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MENINGOCOCCAL INFECTION IN CHILDREN

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МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
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КАФЕДРА ДЕТСКИХ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ

И. Н. Ластовка, Е. Н. Сергиенко

МЕНИНГОКОККОВАЯ ИНФЕКЦИЯ У ДЕТЕЙ

MENINGOCOCCAL INFECTION IN CHILDREN

Учебно-методическое пособие

Минск БГМУ 2020

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Л26

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Отражены вопросы этиологии, эпидемиологии, патогенеза, клиники, лабораторной диагностики, терапии и профилактики менингококковой инфекций у детей.

Предназначено для студентов 4-го курса медицинского факультета иностранных учащихся по учебной дисциплине «Детские инфекционные болезни», обучающихся на английском языке.

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MOTIVATIONAL CHARACTERISTICS OF THE THEME

Theme: Meningococcal disease.

The duration of the study subjects: 5 hours.

Meningococcal disease produces a considerable global burden of disease. Meningococcal disease, which may present clinically as septicemia, as meningitis, or with a mixed picture, is caused by infection with Neisseria meningitidis (N. meningitidis). Recent advances include greater knowledge about the pathogenesis of meningococcal disease, work to facilitate its early diagnosis, and some evidence of improved outcomes after meningococcal disease. A recent study demonstrated that the carriage prevalence increases throughout childhood from 4.5 % in infants to a peak of 23.7 % in 19-year-old subjects, then decreases to 7.8 % in 50-year-old adults.

Early recognition of children with meningococcal infection is mandatory in order to immediately start systemic antibiotic therapy and avoid death or long-term sequelae. Vaccination represents the best strategy to prevent meningococcal disease.

The purpose of the classes: To explore epidemiology, pathogenesis, the clinical symptoms, differential diagnostic criteria for meningococcal infection, to master the methods of qualitative diagnosis, treatment, and immunization of meningococcal infection in children.

Objectives. ***The student must know***:

– the modern data on the etiology and epidemiological features of meningococcal infection in children;

– the pathogenesis of meningococcal disease;

– the classification of clinical forms of meningococcal infection in children;

– the manifestations of localized forms of meningococcal disease;

– the manifestations of generalized forms of meningococcal infection;

– the complications of meningococcal disease;

– the diagnosis of all forms of meningococcal infection;

– the differential diagnosis of meningococcal disease in children;

– the management principles for infants, children with meningococcal disease;

– the prophylaxis principles of contacts on meningococcal disease;

– the vaccination principles of meningococcal disease.

The student should be able to:

– collect complaints, anamnesis of disease and life;

– carry out a systematic clinical examination of the child with infectious diseases with hyperthermia;

– carry out a systematic clinical examination of the child with infectious diseases with rash;

– carry out a systematic clinical examination of the child with infectious diseases with symptoms of meningitis;

– establish a preliminary (working) diagnosis;

– make a plan for examination of a child with meningococcal disease;

– the methods for differential diagnosis of infectious and non-infectious diseases of the central nervous system in children by the leading syndrome;

– evaluate the results of the laboratory and instrumental examinations;

– draw the medical documentation at meningococcal infection in children on the stages of identification, treatment and dispensary observation;

– make a plan of the treatment according to the severity of the disease, the timing of the disease, the course and age.

The student must master the skills:

– learn to estimate the epidemic situation of meningococcal disease;

– learn to detect of clinical symptoms with an emphasis severe forms of infections;

– learn to estimate the degree of severity of the condition of patients with meningococcal disease;

– learn the complex argumentation of the final diagnosis;

– learn to identify indications for isolation, hospitalization, the intensive care unit.

Requirements to initial level of knowledge. Student must repeat from:

– human anatomy — anatomical and physiological features of nervous system in children;

– microbiology and immunology — properties and structural features of N. meningitidis; bases of formation of immunity;

– pathological physiology — basic pathogenesis of meningococcal disease;

– epidemiology — epidemiology features of meningococcal disease;

– infectious diseases — the main diagnostic methods meningococcal infections;

– childhood diseases — differential diagnosis of the clinical manifestations of infectious and somatic diseases in children.

Control questions from the related disciplines:

1. What are the features of bacteria N. meningitides?
2. The structure of the brain. What is the blood-brain barrier?
3. Cerebrospinal fluid: formation, circulation, research methods.
4. How much do you know the degrees of impaired consciousness and their clinical symptoms?
5. What are the main links in the pathogenesis septic shock development mechanism?

Control questions of the classes:

1. What are the features of bacteria N. meningitidis?

2. Describe the epidemiology of meningococcal disease: the source of infection, route of transmission, receptive contingent.

3. What are the mechanisms of development of meningococcal infections?

4. What is the clinical classification of meningococcal disease?

5. Describe the clinical manifestations of localized forms of meningococcal disease.

6. Describe the clinical manifestations of meningococcemia.

7. Describe the clinical manifestations of fulminate meningococcemia.

8. Describe the clinical manifestations of meningococcal meningitis and meningoencephalitis.

9. What do you know about other manifestations of meningococcal disease (meningitis with syndrome of ependimatitis (ventriculitis), chronic meningococcemia, rare forms of meningococcal infection)?

10. The causes of the development and character of complications on meningococcal infection.

11. What the laboratory tests are used at meningococcal disease?

12. What are the indications for hospitalization and prognosis of meningococcal infection?

13. The principles of therapy of meningococcal disease.

14. Recommended chemoprophylaxis regimens for high-risk contacts and persons with invasive meningococcal disease.

15. Specific prevention of meningococcal infection.

INTRODUCTION

The bacterium, meningococcus, recently called Neisseria meningitidis (N. meningitidis), is an exclusively human-encapsulated Gram-negative diplococcus. It colonizes the human nasopharynx (termed nasopharyngeal carriage) and mostly affects children and young people with high mortalities. N. meningitidis was first discovered in 1887 by Weichselbaum from analyzing the cerebrospinal fluid (CSF) of a patient infected with meningitis. It is a human-specific bacterium that causes a multitude of illnesses, collectively termed meningococcal disease. Surprisingly, up to 10 % of the general population carry the bacteria in their nose and throat without any adverse effects. N. meningitidis is associated with many infections. However, its association with fulminant meningococcemia and meningococcal meningitis is what has led to its significant impact. Invasive strains of N. meningitidis may invade across the mucosal surface entering the bloodstream and invading the blood-brain barrier, causing septicemia and meningitis, also called invasive meningococcal disease (IMD). In addition to meningitis and septicemia (meningococcemia), IMD is responsible for a spectrum of infections such as pneumonia, and more

rarely septic arthritis and pericarditis. It also may be associated with long-term sequelae and lifelong morbidity, including limb loss, neurologic impairment, allergic complications, hearing loss, and even death.

