Parasitic causes are very rare due to high hygiene standards. Another reason to differentiate the pathogen classes is the therapeutic approach.

Only concerning bacterial CNS infections treatment with antibiotics is reasonable!

The gold standard for diagnosis of meningitis is a lumbar puncture with cerebrospinal fluid (CSF) examination for certain parameters as shown. The following aspects are examined in the fluid:

- Cell count and cell differentiation
- Glucose and protein
- Microbiological pathogen detection: direct pathogen detection with
Overview of typical cerebrospinal fluid findings at CNS infections

<table>
<thead>
<tr>
<th></th>
<th>Cells</th>
<th>Protein</th>
<th>Glucose</th>
<th>Lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial Meningitis</strong></td>
<td>Often &gt; 1,000 cells/µL, dominantly granulocytic</td>
<td>↑ (100 – 200 mg/dL)</td>
<td>↓ CSF/serum glucose ratio &lt; 0.3</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Tubercular Meningitis</strong></td>
<td>50 – 400 cells/µL, first granulocytes, later lymphocytes and monocytes</td>
<td>↑↑ (100 – 500 mg/dL)</td>
<td>↓ CSF/serum glucose ratio &lt; 0.5</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Viral Meningitis</strong></td>
<td>&lt; 1,000 cells/µL, dominantly lymphocytic</td>
<td>↑ (e.g.: 50 – 150 mg/dL)</td>
<td>↔ CSF/serum glucose ratio</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**CSF/serum glucose ratio**
The CSF/serum glucose ratio gives the relation of glucose in the cerebrospinal fluid compared to glucose in the serum.

Table: A. Bender et al.: mediscript Kurzlehrbuch Neurologie. Elsevier Verlag 2013. S. 191, Tab. 7.2

Bacterial Infections of the Central Nervous System

Acute bacterial meningitis

**Epidemiology of bacterial meningitis**

At acute bacterial meningitis, the meninges and the subarachnoid cavity are infected. Incidence in Europe is 2-6 affected people in a population of 100,000. The disease is significantly more frequent in the meningismus belt in the sub-Saharan regions of Africa. With bacterial meningitis, different pathogens are typical for respective age groups, and they undergo empiric antibiotic therapy.

- **Newborns:** enterobacteria, streptococci, Listeria monocytogenes ⇒ Therapy: cefuroxime and ampicillin
- **Children:** Streptococcus pneumoniae, Neisseria meningitidis ⇒ Therapy: ceftriaxone
- **Adults:** Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes (in > 50-year-olds) ⇒ Therapy: ceftriaxone and ampicillin
Clinical picture of bacterial meningitis

Cardinal symptoms: Headache, neck stiffness, fever, decrease in vigilance (the symptoms do not always occur in this combination!).

Also, patients often show the following symptoms: nausea, vomiting, vertigo and photophobia. One third of the patients display focal neurological deficits like cranial nerve palsies (mostly cranial nerve 3 and 6), sensitivity impairments and speech disorders; one tenth also shows cranial nerve damages. Kerning’s sign and Brudzinski’s sign can be positive (see the article on neurological examination). In infections with Neisseria, skin bleedings in the context of Waterhouse-Friderichsen syndrome are possible.

Diagnostics of Bacterial Meningitis

CSF examination: The examination of the CSF is the diagnostic basis. The pathogens in the CSF can be detected using the Gram stain, CSF cultures, antigen quick tests, PCR and blood cultures. Cases of acute bacterial meningitis produce the following picture (before treatment):

- > 1,000 cells/µL, granulocytes dominate
- Protein and albumin ↑
- Glucose ↓, CSF/serum glucose ratio < 0.3
- Lactate ↑

CAVE: If there is clinical evidence to suggest increased cranial pressure (decrease in vigilance, focal neurological deficits, epileptic seizures), a CCT before lumbar puncture is absolutely necessary. (see scheme below)

Blood: The differential blood count mostly shows leukocytosis with left shift, CRP ↑ and procalcitonin ↑.

