

Purulent meningitis (pediatrics)

Bacterial meningitis is a life-threatening disease. Its main cause is inflammation of the meningeal coverings of the brain or the spinal cord, which very often also affects the adjacent brain tissue. *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* are among the most important bacteria that cause meningitis from infancy. Since the introduction of Hib and meningococcal vaccination, there has been a significant decrease in cases of purulent meningitis. Currently, the most common bacteria that causes this disease is *Streptococcus pneumoniae*, and it usually affects children aged 1-23 months.

Predisposing factors:

- respiratory infection
- otitis media - inflammation of the middle ear
- mastoiditis
- head injury
- immunodeficiency
- hemoglobinopathy



Pneumococcal meningitis

Pathophysiology

Bacteria enter the subarachnoid space most often via the hematogenous route (through the blood). They can enter the subarachnoid space directly in case of intracranial abscess, rupture, but more often through the dura mater during trauma, instrumental procedures or due to the spread of extradural inflammatory foci (otitis, sinusitis). Pathogens affecting the CNS by a non-hematogenic route (a route other than blood) include *Streptococcus* spp., anaerobic bacteria and gram-negative rods. Bacteria enter the nasopharynx intravascularly by passing through tight junctions between mucosal epithelial cells, but transport across the mucosal barrier by endocytosis is also possible (observed in *N. meningitidis* infection). After the entry of bacteria via the intravascular route, the main element of virulence is encapsulation, i.e. the formation of a capsule. This phenomenon can be observed in *S. pneumoniae*, *H. influenzae*, *N. meningitidis* as well as *Streptococcus agalactiae* and *E. Coli*. After the transfer of bacteria to the CNS, the bacteria quickly replicate, because there are not enough immune mechanisms in the CNS that could significantly block the replication. Immunoglobulin-mediated opsonization is particularly inefficient. Once the bacteria enter the subarachnoid space, individual parts of the pathogen's bacterial wall trigger a violent inflammatory response in the host. The released cellular component, teichoic acids, peptidoglycans and lipopolysaccharides after treatment with bacteriocidal antibiotics, also play a role. Bacteria and their components activate the complement, which is important for chemotaxis of leukocytes (neutrophils = microphages and macrophages). Thus, endothelial damage or a new flare-up of the disease continues. Cytokines, which are then released, initiate a host of processes and ultimately lead to neuronal damage and apoptosis. Interleukin 1 (IL-1), tumor necrosis factor alpha (TNF- α) and increased NO production have a major role in triggering the inflammatory response and in neurological damage. The bactericidal action of neutrophils leads to the release of oxygen radicals, which further contribute to CNS damage.

The infectious process moves and continues in the cortical vessels. This results in edema and proliferation of the endothelial cells of the arterioles. A similar process affecting the venous bed leads to life-threatening thrombosis and obstruction of blood flow in the vessel. This will lead to an increase in intracellular sodium and subsequently water. The subsequent development of brain swelling further worsens cerebral blood flow and leads to a rise in intracranial pressure (pressure in the skull) with possible uncal herniation. Edema (swelling) of the brain thus becomes a combination of cytotoxic swelling due to the joint cytotoxic action of bacteria and inflammatory mediators and vasogenic edema due to increased capillary permeability. Due to the fact that there is a disorder in the cerebral autoregulation of circulation, there is also an increase in the volume of blood in the CNS, and thus the intracranial pressure continues to increase, which leads to severe intracranial hypertension. Later obstruction of the arachnoid villi leads to violation of the outflow of liquor. Hydrocephalus or subdural effusions will occur.

In many patients with purulent meningitis, there is an increased secretion of antidiuretic hormone, which is the cause of SIADH and leads to further retention of free water. All these factors play a role in the development of focal or generalized convulsions. In case of severe brain edema, there will be a caudal shift of midline structures of the CNS with their "trapping" in the area of the tentorium or foramen magnum. Caudal displacement causes herniation of the parahippocampal gyri and/or cerebellum. These intracranial lesions manifest clinically as disorders of consciousness and postural reflexes. Displacement of the brainstem in the caudal direction leads to disorder III. and VI. cranial nerve. If these changes are not treated, decortication and decerebration occur, followed by respiratory and cardiac arrest.