ETIOLOGY

N. meningitidis is an anaerobic, Gram-negative diplococcus that exclusively infects humans. There are at least 13 serogroups on the basis of the immunochemistry of their capsular polysaccharides; however, only five serogroups (A, B, C, W-135, Y, and X) are responsible for most IMD cases around the world.

The serogroups causing IMD vary geographically, mostly likely due to differences in population immunity and environmental factors. Meningococcus serogroup A (MenA) occurs in Africa and some areas of Asia, whereas serogroups B (MenB), C (MenC) and Y (MenY) are predominant in the other continents, including Europe and North America. In the 13 countries included in the African «meningitis belt», MenA was responsible for the majority of cases in 2007–2009, while meningococcus serogroup W135 (MenW135) predominated in 2010 and 2011. Serotype W is the cause of epidemic outbreaks around the world and had an association with the Hajj pilgrimages to Saudi Arabia. Although MenC is rare in Africa, in 2013 and 2014 two outbreaks due to a novel strain of MenC were reported in Nigeria and Kebbi, respectively. Moreover, during 2006–2010 outbreaks of MenX were described in Niger, Togo, Kenya, Uganda, and Burkina Faso. In Europe, MenB is the main cause of IMD, followed by MenC and MenY. In countries with established MenC vaccination programs, the incidence of MenC disease has significantly declined. In comparison with the US, IMD caused by MenY is rare in Europe. However, an increase in this serogroup has been reported in recent years, particularly in the Nordic European countries.

It is a devastating infection with high mortality if not recognized, and treatment started promptly. Other infections that N. meningitidis can cause are meningococcemia (defined as a blood infection due to N. meningitidis), pneumonia, septic arthritis, pericarditis, and urethritis. N. meningitidis can also cause both endemic and epidemic infections and can even infect young, healthy adults.

EPIDEMIOLOGY

The highest incidence of meningococcal disease appears in infants less than 1-year-old at 5,38 cases per 100 000. It can cause endemic and epidemic outbreaks and is a significant cause of bacterial meningitis in sub-Saharan Africa, which has even lead to the region being called the «meningitis belt». Mortality rate range

from approximately 10 to 14 % of patients who receive treatment and up to 50 % in those that don't. The incidence of meningococcal disease has declined with routine use of meningococcal vaccination, starting in adolescents with an estimated 1,2 million cases per year. For example, in the United States, the incidence of meningococcal disease is less than 1 case per 100000 per year, with the highest infection rates in February through March.

PATHOGENESIS

Humans are the only natural host to carry N. meningitidis and do so in their nasopharynx before systemic infection. Humans so colonized may be asymptomatic carriers. Colonizing the nasopharynx puts close contacts, such as family members, college roommates, and military recruits at an increased risk of contracting N. meningitidis and possible infection. Those involved in laboratory or medical care exposure, such as intubating an infected patient with no face shield or mask, are also at increased risk. N. meningitidis colonization of the nasopharynx via inhalation of aerosolized particles containing the bacteria. The incubation period varies and ranges from 1 to 14 days.

Once colonized, it possesses several virulence factors that aid in its invasion and infection of humans: capsule, pili, opacity proteins, meningococcal serine protease A (MspA), lipooligosaccharide (LOS), and human factor H-binding protein. Although N. meningitidis may or may not have a capsule, systemic infection isolates are invariably capsulated, aiding in surviving the immune response. The pili are considered a primary adhesion factor and have high tropism to the nasopharyngeal epithelium and to increased rates of meningitis and septicemia. Opacity proteins, Opa and Opc, also facilitate adhesion to and invasion via receptors found on human epithelial cells, endothelial cells, and cells belonging to the immune system. MspA may also aid epithelial and endothelial cell binding. After N. meningitidis invades the bloodstream, it activates and produces a robust immune response. LOS is an essential component for eliciting the immune response, and via cytokine release leads to endothelial damage, capillary leakage, tissue necrosis, organ failure, and meningococcal sepsis. Meningococcal LOS interacts with human cells, resulting in the production of proinflammatory cytokines and chemokines, including interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF), that are important in the pathogenesis of meningococcal disease. Human factor H-binding proteins also aid in surviving a strong immune response by binding human factor H and negatively regulating the complement pathway of the immune system. The invasion of the bloodstream is thought to be the primary route to the brain but can also cross the cribriform plate of the ethmoid bone.

Bacterial meningitis is the leading cause of central nervous system (CNS) infection. The blood–brain barrier (BBB) protects the CNS from most bacteria that may have reached the bloodstream. Most of the few types of bacteria, which can cross BBB to invade the meninges, are extracellular pathogens: Escherichia coli and Streptococcus agalactiae (Group B Streptococcus) in the newborn, N. meningitidis, Haemophilus influenza type b, and Streptococcus pneumonia in children and adults. Once inside the cerebrospinal fluid (CSF), bacterial multiplication is thought to be uncontrolled, owing to the local deficiency in complement and immunoglobulins, and despite the influx of polymorphonuclear leukocytes induced by the local inflammatory response. The small number of bacterial species capable of invading the meninges suggests that specific virulence factors are required for bacteria to enter the subarachnoidal space. Among the above-mentioned extracellular bacteria, N. meningitidis is the pathogen that once in the bloodstream, is able to invade the meninges the most effectively. It has been estimated that 63 % of the cases of bacteremia owing to N. meningitidis are associated with meningitis.

CLINICAL MANIFESTATIONS

The clinical features of meningococcemia are dependent on bacterial load. A low level of bacteremia is likely to be associated with limited vascular colonization and few purpuric lesions. Some colonies in the brain capillaries may breach the blood–brain barrier and proliferate into the central nervous system (CNS). Thus, few colonies are sufficient to induce meningitis. On the other hand, high bacteremia is associated with an important colonization of the peripheral blood vessels that results in a fast and strong vascular leakage.

In purpuric lesions, endothelial cell retraction is observed at the site of bacterial endothelial cells interaction, associated with a loss of the integrity of the capillary resulting in an increase in permeability, hemorrhages, leukocyte aggregation and formation of thrombi hemorrhages, and adhesion of leukocytes. The colonization of a large number of vessels by a high number of bacteria as those seen in purpura fulminans and the consequences of the corresponding signaling may explain the extensive purpuric lesions and thrombosis as well as the loss of vascular integrity responsible for the severity of the shock.

The spectrum of clinical manifestations of infection with N. meningitidis ranges from asymptomatic carriage, the most common form of infection, to death within hours with fulminant meningococcal septicemia (meningococcemia). Meningococcal meningitis and septicemia are the most frequently reported clinical syndromes associated with N. meningitidis.

Clinical forms:

1. Primarily localized forms of Meningococcal Disease:
a) meningococcal carrier state;
b) acute nasopharyngitis
2. Generalized forms:
a) meningococcemia: typical, acute meningococcal sepsis; chronic;
b) meningitis; meningoencephalitis;
c) mixed forms (meningococcemia + meningitis, meningoencephalitis);
d) rare forms (pneumonia, endocarditis, arthritis, iridocyclitis).

