Invasive meningococcal diseases

Invasive meningococcal diseases (IMDs) are highly feared infectious diseases caused by the Gram-negative diplococci **Neisseria meningitidis**. Younger age groups are most often affected with the maximum incidence observed in the age group of 0–4 years (prevalence of the so-called serogroup B) and between 15–19 years (prevalence of the so-called serogroup C). IMD usually starts from full health and within a few hours the patient's condition worsens dramatically. In the Czech Republic, N. meningitidis is susceptible to penicillin, and third generation cephalosporins (cefotaxime, ceftriaxone) are recommended as part of initial empirical therapy as another etiology cannot be ruled out with certainty. Sometimes, even after early initiation of antibiotic therapy, a systemic inflammatory response may develop leading to severe multiorgan failure. Vaccination is available against the most common serotypes. IMDs are rare in the Czech Republic; however, their mortality is relatively high (10%), especially for children under 1 year of age. It is one of the fastest progressing deadly infectious diseases.[1][2]

There are three basic clinical forms of IMD:

- **meningococcal sepsis** (lethality rate of 25%)
  - tachycardia, tachypnea, hypotension, petechiae and suffusions, restlessness, development of **septic shock** to multiorgan failure within hours;
  - most severe form: Waterhouse-Friderichsen syndrome with extremely high lethality (95%);
- **meningococcal meningitis** (lethality rate of 2%);
  - fever, headache, vomiting, restlessness, mild to severe impaired consciousness, convulsions, focal neurological symptoms, meningeal symptoms, **intracranial hypertension** → respiratory insufficiency; no petechiae are present;
- **meningococcal sepsis with meningitis** (lethality 5%) - the most common form of IMD.[2]

Pathophysiology

Neisseria meningitidis is an immobile Gram-negative diplococcus, mostly in the shape of a coffee bean, stored inside granulocytes. In the population, asymptomatic carriers of meningococci carry them in the nasopharynx (2-5%[1] to 10-25%[2] of the population, mostly in the age group around 25 years). It is transmitted via respiratory droplets (aerosol, kissing, sharing glasses with drinks, etc.). It causes superficial infections of the nasopharynx (catarrhal infection) and urogenital tract (urethritis, cervicitis, vaginitis), pneumonia, bronchitis, and IMD (bacteria are massively transmitted by blood to various organs).[1][2]

According to the immunological reactivity of capsular polysaccharides, 13 different serogroups of N. meningitidis are distinguished, of which 6 cause the vast majority of diseases (**A, B, C**, D, 29E, H, I, K, L, **W-135, X, Y,** Z), Groups B, C, Y and W-135 are the most common in the Czech Republic (descending), serogroup Y has the highest lethality.[2][3]

Virulence factors include adhesins and the polysaccharide of the capsule (formation of carrier status and immunity), endotoxin (triggers the inflammatory and coagulation cascade) is essential for the clinical course. The incubation period is usually 1–8 days, in the short period of time non-specific symptoms sometimes appear (temperature, flu problems, headache, fatigue, muscle and joint pain). IMD usually develops during primary infection of N. meningitidis in the first days after nasopharyngeal colonization. IMD development is facilitated by impaired nasopharyngeal mucosal integrity, smoking, exposure to low humidity and dust, co-infection and immunodeficiency. Meningococci penetrate the mucosa into the bloodstream (sepsis), and meningitis develops when the blood-brain barrier crosses the meningitis. Endotoxin triggers a coagulation cascade, petechiae develop throughout the body, and disseminated intravascular coagulopathy develops. Endotoxin also triggers the inflammatory response and complement cascade, which further worsens the clinical course even when antibiotic therapy is initiated. IMD can very rarely manifest as purulent arthritis, pericarditis, pleurisy, and endocarditis.[2]

Up to 30% of adolescents and 10% of adults are carriers of meningococcus in the upper respiratory tract (evidence of pharyngeal cultivation). Carriers are not at risk of invasive infection because they are usually immunized. This is probably due to the "travel" of meningococci through the nasopharynx and the antigenic cross-reaction with enterogenic bacterial flora during the first two decades of life. On the contrary, **carrier status essentially provides "protection" against invasive infection.**[4]