Imaging: The CT of the skull checks for:

- Signs of increased cranial pressure as result of diffuse brain edema or hydrocephalus
- Changes in density due to accumulations of purulence in the ventricles
- Abscesses
- Inflammatory foci in the paranasal sinus and the mastoid
**Therapy of bacterial meningitis**

**Important**: Antibiotic therapy should start as soon as possible! The antibiotic therapy should – if possible – be started within 60 minutes after hospitalization. Since waiting leads to a worse prognosis, the antibiotic therapy is initiated before final pathogen detection according to the typical pathogens of the respective age group (see above under epidemiology). If the pathogen detection has been made, the antibiotic therapy has to be adjusted. Of course, blood cultures are taken BEFORE medicamentous therapy!

For adults with pneumococcal meningitis, an adjuvant therapy with **dexamethasone** is currently (as of 2015) suggested. Studies show decreased occurrence of consequential damages like hearing impairment and lethality.

**Learning tip**: The IMPP and oral exams often ask for the ‘listeria gap’: For adults, ampicillin has to be given in addition to ceftriaxone since ceftriaxone has no effect on listeria.

**Prognosis of bacterial meningitis**

**Lethality** of bacterial meningitis is **high**. 20 % of all patients die of infections caused by the pathogens pneumococci and listeria. With S. aureus as the actuator of acute bacterial meningitis, lethality reaches as high as 20—40 %. Possible consequential damages are – among others—hearing impairment, neuropsychological deficits, hemiparesis, epileptic seizures and cranial nerve palsies.

**Features of meningococcal meningitis**

N. meningitidis is transmitted via **droplet infection**. In case of suspicion, the affected persons have to be isolated until 24 hours after the start of antibiotic therapy. Contact persons should be treated with a combined chemoprophylaxis consisting of rifampicin, ciprofloxacin/or ceftriaxone in the sense of post-exposition prophylaxis.

Meningococcal meningitis is subject to mandatory reporting at the public health department.

**Tubercular meningitis**

**Epidemiology of tubercular meningitis**

The pathogens responsible for tubercular meningitis are **mycobacteria** out of the Mycobacterium tuberculosis complex. This subacutely or chronically proceeding disease often presents itself as basal meningitis (infectious reaction concentrates on basal cerebral areas, especially the brain stem).

**Number-facts for active tuberculosis:**

- Worldwide 10 million people
- Germany: 4,500 cases

**Clinical presentation of tubercular meningitis**

Clinical symptoms of tubercular meningitis are primarily **fever, meningismus, headaches, nausea and vomiting**. In 50 % of the patients, cranial nerve palsies, disorders in vigilance and confusion syndromes occur. If encephalitis or tuberculomas form, epileptic seizures are also possible.
Diagnosis of tubercular meningitis

**CSF examination:** pleocytosis with 50-400 cells/µL, protein ↑↑, glucose ↓ (CSF/serum glucose ratio < 0.5), lactate ↑.

**Interferon-γ release assays:** Blood lymphocytes are stimulated with tuberculosis-antigens. In the case of undergone or current infection, the gained cells produce interferon-γ.

**Microbiology:** At pathogen detection in CSF with Ziehl-Neelsen stain, Auramin stain, PCR and cultures, acid-fast rods can be found in tuberculosis. Do not wait until the final pathogen detection (like at acute bacterial meningitis) before beginning therapy!

**Imaging:** Cerebral changes at tuberculosis are often visible in MRI or CCT.
- Hydrocephalus
- Basal contrast agent accumulation
- Masses at CNS tuberculomas
- Ischemic infarction in case of associated vasculitis

**Therapy of tubercular meningitis**

Involves the use of anti-tubercular medications that take the forms of:

**An intensive phase:**

It is a fourfold-combination is used as standard therapy. Mostly, it consists of isoniazid, rifampicin, pyrazinamide and ethambutol. The drugs are administered under direct supervision for compliance.

Dexamethasone is administered before or together with the initial dose. It has been shown to reduce mortality if properly administered as per the guidelines.