Localized forms of meningococcal disease

N. meningitidis is an important cause of meningitis and septicaemia, but most infected individuals experience a period of asymptomatic carriage rather than disease. Historically, carriage of the bacterium was estimated to occur in approximately 10 % of the general population, with most people becoming a carrier multiple times in their lifetime. Since N. meningitidis is a strict human pathogen and most patients have not been in contact with other cases, asymptomatic carriers are presumably the major source of the pathogenic strains. Carriage itself can be an immunizing process resulting in systemic protective antibody responses. A meta-analysis of 89 studies from across the world published in 2010 in the Lancet showed that carriage is lowest in infancy (4,5 %) but then increases through childhood to a peak in late adolescence (27,7 % at 19 years). The rates of carriage then reduce again throughout adulthood.

The most common complains of the patients are headache, mainly in the frontal-parietal region, sore throat, dry cough, blocked nose, fatigue, weakness, loss of the appetite, violation of the sleep. In the most of the patient's body temperature rises up to subfebrile and lasts for not more than 3–7 days. The skin is pale, conjunctival vessels and sclera are injected. There are hyperemia and edema of the mucous membrane of the nose. The follicles of the posterior pharyngeal wall are hypertrophied. In many patients the posterior wall of the pharynx is covered by mucous or mucous — purulent exudation. In the peripheral blood moderate leukocytosis with neutrophylosis and a shift of leukocyte formula to the left. Nasopharyngitis often precedes the development of generalized forms of the disease.

Generalized forms of meningococcal infection

Generalized (invasive) meningococcal disease describes the process when the bacteria N. meningitidis crosses from the respiratory mucosa and invade the host. In most people carriage is asymptomatic but in a minority the bacteria cross

the mucosa and enter the blood. Once the N. meningitidis bacteria cross from the nasopharynx to the blood, it multiples rapidly with resultant bacteraemia and an associated cytokine storm. This leads to increased host vascular permeability, organ dysfunction and disseminated intravascular coagulation. The bacteria may also cross the BBB resulting in meningitis. Part of the clinical challenge in diagnosing meningococcal disease is the varied and often non-specific ways it can present. This is exemplified by studies suggesting that half of meningococcal disease is not recognised at initial presentation.

The most common clinical manifestations of meningococcal infection are meningitis and septicemia, although in some cases both clinical pictures are present. However, signs and symptoms at the onset of the disease, such as coryza and sore throat, may resemble those of common respiratory viral infections. The incubation period varies from 1 to 14 days, although it usually lasts less than 2 days.

The current UK standard of care is the National Institute for Health and Care Excellence (NICE) guideline «Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management clinical guideline [CG102] ». Symptoms described in the NICE guidance such as lethargy, irritability and poor feeding are likely to feature in any child who is unwell, while others such as coryzal symptoms, nausea and vomiting and abdominal pain could lead a clinician to consider other potential viral or bacterial infections rather than meningococcal disease. The vague nature of these symptoms means any clinician ought to consider the possibility of meningococcal disease when assessing any unwell child. It is also important to appreciate that many of these symptoms should also raise suspicion of possible early sepsis. In the NICE guidance there are 31 potential symptoms and signs of meningococcal infection. These are divided into common and non-specific signs, less common and non-specific signs and more specific signs, table 1.

Table 1

Symptoms and signs of invasive meningococcal disease (NICE CG102)

Non-specific signs	Specific signs (sepsis)	Specific signs (meningitis)
Abdominal pain	Purpura	Headache
Nausea and vomiting	Non-blanching rash	Reduced GCS
Diarrhoea	Reduced Glasgow Coma Scale (GCS)	Neck stiffness
Lethargy	Myalgia	Photophobia
Irritable	Cold extremities	Seizure
Coryzal symptoms	Tachycardia	Neurological deficit
Fever	Ill appearance	
Tachypnoea	Pallor	
Sore throat	Shock	
Refusing food/drink	Leg pain	

Risk Factors for invasive Meningococcal Disease (Long, Sarah S et al., 2012):

– Lack of bactericidal antibody to acquired strain;
– Age < 1 year or 15–24 years of age;
– Crowded living conditions/close contact (poor housing, military barracks, students in dormitories);
– Cigarette smoking, active or passive;
– Prior viral respiratory infection (especially influenza);
– Inherited properdin or factor D deficiency;
– Inherited terminal complement component deficiency (C5–C9);
– Family/household contact of person with meningococcal disease.
– Meningococcemia.

The incubation period varies from 1 to 14 days, although it usually lasts less than 2 days. In initial stage of meningococcal infection signs of septicaemia and circulatory shut-down were next to develop: approximately 72 % of children had limb pain, cold hands and feet, or pale or mottled skin at a median time of 8 hours from onset of illness. Parents of younger children also reported drowsiness, rapid or labored breathing, and sometimes diarrhoea. Thirst was reported in older children. A subsequent MRF-funded study 10 found limb pain to be highly specific and cold hands / feet moderately specific to meningococcal disease. Pallor was frequently found in children with minor infections, and was not a discriminating symptom for meningococcal disease.

The classic features of meningococcal sepsis are fever and a non-blanching rash, which appear at 8-9 hours (median time) in an ill child, fig. 1.

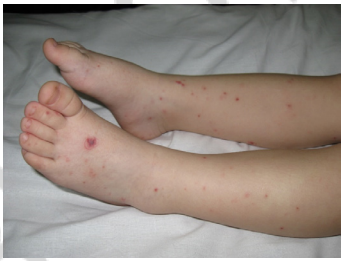

Fig. 1. Meningococcemia: petechial, purpuric elements of rash

Support literature promotes the «tumbler test» to parents as a way of confirming the non-blanching nature of the rash. If the non-blanching rash is purpuric (more than 2 mm diameter) in an ill, febrile child then meningococcal disease is very likely. Up to 11 % of children with an exclusively petechial rash will have meningococcal disease; most of the rest have viral infections. The classic features may be preceded by viral infection-like non-specific symptoms. In the early stag-

es the rash may be blanching and maculopapular, but it nearly always develops into a non-blanching red or brownish petechial rash or purpura. Isolated pinprick spots may appear where the rash is mainly maculopapular, so examining the whole skin surface is worthwhile Up to 30 % of children with meningococcal disease may present with a non-specific maculopapular rash, although most will have non-blanching elements. Differentiating the non-blanching rash of meningococcal disease from viral rashes is almost impossible.

Fulminate meningococcemia (acutest meningococcal sepsis, Waterhause-Friedrichsen syndrome). It is the most severe, unfavorable form of meningococcal infection. Its base is infectious-toxic shock. The NICE Guideline on Bacterial Meningitis and Meningococcal Septicaemia identified recognizing shock as one of the key priorities for implementation. Early signs of circulatory shutdown and shock include pale or mottled skin, and cold hands and feet due to vasoconstriction and prolonged capillary refill, tachycardia, and fast or labored breathing.

