FEDERAL STATE BUDGETARY EDUCATIONAL INSTITUTION OF HIGHER EDUCATION
"NORTH OSSETIAN STATE MEDICAL ACADEMY»
MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

Department of Infectious diseases

METHODOLOGICAL GUIDE

LEPTOSPIROSIS

for students studying in the specialty
31.05.01 General medicine (specialty)

Vladikavkaz, 2020

UDC 619:616.98
BBK 55.146

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Leptospirosis - 2020

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Approved and recommended for publication by the Central Coordinating Educational and Methodological Council of the Federal State Budgetary Educational Institution SOGMA of the Ministry of Health of the Russian Federation (protocol N 6 of 06.07.2020).

North Ossetian State Medical Academy, 2020

LEPTOSPIROSIS

Leptospirosis (Vasiliev-Weil's disease, bathers 'fever, canine disease, swamp fever, swineherd's disease, Japanese seven – day fever, rice farmers' disease) is an acute zoonotic natural-focal infectious disease with a predominantly aquatic pathway of transmission of the pathogen. Characterized by intoxication, fever, lesions of the blood vessels, kidneys, liver, Central nervous system and muscles. The incidence of it in humans can be sporadic or in groups, and outbreaks may occur.

Leptospirosis is the most common zoonosis in the world. Cases of this disease have been reported on all continents of the world, except Antarctica. The most powerful natural focus of leptospirosis in the world is in Indonesia, where rodent infestation reaches 10-50%. In Europe, the incidence is highest in areas where the main sources of infection - gray rats-are concentrated, i.e. in port cities, fisheries, meat processing plants, and rice-growing areas (France, Italy, Spain, and the Netherlands).

In Russia, leptospirosis is one of the most common natural focal infections, about 1500 cases of human diseases are registered annually, the incidence is 0.9-1.5 per 100 thousand of the population. On the territory of the Russian Federation, there are 3 main regions that are not affected by leptospirosis and are characterized by a stable tendency to increase in morbidity: the North-Western, Central and especially the North Caucasus. In the Krasnodar territory in recent years, the incidence is 8.1-29.6 per 100 thousand of the population, and the mortality rate is about 1.4 per 100 thousand.

Lethality from leptospirosis is high – on average about 7-8 %, and with a severe form of icterohemorrhagic leptospirosis reaches 25-30%.

The lack of experience of General practitioners in diagnosing leptospirosis, the lack of alertness to the manifestation of this infection makes it difficult to detect sporadic diseases, which often leads to diagnostic errors. Timely diagnosis allows to provide adequate etiopathogenetic therapy and prevent possible adverse outcome.

Purpose of the lesson.

Master the principles of clinical and laboratory diagnostics of leptospirosis, get acquainted with the basics of treatment and prevention.

Medical practical skills mastered by students on the topic

After completing the study of the topic, the student should be able to:

- purposefully find out the epidemiological history;
- based on clinical data, determine the severity of damage to various organs and systems (kidneys, liver, CNS, heart, adrenal glands), hemorrhagic manifestations, assess the severity of leptospirosis;
- evaluate the results of clinical, biochemical and serological studies confirming leptospirosis;
- Make a differential diagnosis with influenza, typhoid fever, acute glomerulonephritis and pyelonephritis, viral hepatitis, poisonings, meningitis;
- make a treatment plan for leptospirosis patients;
- make a plan of rehabilitation measures for leptospirosis reconvalescence.

Etiology

The causative agent is an aerobic mobile spiral-shaped bacterium Leptospira interrogans of the family Leptospiraceae. The term Leptospira (Leptospira: Leptos –soft, delicate, speira – spiral, Greek.) to refer to newly discovered microbes was proposed by the famous microbiologist Noguchi in 1917. The spirals are very close to each other, which gives them the appearance of a "string of pearls" under microscopy in a dark field; one or both ends can be curved. Gram-negative, spores and capsules do not form, strict aerobes. They are cultivated on special nutrient media containing rabbit or sheep blood serum (sera of other animals have a bactericidal effect against these microbes), at a pH of 7.2 – 7.4 and a temperature of 25-35°C. In order to clone Leptospira, study their variability and sensitivity to antibiotics, determine the antagonistic relationships between Leptospira of different serogroups and in relation to other microorganisms, dense nutrient media are used to