The genetic influence on host sensitivity is already known in many cases. Deficiency of the terminal complement cascade predisposes those affected to meningococcal disease. A genetic variant of mannose-binding lectin, a plasma opsonization factor that initiates another pathway of complement activation, may explain almost 1/3 of the disease. The intrinsic anti-inflammatory profile of cytokines, specifically low levels of TNF and high levels of interleukin 10 (IL-10), are responsible for the fatal course of meningococcal infection. Patients with the Leiden mutation have a significantly higher risk of thrombotic complications, there is a more frequent need for amputations and skin transplants, but mortality is not increased. Patients with asplenia are also at increased risk for meningococcal infection.[4]

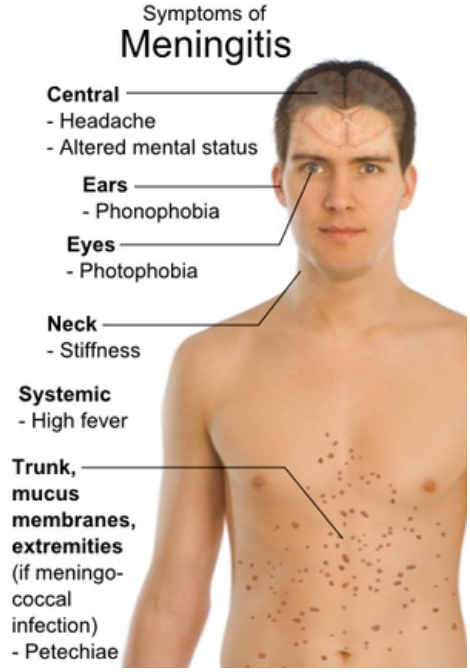
Clinical picture

Meningitis and sepsis

The disease occurs **suddenly**, mostly in previously healthy children and adolescents. Initially, the clinical picture is **uncharacteristic** (flu symptoms, fever, fatigue, joint pain). Already at this stage, they may appear in patients with meningococcal sepsis and in patients with a mixed form of the disease of diagnostically important **painless petechiae**. The IMD is characterized by emerging petechiae that are larger than 2 mm, can coalesce, and are also found in the lower limbs and abdomen. IMD is unlikely to be located on the head, neck and upper torso. Distinguishing petechiae from other rashes is possible using the "slide" method (rashes under pressure under glass fade until they disappear, petechiae persist).

Distribution of meningococcal meningitis - an epidemic in sub-Saharan Africa

Sepsis is the result of activation and continuous stimulation of the immune system by pro-inflammatory cytokines. This process is caused both directly by bacterial components (especially endotoxins released from the cell wall) and indirectly by the activation of inflammatory cells. The clinical picture of meningococcal sepsis includes **hemorrhagic rash** (petechiae and suffusions), **fever**, and psychological alteration (restlessness, agitation, confusion) and incipient or already developed **septic shock** (tachycardia, tachypnea, cold periphery, delayed capillary return, peripheral or even central **cyanosis, hypotension** and oliguria or even anuria). Muscle and abdominal pain, and diarrhea, the absence of meningeal symptoms, and the afebrile course do not preclude IMD; on the contrary, they can slow down correct diagnosis. There is a high risk of death in patients with advanced shock and severe impaired consciousness. The clinical spectrum of meningococcal sepsis may reach the stage of **multiorgan dysfunction** with predilection of the cardiopulmonary unit, kidneys, GIT and, of course, the CNS.



Symptoms

The clinical picture of the **mixed form** (meningococcal sepsis with meningitis) includes the more or less pronounced symptoms of sepsis, as well as **headache, vomiting, meningeal symptoms and impaired consciousness**.

Meningitis

Neurological impairment is the result of the following three processes: direct bacterial toxicity, indirect pro-inflammatory processes (ischemia, vasculitis, edema, cytokine release) and systemic causes (shock, convulsions, cerebral hypoperfusion). Loss of cerebral circulation self-regulation, cerebral edema, and decreased cerebral perfusion lead to increased **intracranial pressure**. Intracranial hypertension, **vasculitis, and cerebrovascular thrombosis** are responsible for **ischemia** and subsequent **neurological impairment**. The clinical picture of meningococcal meningitis includes headache, vomiting, meningeal symptoms, disorders of consciousness, convulsions, photophobia, neck stiffness, focal neurological symptomatology. The patient is increasingly sensitive and painfully responds to physical examination. Clinically, this form is indistinguishable from other purulent meningitis.