Check capillary refill by pressing for 5 seconds on the big toe or a finger, or on the sternum, and count the seconds it takes for colour to return. Consider meningococcal septicaemia and shock if capillary refill time > 2 seconds, especially if heart and respiratory rate are raised. Check oxygen saturation (if pulse oximeter is available): normal value is >95 % in air. Hypotension is an important sign in adults, but it is a late and ominous sign in children, which limits its diagnostic value. Children and adolescents can compensate for shock and maintain normal blood pressure until septicaemia is far advanced. In conjunction with other signs, postural hypotension in adults may suggest shock. In infectious-toxic shock the development of thrombosis, hemorrhages, necrosis in different organs are observed even in the adrenal glands (Waterhause – Fridrechsen syndrome), fig. 2.

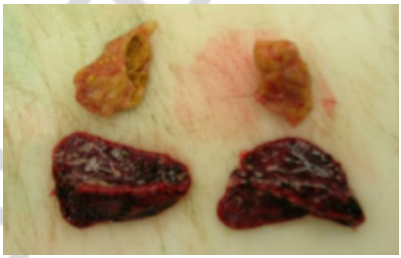

Fig. 2. Normal (top) and hemorrhagic (bottom) adrenal glands

Meningococcal meningitis and meningoencephalitis. It may start after meningococcal nasopharyngitis, but sometimes primary symptoms of the disease arise suddenly. In meningitis three symptoms are revealed constantly: fever, headache and vomiting. Temperature increases quickly with chill and may reach 40-41°C during few hours. Intermittent, remittent, constant, double waved types of the

temperature occur in meningitis. The patients suffer from severe headache, having diffuse or pulsatory character. Headache is very intensive at night. It increases due to change of body position, sharp sounds, bright light. Vomiting arises without precedent nausea. There is no connection with food and relief after vomiting. It is rule abundant, like «fountain», repeated. Vomiting arises on the peak of headache.

In meningitis hyperthermia, hyperkynesia, photophobia, hyperalgesia, hyperosmia are noticed. These symptoms are revealed more frequently in children. The severe convulsions arise in the many patients at the first hours of the disease (clonic, tonic or mixed types). In small children meningococcal meningitis may start with convulsions. The disorders of consciousness occupy the great place in clinical picture (from sopor till coma). The loss of consciousness develops after psychomotoric excitement. The loss of consciousness at the first hours of the disease is unfa vorable sign. During objective examination meningeal symptoms stand at the first place. It is described near 30 meningeal signs. A few meningeal signs are used in practice: rigidity of occipital muscles, Kernig's symptom, Brudzinsky's symptom (upper, middle and lower). The estimate of state of fontanelle is very important in infants. There are three symptoms of meningitis in infant: swelling, tension and fontanelles pulsation. There is no accordance between expression of meningeal syndrome and severity of the disease. The expression of different symptoms is no similar at the same patient. The patient has compulsory pose during serious cases. He lays on side with deflection of the head backwards. The legs are curved in knee-joint and pelvic-femoral joint. The legs are pulled to abdomen. Asymmetry and increased tendinous, periostal and dermal reflexes are observed in the patients. These reflexes may be decreased during expressive intoxication. Pathological reflexes may be revealed (such as Babinski's, Hordon's, Rossolimo's reflexes, foot's clones), and also symptoms of damage cranial nervous (more frequently III, VI, VII, VIII pairs).

The multiple symptoms of the lesion of the other organs and systems are connected with intoxication. There is tachycardia at the first hours of the disease. Then it may be bradycardia. Arrhythmia, tachypnoea (30–40 per minute) are possible. The tongue is covered by dirty brownish coat. It is dry. Abdomen is pulled inside. There is tension of abdomen muscles. The external appearance of the patients is very typical. There is hyperemia of the face and neck. Sclera's vessels are injected.

Fulminate course of meningitis with syndrome of brain's swelling and edema is the most unfavorable variant. There is hypertoxicosis during this form and high percentage of mortality. The main symptoms are consequence of inclination of the brain into foramen magnum and strangulation of medulla oblongata by tonsils of cerebellum. Symptoms of cardiovascular and respiratory systems failure develop rapidly. Bradycardia appears. Then it is changed by tachycardia. Arterial pressure may fall catastrophically, but it increases more frequently till high level. Tachypnoea arises with help of axillary muscles. The disorders of breath lead to its sudden interruption. These symptoms develop in hyperthermia, clonic cramps

and loss of consciousness. Cyanosis of the skin, hyperemia of the face are marked. Pyramidal signs, sometimes symptoms of damage of cranial nerves, decreased corneal reflexes contraction of pupils and its decreased reaction on light are determined. Death occurs due to respiratory failure at the first hours of the disease, rarely on 2–3 day or on 5–7 day.

Meningitis with syndrome of ependimatitis (ventriculitis). Now it is rare form of meningitis. This form develops during late or insufficient treatment of the patients. Especial severity of the disease is connected with spread of inflammation on ventricles membranes (ependime) and involvement of brain's substance in to pathological process. The principal clinical symptoms are total and expressive muscular rigidity. The patients accept the particular pose. The disorder of psychic, sleeping, tonic and clonic cramps are observed. The body temperature is normal or subfebrile during general severe state of the patient. Vomiting is constant symptom. Hydrocephalia and cachexia develop due to prolonged course and/or noneffective therapy of ependimatitis.

Meningoencephalitis. It is rare form of meningococcal infection. In this case the symptoms of encephalitis predominate, but meningeal syndrome is weakly expressed. Meningococcal encephalitis is characterized by rapid onset and impetuous cramps, pareses and paralyses. Prognosis is unfavorable. The mortality is high and recovery is incomplete even in modern conditions.

Chronic meningococcemia. This form of meningococcal infection is rare. The duration of the disease is from some weeks till some years. One case was described with duration of meningococcemia during 25 years. Fever is usually intermittent. The disease is accompanied by polymorphic exudative erythema. The temperature may be normal during period of the remission. Rash becomes pale. It may disappear. The patient's state is improved. In chronic meningococcemia arthritis and polyarthritis are possible. Splenomegaly is revealed inrarely. In the peripheral blood leukocytosis, neuthrophylosis, increased ESR are marked. There is temperate proteinuria in urine. Endocarditis (pancarditis) were described in chronic meningococcemia. It is possible the development of meningitis after some weeks or month from the onset of the disease.

Rare forms of meningococcal infection (arthritis, polyarthritis, pneumonia, iridocyclitis). These forms are consequence of meningococcemia. Prognosis is favorable in opportune and sufficient therapy.