In newborns, the attack of the mother by pathogens plays a role, which are resettled on the newborn after the amniotic sac ruptures. Certain bacteria such as Group B *Streptococcus* (*Streptococcus agalactiae*, GBS), enterogenic bacteria and *Listeria monocytogenes* can also infect newborns through the placenta (transplacentally). Newborns can also acquire meningitis through the nosocomial route. The bacteria enter the subarachnoid spaces

hematogenously. After they enter the CNS, the bacteria spread from the sinuses to the meningeal sheaths, choroid plexus, and ventricles. Using IL-1 and TNF- α , a local inflammatory response is mediated through the induction of phospholipase A2 activity, leading to the production of platelet-activating factor (PAF) and arachidonic acid. is the re-production of prostaglandins, thromboxane and leukotrienes. Thanks to the activation of endothelial cells, leukocytes are attracted and proteolytic enzymes are released. The mentioned processes cause a breakdown of the blood-brain barrier, the coagulation cascade is activated, cerebral edema and tissue damage occur. Thanks to the inflammation of the meningeal covers and ventricles, the response of polymorphonuclear cells, the rise of proteinorrachy and the consumption of glucose in the cerebrospinal fluid will occur. Gram-negative bacteria are more likely to cause empyema or abscess formation in the CNS. Heavy inflammatory exudation can lead to obstruction of the aqueduct of Sylvius and other spaces. This will lead to the development of obstructive hydrocephalus.

Epidemiology

The highest mortality is in the first year of life and in *Streptococcus pneumoniae* infection. Mortality is high in newborns and long-term consequences are significantly higher in survivors. The gender predilection for individual pathogens is interesting – boys have a higher incidence of Gram-negative meningitis, and *Listeria* infection is more common in girls. GBS affects both sexes equally. Prognosis is unfavorable for prolonged or refractory convulsions, especially if they last longer than the 4th day of hospitalization. On the other hand, if convulsions appear within the first 3 days of hospitalization, they are not prognostically significant. Only in 6% of patients can we notice signs of DIC or endotoxin shock. These patients also have a worse prognosis.

Etiology

Neonatal meningitis usually enters the body through the vaginal flora. The most common pathogens are Gram-negative enterobacteria and *Streptococcus agalactiae*, *Listeria monocytogenes* infection is rare.

- **Early-onset** meningitis is caused by GBS and occurs within the first 7 days of life. The pathogen attacks newborns prenatally or intrapartum. The infection is caused by colonization of the mother and subsequent transmission and lack of protective antibodies in the newborn. It is often associated with gynecological complications. The disease often occurs in the group of premature babies and low birth weight newborns.
- **Late-onset** meningitis, also caused by GBS, appears only after the 7th day of life. The pathogen infects newborns intrapartum or is a nosocomial transmission.

Meningitis in children > 4 weeks is most often caused by *Streptococcus pneumoniae* and *Neisseria meningitidis*. *Haemophilus influenzae* is now rare thanks to Hib vaccination.

Clinical picture

In **newborns** the clinic is often quite unremarkable and practically always non-specific. The set of clinical signs includes poor food intake, lethargy, apathy or, conversely, irritability, apnea, bulging fontanel, pallor, shock, hypotonia, high-pitched crying, squealing, hypoglycemia, resistant metabolic acidosis.