**Continuation phase:**

Rifampicin and isoniazid are continued for 6 more months and cure must be confirmed before withdrawing the drug.

**Learning tip:** The ‘IMPP classic’: The initial fourfold-combination of tuberculosis therapy and the side effects of the individual components.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration of Application</th>
<th>Side Effects</th>
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</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>2 months initially, further 10 months</td>
<td>Hepatotoxicity, polyneuropathy (prophylaxis pyridoxine)</td>
</tr>
<tr>
<td></td>
<td>(stabilization phase)</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>2 months initially, further 10 months</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>(stabilization phase)</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2 months initially</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>2 months initially</td>
<td>Impaired vision (ophthalmologic controls are regularly necessary)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>2 months initially</td>
<td>Ototoxicity</td>
</tr>
</tbody>
</table>

**Prognosis of tubercular meningitis**

If no antibiotic therapy is performed, tubercular meningitis mostly ends lethally. If sufficient treatment is performed, lethality is reduced to roughly 20%. Circa 30% of the affected people suffer from consequential damages like hydrocephalus, organic brain syndrome, cranial nerve palsies, ataxia and epileptic seizures.
Brain abscess

Etiology of brain abscesses

A brain abscess is a **bacterial abscessing infection of the brain**.

Brain abscesses can form in different ways: via transmission of meningeal foci, hematogenic, and iatrogenic in the course of surgical interventions. The responsible pathogens responsible are mostly **streptococci, anaerobics, Gram-negative enterobacteria, pseudomonads and S. aureus**. With immunodeficiency, fungi and parasites can also be the actuators of abscesses.

**Clinical presentation of the brain abscess**

Concerning brain abscesses, there is a **broad variety** of symptoms which can develop over days or weeks. They include:

- Headache
- Fever
- Nausea and vomiting
- Epileptic seizures
- Neurological examination: vigilance impairments, meningismus

**Diagnostic of the brain abscess**

**Laboratory, microbiology and imaging procedures**: In laboratory parameters, CRP is mostly increased; CSF examination is not necessary since the findings are too unspecific. More important is the examination of abscess material via bacterial cultivation, PCR and the test for fungi and mycobacteria.

**Therapy of the brain abscess**

| The 3 Pillars of Brain Abscess Therapy |

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Surgical removal of purulence CAT/MRI-controlled stereotactic aspiration. Goal: reduction of the mass, gain of material for microbiological diagnostics. If necessary, excision at foreign bodies and division of abscesses

Systemic antibiosis
Before pathogen detection empiric three-fold therapy:
1. Cephalosporin of 3rd generation (e.g., ceftriaxone)
2. Antibiotic against anaerobics (e.g., metronidazole)
3. Antibiotic against staphylococci (e.g., vancomycin)
⇒ Adjustment according to the antibiogram.

Elimination of the infectious focus
Thorough search for the focus (is the focus located distally?) with surgical elimination if needed

Prognosis of the brain abscess
In case of timely and appropriate therapy, lethality is < 10 %.

Neuroborreliosis

Epidemiology of neuroborreliosis
Neuroborreliosis, triggered by the bacterium Borrelia burgdorferi, which is transmitted by ticks, is one of the most frequent CNS diseases in Germany: 100—50 / 100,000 inhabitants suffer from this disease. The regional dissemination of the infected ticks is very different and should be taken into account for diagnosis.

Clinical features of neuroborreliosis
The symptoms of neuroborreliosis typically proceed in three stages:

Stage I: Formation of erythema migrans: circularly limited skin reddening, which mostly develops ca. 2 weeks after the tick bite. Only half of the patients who reach stage II had erythema migrans.
Stage II: Meningoradiculitis: searing, radicular pain (Bannwarth syndrome), partially radicular palsies, palsy of the facial nerve. Joint involvement, myocarditis, pericarditis and lymphadenosis cutis benigna are also possible.