COMPLICATIONS OF MENINGOCOCCAL DISEASE

A myriad of long-term complications are associated with IMD, some of which are irreversible and disabling. Sequelae occur in 11–19 % of surviving IMD patients, and the most frequently reported conditions are chronic pain, skin

scarring, and neurologic impairment. Other common complications include hearing impairment, visual impairment, motor defects, behavioral problems, and seizures. Other less frequent complications include septic arthritis, conjunctivitis, and chronic meningococcemia. Hearing loss and amputations occur in approximately 3 % of IMD cases.

Careful follow-up of patients with IMD should be routine. Hearing tests are recommended within 4 weeks of hospital discharge. Orthopedic complications may be reported several years after the acute infection due to bone growth plate abnormalities and may need complex orthopedic procedures. Multidisciplinary team involvement for amputation, limb-fitting, and rehabilitation are required in patients who suffer amputation. More recently psychological and psychiatric complications of IMD have become increasingly recognized in up to one third of survivors. These include post-traumatic stress disorder, anxiety, depression, and behavioral/educational abnormalities. Management may require psychiatric and psychological follow-up and intervention. Post-infectious inflammatory syndrome occurs in approximately 6–15 % of individuals with IMD typically within 4–12 days of IMD onset.

Meningococcal arthritis occurs primarily in adults. The overall incidence, as acomplication of bacteremia, is about 2 to 10 %. There are two forms of meningococcal arthritis. The first is seen within the first few days of treatment and is characterized by severe arthralgias and few objective signs of joint inflammation. The second, more common form appears to be a hypersensitivity phenomenon. It is usually noted three to seven days after the recognition of meningococcemia, often at a time when the patient appears to be improving from the meningitis or sepsis. The knee, wrist, elbow, and ankle joints are most commonly involved.

Pericarditis, as a complication of meningococcal disease, occurs in 3 to 5 % of cases. It generally occurs in a patient with meningococcemia but has been reported as an isolated event without septicemia or meningitis. Pericarditis is presumed to be a late complication of meningococcal disease, since clinical symptoms such as fever, dyspnea, or substernal chest pain (or even cardiac tamponade) usually do not appear until the fourth to the seventh day of illness. Myocarditis was noted at autopsy in 78 % of patients with fatal meningococcal disease. Myocarditis was noted most often in adults, and was more severe than in children.

Numerous other complications include cranial nerve palsies, radiculitis, hemiplegia, seizure disorders, ophthalmic complications, associated herpetic lesions (developing on four or five day of disease), hydrocephalus and arachnoiditis.

Orchitis, epididymitis and salpingitis are rare complications.

Usually, treatment of these post-infectious complications requires symptomatic treatment with antipyretics or nonsteroidal antiinflammatory agents. However, once ongoing infection has been excluded, steroid treatment may be required, and theprognosis of these complications is excellent.

DIAGNOSIS

The diagnosis of all forms of meningococcal infection is based on the complex of epidemiological and clinical data. The final diagnosis is established with help of the laboratory examination. Separate methods have different diagnostical significance in various clinical forms of meningococcal infections. The diagnosis of meningococcal carrier is possible only by use of bacteriological method. The material for analysis is the mucus from proximal portions of upper respiratory tract. In diagnostics of meningococcal nasopharyngitis epidemiological and bacteriological methods occupy the main place. Clinical differention of meningococcal nasopharyngitis from nasopharyngitis of the other genesis is not possible or very difficult.

If a child or young person has an unexplained petechial rash and fever (or history of fever) carry out the following investigations:

- full blood count;
- C-reactive protein (CRP);
- coagulation screen;
- blood culture;
- whole-blood polymerase chain reaction (PCR) for N. meningitides;
- blood glucose;
- blood gas.

In children and young people with suspected bacterial meningitis, perform a CRP and white blood cell count:

– If the CRP and/or white blood cell count is raised and there is a non-specifically abnormal cerebrospinal fluid (CSF) (for example consistent with viral meningitis), treat as bacterial meningitis.

– Be aware that a normal CRP and white blood cell count does not rule out bacterial meningitis.

– Regardless of the CRP and white blood cell count, if no CSF is available for examination or if the CSF findings are uninterpretable, manage as if the diagnosis of meningitis is confirmed.

– Procalcitonin (PCT) is to distinguish sepsis from other inflammatory and non-inflammatory states or to predict outcomes.

In recognition of generalized forms, anamnestic and clinical methods of diagnostics have real diagnostic significance, mainly in case of combination of meningococcemia and meningitis. The examination of cerebrospinal fluid (CSF) has great meaning in diagnostics of meningitis. In lumbar punction cerebrospinal fluid flows out under high pressure and by frequent drops. The cerebrospinal fluid may flow out by rare drops only due to increased viscosity of purulent exudation or partial blockade of liquor's ways. Cerebrospinal fluid is opalescent at the initial stages of the disease. Then it is turbid, purulent, sometimes with greenish shade. Pleocytosis achieves up $10–30 \cdot 10^3$ in 1 mcL. Neuthrophils leukocytes predomi-

nate in cytogram. Neuthrophilous compose 60–100 % of all cells. In microscopy neuthrophils cover intirely all fields of vision, inrarely. Quantity of protein of cerebrospinal fluid increases (till 0.66–3.0 gm/L). There is positive Nonne-Appelt's reaction. The reaction of Pandy composed (+++). Concentration of glucose and chlorides are usually decreased. In generalized forms the final diagnosis is confirmed by bacteriological method. In diagnostics immunological methods are used too. Reactions of hemagglutination, latex agglutination are more sensitive.

Serology. Serum antibody tests for the diagnosis of IMD are not routinely available, but are performed in some laboratories. Serological diagnosis is based on the demonstration of a single elevated level of IgM antibody or seroconversion to outer membrane protein (OMP) antigens. As the OMP antigens amongst the Neisseria genus cross-react, the test may be positive in disseminated gonococcal infection. An assay to detect IgM antibody to serogroup C capsule is also available and will detect an antibody response to recent C capsule vaccination or invasive infection with serogroup C N. meningitidis. Serological diagnosis is retrospective but may be useful in circumstances where IMD was suspected clinically and when other tests were negative or not performed; it is not recommended for clinical diagnosis of acute cases.

Strain differentiation. Strain differentiation or typing can assist in establishing linkages between cases or cases and carriers that are identified epidemiologically. Laboratory typing results can exclude true relatedness of apparently linked cases if they emerge as being distinct. Also, if the method used is highly discriminating and the prevalence of particular types is taken into account, detection of indistinguishable case isolates can provide quite strong evidence of relatedness.

Genotyping (molecular) techniques are now used by most state laboratories to type strains in addition to serotyping. Techniques available include pulsed-field gel electrophoresis (PFGE), porA/porB, or fetA sequencing and multi-locus sequence typing (MLST). Whole genome sequencing, where available, can also be used to establish strain relatedness of cases and guide public health interventions.

