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REVIEW ARTICLE

Clinical picture, diagnostics and treatment of bacterial meningitis

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Abstract

Bacterial meningitis is a serious infectious disease of the cerebral meninges, which occurs worldwide and threatens the lives of people of all ages. The largest number of cases in developed countries is caused by the gram-positive bacterium Streptococcus pneumoniae. Other more common agents are Neisseria meningitidis serotype B and Listeria monocytogenes. Fever is the most commonly reported symptom in paediatric patients, occurring in up to 93% of cases. Further, it is possible to observe headache, vomiting and positive meningeal phenomena. The most common symptoms in adults are fever, headache, positive meningeal symptoms and impaired consciousness. Examination of cerebrospinal fluid is essential for the diagnosis of bacterial meningitis. The basis of treatment is the earliest possible administration of antibiotics, initially empirically and then purposefully according to the results. Corticosteroids, traditionally dexamethasone, are also used in therapy.

AETIOPATHOGENESIS

Bacterial meningitis is a serious infectious disease of the cerebral meninges that occurs worldwide and threatens the lives of people of all ages. The introduction of vaccines against bacteria *Haemophilus influenzae* type b, *Neisseria meningitidis* serotype C and pneumococcal conjugate vaccines has changed the epidemiology and spectrum of pathogens, especially in developed countries. In these countries, the incidence of purulent meningitis in children has dropped dramatically, with the majority of patients being productive and elderly. (McIntyre *et al.* 2012). The largest number of cases is caused by the gram-positive, facultatively anaerobic, α-hemolytic bacterium *Streptococcus pneumoniae* (Bodilsen *et al.* 2014, Kim *et al.* 2021). Bacteria are also the most common cause of community-acquired pneumonia in the Czech Republic (Bartoš *et al.* 2020). Other more common causes of acute bacterial meningitis are *Neisseria meningitidis* serotype B, aerobic gram-negative diplococcus, and *Listeria monocytogenes* (Koopmans *et al.* 2013, Bijslma *et al.* 2014). The latter occurs more frequently in the elderly, and patients with cancer or

immunocompromised patients (Koopmans *et al.* 2013, Paciorek *et al.* 2019) and is a gram-positive, facultatively anaerobic rod. In HIV positive patients, cryptococcal meningitis is more common as an opportunistic infection (Beno *et al.* 2016), which is not caused by bacteria but by a fungus. Despite improvements in diagnosis and antibiotic therapy, bacterial meningitis is still associated with high mortality of up to 28%, and approximately 50% of survivors suffer from various neurological problems after undergoing it (Sharma *et al.* 2014).

CLINICAL PICTURE

The symptoms of bacterial meningitis are different in different age categories. In newborns, they are often nonspecific, such as irritability or lethargy, vomiting, lazy sucking, muscle tone and breathing disorders. In a smaller number of cases, opposition of the neck, bulging large fontanelle, convulsions or opisthotonos can be observed (Gaschignard *et al.* 2011, Johansson Kostenniemi *et al.* 2015). In childhood we observe headache, fever, vomiting and positive meningeal phenomena, in children up to about 1 and a half years bulging of the large fontanelle can be observed (Johansson Kostenniemi *et al.* 2015, Nguyen-Huu *et al.* 2022). Fever is the most commonly reported symptom in pediatric patients, occurring in up to 93% of cases. Vomiting is observed in 55–67% of children with bacterial meningitis (Snaebjarnardottir *et al.* 2013). In a small number of cases, photophobia, convulsions and impaired consciousness occur. The most common symptoms in adults are fever, headache, positive meningeal symptoms and impaired consciousness. The classic triad of these symptoms is present in about half of the patients (Dauchy *et al.* 2007, Domingo *et al.* 2013). Disorders of consciousness occur both quantitatively and qualitatively and are often fluctuating in nature. Petechiae occur in up to half of the cases and in most patients (up to 90% of cases) it indicates meningococcal meningitis (van de Beek *et al.* 2004). The observation of the presence of symptoms of bacterial meningitis in adult patients in several European studies is shown in Table 1.

