MENINGEAL SYNDROME

Dejan Bogdanović, Jelena Miljković, Slaviša Đorđević

HEALTH CENTER LEBANE, DEPARTMENT FOR ADULT HEALTHCARE, LEBANE, SERBIA

Summary: Meningitis is an inflammation of the soft tissues of the brain and spinal cord, which are characterized by the presence of polymorphonuclear leukocytes in the cerebrospinal fluid, and are caused by various bacteria, viruses, parasites, etc. The term meningeal syndrome means that it is an irritation of the meninges (meningism) or an inflammatory process on them (meningitis) and is an indication for a cerebrospinal fluid puncture, which is the only way to distinguish meningism from meningitis. Meningism and meningitis cannot be distinguished from each other based on the clinical picture, because there is no: singular sign that occurs in meningitis, but not in meningism, and vice versa, difference in the intensity of meningeal symptoms in meningitis from that in meningism, condition that can be accompanied by meningitis that cannot be accompanied by meningism.
Key words: meningitis, inflammatory process, brain tumors, meningeal syndrome

INTRODUCTION

Meningitis represents inflammation of the meninges and, more rarely, the brain (meningoencephalitis), characterized by the presence of polymorphonuclear leukocytes in the cerebrospinal fluid (CSF). It is caused by various bacteria, viruses, parasites, and other agents.

The term *meningeal syndrome* refers to irritation of the meninges (*meningism*) or an inflammatory process affecting them (*meningitis*) and indicates the need for cerebrospinal fluid puncture, which is the only method to distinguish meningism from meningitis.

Meningism and meningitis cannot be differentiated based on clinical presentation alone because:

There is no sign present in meningitis that does not occur in meningism, and vice versa,

There is no difference in the intensity of meningeal symptoms in meningitis compared to meningism,

There is no condition that could be accompanied by meningitis but not by meningism.

ETIOLOGY OF MENINGEAL SYNDROME

Meningitis can be caused by infectious agents, allergic reactions, toxic, physical, and chemical noxae.

Bacterial meningitis is caused by pyogenic bacteria: *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus), *Staphylococcus*, *Streptococcus*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Proteus*, etc.

Viral meningitis is caused by poliovirus, ECHO virus, Coxsackie virus, Armstrong virus, mumps virus, herpes zoster, influenza virus, mononucleosis, adenoviruses, and arboviruses.

Spirochetal and rickettsial meningitis are caused by *Leptospira*, *Treponema pallidum* (pale spirochete), and all rickettsial species.

Fungal meningitis is typically caused by *Candida*.

Parasitic meningitis is caused by *Ascaris*, *Trichinella*, and tapeworms.

Meningitis caused by chemical agents occurs due to endogenous toxins (e.g., urea) or inhalation of toxic gases [1].

Bacterial meningitis is the most common form of infectious process affecting the central nervous system (CNS). The incidence ranges from 0.13 to 0.4 per 1,000 live births and is higher in preterm infants, at 1.36–2.5 per 1,000 live births. Predisposing factors include low gestational age, premature rupture of membranes, cesarean section, catheterization, and prolonged rehydration. Meningocele and spina bifida can lead to meningitis through direct infection of the meninges [2].

Scheme 1. Classification of Meningitis Causes [3]

Classification:
Microbial meningitis Viral meningitis Rickettsial meningitis Pararickettsial meningitis Bacterial meningitis Fungal meningitis
Concomitant meningitis Para- and post-infectious meningitis Post-vaccinal meningitis
Toxic-allergic meningitis Meningitis collateralis s. sympathica Meningitis occurring during systemic infections Meningitis toxica (in a strict sense) Meningitis allergica
Irritative meningitis Meningitis after cerebrospinal fluid (CSF) puncture Meningitis following the introduction of heterogeneous substances Meningitis after meningeal hemorrhage Meningitis due to sunstroke Meningitis caused by cerebral foci

