

Bacterial meningitis (paediatrics)

Bacterial meningitis is a life-threatening disease. Its main cause is inflammation of meninges that cover brain or spinal cord, that very often affects the adjacent brain tissue. The most important bacteria that cause meningitis, from infancy onwards, are *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*. Following the introduction of vaccination against Hib and meningococcal, the number of cases with this condition purulent meningitis dropped sharply. The most common bacteria that causes this disease is currently *Str. pneumoniae*. *Str. pneumoniae* typically affects children between 1 and 23 months of age.

Predisposing factors:

- respiratory infection
- otitis media - Middle ear inflammation
- mastoiditis
- head injury
- immunodeficiency
- haemoglobinopathy

Pathophysiology

Bacteria enter the subarachnoid space most often haematogeneous pathway (through the blood). They can enter directly into the subarachnoid space during the rupture of the intracranial abscess or more frequently through the dura mater during trauma, instrumental procedure or through the proliferation of extradural inflammatory focus (otitis, sinusitis). Among pathogens affecting CNS via non-haematogenic pathways (other than blood) we include *Streptococcus* spp., anaerobic bacteria and Gram-negative rods. Bacteria are transferred intravascularly from the nasopharynx via tight junctions between mucous epithelial cells, but transport through the mucosal barrier via the endocytosis is also possible (seen in *N. meningitidis* infection). After the entry of bacteria via the intravascular route, the main element of virulence is encapsulation, i.e. capsule formation. We can see this phenomenon in *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, *Streptococcus agalactiae* and *E. Coli*. After bacteria transfer to the CNS, bacteria replicate rapidly as there are insufficient immune mechanisms in the CNS to significantly block replication. In particular, immunoglobulin-mediated opsonisation is inefficient. As soon as the bacteria enters the subarachnoid space, the individual parts of the bacterial wall of the pathogen trigger a rather strong host inflammatory response. Released cellular components such as teichoic acid, peptidoglycans and lipopolysaccharides after treatment with bactericidal antibiotics are also involved. Bacteria and their components activate complement that is important for leukocyte chemotaxis (neutrophils = microphages and macrophages). This will lead to further progress of endothelial damage or new flare-up of the disease. Cytokines, which are then released, initiate a lot of processes and ultimately lead to neuronal damage and apoptosis. The main role in triggering the inflammatory response and in neurological damage have Interleukin 1 (IL-1), tumour necrosis factor alpha (TNF- α), and increased NO production. The bacterial action of neutrophils leads to the release of oxygen radicals, which also causes deepening of CNS damage.

The infection process moves and continues in the cortical vessels. The result is oedema and proliferation of endothelial arterioles cells. A similar process that affects the venous circulation leads to life-threatening thrombosis and obstruction of blood flow in the blood vessel. This increases intracellular sodium and consequently water. The subsequent development of brain swelling further impairs cerebral blood flow and leads to an increase in intracranial pressure (pressure in the skull) with possible uncal herniation. The oedema (swelling) of the brain thus becomes a combination of cytotoxic swelling with the combined cytotoxic action of bacteria and mediators of inflammation and vasogenic oedema in increasing capillary permeability. Due to the fact that the cerebral autoregulation of the circulation is impaired, there is also an increase in blood volume in the CNS and so the intracranial pressure continues to increase, leading to severe intracranial hypertension. Later obstruction of the arachnoid villi leads to a violation of the drainage of the liquor. Hydrocephalus or subdural effusions occur.

A number of patients with purulent meningitis experience increased secretion of the antidiuretic hormone, which causes SIADH and leads to additional retention of free water. All of these factors contribute to the development of focal or generalised convulsions. In severe cerebral oedema, the central line structures of the CNS are causally displaced with their "trapping" in the region of the tentorium or foramen magnum. Caudal displacement causes herniation of parahippocampal gyres and/or cerebellum. These intracranial disabilities become clinically apparent as disturbances of consciousness and postural reflexes. The displacement of the brain-stem in a caudal direction leads to a disturbance of the III and VI cranial nerves. If these changes do not start to be treated, decortication and decerebration occur and consequently respiratory and cardiac arrest.

