If a patient suffers from neurological symptoms, numerous differential diagnoses have to be considered. The following article is organized according to the different pathogens: bacteria, viruses, protozoa, and fungi. Learn and review the clinical presentations, diagnosis, and treatment of diseases such as acute bacterial meningitis, viral CNS infections with HSV, ESME, VZV and CMV, and opportunistic infections in immunodeficient patients.

Gold Standard Cerebrospinal Fluid Examination
Introduction

Meningitis is defined as the infection and inflammation of the pachymeninges.

The various types of meningitis can be classified based on the cause of the infection:

- Bacterial meningitis: The most common cause of meningitis and a common disease in the developing world.
- Viral causes of CNS infections: This includes the herpes and varicella viruses. Encephalitis is also caused by viruses.
- Parasitic causes are very rare due to high hygiene standards, and they have been associated with immunosuppression.

The main reason for classification according to etiology is to:

- Differentiate the pathogen classes and thus determine the accurate therapeutic approach
- For easier diagnosis in the future

Treatment with antibiotics should only be considered if a bacterial central nervous system (CNS) infection is suspected!

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

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

<table>
<thead>
<tr>
<th></th>
<th>Cells</th>
<th>Protein</th>
<th>Glucose</th>
<th>Lactate</th>
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<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, 1st 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>↔</td>
<td>Normal</td>
</tr>
</tbody>
</table>

The CSF/serum glucose ratio is a measure of the glucose in the CSF compared with the blood glucose level.

<table>
<thead>
<tr>
<th>CSF/serum glucose ratio</th>
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Table: A. Bender et al.: mediscript Neurology. Elsevier 2013. p. 191, Tab. 7.2

Bacterial Infections of the Central Nervous System

**Acute bacterial meningitis**

**Epidemiology of bacterial meningitis**

In acute bacterial meningitis, the **meninges** and the **subarachnoid cavity** are infected. In Europe, the incidence is 2–6 cases per 100,000 people. The disease is significantly more frequent in the meningismus belt in the sub-Saharan regions of Africa. Empiric antibiotic therapy is administered based on the age-specific pathogens associated with the disease.

- **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, and decrease in vigilance (the symptoms do not always occur in this combination!).

Also, patients often present with the following symptoms: nausea, vomiting, vertigo, and photophobia. One-third of the patients display focal neurological deficits such as cranial nerve palsy (mostly cranial nerve 3 and 6), sensitivity impairments and speech disorders; 1/10th also present with cranial nerve damage. Kerning’s sign and Brudzinski’s sign can be positive (see the article on neurological examination). In infections with Neisseria, bleeding of the skin is possible in the context of Waterhouse-Friderichsen syndrome.

Diagnosis of bacterial meningitis

CSF examination: The diagnosis is based on the examination of the CSF. 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):

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

Blood: The differential blood count mostly shows leukocytosis with left shift, C-reactive protein (CRP) ↑ and procalcitonin ↑.

Imaging: The CT of the skull reveals:

- Signs of increased cranial pressure as a 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

Treatment 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 for labs leads to a worse prognosis, antibiotic therapy is initiated before
final pathogen detection according to the age-specific pathogens associated with the
disease (see Epidemiology above). Once the pathogen has been detected, antibiotic
therapy can be adjusted. Of course, blood cultures should be taken BEFORE starting
antibiotic therapy!

For adults with pneumococcal meningitis, adjuvant therapy with **dexamethasone** is
currently (as of 2019) suggested. Studies show reduced mortality rates as well as a
decrease in adverse effects such as hearing impairment.

### Prognosis of bacterial meningitis

**Bacterial meningitis is associated with high mortality rates.** Twenty percent of all
patients die of infections caused by the pathogens *Pneumococci* and *Listeria*. In acute
bacterial meningitis caused by *S. aureus*, the mortality rates can be as high as 20–40%.
Possible adverse effects 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
patients have to be isolated until 24 hours after the start of antibiotic therapy. People
who have had contact with the infected patients should be given post-exposition
prophylaxis consisting of rifampicin and ciprofloxacin/or ceftriaxone.

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** of the
*Mycobacterium tuberculosis* complex. This subacutely or chronically proceeding disease
often presents as basal meningitis (infectious reaction is focalized to the basal cerebral
areas, especially the brain stem).