isolate clean cultures. Leptospira reproduce by transverse division, and this occurs more slowly than in other bacteria. The maximum concentration of the culture reaches 6-12 days. Currently, there are more than 200 serological variants of pathogenic Leptospira, United into 25 serological groups. The most important serogroups in the structure of human morbidity Icterohaemorragiaeare Icterohaemorragiae , Canicola, Grippotyphosa, Pomona, and Hebdomadis. Saprophyte serotypes of leptospir are about 60.

L can be detected in water and moist soil L. Biflexa, morphologically they are indistinguishable from L. Interrogans. One of the criteria for differentiating pathogenic and saprophytic Leptospira is to determine the timing of their survival in the body of a laboratory animal. Saprophytic Leptospira disappear in 2 to 3 hours from the peritoneal fluid of a Guinea pig, after their intraperitoneal administration, and pathogenic Leptospira persist for 4 to 5 hours. Saprophytes, unlike pathogenic Leptospira, do not possess adhesive properties in relation to cells of primary cultures of mammalian kidney tissues and do not have a cytopathic effect on these cells.

The pathogenicity factors of leptospir are:

- exotoxin-like substances with cytotoxic and hemolytic properties;
- pyrogenic with endotoxin, skin-necrotizing, and lethal properties;
- enzymes (fibrinolysin, plasmahouse, lipase, etc.).

The virulence of Leptospira is also due to the inherent invasiveness and adhesiveness.

Leptospira are hydrobionts adapted to life in water, and when dried quickly die. Sensitive to high temperatures, boiling kills them instantly, and heating to 60°C-after 20-30 minutes. At low temperatures, they can remain viable for several months, survive the winter in moist soil and in reservoirs, without losing virulence. On food products, they survive 1-2 days, do not lose activity when frozen. The duration of leptospir storage in food products is influenced by two factors: the acidity of the medium and the presence of moisture in the products. On dry products (bread, sausage), Leptospira do not last long, in products with a weakly alkaline reaction and a liquid or semi – liquid consistency (potato soup, millet porridge), Leptospira live for several days; maximum 1-2 weeks. Solutions of 0.1% hydrochloric acid, 0.5% phenol kill leptospir within 20 minutes, active chlorine in a dose of 0.3-0.8 mg/l-after 2 hours.

Epidemiology

Leptospirosis is a natural focal zoonosis. The source of the infectious agent is animals – wild, agricultural, domestic and commercial animals. The natural reservoir of leptospirosis consists of rodents and insectivores (voles, rats, mice, shrews, hedgehogs), in which the infectious process occurs latently, and leptospirosis continues for several months (up to 6) . The urine of sick animals can contaminate water bodies, soil, vegetation, food products, etc.

Infection of people is carried out mainly by water, less important are the contact and food routes.

Human infection in natural foci is characterized by summer-autumn seasonality (June – September). It occurs during agricultural activities (mowing, harvesting hay, cultivating rice and other moisture-loving crops, logging), as well as during swimming in freshwater reservoirs, hunting, fishing, collecting mushrooms, drinking water from random water sources, walking barefoot on the ground, etc.Leptospira usually enter the human body through the skin.

In natural foci, agricultural animals (pigs, cattle, horses), as well as rodents and dogs living near humans can also become infected. Thus, anthropological foci of leptospirosis are formed; infection of people in them is possible by water, contact (when caring for sick animals, slaughtering and butchering carcasses) and food (when consuming milk, meat and other infected products) ways. Leptospirosis in farm animals occurs acutely and chronically without pronounced clinical manifestations.

Leptospira of a particular serovar affects mainly populations of certain animal species, and the etiological structure of diseases in each focus is generally determined by the predominant type of animal host of the pathogen. In particular, in Russia, gray rats are carriers of the most virulent Leptospira – L. icterohaemorragicae, dogs-L. canicola, pigs - L. Pomona, etc.