In **infants and children** we observe nuchal rigidity, opisthotonus, bulging fontanel, convulsions, photophobia, headaches, lethargy or irritability, loss of appetite, nausea, vomiting, fever or hypothermia and again the characteristic high-pitched cry. Bacterial meningitis is often preceded by a viral infection of the upper respiratory tract, and a peracute course is also common. Patients may also have another infectious focus, and the diagnosis of meningitis may thus be significantly delayed. The so-called meningeal syndrome is characteristic, characteristic for the age group of children > 1 year. It atypically occurs in infants. It is characterized by cephalgia, vomiting, disturbances of consciousness, symptoms from irritation of the anterior and posterior spinal roots:

- opposition of the neck (meningismus) = the child cannot touch the chest with the chin while lying down
- Brudzinski = passive forward tilt of the head causes spontaneous flexion in the hip joints
- Kernig = flexion of the hip joints at a right angle followed by passive extension of the knees causes pain
- Lasegue = painful elevation of stretched lower limbs when we do not reach 90 degrees
- Amoss ("tripod" sign) = when sitting on the bed, the child cannot hold himself in a sitting position, he has to help himself by supporting his upper limbs
- spine sign = pain when trying to touch the head with bent knees

In addition to neuroinfections, the differential diagnosis of neck opposition (meningism) also includes subarachnoid hemorrhage, abscesses or tumors in the posterior cranial fossa, rarely so-called deep neck infections or pneumonia. Sometimes patients arrive in a serious condition with impaired consciousness, a pathological reaction of the pupils and breathing pattern (Cheyne-Stokes pattern). Physical findings characterizing intracranial hypertension in bacterial meningitis include a bulging and/or pulsating fontanel, altered mental status, hyperreflexia with a positive Babinski sign. There are also disorders of the functions of the cranial nerves. Some patients may also show signs of circulatory failure..

Focal neurological findings can be observed in 20% of patients with purulent meningitis. By irritation of the nervus vagus vomiting and bradycardia occur. Irritation of the sensitive roots of the spinal cord can cause skin hyperesthesia, hyperacusis and also photophobia. Thanks to the increased vasomotor activity, we also observe skin dermographism. The inflammation regularly affects the adjacent cortical layer, which ultimately causes thrombosis and the development of a heart attack. Up to 80% of patients with meningitis develop SIADH in the first 48-72 hours. Patients who develop focal neurological symptoms are at higher risk of permanent neurological sequelae. In

33% of patients we can diagnose generalized or focal convulsions. Convulsions lasting during the first three days from the onset of the disease have no major prognostic significance. On the other hand, convulsions that appear even after the fourth day from the onset of the disease or convulsions that are difficult to control with treatment represent a high risk of complications, and permanent neurological consequences. Meningococcal meningitis is characterized by petechiae and suffusion on the skin, but can also occur with *H. influenzae* infection. Skin changes may often be nonspecific, including pallor or maculopapular erythema. In neuroinfections in the acute stage of the disease with brain edema, the surrounding tissues are relatively often oppressed. of the cranial nerve during its course at the base of the skull. Its clinical correlate is diplopia, which disappears with the resolution of brain edema. A subacute or chronic course is typical for fungal and mycobacterial meningitis.

At the beginning and during the course of purulent meningitis, the development of pericardial or joint effusions can be observed. During the development of these symptoms in the initial phase of meningitis, we can cultivate pathogens causing purulent meningitis from effusions. Effusions that form more than a week after the onset of the disease are mostly sterile.

Any worsening of the neurological status during purulent meningitis must be promptly clarified CT scan is the method of choice, as most CNS complications (brain abscess, heart attack, brain edema, vasculitis, subdural effusion) are anatomically correlated. In infants with a sufficiently open fontanel, we can also use ultrasound of the head.

Diagnosics

Diagnosis of purulent meningitis must be quick and accurate. Treatment should be started within 30 minutes after the patient is suspected of having this disease. The diagnosis is based on the clinical picture (which can sometimes be very typical, other times atypical, often mitigated after treatment with antibiotics for another cause) and findings in the cerebrospinal fluid. Cytology and biochemistry indicate a purulent finding. The diagnosis is confirmed by the detection of the pathogen in the cerebrospinal fluid and/or blood.

Lumbar puncture is contraindicated in the following conditions:

- moribund patient in serious condition, has hypotension, respiratory distress
- brain abscess, CNS tumor and other cases of intracranial hypertension
- focal neurological symptoms
- protracted convulsive state
- anizokorie
- infection at the site of the intended injection
- hemorrhagic diatheses

LP is then performed after stabilization of the patient's general condition. As soon as the intracranial pressure drops, we choose diagnosis via CT or MRI scan. CT can demonstrate cerebral edema (we detect a loss of differentiation between the white and gray matter of the brain) or obliteration of the ventricles and cisterns.