DIFFERENTIAL DIAGNOSIS

In meningococcemia the presence of rash requires of differential diagnostics with measles, scarlet fever, rubella, diseases of the blood (thrombocytopenic purpura, Werlgoff's disease, hemorrhagic vasculitis — Sheinlein-Henoch's disease). Sometimes it is necessary to exclude epidemic typhus, grippe, hemorrhagic fevers.

It is necessary to differentiate meningococcal meningitis with extensive group of the diseases:

1. Infectious and noninfectious diseases with meningeal syndrome but without organic damage of central nervous system (meningism or meningismus).

Meningism may be in influenza, acute shigellosis, uremia, lobar pneumonia, toxical food-borne infectious, typhoid fever, epidemic typhus, infectious mononucleosis, pielitis, middle otitis.

2. Diseases with organic damage of central nervous system, but without meningitis (brain abscess, tetanus, subarachnoid hemorrhage).

3. Meningitis of other etiology. In purulent meningitides etiological factors may be pneumococci, staphylococci, streptococci, Bacterium coli, salmonella, fungi, Haemophilus influenzae. In purulent meningitis of nonmeningococcal etiology it is necessary to reveal primary purulent focus (pneumonia, purulent processes on the skin, otitis, sinusitis, osteomyelitis).

TREATMENT

Treatment guidelines have been developed over many years. These are regularly updated and are useful reminders of the management principles for infants, children, and young adults with meningococcal septicemia and meningitis, leading to substantial improvements in mortality. Recognition and management of shock and/or raised ICP is the priority in effective treatment of IMD. Early and aggressive fluid resuscitation is associated with improved survival in pediatric septic shock. In the absence of shock, ICP can be treated with osmotherapy to reduce cerebral edema and improve brain perfusion.

The priority in management of meningococcal disease is treatment of shock in meningococcemia and of raised intracranial pressure in severe cases of meningitis, fig. 3. Fluid replacement should be administered initially as 0.9 % sodium chloride solution in a volume of 20 mL/kg over 5 to 10 minutes and repeated until shock improves (reduction in heart rate and increased tissue perfusion). Empirical therapy for suspected meningococcal disease should include an extended spectrum cephalosporin, such as cefotaxime or ceftriaxone:

– Cefotaxime (200 mg/kg per day, maximum 8 g/day, in 4 divided doses, intravenous);

– Ceftriaxone (100 mg/kg per day, maximum 4 g/day, in 1 to 2 divided doses, intravenous).

In the newly diagnosed patient, parenteral antimicrobial therapy is a top priority and should be given as quickly as possible and certainly within 1 hour of recognition of IMD as recommended in the most recent national and international guidelines, table 2. It should be noted that patients with IMD can transmit meningococci within the first 24 hours of antibiotic therapy, therefore, measures such as droplet precautions should be taken to minimize exposure to health care workers. Antibiotic therapy rapidly reduces circulating plasma endotoxin levels in patients with IMD;

increased endotoxin levels have been associated with severity of illness, including the presence of septic shock, multiple organ failure, and death in patients with IMD.

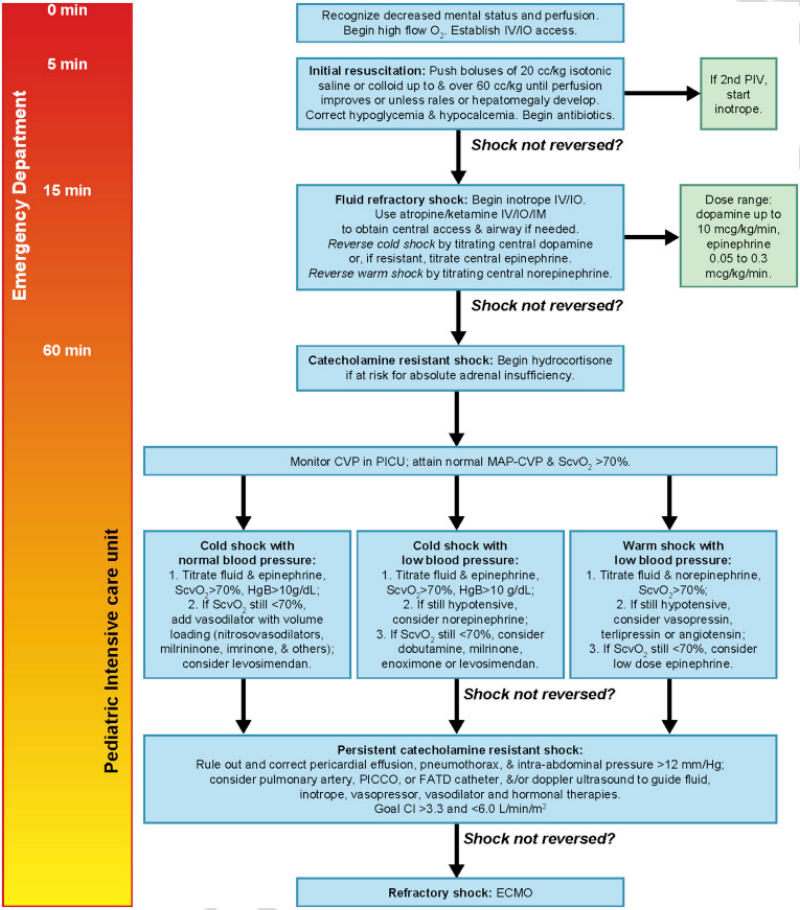

Fig. 3. Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in infants and children. CI — cardiac index; CRRT — continuous renal replacement therapy; CVP — central venous pressure; ECMO — extracorporeal membrane oxygenation; FATD — femoral arterial thermodilution; Hgb — hemoglobin; IM — intramuscular; IV — intravenous; IO — interosseous; MAP — mean arterial pressure; PICCO — pulse contour cardiac output; PICU — pediatric intensive care unit; PIV — peripheral intravenous; $ScvO_2$ — central venous oxygen saturation [13].

Table 2

Antibiotics and dosages used to treat meningococcal meningitis in children

Antibiotic	Total daily dose
Penicillin G	200 000 to 300 000 units/kg/day IV or IM divided every 4 to 6 hours (Max: 24 million units/day)
Ceftriaxone	50 mg/kg, q 12 hours, IV
Cefotaxime	50 mg/kg, q 6 hours, IV
Ceftazidime	50 mg/kg, q 8 hours, IV
Cefepime	2 g, q 12 hours, IV
Ampicillin	75 mg/kg, q 6 hours, IV
Rifampin	6,7 mg/kg, q 8 hours, IV
Meropenem — a,b	40 mg/kg, q 8 hours, IV
Chloramphenicol — b	50 mg/kg, qid 4 hours, IV

q = every; qid = every day.
a Use restricted to >3 months of age.
b Use in the case of penicillin allergy.
IV — intravenous dosage.
IM — intramuscular dosage.