For leptospirosis, as for other zoonoses, in the last 10 -15 years, a pronounced trend towards urbanization is characteristic – most of the patients are urban residents, which is due to a variety of reasons, including the expansion of urban boundaries with the development of natural focal areas, a passion for gardening, the desire of citizens to keep Pets (primarily dogs).

People's susceptibility to leptospirosis is high. There may be both sporadic cases and epidemic outbreaks associated with bathing in open reservoirs that serve simultaneously for watering livestock, or with the use of unboiled water from one source, or with agricultural work, etc.

Previously, the incidence of leptospirosis was largely professional in nature (animal technicians, veterinarians, meat-processing plant workers, animal breeders, deratisers, miners, plumbers, janitors, etc.). due to the planned vaccination of individuals with these groups of diseases, leptospirosis was rarely registered in them.

A person with leptospirosis does not pose an epidemiological danger to others, although isolated cases of sexual infection have been described.

Pathogenesis

Leptospiruses enter the human body both through the skin (if there is at least the smallest damage on it), and through intact mucous membranes of the eyes and mouth.

There are 5 phases of pathogenesis of leptospirosis.

Phase 1 corresponds to the incubation period. At the entrance gate, no visible changes are detected, microbes are captured by mobile macrophages and enter the blood. This primary bacteremia is very short-term (in the experiment it lasts 2 – 3 hours) and is asymptomatic. From the blood, Leptospira penetrate into various organs – kidneys, liver, lungs, spleen, etc., in which for 7 to 20 days their intensive reproduction occurs.

Phase 2 is caused by secondary bacteremia, Leptospira re-enter the blood in large quantities from various organs. In addition to the leptospiruses themselves, their toxins, products of metabolism and decay circulate in the blood, which is accompanied by fever, intoxication, characteristic of the initial period of leptospirosis. The duration of this phase is 3-7 days. During this period, there is a secondary dissemination of leptospir in the body, their penetration into the Central nervous system is possible due to the ability of leptospir to overcome the BBB.

Phase 3-toxic (toxemic), clinically corresponds to the peak period (the end of the 1st – 3rd week of the disease), characterized by damage to many organs (primarily kidneys, liver, muscles), brain membranes, the development of universal capillarotoxicosis. Inside the cells of organs, Leptospira do not penetrate, they are located in the intercellular space, on the surface of cells. Having adhesive properties, Leptospira adhere to hepatocytes, nephrotelium of the proximal tubules and colonize the corresponding cells. Damage to the kidneys and liver, which is most pronounced clinically since the end of the 1st week of the disease, is caused both by the cytopathic action of leptospir, and by a violation of microcirculation in these organs. The effect of leptospir toxins is diverse, one of its main manifestations is a violation of the integrity of the endothelium of capillaries, leading to an increase in their permeability and the development of generalized capillarotoxicosis, resulting in bleeding and hemorrhage. In the pathogenesis of hemorrhagic syndrome in leptospirosis, violations of hemocoagulation due to the action of the endotoxin leptospir on platelets are no less important, which leads to an increase in their aggregation activity. In leptospirosis, all the links of hemostasis (vascular-platelet and plasma) are disrupted, especially in severe cases. Intravascular blood clotting and platelet aggregation lead to impaired microcirculation, subsequent necrosis of the vascular wall and secondary bleeding. Platelet aggregation causes thrombocytopenia and a tendency to bleed from the vessels of the microcirculatory bed.

During leptospiremia and toxinemia, jaundice may occur due to the development of hepatitis, cholestasis, hemolysis of red blood cells caused by leptospir hemolysin, as well as myoglobinemia (damage to muscle tissue by leptospirs and their toxins is accompanied by the entry of the muscle protein myoglobin into the bloodstream). Damage to the epithelium of the renal tubules leads to a violation of the process of urination with the possible development of acute kidney failure. In severe cases, mixed acute renal-hepatic insufficiency (OPPN) may develop.