In newborns, the role is played by the attack of the mother by pathogens, which are resettled in the newborn after the rupture of the amniotic membranes. Certain bacteria such as *Streptococcus* group B (*Streptococcus agalactiae*, GBS), enterogenic bacteria and *Listeria monocytogenes* can also infect newborns through the placenta (transplacental transmission). Newborns can also acquire meningitis via the nosocomial route. Bacteria enter subarachnoid spaces haematogenously. After they reach the CNS, the bacteria spread from the sinuses to the meningeal sheaths, the choroidal plexus and the ventricles. IL-1 and TNF- α mediate a local inflammatory response due to the induction of phospholipase A2 activity, leading to the production of platelet activating factor (PAF) and arachidonic acid. The result is the re-production of prostaglandins, thromboxane and leukotrienes. Due to the

activation of endothelial cells, leukocytes are attracted and proteolytic enzymes are released. These processes cause a disorder of the blood-brain barrier, the coagulation cascade is activated, brain oedema and tissue damage occur. Inflammation of the meningeal sheaths and ventricles will result in a polymorphonuclear response, an increase in proteinorachia, and cerebrospinal fluid consumption. Gram-negative bacteria more often cause the formation of empyema or abscesses in the CNS. Severe inflammatory exudation can lead to obstruction of the aqueductus Sylvii and other areas. This will develop in an obstructive hydrocephalus.

Epidemiology

Mortality is highest in the first year of life and in *Streptococcus pneumoniae* infection. Neonatal mortality is high and survivors have significantly higher long-term sequelae. The gender predilection for individual pathogens is interesting - boys have a higher incidence of gram-negative meningitis, while girls have a higher incidence of listeria infection. GBS affects both sexes equally often. In terms of prognosis, prolonged or refractory convulsions are unfavourable, especially if they last longer than after the 4th day of hospitalisation. On the other hand, if convulsions occur within the first 3 days of hospitalization, they are not prognostically significant. Only 6% of patients show signs of DIC or endotoxin shock. These patients are also prognostically worse off.

Etiology

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

- **Early-onset** meningitis is caused by GBS and occurs within the first 7 days of life. The pathogen attacks the newborn prenatally or intrapartally. Infection is caused by maternal colonization and subsequent transmission and lack of protective antibodies in the newborn. It is often associated with gynaecological complications. The disease often occurs in the group of premature and low birth weight newborns.
- **Late-onset** meningitis also caused by GBS occurs after the 7th day of life. The pathogen infects newborns intrapartally or by nosocomial transmission.

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

Clinical picture

In **newborns** the clinic is often rather bland and almost always non-specific. The set of clinical signs includes poor food intake, lethargy, apathy or irritability, apnoea, fever or hypothermia, convulsions, icterus, bulging fontanelle, pallor, shock, hypotonia, high-pitched crying, screeching cries, hypoglycaemia, resistant metabolic acidosis.

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

- Neck opposition (meningism) = the child cannot touch the chest with the chin when lying down
- Brudzinski = passive head tilt causes spontaneous flexion in the hip joints
- Kernig = right-angle hip flexion followed by passive knee extension causes pain
- Lasségue = painful elevation of the stretched lower limbs when we do not reach 90 degrees
- Amoss (tripod symptom) = 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 = soreness when trying to touch the forehead of the bent knees

In addition to neuroinfections, the differential diagnosis of neck opposition (meningismus) includes subarachnoid haemorrhage, abscesses or tumours in the posterior cranial fossa, and rarely deep neck infections or pneumonia. Sometimes patients come in serious condition with impaired consciousness, pathological reaction of the pupils and breathing pattern (Cheyne-Stokes pattern). Physical findings characterizing intracranial hypertension in bacterial meningitis include bulging and/or pulsatile fontanelle, altered mental status, hyperreflexia with positive Babinski's sign. There are also disturbances in 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. Irritation of the n. vagus results in vomiting and bradycardia. Irritation of the sensitive roots of the spinal cord can cause cutaneous hyperesthesia, hyperacusis and also photophobia. Due to increased vasomotor activity, we also observe skin dermographism. Inflammation periodically extends to the adjacent cortical layer, which ultimately causes thrombosis and the development of infarction. 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 after the onset of the disease are not essential to prognostic significance. Conversely, convulsions that continue after the fourth day after the onset of the disease or convulsions that are difficult to control with treatment present a high risk of complications, as well as permanent neurological consequences. Meningococcal meningitis is characterised by petechiae and suffusions on the skin, but can also occur in *H. influenzae* infection. Changes on the skin may often not be specific, include blanching or maculopapular erythema. In neuroinfections in the acute stage

of the disease with cerebral oedema, the surrounding tissues of the VI cranial nerve are relatively often oppressed during its course at the base of the skull. Its clinical correlate is diplopia, which disappears with the retreat of cerebral edema. Subacute or chronic course is typical for mycotic and mycobacterial meningitis.