Even with antibiotic treatment, IMD carries a 10 % mortality rate, but this is considerably lower than the 70–85 % mortality rate observed before the availability of antibiotics. Cefotaxime, ceftriaxone, and penicillin are preferred as initial therapy in patients with a clinical diagnosis of IMD. Chloramphenicol and meropenem can be used in cases of penicillin allergy. Empiric treatment with a third-generation cephalosporin is recommended in developed countries until a positive microbiological diagnosis is available, as there remains the possibility of either penicillin resistance or alternative diagnoses that might not be adequately treated by penicillin therapy alone. The recommended duration of antibiotic therapy for IMD is a 5- to 7-day course of a third-generation cephalosporin for both meningococcal meningitis and septicemia.

Dexamethasone may be administered as adjunctive therapy in children aged 6 weeks with meningococcal meningitis, but the risk/benefit ratio needs to be considered, and dosing should occur before or concomitant with the first dose of antibiotics. High-dose dexamethasone should be given in cases of suspected bacterial meningitis before (ideally within 4 hours), and no longer than 12 hours following, the first dose of parenteral antibiotics; a dose of 0,15 mg/kg 4 times per day for 2-4 days is recommended. High-dose corticosteroid therapy is contraindicated in meningococcal septicemia with shock in the absence of meningitis because high-dose corticosteroids have been shown to worsen the outcomes of adults with septic shock.

PROPHYLAXIS OF CONTACTS

Of special note, all individuals in close contact with an IMD-infected individual should receive chemoprophylaxis, regardless of previous meningococcal immunization. A number of antimicrobial agents are effective for chemoprophylaxis against N. meningitides, table 3.

Table 3

Recommended chemoprophylaxis regimens for high-risk contacts and persons with invasive meningococcal disease [5]

Drug	Dose	Duration	Efficacy (%)	Cautions
Rifampin				
<1 month	5 mg/kg, orally, every 12 hours	2 days		
≥1 month	10 mg/kg (maximum 600 mg), orally, every 12 hours	2 days	90–95	Can interfere with efficacy of oral contraceptives and some seizure prevention and anticoagulant medications; may stain soft contact lenses. Not recommended for pregnant women.
Ceftriaxone				
<15 years	125 mg, intramuscularly	Single dose	90–95	To decrease pain at injection site, dilute with 1 % lidocaine.
≥15 years	250 mg, intramuscularly	Single dose	90–95	To decrease pain at injection site, dilute with 1 % lidocaine.
Ciprofloxacin				
≥1 month	20 mg/kg (maximum 500 mg), orally	Single dose	90–95	
Azithro-mycin - a	10 mg/kg (maximum 500 mg)	Single dose	90	Not recommended routinely. Equivalent to rifampin for eradication of N. meningitidis from nasopharynx in one study

a — Use only if fluoroquinolone-resistant strains of N. meningitidis have not been identified in the community.

MENINGOCOCCAL VACCINES

Attempts to create an effective vaccine against N. meningitidis date back to the early 20th century with the first, unsuccessful, attempt at a meningococcal vaccine prepared from heat killed bacterial cultures in the 1910s. The first successful polysaccharide vaccines targeting serogroups A and C were developed based on the work of Gotschlich and colleagues between 1969 and 1971. Clinical trials

revealed vaccine efficacy of 89.5 % against serogroup C disease. The quadrivalent A, C, Y, W-135 meningococcal polysaccharide vaccine was first approved for use in 1978. Major limitations of meningococcal polysaccharide vaccines are that they are, except for the serogroup A polysaccharide, poorly immunogenic in children under age 2 and they are unable to induce long term immunologic memory since they behave as T-cell independent antigens and generate a predominant IgM antibody response.

Late in the 20th century meningococcal vaccine development efforts became focused on improving the T-cell mediated immune response through conjugation of the polysaccharide to a protein. The success of the Haemophilus influenzae type b (Hib) protein-polysaccharide conjugate vaccines provided a model for meningococcal conjugate vaccine development. Conjugation, covalently coupling the capsular polysaccharide to a protein carrier, changes the human immune response from T-cell independent to T-cell dependent engaging helper T cells in maximizing a predominant high affinity IgG immune response. Conjugation ultimately results in an improved primary antibody response, especially in young children, creates affinity maturation, immunologic B cell memory and an amnestic IgG response at re-exposure.

The first meningococcal conjugate vaccines targeted serogroup C and were introduced in the United Kingdom in 1999 as a broad-catch up campaign in adolescents (who have the highest meningococcal carrier rates). Serogroup C conjugates vaccines were subsequently incorporated into the routine vaccination program for infants and young children. Serogroup C disease decreased dramatically in the first 2 years after vaccine introduction and virtually disappeared by 2005. A major contributor (approximately 50 % of effectiveness) to this rapid decline was herd protection created by the generation of mucosal immunity by these vaccines and the interference with transmission of serogroup C expressing meningococci. Vaccine effectiveness for reducing nasopharyngeal carriage of serogroup C in adolescents was more than 75 % (serogroup C specific carriage decline from 0.42 % to 0.09 %), and the reduction in serogroup C meningococcal disease has persisted now for almost two decades.

Similar MenC conjugate vaccine effectiveness was demonstrated recently in Brazil. Routine immunization with serogroup C meningococcal conjugate vaccines was started in 2010 in infants at 3 and 5 months, followed by a booster dose at 12 to 15 months. Unlike in the UK, a catch-up campaign was not implemented. After four years MenC invasive disease was reduced 64 %-92 % in the target population due to direct vaccine effects but overall population impact in older children and adults was not observed. Overall, the improved efficacy of meningococcal vaccines for serogroups A, C, W, Y in the last 15 years can largely be attributed to the success of protein-polysaccharide conjugation.

Serogroup B has presented significant challenges in vaccine development, as previously described. While some work has looked at vaccines based on unique structural aspects of the meningococcal serogroup B polysaccharide capsule, the targeting of N. meningitidis outer membrane proteins rather than the serogroup B capsule has been a major focus. However, meningococcal outer membrane proteins and lipoproteins demonstrate significant genetic and structural variability. Outer membrane vesicle (OMV) based vaccines such as "tailored" OMV vaccines were used successfully in outbreak settings such as in Cuba, Norway and New Zealand. Recently, two meningococcal protein based serogroup B vaccines were licensed for routine and outbreak use in the US in persons aged 10–25 years old, and in the UK, one is now used in infants and young children.

While meningococcal polysaccharide vaccines are still in use, meningococcal protein-polysaccharide conjugate vaccines and serogroup B based vaccines are now the standard for meningococcal disease prevention and outbreak management. Polysaccharide vaccines are being phased out. Table 4 details the current available US and WHO prequalified meningococcal vaccines composition, dosage, administration, and adverse effects.