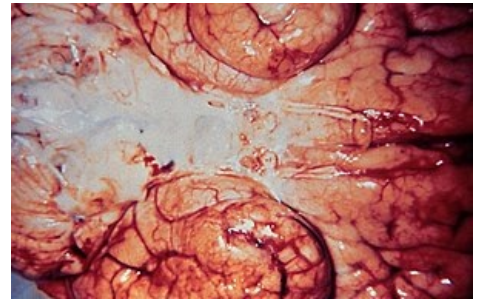
A characteristic finding in the cerebrospinal fluid. which indicates purulent meningitis is:

- opalescent to cloudy liquid
- proteinorrhachie > 1 gram
- thousands to tens of thousands of polymorphonuclear cells with a predominance of about 90% over mononuclear cells
- reduced glycorrachia (significant is glycorrachia < 1/3 of the blood glucose value, which is performed in parallel with the collection of cerebrospinal fluid)

If strongly opalescent to cloudy cerebrospinal fluid flows out during a lumbar puncture, we do not wait for the results of biochemistry and cytology and start therapy immediately. In some cases, the cerebrospinal fluid is so cloudy that sampling is not possible even with a standard needle and a stronger needle must be used (usually a 20 G needle). In the very early phase of purulent meningitis, the findings in the cerebrospinal fluid may not be very convincing, and it is therefore necessary to repeat the puncture at least 24 hours apart. If there is blood in the cerebrospinal fluid, it is good to find out the ratio between the number of erythrocytes and leukocytes. If the ratio is < 500:1 and if the cerebrospinal fluid is xanthochromic after centrifugation, there is a probability of finding an intracranial hemorrhage (subarachnoid hemorrhage). If the ratio is > 500:1 and if the cerebrospinal fluid is not xanthochromic after centrifugation, it is probably a fresh, artificial bleeding in connection with the puncture.

The diagnosis is confirmed by proof of the pathogen that caused the disease. Mainly cerebrospinal fluid and blood are examined. For confirmation, we can use microscopic examination, culture, latex agglutination or detection of *Streptococcus pneumoniae* antigen in the cerebrospinal fluid. Cross-reactivity between *Streptococcus pneumoniae* and *Hemophilus influenzae* and between GBS and *E. Coli* is possible in antigen detection. The modern method is then identification of the pathogen using PCR. As part of the triple test, we demonstrate the three most common pathogens – meningococcus, pneumococcus and haemophilus. However, we can also detect *Staphylococcus aureus*, *Listeria monocytogenes* and *Mycobacterium tuberculosis*.

If meningitis or a septic condition of unclear etiology is suspected, a lumbar puncture must be performed, unless there are contraindications! ("whenever you think of an LP, you should do it")



Hemophilic meningitis

	a normal finding	serous meningoencephalitis	purulent meningitis	TB meningitis	brain abscess
pressure	0,7–2,5 kPa (depending on the patient's age and position)	increased	increased	increased	increased
appearance	clear, colourless	clear, colourless	cloudy to purulent	clear, colourless, slightly cloudy	clear, colourless
Pandy's reaction	0	+ - ++	++ - +++	++ - +++	0 - +
cytology	in children > 1 month: up to 5/mm ³ = up to 15/3 in the Fuchs-Rosenthal chamber and only mononuclear cells (> 1/mm ³ poly is already a pathological finding) ! in children < 1 week < 40/mm ³	increased, predominance of mononuclear cells	high, predominance of polymorphonuclears	increased, predominance of mononuclear cells	dozens of mono ev. and polymorphonuclears
proteinorrhachie	0,15–0,4 g/l	increased	high	high	increased
glycorrhagia (norm 1/2–2/3 glycemia)	normal	normal	reduction to zero	reduction to zero	normal
lactate	1,2–2,1 mmol/l	normal	increased	increased	lightly increased
chlorids	116–130 mmol/l	normal	reduced	reduced	normal