Phase 4-formation of non-sterile immunity. In the blood of patients, the concentration of specific antibodies increases, but Leptospira is still preserved in the organs, most often in the kidneys, since due to gross microcirculatory disorders, antibodies do not penetrate well into the kidney tissue, and the conditions for preserving Leptospira in the renal tubules are favorable (liquid medium, neutral reaction).

During the period corresponding to the 4th phase of pathogenesis (3rd – 4th week of the disease), there may be relapses of leptospirosis, complications from the eyes, heart, etc.

The 5th phase – the formation of sterile immunity falls on the 5th-6th week of the disease, which clinically corresponds to the period of convalescence. Meanwhile, leptospir antigens can be detected in the CEC even after 2-3 months, which indicates the incompleteness of the infectious process and explains the possibility of long-term complications a few months after leptospirosis.

Pathomorphology

Pathomorphological changes are better studied in the severe form of leptospirosis (icterohemorrhagic, caniculosis) with a fatal outcome. They are similar to those in cases of death from ITSF, acute respiratory failure, OPPN, and multiple organ failure. With ITS, which develops in the first days of the disease, there is fullness and edema of the internal organs, numerous hemorrhages in the serous membranes and internal organs. It is characterized by intense jaundice of the skin and mucous membranes. When histological examination of internal organs at the height of the disease, in addition to signs of a sharp violation of microcirculation, pronounced changes in the kidneys, liver and other organs are detected. In the kidneys, dystrophic changes of the parenchyma, necrosis of the glomerular epithelium and epithelium of the proximal tubules are detected; in the liver, dystrophy and necrosis of hepatocytes, edema of the intervertebral tissue, infiltration of portal fields by mononuclears, bile clots (in the Central zone of the lobules). It is characterized by damage to skeletal muscles, especially the calf and thoracic; they show hemorrhages, uneven swelling of fibers, degenerative changes, sometimes foci of necrosis, which explains the presence of typical for leptospirosis myalgia. The spleen is usually enlarged, its consistency is not changed.

There is a fullness and swelling of the brain substance, and almost a third of patients have serous meningitis.

Immunity

After undergoing leptospirosis, the immune system is long-lasting and strong, but serovarospecific, so it is possible to repeat the disease caused by leptospiras of other serovars.

Clinical picture

The duration of the incubation period is from 3 to 30 days (usually within 7-14 days).

The course of leptospirosis depends on the virulence of the pathogen, the infecting dose, and the fullness of the immune response of the macroorganism at the cellular and humoral levels.

There is no single clinical classification. There are two main forms: jaundice and Busselton: according to the severity there are mild, moderate and severe. It is advisable to consider the following syndromes – renal, hepatorenal, hemorrhagic, meningeal.

The jaundice form is usually more severe than the non-jaundice form. The main criteria of severity are the height of fever, the severity of intoxication, kidney damage, hemorrhagic syndrome and the intensity of jaundice.

Leptospirosis refers to diseases that are characterized by an acute, non-prodromal onset. Usually, patients accurately indicate the day of the onset of the disease, the first symptoms of which are chills, a sharp deterioration in health and high body temperature (fever reaches 39 - 40° C by the end of 1 – 2 days). In the cyclical course of leptospirosis, three main periods can be distinguished: initial, peak, and reconvalescence.

The duration of the initial period is 4-5 days. From the first hours of the disease, patients complain of severe headache (usually without a specific localization), low back pain, General malaise. Appetite disappears, nausea appears. Possible vomiting. Leptospirosis is characterized by muscle pain, especially in the calf, occipital, as well as in the muscles of the back and abdomen. Myalgia is also observed at rest, but it is significantly increased when moving. Some patients may not have independent pain in the muscles, but palpation reveals soreness, usually of the calf mus-

cles. Massive muscle necrosis with the development of myoglobinemia may be one of the causes of subsequent kidney damage.