Table 4

US, European, and Globally-Licensed and WHO prequalified meningococcal vaccines

Vaccine	Manufacturer	Composition	Dose	Year first licensed	Administration
Meningococcal A+C (MenAC) WHO	Sanofi Pasteur	Bivalent meningococcal polysaccharide vaccine covering Serogroups A and C	0.5 mL dose contains 50 μg purified capsular polysaccharide from Serogroup A and C	1997	Intramuscular injection
MenACWY-D (Menactra) US and WHO	Sanofi Pasteur	Quadrivalent meningococcal polysaccharide vaccine covering Serogroups A, C, Y, and W each conjugated individually to diphtheria toxin	0.5 mL dose contains 4 μg of each of the 4 serogroup polysaccharides conjugated to approximately 48 μg of diphtheria toxoid protein carrier	2005	Intramuscular injection

End table. 4

Vaccine	Manu-facturer	Composition	Dose	Year first licensed	Admi-nistration
MenACWY-CRM (Menveo) US and WHO	Glaxo-Smith-Kline/ Novartis	Quadrivalent meningococcal polysaccharide vaccine covering Serogroups A, C, Y, and W each conjugated individually *to Corynebacterium diptheriae* CRM197 toxin	0.5 mL dose contains 10 µg MenA oligosaccharide, 5 µg of each of MenC, MenY and MenW-135 oligosaccharides and 32.7 to 64.1 µg CRM197 protein	2010	Intra-muscular injection
MenACYW (Nimenrix) WHO	Pfizer	Quadrivalent meningococcal polysaccharide vaccine covering Serogroups A, C, W, and Y each conj-ugated to tetanus toxin	0.5 mL dose contains 5 µg of each of the 4 serogroup polysaccharides conjugated to 2016 approximately 44 µg of tetanus toxoid protein carrier	2016	Intra-muscular injection
PsA-TT (MenAfriVac) US and WHO	Serum Institute of India, Ltd.	Purified serogroup A polysaccharide conjugated to tetanus toxoid	10 µg of purified MenA polysaccharide antigen conjugated to 10 to 33 µg tetanus toxoid protein	2010 (African menin-gitis belt)	Intra-muscular injection
MenAfriVac 5 micrograms (pediatric dose) WHO	Serum Institute of India, Ltd.	Purified serogroup A polysaccharide conjugated to tetanus toxoid	5 µg of purified MenA polysaccharide antigen conjugated to 10 to 33 µg tetanus toxoid protein	2014 (African menin-gitis belt)	Intra-muscular injection
MenB-FHbp (Trumenba) US	Pfizer	Two purified recombinant factor H binding protein antigens, one from each FHbp subfamily	0.5 mL dose contains 60 µg of each fHBP variant (total of 120 µg of protein)	2014	Intra-muscular injection
MenB-4C (Bexsero) US	Glaxo Smith-Kline	Three recombinant proteins (FHbp, NadA, and NHBA) formulated with OMVs containing outer membrane protein PorA serotype P1.4	0.5 mL dose contains 50 µg each of recombinant proteins NadA, NHBA, and fHbp, with 25 µg of OMV	2015	Intra-muscular injection

SELF-CONTROL OF MASTERING THE TOPIC

Task 1

The child is 9 months old. According to the mother, the child fell ill 6 hours ago. The disease began with an increase in temperature to 38,9 °C. Objectively: The child is sluggish, pale, upon examination — on the back there are isolated elements of a spotted rash, on the right lower leg — a hemorrhagic element.

1. What is your diagnosis?
2. Assign laboratory tests.
3. Prescribe treatment.

Task 2

The dose of ceftriaxone for the treatment of purulent meningitis in children under 12 years is

1. 250 mg / kg / day;
2. 200 mg / kg / day;
3. 150 mg / kg / day;
4. 100 mg / kg / day;
5. 50 mg / kg / day.

Task 3

Pathogenetic therapy of meningitis includes:

1. antibiotics;
2. antipyretic drugs;
3. dehydration;
4. spasmolytics.

LITERATURE

1. *Principles* and Practice of Pediatric Infectious Diseases / Long Sarah S. [et al.]. / 4th Edition. 2012. p. 1744.

2. *National* Institute for Health and Clinical Excellence. Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. Clinical guideline 102; 2010. p. 276.

3. https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_12_Meningococcus_R2.pdf?ua=1 Date of access: 12.11.2019.

4. *Meningococcal* carriage by age : a systematic review and meta-analysis / Christensen H. [et al.]. Lancet Infect Dis. 2010 Dec ; 10(12) : 853–861.

5. *Red* book. Menigococcal infections. American Academy of Pediatrics Committee on Infectious Diseases / D. W. Kimberlin, M. T. Brady, M. A. Jackson, Elk Grove Village, IL2015: 547–558

6. *Greenlee, J. E.* Acute bacterial meningitis. Merck manual, professional version. Merck Publishing Group, Rahway, NJ. 2015.

7. *Practice* guidelines for the management of bacterial meningitis / A. R. Tunkel [et al.]. Clin Infect Dis. 2004; 39: P. 1267–1284.

8. *Pace, D.* Meningococcal disease : Clinical presentation and sequelae / D. Pace, A. J. Pollard. Vaccine. 2012 ; 30: B3-B9

9. *Meningococcal* carriage by age : A systematic review and meta-analysis / H. Christensen, [et al.]. Lancet Infect Dis. 2010; 10: P. 853–861.

10. *Trotter, C. L.* Vaccination against meningococcal disease in Europe : Review and recommendations for the use of conjugate vaccines / C. L. Trotter, M. E. Ramsay. FEMS Microbiol Rev. 2007; 31: P. 101–107.

11. *Nadel, S.* Treatment of Meningococcal Disease. J Adolesc Health. 2016 Aug; 59(2 Suppl): P. 21–28.

12. *Neisseria* meningitidis : biology, microbiology, and epidemiology. / N. G. Rouphael, D. S. Stephens. Methods Mol Biol. 2012; 799. P. 1–20.

13. *Clinical* practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine / J. Brierley [et al.]. Crit Care Med 2009; 37:P. 666–688.

14. *Functional* genomics of Neisseria meningitidis pathogenesis / Y. H. Sun [et al.]. 2000. Nat Med 6: P. 1269–1273.

15. *Current* epidemiology and trends in meningococcal disease-United / J. R. StatesMacNeil [et al.]. 1996–2015. Clin Infect Dis. 2017.

16. *Dretler, A. W.* Progress toward the global control of Neisseria meningitidis: 21st century vaccines, current guidelines, and challenges for future vaccine development / A. W. Dretler, N. G. Rouphael, D. S. Stephens / Human vaccines & Immunotherapeutics. 2018, Vol. 14, N. 5, P. 1146–1160.

17. *Sophian, A.* Prophylactic vaccination against epidemic meningitis / A. Sophian, J. Black. JAMA. 1912 ; 59 : P. 527–32.

18. *Meningococcal* disease / N. E. Rosenstein [et al.]. N Engl J Med. 2001 ; 344 : P. 378–388.

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MENINGOCOCCAL INFECTION IN CHILDREN

Учебно-методическое пособие

На английском языке

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