Capillary leak

The extreme **increase in capillary permeability** during meningococcal sepsis is well known. Pathophysiologically, this is probably a multifactorial issue. Meningococci together with neutrophils lead to a loss of negative charge of glycosaminoglycans in the endothelium. **Fluid requirements** are therefore tremendous in the first hours of infection, often **40-60 ml / kg / hour,** with some sources reporting up to 200 ml / kg in the first hour. Patients usually require a volume several times their total blood volume during the first 24 hours. The risk of this necessary fluid substitution is the development of pulmonary edema, which may occur after a dose of 40 ml / kg. Its prevention and the treatment is artificial lung ventilation.

Coagulopathy

Meningococcemia is a known cause of DIC, which causes microcirculation thrombosis and subsequent severe bleeding with coagulation factor consumption. The result can be amputation of the fingers of the limbs, and in extreme cases the death of the patient. Meningococcal infection affects three main routes of coagulation that lead to a hypercoagulable state:

- Endothelial involvement leads to local vasoconstriction, platelet activation with the development of thrombosis. Because consumption coagulopathy and down-regulation of natural coagulation inhibitors (tissue factor inhibitor, antithrombin III) occur at the same time, coagulopathy is further exacerbated.
- The importance of protein C is crucial in the development of purpura fulminans. A similar rash is seen in neonates with congenital protein C deficiency or in older children after varicella, where antibodies to protein S may develop. Protein C and S levels are reduced in children with meningococcemia. The same picture can be

found in patients with septic shock. The inability to activate protein C in the microvascular system certainly plays a role.
- The fibrinolytic system is also subject to down-regulation. Consumption and insufficient plasmin production cause insufficient feedback on clot formation. Another cause is a significant increase in PAI (plasminogen activator inhibitor) levels and, conversely, decreased efficacy of endogenous TPA (tissue plasminogen activator).

Meningococcal infection affects three major coagulation pathways that lead to hypercoagulable status: endothelial involvement, protein C deficiency, and down-regulation of the fibrinolytic system.

Metabolic disorders

The most important is the development of severe MAC together with ionogram disorders - hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia.

Myocardial dysfunction

Myocardial dysfunction leads to a decrease in ejection fraction and an increase in cardiac enzymes as a marker of myocardial damage. We find heart rhythm disorders (audible gallop), increased central venous pressure and hepatomegaly. The cause of myocardial dysfunction is hypovolemia, the above-mentioned ionic imbalances, and myocardial depression in the septic state.

Diagnostics

Biological material should be collected to identify the agent before initiating antibiotic treatment. Carrying out diagnostic tests must not be a reason for delaying treatment.

Basic examination

The basic examinations include:

- blood samples: complete blood count+ diff. including platelets, biochemical examination (glycemia, mineralogram, urea, creatinine, bilirubin, transaminases, lactate, albumin, acute phase proteins - CRP, procalcitonin), acid - base balance.

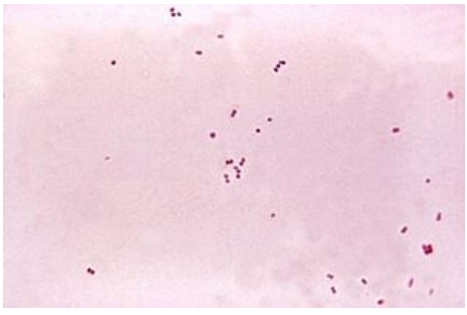
Due to the high risk of developing DIC, it is necessary:

- hemocoagulation examination: aPTT, INR, fibrinogen, D-dimers, antithrombin III, EGT.

It should be borne in mind that children at the onset of an infection may have a normal leukocyte count and only non-specifically elevated CRP. The prognostic finding is leukopenia, which poses a risk of rapid disease progression. Collection of biological material from blood includes **blood cultures** (ideally two, for children a volume of 1–5 ml), latex agglutination of serum, and blood collection for PCR.