**Statistics for active tuberculosis:**

- Tuberculosis is 1 of the top 10 causes of death worldwide
- In 2018, an estimated 10 million people were affected by tuberculosis

#### Clinical presentation of tubercular meningitis

The 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
occur, 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), and lactate ↑.
**Interferon-γ release assays:** These assays measure the T cell release of interferon-γ, after being stimulated by antigens specific to tuberculosis.

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

**Imaging:** Cerebral changes in tuberculosis are often visible in magnetic resonance imaging (MRI) or computed tomography (CT) scans.

- Hydrocephalus
- Basal contrast agent accumulation
- Masses of CNS tuberculomas
- Ischemic infarction in case of associated vasculitis

**Treatment of tubercular meningitis**

Anti-tuberculosis medications are administered in the following phases:

**An intensive phase:**

It is a 4-fold-combination used as standard therapy that includes isoniazid, rifampicin, pyrazinamide, and ethambutol. The drugs are administered under direct supervision for compliance.

Dexamethasone is administered before or in combination 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 the cure must be confirmed before withdrawing the drugs.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration of Application</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td>2 months initially and an additional 10 months (stabilization phase)</td>
<td>Hepatotoxicity, polyneuropathy (prophylaxis pyridoxine)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>2 months initially and an additional 10 months (stabilization phase)</td>
<td>Hepatotoxicity</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 (regular ophthalmologic controls are necessary)</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 administered, tubercular meningitis can be fatal. If appropriate treatment is administered, the mortality rate is reduced by roughly 20%. Approx. 30% of the affected people suffer from accompanying symptoms such as hydrocephalus, organic brain syndrome, cranial nerve palsies, ataxia, and epileptic seizures.

**Brain abscesses**

**Etiology of brain abscesses**
A brain abscess is a **bacterial infection of the brain**.

Brain abscesses can form in multiple ways: via the transmission of meningeal foci, via hematogenic transmission, and through iatrogenic causes during surgical interventions. The pathogens responsible are mostly **streptococci, anaerobics, Gram-negative enterobacteria, pseudomonads, and S. aureus**. Fungi and parasites may also be responsible for immune-deficiency-related abscesses.

**Clinical presentation of brain abscesses**

There is a **broad variety** of symptoms that can develop over the course of days or weeks. These include:

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

**Diagnosis of brain abscesses**

**Laboratory, microbiology, and imaging procedures**: Among laboratory parameters, CRP is mostly increased. CSF examination is not necessary since the findings are too vague. It is extremely important to examine the abscess material via bacterial cultivation, PCR, and tests for fungi and mycobacteria.

**Treatment of brain abscesses**

<table>
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<tr>
<th>The 3 Pillars of Brain Abscess Therapy</th>
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*Image: “Brain abscess imaging” by Hellerhoff. License: CC BY-SA 3.0*
Surgical removal of purulence

Computerized axial tomography (CAT)/MRI-controlled stereotactic aspiration.

Goal: reduction of the mass and gain of material for microbiological diagnostics. If necessary, excision of foreign bodies and division of abscesses.

Systemic antibiotics

Before pathogen detection, empiric 3-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 foci

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

Prognosis of brain abscesses

With timely and appropriate therapy, the mortality is < 10%.

Neuroborreliosis

Epidemiology of neuroborreliosis

Neuroborreliosis is triggered by the bacterium *Borrelia burgdorferi*, which is transmitted by ticks. The incidence of this disease is 50–100 cases per 100,000 people. The regional dissemination of 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 1:** Formation of erythema migrans - circularly-limited skin reddening, which mostly develops approx. 2 weeks after the tick bite. Only half of the patients who reach stage 2 present with erythema migrans.
**Stage 2:** Meningoradiculitis – searing, radicular pain (Bannwarth syndrome), partially radicular palsies, and palsy of the facial nerve. Joint involvement, myocarditis, pericarditis, and lymphadenosis cutis benigna are also possible.

**Stage 3:** 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. Antibodies are not suitable for therapy assessment! The antibodies can circulate in the CSF over the course of months to years after successful antibiotic therapy.

**Treatment of neuroborreliosis**

Erythema migrans is treated with an oral 14-day antibiotic therapy of amoxicillin, cefuroxime, doxycycline, or penicillin. If neuroborreliosis has reached stage 2 or 3, oral therapy should be administered with doxycycline over 14 days. The alternative is intravenous (IV) treatment with ceftriaxone, cefotaxime, or penicillin.