The most common causes of neonatal meningitis are Gram-negative bacteria, with *Escherichia coli* (E. coli) being the most significant. Neonatal meningitis occurs in two forms: early neonatal meningitis, caused by Gram-positive cocci, affects 1/3 of affected neonates. *E. coli* may occur sporadically or occasionally as an epidemic in neonatal wards [3]. Other causative agents include *Proteus*, *Pseudomonas aeruginosa*, *Klebsiella*, *Salmonella*, *Streptococcus pneumoniae* (pneumococcus), and *Staphylococcus*, while *Neisseria meningitidis* (meningococcus) and *Listeria monocytogenes* are less frequently isolated. Other bacteria such as *Citrobacter* and *Campylobacter* are rarely encountered [3,4].

PATHOANATOMICAL CHANGES IN MENINGEAL SYNDROME

In purulent meningitis, changes occur in the meninges with the accumulation of purulent exudate in the subarachnoid space and ventricles. This leads to increased intracranial pressure and sometimes to ventricular occlusion, which may cause pyocéphaly. Purulent exudate accumulates at the base of the brain and on the convexities, commonly in pneumococcal meningitis. Inflammation can affect cranial nerves, causing blindness, deafness, or paralysis.

Endotoxin from meningococcus causes thrombosis, hemorrhages, and perivascular infiltrates, leading to degenerative changes in organs and tissues, particularly in the skin, brain, and adrenal glands. Brain edema may occur due to decreased cerebrospinal fluid pH and bacterial toxic factors, resulting in ischemia and altered consciousness. The exudate may organize, forming adhesions that can cause hydrocephalus [5].

PATHOGENESIS OF MENINGEAL SYNDROME

Bacteria such as *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *E. coli* evade the body's defense mechanisms by adhering to mucosal cells. The bacterial capsular polysaccharide prevents phagocytosis, allowing bacteria to avoid the complement system. After surviving in the intravascular space, bacteria enter the subarachnoid space, where the body's defenses are insufficient.

Inflammation in the subarachnoid space leads to increased complement levels in the cerebrospinal fluid, while immunoglobulin concentrations remain low, contributing to the immune deficiency in this space during bacterial meningitis [5].

PATHOPHYSIOLOGY OF MENINGEAL SYNDROME

In experimentally induced infections, subcapsular components of bacteria (cell wall and lipopolysaccharide or endotoxin) are significant determinants of pathogenicity compared to surface components. For example, in the cell wall of *Streptococcus pneumoniae*, two main polymers are present: peptidoglycan and ribitol-phosphate teichoic acid. The former causes inflammation within 24 hours, while the latter does so within 5 hours [5].

Blood-Brain Barrier (BBB) Damage

The blood-brain barrier (BBB) separates cerebrospinal fluid and brain tissue from the intravascular space. The main sites are the arachnoid membrane, the epithelial layer of the choroid plexus, and the endothelium of cerebral capillaries. These capillaries are the primary sites of damage due to the endothelium's unique ultrastructural properties—sparse plasmalemmal vesicles and continuous

intracellular tight junctions, which make them resistant [5,6].

Interaction Between Leukocytes and Endothelial Cells

An essential component of the inflammatory response during bacterial meningitis is the migration of circulating leukocytes, primarily neutrophils, from the bloodstream into the cerebrospinal fluid. This process depends on interactions between endothelial cells and leukocytes.

During acute inflammation, circulating leukocytes are activated by various inflammatory mediators, such as complement components, cytokines, and bacterial lipopolysaccharide. This activation leads to leukocyte sequestration in the microcirculation, partly due to reduced deformability and increased endothelial adhesiveness [5].

Changes in Intracranial Pressure and Cerebral Blood Flow

Intracranial pressure (ICP) is often elevated during bacterial meningitis and may cause cerebral herniation, which is life-threatening. During the early hours of infection, cerebral blood flow (CBF) increases by 100–200%, which, along with brain edema, leads to intracranial hypertension.