Stage III: Detection of antibodies against *B. burgdorferi* in the enzyme-immune-assay. The detection of antibodies has to occur in both the serum and the CSF. The antibodies are not suitable for therapy assessment! The antibodies can circulate in the CSF over the course of months to years after successful antibiosis.

Therapy of neuroborreliosis

Erythema migrans is treated with an oral 14-day antibiosis: amoxicillin, cefuroxime, doxycycline, or penicillin. If neuroborreliosis has reached stage II or III, oral therapy should be performed with doxycycline over 14 days. The alternative is intravenous treatment with ceftriaxone, cefotaxime, or penicillin.

Prophylaxis of neuroborreliosis

If a tick is removed within the first 12 hours after the bite, the risk of borrelia infection is decreased. There is no vaccination against borrelia.

Viral Infections of the Central Nervous System

The most common viruses causing CNS infection are herpes-simplex-virus (HSV), varizella-zoster-virus (VZV), HIV, Ebstein-Barr-virus (EBV) and enteroviruses.
Herpes-simplex-virus-encephalitis

Epidemiology of herpes-simplex-virus-encephalitis

The herpes-simplex-virus-encephalitis is rare, but it has a fulminant course. Incidence amounts to 1/250,000 inhabitants.

Clinic of herpes-simplex-virus-encephalitis

Besides possible aphasia, ataxia, hemiparesis, cranial nerve palsies and visual field deficits, especially these cardinal symptoms of herpes-simplex-virus-encephalitis occur:

- High fever
- Headache
- Personality changes
- Epileptic seizures in 60 %
- NO meningismus

Diagnostic of herpes-simplex-virus-encephalitis

**CSF:** CSF findings mostly show a typical relation: lymphomonocytic pleocytosis, elevated protein and albumin and non-decreased glucose (see above table concerning typical CSF findings in bacteria and viruses).

**Microbiology:** With PCR, HSV-DNA is detected in the CSF.

**Imaging procedures and EEG:** Mostly, the temporal lobe is affected. Necrosis and hemorrhages are typical signs. The EEG often shows temporal slowdowns.
Therapy and prognosis of herpes-simplex-virus-encephalitis

Treatment consists of the intravenous injection of acyclovir five times a day for 14 days. Despite timely introduced therapy, 20% of all diseased people die. Most survivors suffer from consequential diseases.

Viral meningitis

Epidemiology of viral meningitis

Incidence of viral meningitis is 6-10/100,000 inhabitants. In Germany, mostly enteroviruses are the actuating pathogens. HHV6, VZV, measles viruses, mumps viruses and EBV should also be taken into account.

Clinic of viral meningitis

Viral meningitis causes the typical picture of a meningitic disease: fever, neck stiffness and headache. Often, patients also display flu symptoms.

Diagnostic and therapy of viral meningitis

The CSF findings show the typical picture for viruses with elevated protein and non-decreased glucose levels. Microbiologically, PCR and indirect serological pathogen detections are used.
If viral meningitis is caused by VZV or HSV, treatment with aciclovir is reasonable. If, however, enteroviruses are the cause, only symptomatic treatment occurs.

Herpes zoster: the shingles

Etiology of herpes zoster

If an earlier varizella-zoster-infection (chickenpox) reactivates, herpes zoster develops. This is often an expression of immunodeficiency. However, herpes zoster may also occur in immunocompetent people.

Clinical presentation

Typically, after a painful phase, skin reddening with blister formation in the dermatome of a nerve root sets in. Especially severe are disease courses in facial dermatomes: zoster oticus and zoster ophthalmicus. A frequent complication is poster-zoster-neuralgia with pain and allodynia.

Diagnostic and therapy of herpes zoster

Mostly, the diagnosis of herpes zoster is made on the basis of the dermatological picture. Rarely, pathogen detection with blister secretion and biopsy material is used.

The virostatics aciclovir, brivudin, famciclovir or aciclorvir can be used orally for treatment of uncomplicated herpes zoster. In severe cases, intravenous therapy is indicated.