Next, a blood sample is taken. In KO+diff. we demonstrate leukocytosis with a shift to the left. Thrombocytopenia may be associated with DIC and thus portends a much worse prognosis. In biochemistry, we can find an elevation of CRP and procalcitonin, depending on the development of the disease and other biochemical deviations. Lactic acidosis may indicate asprup. A comprehensive examination of coagulation parameters is crucial. In particular, this comprehensive examination can point to ongoing DIC, especially in the case of meningococcal meningitis. We examine APTT, INR and Quick, EGT, antithrombin III, D-dimers and fibrinogen, and of course platelets.

Therapy

We start treatment as soon as meningitis is suspected. Ideally, a blood and cerebrospinal fluid culture is taken before ATB is used. If the patient is in a serious condition, we postpone the LP for several days until the general condition stabilizes. As a rule, it is no longer possible to prove the pathogen, but biochemical and cytological changes are present and thus confirm the diagnosis of purulent meningitis. We monitor parenteral fluid intake very carefully, because especially newborns are more prone to developing hyponatremia as a result of SIADH. These changes can also be associated with convulsions that can be observed during the first 72 hours. However, most children with purulent meningitis present with severe sepsis and require sufficient volume expansion. Increased intracranial pressure caused by brain edema is rarer in newborns, mainly due to greater intracranial compliance. It is also a good idea to check the circumference of the head daily in children who have an open fontanel. We monitor blood gases and metabolic stability. After meningitis in all children, including newborns, it is necessary to examine BAER auditory evoked potentials. Purulent meningitis is treated with antibiotics and supportive measures are provided..

Antibiotic therapy

- **Age < 6 weeks:** For newborns and children < 6 weeks of age, a combination of ampicillin and cephalosporin

III is recommended when purulent meningitis is suspected. generation. Ampicillin is good for coverage against GBS, *Listeria monocytogenes*, Enterococci and some strains of enterobacteria. It penetrates perfectly into the cerebrospinal fluid, which is why we prefer it to Gentamycin, which, although it also has a good antimicrobial spectrum, does not reach such levels in the cerebrospinal fluid as Ampicillin. Cephalosporin III. generation is good at covering GBS and enterobacteria. *Listeria monocytogenes* and enterococcus are always primarily resistant. Ceftriaxone or cefotaxime is used. Cefotaxime binds less to albumin, therefore it penetrates better and is less competitive with bilirubin when binding to albumin. Ceftriaxone also causes biliary sludge.

The course of the disease and the particular pathogen determine how long the treatment will last. GBS meningitis is treated for about 10-21 days. For gram-negative bacteria, it takes longer for the cerebrospinal fluid to be sterile, and a treatment of 3-4 weeks is recommended. Repeated lumbar puncture is indicated if the patient's condition does not improve after starting treatment or after meningitis caused by gram-negative bacteria. Control LP is performed with an interval of 48 - 72 hours. If the treatment is correct, the cerebrospinal fluid will be sterile. And if there were no better results, a sonographic examination and a change of antibiotics are necessary. We perform further LP according to the clinical response or if the initial treatment fails and the antibiotics are changed. Sonography can reveal ventriculitis and other parenchymal changes that indicate a complicated course. If the findings in the cerebrospinal fluid and the general condition improve, it is enough to check the cerebrospinal fluid after 7 days..

In the last puncture before the end of the treatment, the number of leukocytes may not be completely normal, but glycorrhagia, proteinorrhagia and a negative culture of the cerebrospinal fluid must be clearly normal.

antibiotic	newborns > 2000g, age 0-7 days	newborns > 2000g, age > 7 days
ampicilin	150-300 mg/kg/day every 8 hours	200-400 mg/kg/day every 6 hours
cefotaxime	150 mg/kg/day every 8 hours	200 mg/kg/day every 6 hours
ceftriaxone	50 mg/kg/day every 24 hours	75-100 mg/kg/day every 12-24 hours