Symptoms associated with damage to the gastrointestinal tract are relatively common. They are especially pronounced in diseases associated with infection with Leptospira Icterohaemorrhagiae. Many authors consider the characteristic lesion of the gastrointestinal tract for this leptospirosis. Signs of damage often appear at the beginning of the disease in the form of nausea, vomiting, often indomitable, abdominal pain, lack of appetite or complete aversion to food, a bitter taste in the mouth, constipation or diarrhea. Abdominal pain is localized more often in the submandibular region and in the right hypochondrium. Abdominal pain resulting from hemorrhages in the rectus abdominis or retroperitoneal hemorrhages is sometimes so intense that it leads to the assumption of an acute surgical disease, in connection with which some patients with a preliminary diagnosis of "appendicitis", "cholecystitis", "peritonitis" are even operated on. According to the observations of most authors, diseases caused by representatives of other serogroups of leptospir are also marked by loss of appetite, nausea, often turning into vomiting, constipation, rarely abdominal pain and liquid stool, sometimes with an admixture of mucus. Despite the fact that myalgia is considered one of the earliest and most characteristic symptoms of leptospirosis, it should be borne in mind that in some patients, even with the most thorough survey and examination, this sign can not be detected. In addition to muscle pain, some patients worry about aches in their bones and joints.

The appearance is quite typical of patients with diseases: they are usually lethargic, adynamic, the face is slightly puffy and hyperemic, injected sclera vessels, lips and wings of nose herpetic vesicles, sometimes hemorrhagic content. Approximately 30% of patients in 3 to 5 days after the onset of the disease on the skin of the chest, back, abdomen, side surfaces of the trunk, arms and legs, a rash appears: bright pink dot, spot-papular, rarely petechial with the development of hemorrhagic syndrome. The rash elements are similar to those of measles, rubella, or scarlet fever. It is possible to develop thrombohemorrhagic syndrome, which is manifested in addition to petechial rash by hemorrhages into the skin at the injection sites, nosebleeds, and hemorrhages into the sclera. Rashes usually disappear after 1 to 2 days, in some cases they persist longer, accompanied by a burning sensation or a slight itch. After the rash disappears, bran-like peeling of the skin is possible.

Some patients feel slight pain in the throat when swallowing, cough. When examining the oropharynx, there is a moderate hyperemia of the arches, tonsils, and soft palate (occasionally a spotty enanthema or hemorrhage appears on it). There may be a slight increase in occipital, submandibular, and axillary lymph nodes. The tongue from the second day of the disease becomes dry, covered with a yellowish-brown plaque. During palpation of the abdomen, there may be pain in the epigastrium and right hypochondrium.

From 2 to 3 days from the beginning of the disease, the liver increases, it is dense in consistency, painful on palpation. In patients, the spleen is palpated.

Changes in the cardiovascular system are manifested from the first days by muffled heart tones, relative bradycardia, hypotension (sometimes up to collapse) – due to intoxication. On the ECG-signs of diffuse myocardial damage. In more severe cases, there may be a detailed clinical picture of specific leptospirosis myocarditis.

Kidney damage is manifested from the first days of the disease in the form of oliguria. In many patients, a positive symptom of pounding is determined (some clinicians associate the presence of this symptom not with renal pathology, but with an increase in the liver and stretching of the glisson capsule).

Even in the initial period, the Central nervous system is characterized by an intense headache, dizziness, insomnia, and delirium. With a severe course of leptospirosis, 1-40% of patients develop meningeal syndrome: rigidity of the occipital muscles, symptoms of Kernig, Brudzinsky, Neri. Clinical manifestations of meningitis is confirmed by laboratory studies: CSF cell count is noted, usually within 400 – 500 in 1 MCL with a predominance of neutrophils, but some patients may change as the cerebrospinal fluid in purulent meningitis with number of cells up to 3 – 4 thousand in 1 mm and more, also with a predominance of neutrophils.

The hemogram during this period is characterized by a pronounced neutrophilic leukocytosis with a sharp shift to the left up to myelocytes, aneosinophilia, relative lymphopenia, an increase in ESR.

In the General urine analysis – minor or moderate proteinuria, cylindruria, microhematuria, leucocyturia

In some patients, nosebleeds appear in the first days of the disease, but the hemorrhagic syndrome characteristic of leptospirosis is more often expressed during the peak period, from 5 to 6 days of the disease. By this time, intoxication increases, headache and weakness are even more severe; anorexia can be accompanied by an aversion to food. Frequent vomiting is possible.