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

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

Diagnostics

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

The following conditions are contraindications to lumbar puncture:

- moribund patient in severe condition, has hypotension, respiratory distress
- brain abscess, CNS tumor and other cases of intracranial hypertension
- focal neurological symptoms
- prolonged seizures
- anisokoria
- infection at the expected injection site
- haemorrhagic diathesis

We then perform the LP after stabilizing the overall condition of the patient. As soon as the intracranial pressure drops, we choose diagnostics via CT or MRI scan. CT can show cerebral edema (we find a loss of differentiation between white and gray matter) or obliteration of the ventricles and cisterns. A characteristic finding in cerebrospinal fluid that indicates purulent meningitis is:

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

If a strongly opalescent to turbid cerebrospinal fluid leaks during 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 hardened that it is not possible to take it with a standard needle and it is necessary to use a thicker needle (usually a 20 G needle). In the very early stage of purulent meningitis, the finding in cerebrospinal fluid may not be very convincing and it is 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. At a ratio of <500: 1 and if the cerebrospinal fluid is also xanthochromic after centrifugation, there is a likelihood of finding intracranial hemorrhage (subarachnoid hemorrhage). At a ratio of > 500: 1 and if the cerebrospinal fluid is not xanthochromic after centrifugation, it is probably fresh, artificial bleeding due to puncture. If we have a large amount of blood in LP, then 1 leukocyte can be counted per 700 erythrocytes and 10 mg protein / liter can be counted per 1000 erythrocytes.

The diagnosis is confirmed by the identification of the pathogen that caused the disease. The cerebrospinal fluid and blood are mainly examined. We can use microscopic examination, culture, latex agglutination or detection of *Streptococcus pneumoniae* antigen in 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 to detect the pathogen by PCR. In the tripple test, we detect the most common three main pathogens - meningococcus, pneumococcus and *Haemophilus*. However, we can also detect *Staphylococcus aureus*, *Listeria monocytogenes* and *Mycobacterium tuberculosis* by PCR. right[thumb|300px|Hemofilová meningitida

When suspected of meningitis or a septic condition of unclear etiology, lumbar puncture must be performed, unless contraindications are present ! („whenever you think of an LP, you should do it“)

	normal finding	serous meningoencephalitis	purulent meningitis	TBC meningitis	brain abscess
pressure	0,7-2,5 kPa (depending on the age and position of the patient)	increased	increased	increased	increased
appearance	clear, colorless	clear, colorless	cloudy to purulent	clear, colorless, slightly turbid	clear, colorless
Pandy's reaction	0	+ - ++	++ - +++	++ - +++	0 - +
cytology	in children > 1 month : to 5/mm ³ = 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 polymorphonuclear cells	increased, predominance of mononuclear cells	dozens of mono and polymorphonuclear
proteinorrachia	0,15-0,4 g/l	increased	high	high	increased
glykorrhachie (standard 1/2-2/3 glycaemia)	normal	normal	reduction to zero	reduction to zero	normal
lactate	1,2-2,1 mmol/l	normal	increased	increased	slightly increased
chlorides	116-130 mmol/l	normal	reduced	reduced	normal

Blood is also taken. In bloodcount+dif. we demonstrate leukocytosis with a left shift. Thrombocytopenia may be associated with DIC and thus represents a much worse prognosis. In biochemistry we can find elevation of CRP and procalcitonin, based on the development of the disease and other biochemical abnormalities. Lactic acidosis may be indicated by an astrup. A comprehensive examination of coagulation parameters is crucial. In particular, this comprehensive examination may indicate ongoing DIC, especially in meningococcal meningitis. We investigate 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, the culture is removed from the blood and cerebrospinal fluid before the ATB is applied. If the patient is in a severe condition, we will postpone the LP for several days until the overall 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 due to SIADH. These changes may also be associated with convulsions that may be observed during the first 72 hours. However, most children with purulent meningitis come under severe sepsis and require adequate volume expansion. Increased intracranial pressure due to cerebral edema is rarer in neonates, mainly due to greater intracranial compliance. It is also a good idea to check the head circumference daily in infants who have an open fontanelle. We monitor blood gases and metabolic stability. After meningitis in all children, even newborns, it is necessary to examine the auditory evoked potentials of BAER. Purulent meningitis is treated with antibiotics and supportive measures are provided.