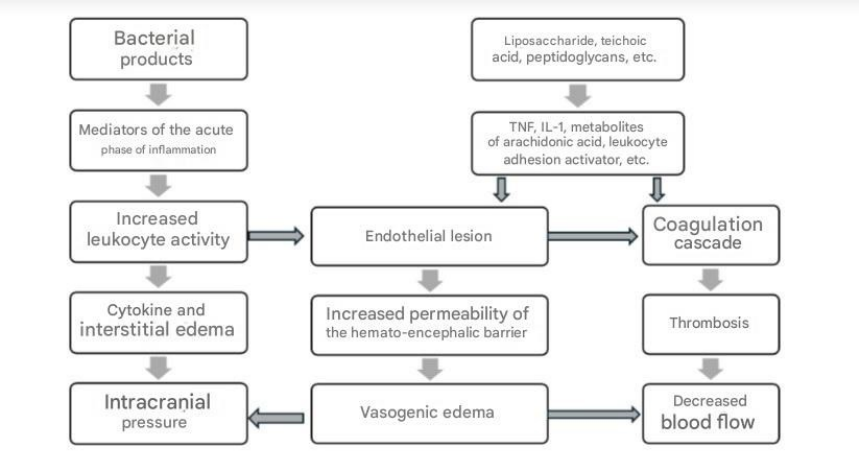
As the infection progresses, cerebral blood flow decreases while ICP continues to rise, and vasculitis develops. In approximately 30% of infants and children with bacterial meningitis, cerebral blood flow is reduced by 30–70%. Factors explaining the association between reduced cerebral blood flow and poor outcomes include inadequate delivery of energy substrates, increased metabolic demands, or inefficient substrate utilization.

Metabolic encephalopathy is believed to result from free radicals, endotoxins, prostaglandins, or other neurotoxins released during infection. Brain edema correlates with the degree of protein in cerebrospinal fluid (proteinorachia) but may also occur due to hyponatremia, which results from inappropriate antidiuretic hormone secretion [5].

Outcome of Bacterial Meningitis

The outcome of bacterial meningitis depends on cerebral perfusion pressure (CPP). The highest morbidity and mortality are observed in children with CPP below 30–50 mmHg.

Image 1. Pathophysiology of Bacterial Meningitis [3]



CLINICAL PICTURE

Meningitis cerebrospinalis epidemica

The clinical manifestations of bacterial meningitis in newborns are not characteristic.

Scheme 2. Symptomatology of Meningitis [2]

Symptomatology
Headache
Signs of irritation of spinal roots Stiff neck Vujić's phenomena: Rotational phenomena of the legs and pronation phenomena of the arms Neck phenomenon (upper Brudzinski's sign) Kernig's sign Collateral phenomenon of the legs (lower Brudzinski's sign)
Signs of irritation of bulbar centers Vomiting Bradycardia Respiratory disturbances
Signs of irritation of the brainstem at the base of the brain (basilar signs) Motor nerve injuries: III - Strabismus, miosis V - Trismus VII - Rictus sardonicus Neuritis of the optic nerve Papilledema
General neurological signs Vasomotor disturbances: Increased dermographism Sensory disturbances: Hyperesthesia Sensory disturbances: Photophobia

Symptomatology of meningitis encompasses three main syndromes: infectious, meningeal, and cerebrospinal fluid (CSF) syndromes.

INFECTIOUS SYNDROME

Initial symptoms include fatigue, general weakness, and anorexia.

MENINGEAL SYNDROME

This syndrome arises due to increased intracranial pressure and develops rapidly (within 1-3 days). Clinical manifestations include:

Headache – Intense and persistent, unrelieved by analgesics. In children, manifests as restlessness, crying, and constant head movement.

Vomiting – No relief after vomiting; referred to as "central vomiting."

Fontanelle tension – Increased intracranial pressure in infants with an open fontanelle.

Meningeal signs – Neck stiffness, Kernig's sign, Brudzinski's sign; reflexes due to pressure on the brain.

Increased sensitivity – Photophobia, hyperacusis, painful palpation of muscles.

Neurovegetative disorders – Cerebral vomiting, bradycardia, constipation, pronounced dermographism.