From the end of the 1st week, sometimes a little earlier, 12-20% of patients develop jaundice of various intensity, which usually has a bright hue and persists for several days to several weeks. Unlike viral hepatitis, the intensity of jaundice in leptospirosis in most cases corresponds to the severity of the disease. The amount of urine released during this period decreases, and it is much darker than normal; the feces are light yellow in color. After 2-3 days after the appearance of jaundice, the body temperature may decrease (the duration of the first fever wave in leptospirosis is usually 5 to 9 days), but the condition of patients continues to deteriorate. The most severe manifestations and complications of leptospirosis occur at the end of the 1st-beginning of the 2nd week of the disease. It is during this period that the most pronounced hemorrhagic syndrome – usually in the form of petechiae rash on the skin, bleeding from the nose and gums, subconjuctival hemorrhages, extensive bruising at the injection sites; possible gastrointestinal and uterine bleeding, hemoptysis, brain hemorrhage, etc. bleeding can be massive and repeated several times. The most severe and prognostically unfavorable are bleeding from the gastrointestinal tract. Hemorrhagic syndrome occurs more often in the jaundice form of leptospirosis, but can be in patients without jaundice.

Changes in the cardiovascular system during the height of the disease are characterized by deafness of heart tones, tachycardia, hypotension; possible extrasystole, atrial fibrillation. On the ECG-diffuse changes in the myocardium.

During the height of the disease, renal pathology worsens: the amount of urine released decreases sharply (sometimes up to anuria), the development of acute renal failure, which is one of the causes of death of patients, is possible.

Meningeal syndrome is first detected or reaches its greatest severity during the peak period. Changes in CSF indicate the development of serous meningitis (moderate lymphocytic pleocytosis with a slight increase in protein content). In some cases, purulent meningitis, meningoencephalitis are possible, in some patients the liquor appears unchanged, i.e. there is meningism or, on the contrary, inflammatory changes in the liquor can be detected in the absence of meningeal symptoms. The prognosis for leptospirosis meningitis is favorable.

Special attention during this period should be paid to the study of urine. Proteinuria can reach 1-3 g/l or more. In the urine sediment, fresh and altered red blood cells, white blood cells,hyaline and granular cylinders, and cells of the renal epithelium. Urea and creatinine levels increase in the blood.

The hemogram is characterized by an increasing anemia of a hyporegenerative nature, due to the inhibitory effect on erythropoiesis of the toxic substances leptospir, in some patients the number of red blood cells decreases to 1.5×10^{12} /l. In patients with hemorrhagic syndrome, marked thrombocytopenia, a decrease in platelet aggregation function are noted. Compared with the initial period of leptospirosis, leucocytosis is even more pronounced, the number of white blood cells can reach 20.0-25.0 $\times^{109}$ /l, stick-nuclear shift persists, pronounced lymphopenia; especially in severe cases, the content of lymphocytes can be less than 10%; ESR reaches 40-60 mm/h.

Biochemical studies indicate liver damage. In patients with jaundice, the content of bilirubin in the blood (both bound and free) increases, the violation of pigment metabolism is caused by degenerative changes in hepatocytes, as well as myolysis and cholestasis. Hyperbilirubinemia is accompanied by a mild elevation of transaminases, but a significant disorders of protein-synthetic function of the liver, which is characteristic for a decrease in the content of albumin, increased levels of $\alpha_1$and α_2 – globulin and γ-globulin, and these changes are detected as in jaundice and in the

absence of such. Typically, an increase in creatine phosphokinase activity due to damage to muscle tissue.

With a favorable course of leptospirosis, the absence of complications in most patients from the end of the 2nd week from the beginning of the disease, the condition gradually begins to improve, the intensity of jaundice decreases, body temperature decreases, muscle pain and meningeal syndrome pass, bleeding does not repeat, the amount of urine released increases.