**Prophylaxis of neuroborreliosis**

If a tick is removed within the 1st 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 that cause CNS infection are herpes simplex virus (HSV), varicella zoster virus (VZV), human immunodeficiency virus (HIV), Epstein Barr virus (EBV), and enteroviruses.
Herpes simplex encephalitis

Epidemiology of herpes simplex encephalitis

Herpes simplex encephalitis is a rare disease, but has a rapid onset and develops very quickly. It occurs when the herpes simplex virus enters the brain. The incidence of this disease is 1 per 250,000 people.

Clinical features of herpes simplex encephalitis

Besides possible aphasia, ataxia, hemiparesis, cranial nerve palsies, and visual field deficits, these are the most common cardinal symptoms of herpes simplex encephalitis:

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

Diagnosis of herpes simplex encephalitis

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

Microbiology: Herpes simplex virus (HSV)-DNA is detected in the CSF using a PCR assay.

Imaging procedures and EEG: In most cases, the temporal lobe is affected. Necrosis and hemorrhages are typical signs. The electrocardiogram (EEG) often shows temporal slowdowns.
Treatment and prognosis of herpes simplex encephalitis

The treatment consists of the IV injection of **acyclovir 5 times a day for 14 days.** Despite timely therapy, 20% of all cases result in death. Most survivors suffer from consequential diseases.

Viral meningitis

**Epidemiology of viral meningitis**

The incidence of viral meningitis is 6-10/100,000 people. Enteroviruses are the most common causative pathogens, accounting for around 85% of all cases of viral meningitis. Human herpesvirus-6 (HHV-6), VZV, measles viruses, mumps viruses, and EBV should also be associated with viral meningitis.

**Clinical features of viral meningitis**

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

**Diagnosis and therapy of viral meningitis**

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

Herpes zoster: shingles

Etiology of herpes zoster

If a past varicella zoster infection (chickenpox) is reactivated, 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 occurs over the dermatome of a nerve root. It is especially severe if the infection develops in the facial dermatomes where it is classified as herpes zoster oticus and herpes zoster ophthalmicus. A frequent complication is postherpetic neuralgia that is accompanied by pain and allodynia.

Diagnosis and therapy of herpes zoster

The diagnosis of herpes zoster is most often 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 the treatment of uncomplicated herpes zoster. In severe cases, IV therapy is indicated.

Early summer meningoencephalitis (ESME)

Etiology of ESME

ESME is actuated by the flavivirus, which is - like borrelia - transmitted by ticks.

Clinical features of ESME
ESME proceeds in 2 phases:

- **Phase 1**: 8–10 days after the infection; the patient has flu-like symptoms

- **Phase 2**: 1 week fever-free interval, then vigilance disorders, confusion syndrome, stance and gait ataxia, intention tremor, and extrapyramidal symptoms

**Diagnosis, treatment, and prevention of ESME**

Typical clinical features for ESME are: CSF syndrome with lymphocytic pleocytosis, blood-liquor barrier disorders, positive detection of ESME-immunoglobulin M (IgM) and immunoglobulin G (IgG)-antibodies, and intrathecal ESME-specific antibody production 2 weeks after disease onset.

In ESME, only symptomatic treatment is recommended. People living and working in high-risk areas should be vaccinated.

**Progressive multifocal leukoencephalopathy (PML)**

**Etiology of PML**

The pathogen responsible for PML is the JC-virus, which leads to demyelination of white matter in infected areas. 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.

**Clinical features 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.

**Diagnosis and treatment of PML**

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

Only an improvement of immunocompetence is possible with the available treatments. Antiviral therapy does not (yet) exist. Affected patients with PML do not have a good prognosis: Often, patients die within 2 years.

**Cytomegalovirus (CMV) infection**

CMV-infection occurs in HIV-infected patients with very severe immunosuppression. In imaging procedures, the infection shows micronodular changes in the brain and/or hydrocephalus. The viruses can be detected in CSF using PCR. Ganciclovir is used for therapy.

**Protozoan and Fungal Infections of the CNS: Facts-Overview**

The following overview allows quick access to facts concerning the most important CNS-diseases caused by protozoa and fungi.
Opportunistic Infection in Patients with HIV

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

- **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)

**References**


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