Altered consciousness – Ranges from drowsiness to coma, caused by fever, inflammation, edema, and intracranial pressure.

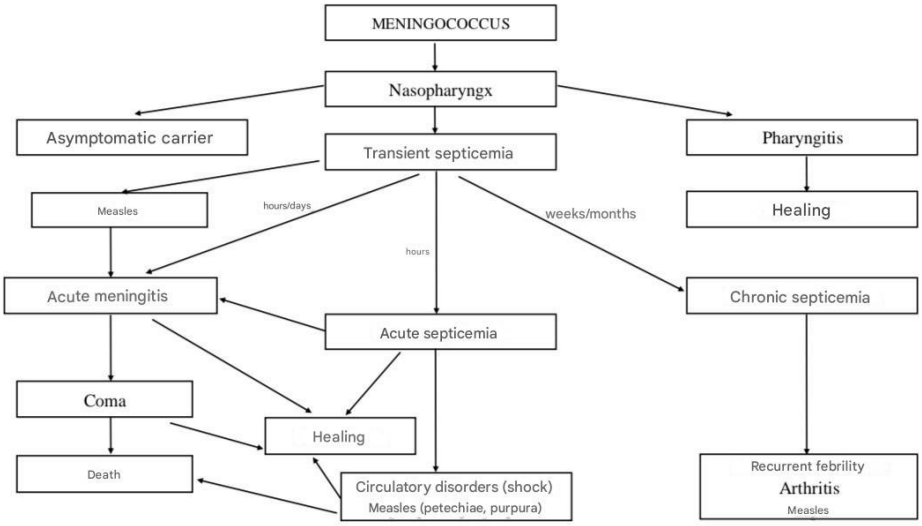
CEREBROSPINAL FLUID (CSF) SYNDROME

This includes changes in CSF accompanying acute leptomeningeal inflammation:

Clear CSF – Normal, as in serous meningitis, with a positive Pandy's reaction.

Cloudy CSF – Indicates purulent meningitis.

Figure 2. Course of Meningococcal Infection [1]



DIAGNOSIS OF MENINGEAL SYNDROME

The diagnosis of neonatal meningitis is established through medical history, clinical examination, and laboratory tests, primarily lumbar puncture. The cerebrospinal fluid (CSF) analysis includes:
White blood cell count in CSF,
Differentiation of cellular elements,
Preliminary protein level determination using Pandy's reagent,
Microscopic examination of Gram-stained CSF,
Microscopic examination of CSF sediment,
Glucose levels in CSF and blood,
Quantitative protein analysis in CSF,
CSF culture.
Other laboratory tests include:
Fundoscopic examination,
EEG,
Brain ultrasound (ECHO),
Stool culture,
Urine culture,
Blood culture,
Throat swab,
Complete blood count,
Erythrocyte sedimentation rate,
Ionogram,
C-reactive protein.
Additional methods such as immunoelectrophoresis, latex agglutination, ELISA test, and Limulus test can also be used. The diagnosis is based on the clinical presentation and CSF findings from lumbar puncture, where the CSF is typically cloudy. The primary method for bacterial detection is the microscopic examination of Gram-stained CSF sediment.

Table 1. Characteristics of Normal Cerebrospinal Fluid and Cerebrospinal Fluid from Patients with Different Types of Meningitis [3]

TYPES OF MENINGITIS				
Characteristics of cerebrospinal fluid	Normal	Bacterial	Viral Leptospirosis	Tuberculous
Appearance	clear	cloudy/purulent	Clear opalescent	Clear opalescent
Leukocyte count in mm3	(<10)	(10-3000)	(10-1000)	(10-1000)
Normal count	0-5	>1000	<200	<200
Type of leukocyte	lymphocytes	polymorphonuclear and (PMN)	lymphocyte (in the initial 10% PMN)	lymphocyte (in the initial 20-30%)
Proteins g/l	0.15-0.4	0,5-5,0+	0.5-1,0	1,0-6,0+
Glucose in mmol/l	2.55-5.5 or 55-60% blood glucose	Very low level (as low as 0)	normal	low level
Gram staining of sediments	no bacteria	+(80%)	no bacteria	+(80%) Ziehl Nielson staining-
Bacterial culture	negative	+ (90%)	negative	+ (85%)