Antibiotic therapy

- **Age <6 weeks:** A combination of ampicillin and cephalosporin III generation is recommended for neonates and children <6 weeks of age when purulent meningitis is suspected. Ampicillin is good for coverage against GBS, *Listeria monocytogenes*, Enterococci and some strains of Enterobacteriaceae. It penetrates well into cerebrospinal fluid, which is why we prefer it to Gentamycin, which also has a good antimicrobial spectrum, but does not reach such levels in cerebrospinal fluid as ampicillin. Cephalosporin III. generation is good for covering GBS and Enterobacteriaceae. The primarily resistant ones are always *Listeria monocytogenes* and enterococcus. Ceftriaxone or cefotaxime is used. Cefotaxime binds less to albumin, therefore it penetrates better and competes less with bilirubin to bind albumin. Ceftriaxone also causes biliary sludging.

The course of the disease and a particular pathogen determine how long the treatment will last. GBS meningitis is treated for about 10-21 days. In gram-negative bacteria, it takes longer than the cerebrospinal fluid is sterile and treatment lasting 3-4 weeks is recommended. The indication of recurrent lumbar puncture is indicated by the patient's non-improving condition after the start of treatment or after meningitis caused by gram-negative bacteria. The control LP is performed with an interval of 48 - 72 hours. If the treatment is correct, the cerebrospinal fluid will be sterile. And if the results are not better, sonography and antibiotic changes are needed. We perform additional LPs according to the clinical response or in case of failure of the initial treatment and change of antibiotics. Sonography can reveal ventriculitis and other parenchymal changes that are indicative of a complicated course. When the findings in the liquor and general condition improve, a check of the liquor after 7 days is sufficient. In the last puncture before the end of treatment, the number of leukocytes may not be completely normal, but there must clearly be normal glykorrhachia, proteinorrachia and negative cerebrospinal fluid cultures.

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antibiotic	newborns > 2000g, age 0–7 days	newborns > 2000g, age > 7 days
ampicillin	150–300 mg/kg/d every 8 hrs.	200–400 mg/kg/d every 6 hrs.
cefotaxime	150 mg/kg/d every 8 hrs.	200 mg/kg/d every 6 hrs.
ceftriaxone	50 mg/kg/d every 24 hrs.	75–100 mg/kg/d every 12–24 hrs.

- **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 in children older than 6 weeks is determined on the basis of the 3 most common pathogens - *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Hemophilus influenzae* type b. Cephalosporins III generation remain the main choice. We administer ceftriaxone 50 mg / kg every 12 hrs. i.v. or cefotaxime 50 mg / kg every 6 hrs. i.v. If pneumococcus or meningococcus is detected, treatment can be completed with good sensitivity with crystalline penicillin at a dose of 50 mg / kg every 4 hrs. i.v.

Supportive therapy

- Stabilization of circulation
- Corticosteroids
- Anticonvulsant treatment
- Anti-edematous 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. Persistent convulsions, development of convulsions during the course of the disease and focal nature of convulsions are prognostically unfavourable. In these cases, there may be a high risk of permanent neurological disability. Complications of purulent meningitis by age

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

Prevention

- **Chemoprophylaxis**

If invasive pneumococcal disease is suspected, the epidemiologist records the clinical form of the disease and possible death as possible epidemiological measures. He also verifies how biological material is collected from the patient for laboratory evidence of etiology and checks whether the patient has been vaccinated against invasive pneumococci in the past. Antibiotic precautions are not recommended for people in contact with the patient. Epidemiological measures related to invasive Hib disease include four-day medical supervision of children under 6 years of age. The parents of these children are instructed to contact a doctor if symptoms of the disease are suspected, including fever. Preventive administration of antibiotics to loved ones is not recommended. For invasive meningococcal diseases, medical supervision is recommended for loved ones for 1 week. In these people, the doctor is looking for symptoms of suspected meningococcal disease. During medical supervision, special attention must be paid to persons in close contact with the patient (in families, in dormitories) 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 support antibiotic treatment. Protective chemotherapy is indicated for at-risk contacts or with the first symptoms that theoretically do not rule out suspected meningococcal disease. During medical supervision for one week from the last contact with the patient, the doctor identifies other possible contacts, in which there is an indication to immediately start protective chemotherapy. In the Czech Republic, V - penicillin orally in therapeutic doses for one week is recommended for targeted protective chemotherapy. In young children, ampicillin may alternatively be used in therapeutic doses. Examination of nasopharyngeal and laryngeal swabs at contacts is provided by an epidemiologist or a physician performing medical supervision.

- **Immunization**

For meningococcus, we use 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 for pneumococcus. It is recommended in immunocompromised patients (asplenia,

nephrotic syndrome, immunosuppression, HIV). For Haemophilus, a conjugated vaccine against H. influenzae type b is used as part of the routine vaccination schedule.

Links

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