DIAGNOSTICS

Examination of cerebrospinal fluid is essential for the diagnosis of bacterial meningitis. Without lumbar puncture and subsequent examination of the fluid, the appropriate diagnosis cannot be clearly established (van de Beek *et al.* 2016). If cerebrospinal fluid examinations cannot be performed for objective reasons, serum parameters of inflammation may provide support for diagnostic considerations (Brouwer *et al.* 2010). The classic findings in cerebrospinal fluid with bacterial meningitis are polynuclear-predominant leucocytosis, low glucose levels, and high protein levels (van de Beek *et al.* 2016). However, observations of some authors show that with concurrent septic shock, the number of leukocytes in the cerebrospinal fluid may be only slightly increased or even normal. Some authors suggest that the diagnostic accuracy of lactate levels in the cerebrospinal fluid is higher than the amount of leukocytes (Huy *et al.* 2010, Sakushima *et al.* 2011), especially at the beginning of the disease. Lactate levels are also affected by antibiotic administration before performing lumbar puncture. The lactate concentration then has a significantly lower susceptibility to purulent meningitis (Sakushima *et al.* 2011). Even more important is the determination of the energy balance coefficient, which expresses the number of ATP molecules produced at current energy conditions in the cerebrospinal fluid from one molecule of glucose (normal value 28.0–38.0). In bacterial meningitis, its value is significantly reduced and can reach negative values.

Most acute bacterial meningitis are caused by bacteria *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Listeria monocytogenes*, only 5–26% is caused by other bacteria, and therefore only the above-mentioned pathogens are detected in the first line by default using the PCR method (Bargui *et al.* 2012). The PCR method for the detection of pathogens has different sensitivities, which are 79–100% for *Streptococcus pneumoniae*, 91–100% for *Neisseria meningitidis* and for example 67–100% for *Haemophilus influenzae* (Brouwer *et al.* 2012). A suitable diagnostic method is also latex agglutination, by means of which the active microorganism can be determined relatively quickly. In the most common purulent meningitis causing pneumococcus, the sensitivity of latex agglutination is described as 59–100%, and it is 22–93% for *Neisseria meningitidis* (Brouwer *et al.* 2010). To determine the aetiology of the disease, a culture examination of the cerebrospinal fluid is irreplaceable, even if it is a method with a time-delayed result. The urinary antigen test can also be a valuable tool in the diagnosis of pneumococcal aetiology of the disease in adults (Vančíková *et al.* 2013).

Mainly, in order to exclude lumbar puncture in a patient with cerebral herniation or haemorrhagic stroke, CT examination of the brain was previously performed as standard. Systematic observations have shown that the routine performance of this test sometimes leads to a significant delay in the initiation of antibiotic therapy, which is subsequently associated with poorer patient treatment outcomes. (Proulx *et al.* 2005). For this reason, criteria have been established, which if met serve as a recommendation to perform a CT examination before performing a lumbar puncture and administering an antibiotic. They apply to cases with focal neurological deficits, new onset of convulsions, patients with Glasgow Coma Scale below 10 and immunocompromised (Brouwer *et al.* 2012). If the patient does not meet any of the above criteria, a CT scan of the brain does not need to be performed before puncture. However, after its X-ray examination, it is

Tab. 1. Symptoms of bacterial meningitis in adult patients in several European studies

state	Netherlands	France	Spain	Denmark
autors	**van de Beek et al. 2004**	**Dauchy et al. 2007**	**Domingo et al. 2013**	**Bodilsen et al. 2014**
reporting period	**1998-2002**	**2001-2004**	**1996-2010**	**1989-2010**
number of patients	696	60	295	172
headache	87%	87%	-	58%
nausea/vomiting	74%	-	45%	-
opposition of the neck	83%	-	69%	65%
rash	26%	-	20%	-
fever	77%	93%	95%	87%
impaired consciousness	69%	30%	54%	68%
coma	14%	-	7%	16%
focal neurological deficit	34%	23%	15%	21%
fever + opposition of the neck + impaired consciousness	44%	-	41%	45%

recommended for possible clarification of mastoiditis or sinusitis as a source of inflammation of the brain meninges. (van de Beek *et al.* 2016).

Blood cultures can also be a valuable diagnostic source, especially in cases where it is not possible to perform lumbar puncture or there are negative cerebrospinal fluid cultures. The degree of blood culture positivity varies from pathogen to pathogen, representing 75% of patients with pneumococcal meningitis, 50-90% of patients with *Haemophilus influenzae* and 40-60% of patients with meningococcal meningitis. (Brouwer *et al.* 2010). As a standard, two sets of blood cultures are taken from two different veins, regardless of the currently measured body temperature.