The convalescence period begins with the 20th-25th day of the disease. By this time, the body temperature is stable normal, polyuric crisis is possible. Restoration of functions of organs naturally affected by leptospirosis (kidneys, liver. Central nervous system), occurs very slowly, signs of functional insufficiency of the renal tubular apparatus (low relative urine density and proteinuria) and asthenic syndrome persist for a long time. In some patients, it is during the convalescence period (at the 4th – 5th week) that anemia is expressed even more than at the height of the disease.

In 20-60% of cases of leptospirosis, relapses occur, which are characterized by the resumption of fever and other manifestations that were during the first wave of the disease. Relapses occur 5 to 7 days after the end of the first febrile period. The body temperature usually does not reach such high figures as in the first days of the disease, the duration of the febrile period is shorter, intoxication is less pronounced, and relapse usually occurs more easily than the first wave of the disease. There may be several relapses (up to 4 or more).

Clinical picture of the disease caused by L. Icterohaemorrhagiaeis characterized by the most severe course, deep damage to the kidneys and liver, and the highest mortality rate.

In addition to the classic forms of leptospirosis, abortive and erased with short – term (2-3 days) and low fever, occurring without jaundice, myalgia, hemorrhagic and meningeal syndromes are possible. In some patients, leptospirosis manifests as a fever of about 7 days in combination with moderate headache and oliguria.

Complications

Among the most serious complications include ITCH, surge arresters, OPEN and ONE.

ITS can develop from the 3rd-4th day of the disease, but more often at the end of the 1st – beginning of the 2nd week. Clinical manifestations of ITCH in leptospirosis are similar to those in other infectious diseases. ITSH can be the cause of death of patients at the 1st week of the disease.

Acute kidney injury in leptospirosis has several stages, the first of which occurs latently and can be detected under water load in the form of a decrease in diuresis. In the 2nd stage of acute renal failure, persistent oligoanuria is noted, the content of urea and creatinine increases in the blood. At the same time, due to increased potassium excretion, significant hyperkalemia is rarely observed. The relative density of urine decreases, proteinuria can reach 30 g / l, red blood cells, various cylinders, and cells of the renal epithelium are detected in the urine sediment. In cases where anuria is short-lived and the prognosis is more favorable, IIstage II of acute renal failure is replaced IIIby stage III, characterized by polyuria and isohypostenuria; IIIstage III lasts about 2 weeks. At this time, it is necessary to carefully monitor the analysis of urine and the content of urea, creatinine and electrolytes in the blood, and correct the detected changes. If anuria lasts more than 4 days, the prognosis is serious.

Despite the development of acute kidney injury, edema and arterial hypertension in leptospirosis usually do not occur. Sometimes acute kidney injury occurs very early, as early as 2 to 4 days after the onset of the disease, leads to uremia and is one of the most frequent causes of death in patients.

Isolated acute liver failure is not typical for leptospirosis, but in severe cases, patients with renal failure develop OPPN.

ODN usually occurs after (or during) ITCH and is currently treated as respiratory distress syndrome (RDS) or shock lung. Clinically, RDS is characterized by severe dyspnea, acrocyanosis, the appearance of bloody sputum, the appearance of hypoxemia, refractory to oxygen therapy; with radiological and follow-up, bilateral infiltrative changes in the pulmonary fields are characteristic.

Among other complications of the acute period of leptospirosis, massive bleeding and hemorrhage, as well as myocarditis, should be kept in mind. In later periods (after 2 weeks – several

months), specific complications are possible – uveitis, iritis, iridocyclitis. There may also be non-specific complications caused by bacterial flora , such as pneumonia, bedsores, abscesses, etc.

Fatal outcomes in sporadic cases are 1-2%, in epidemic outbreaks of leptospirosis - up to 15-20% or more.

Differential diagnosis

In the initial period, leptospirosis should be distinguished from acute febrile conditions, with the development of organ lesions – from viral hepatitis, hemorrhagic fevers, malaria, yersiniosis, sometimes meningitis. In the differential diagnostic search, it is necessary to focus on the acute onset of the disease, two-wave fever, pain in the calf muscles, facial hyperemia with herpetic rashes, injection of sclera and conjunctiva hyperemia, exanthema of a coreobodobny and in the most severe petechial character, multiple hemorrhagic rashes on various parts of the body, lower back pain, micro-and macrohematuria, oligo-or anuria, increase in liver size, in some cases the development of jaundice. At the same time, it is necessary to take into account the data of the epidemiological anamnesis: the patient's stay in areas endemic for leptospirosis, bathing in natural reservoirs and drinking raw water from them, participation in agricultural work.