Examination of cerebrospinal fluid

When meningitis is suspected, we always consider performing a lumbar puncture. However, we always consider the benefits and risks. If it is not possible to perform an LP **within 30 minutes of the IMD being suspected,** there is no further waiting and adequate therapy must be initiated. We also postpone LP in patients with impaired consciousness or septic shock. The following conditions are also **contraindications** for lumbar puncture: dying patient in severe condition with hypotension, respiratory distress, brain abscess, CNS tumor and other cases of intracranial hypertension, focal neurological symptoms, prolonged seizures, mydriasis or anisocoria, absent oculocephalic reflex, infection at the presumed site injection, hemorrhagic diathesis or generalized sowing of petechiae and suffusions. We perform **biochemical** (protein, glucose, lactate), **cytological**, **microbiological examinations** using the cerebrospinal fluid (microscopy in Gram staining - gram-negative intracellularly stored diplococcus, culture and sensitivity, latex agglutination, PCR). PCR is a method with about 90% sensitivity and specificity.



Gram-negative Neisseria meningitidis in Gram cerebrospinal fluid staining

Examination of other material

This is a nasopharyngeal swab or collection of material from skin lesions.

Follow-up examinations

After treatment of acute illness, patients should be evaluated for immunological profiles, including C3, C4, CH50 and properdin levels.

Scoring schemes

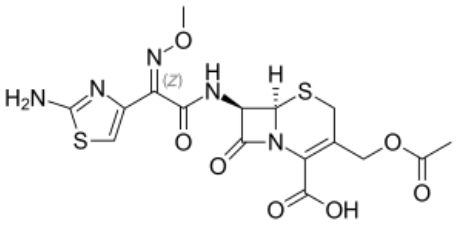
For meningococcemia, there are several scoring schemes that predict the severity of the condition, i.e., the probability of the patient's death. One of the used is the so-called **Rotterdam Score Meningococcal septic shock in children**, which according to the parameters of potassium, base excess, platelets and CRP values expresses a prediction for death in meningococcemia. It exists in the form of a table where, after entering the values of the above parameters, the program calculates the mortality prediction.

Therapy

Initial resuscitation

The primary goal of initial resuscitation is to restore tissue perfusion as quickly as possible in all patients with hypotension and / or clinical signs of tissue hypoperfusion. In most cases, airway management by **tracheal intubation and initiation of ventilatory support** are indicated as soon as possible. For the purposes of initial resuscitation in children, the following can be recommended: capillary return <2 seconds, absence of difference between central and peripheral pulse, warm limbs, diuresis> 1 ml / kg / hour, normal state of consciousness and lactate level <2 mmol / l with MAC adjustment. Evaluation of blood pressure as the only indicator of successful resuscitation should not be used in children. If cardiac output value is available, the target value is considered to be the value of the cardiac index in the range of 3.3–6.0 l / min / m2 as the normal values of the so-called perfusion pressure (difference between mean arterial and central venous pressure) for a given age. Fluid therapy is the initial step in circulatory resuscitation and should be titrated according to clinical goals. As part of the volume expansion, we administer 20 ml / kg of crystalloids within 30 minutes. We can repeat the dose as needed. The initial fluid requirement can be as much as 60 ml / kg / hr. and 120 ml / kg / 2 hours, but may be higher. If extremely high volume expansion is required, careful patient monitoring is required, at least with measurement of CVP and invasive arterial pressure. Colloids or isotonic crystalloids are considered equivalent in terms of achieving resuscitation goals.

Antibiotic treatment



Cefotaxim (cephalosporin antibiotic III. generation)

If IMD is suspected, antibiotics should be given **within 30 minutes**. Resistance of Neisseria meningitidis to penicillin has not yet been demonstrated in the Czech Republic. However, other agents (Haemophilus influenzae, Streptococcus pneumoniae, enterobacteria), which may not be sensitive to penicillin, may cause a very similar clinical course to IMD. Until IMD confirmation, cephalosporin III. generation (ceftriaxone or cefotaxime) is the antibiotic of choice.. If we talk about empirical treatment, it should be noted that in the US, the resistance of pneumococci to penicillin and sometimes III. generation of cephalosporins exists. Therefore, the combination of cephalosporins III. generation and vancomycin is beginning to be promoted in the American recommendations as the empirical therapy of choice until the causative agent is identified. In the case of a proven IMD, the original antibiotic can be continued or replaced with penicillin. The administration of antibiotics is always **intravenous**, the administration time is recommended for **7-10 days.** Administration of steroids before the first dose of antibiotics is recommended especially in patients with meningitis. Antibiotic dosage:

- ceftriaxone 100 mg / kg / day for 12 hours
- cefotaxime 200 mg / kg / day for 6 hours
- penicillin (potassium salt) 400,000 I.U./kg/day 6 hours

Inotropes

They are always indicated when it is impossible to achieve the goals of therapy (inadequate blood pressure, signs of organ hypoperfusion, hyperlactacidemia, SvcO2 <70%) by fluid administration. **Inoconstrictor** of choice is **norepinephrine** in normal doses, only in refractory conditions adrenaline is recommended. Inotropes should be considered in patients with persistent clinical signs of low cardiac output despite fluid administration. The **initiator of choice** is **dobutamine** in conventional doses. Phosphodiesterase inhibitors may be considered in patients with severe tachycardia. Efforts to achieve predefined cardiac output values are generally not recommended, except in conditions where signs of tissue hypoperfusion persist.

Steroids

Acute adrenal insufficiency (**Waterhouse – Friderichsen syndrome**) should always be considered in patients with meningococcal sepsis and higher doses of steroids are recommended. Dexamethasone is recommended in all patients with acute purulent meningitis. According to the Cochrane Database Syst Review 2003, dexamethasone is recommended at a dose of 0.15 mg / kg every 6 hours for 4 days. Steroids, such as hydrocortisone, are recommended in patients with persistent septic shock and concomitant need for vasopressors (see sepsis). However, corticosteroids are not recommended for neonatal purulent meningitis.

Administration of blood and blood derivatives

Blood transfusions are recommended if the **hemoglobin decreases <70 g / l**. Routine plasma administration to correct laboratory abnormalities in the absence of clinical signs of bleeding is not recommended. Antithrombin III administration is recommended in order to reach the normal range (preferably 100-120%). Platelet transfusion is

recommended at <5,000 / mm3 even in the absence of clinical signs of bleeding or at <40,000 / mm3 in patients at risk of bleeding. Achieving a higher platelet count (> 50,000 / mm3) is recommended before invasive surgery (central vein cannulation).

Protein C

PC administration is recommended in patients with a high risk of death but no risk of bleeding. Indications for PC administration are: primary PC deficiency, gram-negative bacterial sepsis (especially meningococcal), DIC, liver disease. Before administration of PC, its plasma level, AT III, D-dimers, PAI-I activity + antigen must be examined. It is recommended that platelet counts be maintained above 30,000 / mm3 when administering PC. The concomitant presence of meningitis and thrombocytopenia in PC treatment significantly increases the risk of CNS bleeding. Protein C (PC) is an **anticoagulant protein** that plays an important role in the regulation of hemostasis. PC is synthesized in the liver as a vitamin K-dependent plasma protein. It is present in plasma at a concentration of 4 ug / ml. PC circulates in the blood in the form of a zymogen (proenzyme). The PC is selectively converted "on site" and "on demand" to activated protein C (APC) during coagulation activation. APC has many "braking effects" on the coagulation cascade: it inactivates coagulation factors Va (thereby reducing thrombin production) and VIIIa, prevents the pro-inflammatory consequences of thrombin production (including platelet activation, adhesion and aggregation, release of vasoactive and pro-inflammatory substances, increased endothelial permeability), promotes fibrinolysis by binding plasminogen activator inhibitor I (PAI-I). PC also has strong anti-inflammatory effects. All patients with a diagnosis of septic shock have lower plasma PC levels and most have elevated APC levels. C protein dosing: initially i.v. bolus 80-120 U.I./kg, then 50 U.I./kg/d divided into 6 doses during the acute phase. We adjust doses and time intervals to the activity of PC in plasma, which we determine once a day, always before the administration of PC concentrate. We infuse the product for about 60 minutes. The increase in plasma PC levels is dose dependent on PC. Conversion of PC to APC has been observed in all patients who have received PC and is also dose dependent for PC. Treatment of PC in children with purpura fulminans and meningococcal sepsis is safe.