TREATMENT

The priority of patient treatment is to ensure his basic vital functions. Above all, ensure airway patency, adequate ventilation and efficient circulation. The patient's primary management should be performed according to the ABCDE algorithm, which is recommended by the European Resuscitation Council as part of extended resuscitation care. In case of medical staff, which has less experience with these procedures, it is appropriate to use a printed cognitive aid, the use of which statistically significantly increases the percentage of treatment procedures in the correct order and thus shorten the duration of management of the initial examination of patients with potentially endangered or failing basic life functions. (Peran *et al.* 2020a). Early recognition and call for help using standardised communication is also essential in the care across boundaries (Peran *et al.* 2020b).

Antibiotic therapy is essential for the continued survival of patients with acute bacterial meningitis. Therefore, the time from admission to hospital to the first dose of antibiotic should not exceed 1 hour (Proulx *et al.* 2005). It is recommended to administer ceftriaxone 3 mg intravenously every 12 hours or 3 g cefotaxime intravenously every 6 hours for adults. Amoxicillin or ampicillin is empirically administered to patients over 50 years of age or immunocompromised patients who may also be expected to have meningitis due to *Listeria monocytogenes* bacteria (van de Beek *et al.* 2016). In such a case, the Czech recommendations also allow the administration of penicillin, possibly in combination with gentamicin.

After the pathogen has been determined, it is necessary to start targeted antibiotic treatment as soon as possible. In the case of *Streptococcus pneumoniae* treatment with penicillin or ampicillin is recommended; in the case of resistance or initial empirical administration of ceftriaxone or cefotaxime, it may be left unchanged. Penicillin resistance is not yet significantly widespread and is described mainly in serotypes 19A, 19F and 15A (Mališová *et al.* 2019). If 3rd generation cephalosporin-resistant pneumococcus occurs, a combination of vancomycin and rifampicin is used as standard, or meropenem may be given. The duration of treatment for pneumococcal meningitis is recommended in international publications in the range of 10-14 days (Erdem *et al.* 2008, van de Beek *et al.* 2012).

If the causative agent is *Neisseria meningitidis*, penicillin or ampicillin is administered. In recent decades, however, meningococcal resistance to penicillin has become increasingly common (Latorre *et al.* 2000), which is why ceftriaxone or cefotaxime are being used more as an alternative, and chloramphenicol may be given at the usual doses. The duration of antibiotic treatment of meningococcal meningitis is 7 days. Meningitis caused by *Listeria monocytogenes* is normally treated

Tab. 2. Targeted antibiotic treatment of bacterial meningitis

bacteria		standard treatment	alternative treatment	duration of treament (days)
Streptococcus pneumoniae	penicilin sensitive	penicilin or ampicilin	ceftriaxon, cefotaxim, meropenem	7-10
	penicilin resistant	ceftriaxon or cefotaxim	meropenem, chloramfenikol	7-10
	cephalosporin 3rd generation resistant	vankomycin plus rifampicin	meropenem, chloramfenikol	7-10
Neisseria meningitidis	penicilin sensitive	penicilin or ampicilin	ceftriaxon, cefotaxim	7
	penicilin resistant	ceftriaxon or cefotaxim	meropenem, cefepim	7
Listeria monocytogenes		penicilin or ampicilin	kotrimoxazol, meropenem, linezolid	minimally 21
Haemophilus influenzae	ß-laktamase negative	ampicilin	ceftriaxon, cefotaxim, meropenem	7-10
	ß-laktamase positive	ceftriaxon or cefotaxim	meropenem, cefepim, chloramfenikol	7-10
	non-enzymatic resistance to beta-lactams	ceftriaxon or cefotaxim	meropenem, chloramfenikol	7-10
Staphylococcus aureus	meticilin sensitive	oxacilin	vankomycin, linezolid, meropenem	minimally 14
	meticilin resistant	vankomycin	kotrimoxazol, linezolid, daptomycin	minimally14
	vankomycin resistant	linezolid	daptomycin	minimally 14
Streptococcus agalactiae		ampicilin or penicilin	cefotaxim, meropenem	10-14
Enterobacteriaceae		ceftriaxon or cefotaxim	meropenem	21-28

with penicillin, amoxicillin or ampicillin (Tunkel *et al.* 2004). Alternatively, meropenem or linezolid may also be selected.

Oxacillin is mainly used in the treatment of staphylococcal meningitis, and flucloxacillin and nafcillin can also be used. In case of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin, possibly linezolid, are recommended. (van de Beek *et al.* 2016). The antibiotic must be given for at least 14 days. Ceftriaxone or cefotaxime, alternatively meropenem, are used against *Enterobacteriaceae* for 21–28 days. An overview of targeted antibiotic therapy of community-acquired bacterial meningitis in the Czech Republic can be seen in Table 2.