Differential Diagnosis

In the differential diagnosis of bacterial meningitis, the following diseases are considered:
Viral meningitis
Tuberculous meningitis
Leptospirosis meningitis
Fungal meningitis
Parasitic meningitis
Brain abscess
Brain tumor
Ruptured blood vessel
Febrile convulsions, and others

I8. Complications of Meningeal Syndrome

Complications of meningitis may include:
Subdural effusion (fluid accumulation in the subdural space, manifesting with fever, convulsions, somnolence, agitation, tense fontanelle, etc.)
Ventriculitis
Abscess formation or hydrocephalus
Damage to cranial and/or spinal nerves

Prognosis of Bacterial Meningitis

The prognosis of acute bacterial meningitis depends on six key factors: the child's age, type of bacteria, speed of diagnosis, consciousness

level, presence of convulsions, and serious mechanical complications. Pneumococcal meningitis has a higher chance of complications and a higher mortality rate (20%) compared to meningococcal and Haemophilus influenzae meningitis (5-10%). The mortality rate is 40-60% in neonates, while neurological consequences (hydrocephalus, convulsions, psychomotor retardation, etc.) are registered in 31-56% of surviving children.

Viral Meningitis

Etiology

Viral meningitis is most commonly caused by enteroviruses (ECHO and Coxsackie viruses), mumps virus, and less commonly by viruses such as lymphocytic choriomeningitis (LCM), herpes virus, adenovirus, cytomegalovirus, Epstein-Barr virus, Herpes-zoster virus, influenza virus, measles, rubella, and arboviruses. In our country, the most common pathogens are enteroviruses and the mumps virus. Viral meningitis accounts for 60-70% of all meningitis cases. Enteroviruses are transmitted fecal-orally, usually during the summer months, and primarily affect children up to 10 years old. The mumps virus is transmitted by droplets, causing epidemics every 3-4 years, most commonly in children between 5-12 years. Lymphocytic choriomeningitis virus occurs sporadically, mostly in winter months, and is transmitted from rodents. Chronic serous meningitis can also be caused by pale treponema, fungi, parasites, and neoplasms.

2. Pathogenesis and Pathoanatomic Changes

Enteroviruses reach the meninges via viremia, while the mumps virus enters the body through the nasopharyngeal mucosa and then spreads through the bloodstream to the CNS. Pathohistological changes in organs are not well known due to the good prognosis of viral meningitis.

3. Clinical Picture of Viral Meningitis

Symptoms are often milder than those of bacterial meningitis, and the incubation period depends on the virus type. The disease may begin abruptly with symptoms such as headache, chills, malaise, abdominal pain, leg and back pain, vomiting, and fever. Meningeal symptoms like neck stiffness and a positive Kernig's sign are present but less pronounced than in bacterial meningitis. Additionally, enteroviral meningitis may cause lymphadenitis, pharyngitis, conjunctivitis, and rash in children under 3 years old. Mumps meningitis is typically associated with parotitis. In rare cases, convulsions or meningoencephalitis may occur during viral meningitis. Recovery is usually complete, though symptoms may last several weeks.

4. Diagnosis of Viral Meningitis

The diagnosis is based on the clinical picture, epidemiological data, and cerebrospinal fluid (CSF) analysis. The CSF is clear, with leukocyte counts ranging from 100 to 1000 per mm^3, and elevated protein levels are present along with normal glucose levels. Specific findings may include the presence of lymphocytes in the CSF. For etiology diagnosis, virus isolation from CSF, throat swab, or stool, or a rise in antibody titers may be used. Peripheral blood may show leukocytosis with lymphocytosis.