Blood glucose control

It is recommended that blood glucose levels be maintained at <8 mmol / l. After stabilization of the glycemia, a glycemic control of 4 hours is recommended. Continuous administration of insulin at values> 10 mmol / l.

Other therapeutic procedures

- Immunoglobulins are administered only in case of presumed or confirmed deficiency.
- Renal replacement is performed only in circulatory unstable patients and with signs of acute renal failure within the MODS.
- We use bicarbonate therapy for refractory acidosis with pH ≤ 7.15.
- Prophylaxis of deep vein thrombosis with heparin or low molecular weight heparin (LMWH) is recommended. In patients with a contraindication to heparin, it is recommended to use mechanical methods to prevent deep vein thrombosis.
- Prophylaxis of stress ulcers is recommended, H2-receptor blockers are preferred.
- Hyperthermia monitoring is recommended.

Experimental therapy

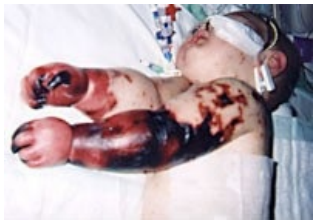
As part of IMD treatment, various pathways of experimental therapy have been and are being tested abroad. Probably the most attention is focused on the use of anti-endotoxin drugs. An international multicenter randomized and controlled study with recombinant bactericidal permeability increasing protein (BPI) has been completed in some centers in the United States and the United Kingdom. Despite a significant reduction in mortality and amputations, the results were not statistically significant. A randomized study of HA1A monoclonal antibodies also showed the same, which also showed a reduction in mortality, but the result was not significant enough.

Complications and prognosis

Complications

The most common complications of meningococcal disease include:

- **cardiopulmonary failure**
- **renal failure** (requiring elimination methods)
- **peripheral gangrene** (sometimes with the need for amputation)
- **peritoneal compartment syndrome** due to extreme abdominal capillary leak (requires the need for abdominal puncture)
- **serum sickness** in the formation of immunocomplexes (arthritis, pericarditis or pneumonitis occurring approximately 10-14 days after the primary infection)



Extensive suffusions can be complicated by gangrene, which sometimes leads to limb amputation.

Prognosis

The incidence of the disease has two peaks. The first between 6 months - 2 years (it is caused by a congenitally low level of protective neutrophil BPI protein). The second peak comes in adolescents and is caused by a change in social behavior and an increase in "intimate" contacts during this age group. The wrong prognosis is:

- hypotension
- shock
- neutropenia
- sowing of petechias during the first 12 hours
- presence of DIC
- persistent MAC
- positive microscopic evidence of meningococcal diplococcus
- low CRP value
- serotype C

Most deaths occur within the first 24 hours of admission. Serotype C disease also poses a greater risk of sequelae and amputations. However, persistent complications are rare in patients with uncomplicated hospitalization. They occur in about 4% of survivors of infections.

Prevention

Vaccination is available in the Czech Republic and is not part of the mandatory vaccination calendar. Meningococcal vaccination is recommended for children and adolescents, in particular:

- children from 2 months to 2 years (against serogroup B);
- children aged 13 to 15;
- adolescents and young adults;
- travelers to high-risk areas; persons at professional risk of infection (ICU, rescue service);
- patients with hyposplenism or splenectomy, patients with immunodeficiency or complement disorders, stem cell hematopoietic stem cell transplantation, bacterial meningitis and septicemia, head injury, prior to eculizumab treatment.

Vaccines:

- combined conjugated tetravaccine against serogroups A, C, W-135 and Y (from 1-2 years of age);
- recombinant 4-component vaccine for serogroup B (serogroup B antigens are highly variable, therefore it is not possible to provide protection against all of them, 74% coverage is assumed).
  An interval of at least 2 weeks is recommended between the two vaccines.

References

External links

- Meningokoková sepse – interaktivní algoritmus + test (https://www.akutne.cz/index.php?pg=vyukove-materialy--rozhodovaci-algoritmy&tid=131)

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