- **Age > 6 weeks:** Regardless of age, antibiotic therapy must be started as soon as possible. Most often, however, within 30 minutes of the suspicion of purulent meningitis. The choice of antibiotic for children older than 6 weeks is determined based on the 3 most common pathogens - *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Hemophilus influenzae* type b. Cephalosporins III remain the main choice. generation. We administer ceftriaxone 50 mg/kg every 12 hours IV or cefotaxime 50 mg/kg every 6 hours IV If pneumococcal or meningococcus is detected, treatment can be completed with crystalline penicilin at a dose of 50 mg/kg every 4 hours intra-venously

Supportive therapy

- Stabilization of circulation
- Corticosteroids
- Anticonvulsant treatment
- Treatment of coagulopathy
- Experimental therapy

Complications

The most common complications of purulent meningitis include the development of convulsions, which affect up to 1/3 of patients. Prognostically unfavorable are persistent convulsions, the development of convulsions during the course of the disease, and the focal nature of convulsions. In these cases, the risk of permanent neurological impairment may be high. Complications of purulent meningitis according to age

0-3 months	3 months - 1 year	1-6 years
<ul style="list-style-type: none"> ▪ obstructive non-communicating or communicating hydrocephalus (in case of obstruction of the external urinary tract) ▪ psychomotor retardation ▪ ventriculitis 	<ul style="list-style-type: none"> ▪ subdural effusion 	<ul style="list-style-type: none"> ▪ irreversible deafness

Prevention

- **Chemoprophylaxis**

When invasive pneumococcal disease is suspected, the epidemiologist records the clinical form of the disease and possible death as possible epidemiological measures. It also verifies how the collection of biological material from the patient is carried out for laboratory proof of etiology and checks whether the patient has been vaccinated against invasive pneumococci in the past. Preventive measures of antibiotics are not recommended for people who are in contact with the sick person. Epidemiological measures related to invasive Hib disease include four-day medical surveillance in children under 6 years of age. The parents of these children are advised that it is necessary to contact a doctor if symptoms of the disease are suspected, including an elevated temperature. Preventive

administration of antibiotics to close people is not recommended. For invasive meningococcal disease, close family members are recommended to be under medical supervision for 1 week. In these persons, the doctor looks for symptoms of suspected meningococcal disease. During medical supervision, it is necessary to pay particular attention to persons in close contact with the patient (in families, in boarding schools) and so-called risk contacts: persons under one year of age, adolescents and persons over 65 years of age, persons with known immunodeficiency, persons with previous respiratory disease, persons weakened by another disease. Mere evidence of *N. meningitidis* does not warrant antibiotic treatment. Protective chemotherapy is indicated for high-risk contacts or with the first symptoms, which theoretically do not rule out suspected meningococcal disease. During medical supervision for a period of one week from the last contact with the patient, the doctor detects other possible contacts, in which there is an indication for the immediate initiation of protective chemotherapy. In the Czech Republic, V - penicillin orally in therapeutic doses for a period of one week is recommended for targeted protective chemotherapy. Alternatively, therapeutic doses of ampicillin can be used in young children. Examination of nasopharyngeal and laryngeal swabs in contacts is carried out by an epidemiologist or a doctor performing medical supervision

▪ Immunization

For meningococcus, we use the meningococcal polysaccharide vaccine A+C. It is indicated according to the epidemiological situation in risk groups, including asplenia after the 2nd year of life. We have a polyvalent polysaccharide vaccine available for pneumococcus. It is recommended for immunocompromised patients (asplenia, nephrotic syndrome, immunosuppression, HIV). When it come to *Haemophilus a* conjugate vaccine against *H. influenzae* type b is used, which is part of the routine vaccination calendar.

Links

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- Infectious diseases of the brain • Neuroinfections, CNS/PGS inflammations • Encephalitis

Sources

- HAVRÁNEK, Jiří, et al. *Purulentní meningitidy v dětském věku* [online]. [cit. 2017-06-04]. <<https://www.pediatricpropraxi.cz/pdfs/ped/2009/01/05.pdf>>.