5. Treatment of Viral Meningitis

The treatment is primarily symptomatic, including analgesics, antipyretics, antiemetics, and infusions. Main therapeutic measures include:

Fluid intake: Initial fluid intake should be 800-1000 mL/m^2 body surface area, and it should be gradually increased. If sodium levels are low, diuretics and sodium chloride are used.

Intracranial hypertension treatment: This includes general and specific measures, such as raising the head by 30°, and using mannitol (0.5-2.0 g/kg) to reduce pressure.

Seizure treatment: Diazepam (0.25-0.5 mg/kg i.v.) is used to stop seizures, along with phenytoin or phenobarbital for anticonvulsant effects.

Infants, Toddlers, Preschool and School-Age Children

Etiology and Pathogenesis

Purulent meningitis in children of this age group is usually caused by *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus), and *Haemophilus influenzae*. Less common pathogens include *Staphylococcus aureus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, *Klebsiella*, and others. Meningitis may result from the direct spread of bacteria from nearby inflamed sites, such as otitis, sinusitis, or otitis media. Meningococcus most commonly enters the body via droplets through the nasopharynx, where it may remain latent or cause nasopharyngitis, which spontaneously resolves after a few weeks. In some cases, meningococcus enters the bloodstream and causes bacteremia, which may

progress to meningitis by crossing the blood-brain barrier.

Clinical Picture

Infants: Meningitis may start abruptly with convulsions or coma, although it often begins gradually. The child becomes febrile, lethargic, irritable, refuses to feed, vomits, has diarrhea, and often becomes dehydrated. Neck stiffness may be mild, and hypotonia is common, with the head often falling backward. The key sign is a "tense fontanelle," indicating increased intracranial pressure. Other signs may include vasomotor disturbances like pale or flushed face, spleen swelling, joint swelling, and petechiae.

Preschool and school-age children: Meningitis often begins abruptly with high fever (39-40°C), headache, and vomiting. The headache becomes severe and worsens with head movements. Vomiting is frequent, and the patient complains of malaise, muscle, and joint pain. As the disease progresses, meningeal symptoms appear: neck stiffness, increased sensitivity to light (photophobia), hyperacusia, irritability, and the presence of reflexes such as Kernig's and Brudzinski's signs. In some cases, somnolence, stupor, or coma may develop. Bradycardia, dermographism, and hyperactive tendon reflexes may also be present. If the condition worsens, cranial nerve paralysis or a positive Babinski sign may occur. In 20-30% of cases, febrile herpes appears, which has diagnostic significance in epidemic meningitis.

Diagnosis and Treatment

The diagnosis and treatment of meningitis in this age group depend on the exact identification of the pathogen and prompt initiation of therapy.

1. Therapy for Infants Aged 29 to 60 Days

Due to the unpredictability of bacterial meningitis pathogens in infants of this age, treatment should start with a three-component therapy before the pathogen is identified. The recommended drug combination includes:

Ampicillin – for controlling infections caused by *Listeria monocytogenes* and *Streptococcus agalactiae*

Amikacin – for its effectiveness against gram-negative bacteria

Chloramphenicol – which covers many bacteria, including *Haemophilus influenzae* and *Streptococcus pneumoniae*

This combination provides broad-spectrum protection until the specific pathogen is identified.

Therapy for Infants Over 2 Months, Preschool, and School-Age Children

For children older than 2 months, a combination of penicillin and chloramphenicol is commonly used, while newer cephalosporins are indicated in cases where bacterial resistance is identified (particularly against *Haemophilus influenzae* and *Streptococcus pneumoniae*).

Benzylpenicillin G: 400,000 IU/kg or 10,000,000 IU/m daily, divided into 8-12 doses or continuously via infusion.

Chloramphenicol succinate: 2.5 g/m^2 daily, divided into 4-6 doses.

2. Therapy for Purulent Meningitis

Treatment for purulent meningitis requires immediate administration of antibiotics and symptomatic therapy. Antibiotic therapy should begin immediately after blood and CSF samples are taken.