In the case of antibiotics, when the anamnesis of allergies cannot be reliably removed, especially in patients with impaired consciousness, it is always necessary to take into account the possibility of developing an allergic or exacerbated anaphylactic reaction. Of all possible noxious substance, anaphylactic reactions are most often caused by drugs, and the mortality rate is up to 0.76 cases per million population (Cmorej *et al.* 2019). The first aid is 0.5 mg of adrenaline intramuscularly in an adult, 0.3 mg in a child, and an antihistamine and corticosteroid. Adequate infusion therapy of crystalloid solution is also important.

The standard part of pharmacotherapy of bacterial meningitis is the administration of corticosteroids. Dexamethasone has been shown to reduce the incidence and severity of hearing loss and to reduce neurological sequelae. However, it does not reduce mortality in the whole group of bacterial meningitis, this phenomenon was observed only in a subgroup of patients with pneumococcal meningitis (Brouwer *et al.* 2015). It should be administered before or with the first dose of antibiotics to effectively prevent bacteriolysis-induced inflammatory reactions, if possible (Mai *et al.* 2007). Dexamethasone treatment is recommended for adults at a dose of 8-10 mg intravenously after 6 hours for a total of 4 days and for children except neonates at a dose of 0.15 mg / kg at the same intervals and for the total duration.

A dangerous complication of bacterial meningitis is intracranial hypertension. It can often lead to the rapid death of the patient. Hyperosmolar therapy with mannitol or hypertonic saline represents the cornerstone of medical treatment of intracranial hypertension (Schizodimos *et al.* 2020). Mannitol treatment is recommended at a dose 0.25 to 1.0 g / kg intravenously after 6 hours. Intracranial monitoring of intracranial pressure and monitoring of cerebral perfusion are not universally recommended due to the lack of convincing

evidence and the risk of complications but in indicated cases they may be beneficial in guiding antiedematous and sedative treatment.

In bacterial meningitis, neutrophils cope with bacterial infection but also lead to tissue damage. The balance of beneficial and harmful effects may depend on the lifespan of the neutrophils in the central nervous system (Recher *et al.* 2013). Neutrophil extravasation into the central nervous system during pneumococcal meningitis influences the pro-inflammatory response and is central to control of the bacterial load, an increase in which may lead to death (Too *et al.* 2016). The possibility of creating neutrophil extracellular traps, which can have a positive effect on the course of the infection in the early phase, is still being studied. Neutrophil extracellular trap is associated with reactive oxygen species production (Appelgren *et al.* 2020). Also the critical role of metalloproteinases in mechanism of neuronal repair and regeneration has only recently been recognized. Currently the use of metalloproteinase inhibitors is being discussed in the treatment of neuroinfections (Muri *et al.* 2019).

Early and effective treatment of meningitis complications is necessary, which most often include convulsions (17% of cases), hydrocephalus (3–5%), ischemic stroke (14–25%), haemorrhagic stroke (3%), subdural empyema (3%), brain abscess (2%), severe sepsis (15%), or hearing loss in up to 22% of cases (Jim *et al.* 2012, Schut *et al.* 2012, Bodilsen *et al.* 2014). It is estimated that 5–35% of patients with bacterial meningitis develop sensorineural hearing loss and 4% of patients have severe bilateral hearing loss (Worsøe *et al.* 2010). Some of the surviving patients are also affected by cognitive impairment, which, however, improves significantly over time (Hoogman *et al.* 2007).

CONCLUSION

Bacterial meningitis is a serious life-threatening infectious disease of the meninges. Despite significant advances in diagnosis and treatment options, mortality is still relatively high. Permanent consequences are common in surviving patients, sometimes even fully disabling. The main diagnostic method is the examination of cerebrospinal fluid obtained by lumbar puncture. Early initiation of empirical antibiotic therapy and subsequent precise targeting of the confirmed pathogen is crucial. The most common causes of bacterial meningitis are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Listeria monocytogenes*. Based on international recommendations, corticosteroids play a clear role in treatment, with dexamethasone being standard. In most cases, pneumococcal meningitis can be prevented by voluntary vaccination Meningitis caused by the bacterium *Haemophilus influenzae* type b is rather a thing of the past due to widespread vaccination in infancy in our region.

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