Early summer meningoencephalitis (ESME)

Etiology of ESME

Early summer meningoencephalitis is actuated by the flavivirus, which is – like borrelia – transmitted by ticks. Also, there is a different regional dissemination in Germany.
Clinic of ESME

Early summer meningoencephalitis proceeds in two phases:

- **Phase I**: 8—10 days after the infection, the patient has flu-like symptoms
- **Phase II**: 1 week fever-free interval, then vigilance disorders, confusion syndrome, stand and gait ataxia, intention tremor, extrapyramidal symptoms

Diagnostic, therapy and prevention of ESME

Typical for early summer meningoencephalitis is a CSF syndrome with lymphocytic pleocytosis, blood-liquor barrier disorders, positive detection of ESME-IgM and IgG-antibodies, and intrathecal ESME-specific antibody production 2 weeks after disease onset.

At ESME, therapy can only occur symptomatically. People living and working in risk areas should **vaccinate**.

Progressive multifocal leukoencephalopathy (PML)

Etiology of PML

The pathogen of PML is the JC-virus, which leads to **demyelination of white matter** at infections. Mostly, the disease occurs due to immunodeficiency, like T-cell-defects. While it almost exclusively affected HIV-patients in the past, PML now also frequently affects people who are medically immunosuppressed due to **multiple sclerosis**.

Clinic of PML

Depending on the localization of the demyelination focus, symptoms like behavioral problems, cognitive deficits, palsies, visual impairments, vigilance disorders and speech disorders can be observed.

Diagnostic and therapy of PML

JC-viruses can be detected in CSF via **PCR**. In the **MRI**, typical signs of PML are confluent demyelination foci without contrast agent accumulation.

Therapeutically, only an improvement of immunocompetence is possible. Antiviral therapy does not (yet) exist. Affected patients with PML do not have a good prognosis: Often, the patients die within two years.

Cytomegalovirus (CMV) infection

CMV-infection occurs in the course of AIDS-disease at very severe immunosuppression. In imaging procedures, the infection shows micronodular changes in the brain and/or hydrocephalus. With PCR, the viruses can be detected in CSF. Concerning therapy, ganciclovir is used.

Protozoa- and Fungal Infections of the Central Nervous System: Facts-Overview

The following overview allows a quick access to facts concerning the most important CNS-diseases caused by protozoa and fungi.
Opportunistic Diseases With HIV

Immunosuppression in AIDS-patients leads to several diseases, which manifest in the CNS. Mostly, the diagnosis of AIDS is made on the basis of so-called AIDS-defining diseases. They occur if certain levels of CD4-cells are undercut.

- CNS-toxoplasmosis (at < 100/µL)
- Primary CNS-lymphomas (no limit)
- Cerebral Cryptococci-infections (at < 100/µL)
- CNS-tuberculosis (no limit)
- CMV-encephalitis (at < 50/µL)
- PML (at < 250/µL)

Review Questions

The answers can be found below the references.

1. Which medicament is not used at neourtuberculosis?
   
   A. Isoniazid
   B. Rifampicin
   C. Amphoteracin
   D. Pyrazinamide
   E. Ethambutol

2. The CSF finding presents like this: > 1,000 cells/µl with dominantly granulocytes, protein and albumin ↑, glucose ↓, CSF/serum glucose ratio < 0.3, lactate ↑. For which disease are those parameters typical?
   
   A. Cryptococci-meningoencephalitis
   B. Bacterial meningitis
   C. CMV-meningitis
   D. Neuroborreliosis
   E. Brain abscess
3. Which assignment of typical bacteria, age and treatment is not correct concerning bacterial meningitis?

A. Newborns: streptococci group B, cefuroxime and ampicillin
B. Children: Streptococcus pneumoniae, ceftriaxone
C. Adults: Neisseria meningitidis, ceftriaxone and ampicillin
D. Children: Listeria monocytogenes, ceftriaxone
E. Newborns: enterobacteria, cefuroxime and ampicillin

References


**Correct answers:** 1C, 2B, 3D

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