Meningococcal meningitis: The drug of choice is **Penicillin G**, administered intravenously in infusions, in a dose of 300,000 IU/kg/day divided into 6 doses over 7 days. If resistance or hypersensitivity to penicillin exists, third-generation cephalosporins (e.g., cefotaxime) or chloramphenicol should be used.

Haemophilus influenzae: The preferred treatment for purulent meningitis caused by *H. influenzae* is chloramphenicol, which can be used alone or in combination with ampicillin, at doses of 300-400 mg/kg/day, divided into 4-6 doses for 10-14 days.

Gram-negative bacteria: For meningitis caused by gram-negative bacteria, second-generation cephalosporins are more effective than aminoglycosides or ampicillin.

Symptomatic therapy includes:

Fluid and electrolyte replacement via saline and

Table 2. Antibiotics Most Commonly Used in the Treatment of Neonatal Meningitis [3]

Name of the medicine	T.M.	<2000	T.M.	>2000
	Age from 0-7 days	7 days	0-7 days	7 days
Amikacin	15mg/kg (2)	15-22,5mg/kg (2)	20mg/kg (2)	30mg/kg (3)
Gentamicin	5mg/kg (2)	7,5mg/kg (3)	5mg/kg (2)	7,5mg/kg (3)
Ampicillin	100mg/kg (2)	150mg/kg (3)	150mg/kg (2)	200mg/kg (4)
Penicillin G	100.000ij/kg (2)	150.000ij/kg (3)	150.000ij/kg (3)	200.000ij/kg (4)
Cefotaxime	100mg/kg (2)	150mg/kg (3)	100mg/kg (2)	150mg/kg (3)
Methicillin	100mg/kg (2)	159mg/kg (2)	150mg/kg (3)	200mg/kg (4)
Chloramphenicol	25mg/kg (2)	25-59mg/kg (2)	25mg/kg (1)	50mg/kg (2)

CONCLUSION

Based on the presented facts and data, we can conclude the following:

Purulent meningitis is a disease that is widespread worldwide, occurring sporadically, except when caused by meningococcus, which can appear endemically and epidemically.

Epidemics are usually caused by meningococcus group A, and they most commonly occur at the end of winter and the beginning of spring.

The source of infection is more often a healthy carrier (about 10% of the general population are healthy carriers, and among those who have been in contact with individuals suffering from meningeal meningitis, this percentage is higher, around 25%), and less frequently a patient.

Viral meningitis is usually a disease of school-age children and younger individuals.

Serous meningitis is usually a disease of school-age children and younger individuals.

Tuberculous meningitis always ends in death if treatment is delayed.

Clinical study results have shown that early adjuvant therapy with dexamethasone significantly reduces the frequency of neurological sequelae in affected children.

The most commonly used therapy is penicillin, followed by third-generation cephalosporins or chloramphenicol.

The fatal outcome occurs in 40 to 60% of affected neonates, while neurological sequelae are observed in 31 to 56% of surviving children.

Based on all the above, we can conclude that meningeal syndrome represents a significant practical and theoretical problem that requires extensive epidemiological and clinical investigations.

LITERATURE:

1. Problemi u pedijatriji 2022. Zbornik, Medicinski fakultet Beograd, 2022; 52:76-93.
2. Wadsworth AW, Garvey KL, Goodman DM, Landerdare DS, The Journal of Pediatrics. 2023; 254-260.e1.
3. Kolar J. Neurologija. Stomatološki fakultet u Pančevu. 2021; 10:110-2.
4. Kostić V. Neurology for Medical Students. 2024; 7:120-43.
5. Problemi u pedijatriji 2023.Zbornik, Medicinski fakultet Beograd, 2023; 70:93-110.
6. Božić M. Infektivne bolesti, Naučna knjiga Beograd, 2021; 10:68/13.
7. Ropper A.H, Samuels M.A, Klein J.P., Prasad S. Principles of neurology 12e. Adams and Victor's. 2023.
8. Bašić-Kes V. Hitna stanja u neurologiji. Medicinska – Naklada 2024.