In **influenza**, in contrast to leptospirosis, headache has a certain localization (brow arches), pain in the calf muscles is not typical, the liver and spleen do not increase, there are no signs of kidney damage, rarely and slightly expressed hemorrhagic manifestations, fever is more short-lived, catarrhal phenomena are characteristic, normal ESR; there are no relapses with influenza. Leptospirosis is usually contracted in the summer, and the flu is more common in the cold season.

Blood in influenza: leukopenia, neutropenia (sometimes with a moderate shift to the left), relative lymphocytosis, eosinopenia, ESR increased to 18-20 mm/h. Leptospirosis symptoms include leukocytosis with a left shift (often with icterohemorrhagic leptospirosis) or normal white blood cell count (or upper norm), but with a shift of leukocyte formula to the left, gipoazotemia or aneozinofiliya.

It should be taken into account that with complicated influenza, there may be leucocytosis with neutrophilosis. You should also keep in mind the contagiousness of influenza and its characteristic winter-spring seasonality. During this period, only certain professional groups of the population are most susceptible to leptospirosis infection (workers of meat processing plants, slaughterhouses, pig farms, cooks, veterinary workers and other persons who come into contact with farm animals or slaughtered raw materials).

Unlike the jaundice form of leptospirosis, viral hepatitis is not characterized by chills, high body temperature and muscle pain in the pre – jaundice period, there is no conjunctivitis and scleritis, the liver is usually painless on palpation, petechial rash is noted only in severe cases; when jaundice occurs, the body temperature normalizes, meningeal and renal syndromes do not occur, the activity of aminotransferases increases sharply, sediment samples change, decreases the prothrombin index, in the hemogram-leukopenia, low ESR, jaundice is more prolonged.

Leptospirosis is often mistaken for hemorrhagic fever with renal syndrome (HFRS). But in HFRS there are no strong pain in the calf muscles, and a natural pain in the lower back, abdomen, sharply positive symptom of a beating; petechial rash often localized in the shoulders and armpits; there is a high proteinuria, in urine sediment, in addition to fresh erythrocytes, detected waxy cylinders and degenerative modified cells of renal epithelium; no jaundice and meningeal syndrome; in the hemogram in the beginning of the disease, leucopenia and not leucocytosis. In addition, the incidence of HFRS increases in the autumn-winter period, not in the summer.

Pseudotuberculosis is characterized by a "scarlet-like" rash, a "crimson" tongue, symptoms of "hood", "gloves" and "socks", severe arthralgias, pain in the right iliac region, rapid stool, minor and rapidly passing jaundice (if it occurs at all), eosinophilia, large-plate peeling of the skin of the fingers and toes. Unlike leptospirosis, pseudotuberculosis rarely involves a combination of kidney, liver and meningeal damage, and hemorrhagic syndrome is generally uncommon.

In leptospirosis, accompanied by meningitis, there is a need for a differential diagnosis with meningitis (mainly serous) of another etiology. It is significant that in leptospirosis, meningitis develops not in the first days of the disease, but by the end of the 1st week and is preceded by fever,

myalgia, and severe intoxication. Leptospirosis meningitis, unlike others, is combined with an increase in the liver and increased activity of transferases (sometimes with hyperbilirubienemia), signs of kidney damage and hemorrhagic syndrome.

In the presence of hemorrhagic rash, meningeal syndrome, it is necessary to make a differential diagnosis with meningococcal infection, in which the rash appears earlier (on the 1-2 th day of the disease), the CSF is purulent.

The jaundiced form of infectious mononucleosis can be mistaken for the icteric form of leptospirosis. Similar are the following manifestations: acute onset, the nature of the temperature reaction, the presence of hepatolienal syndrome and moderate jaundice. In contrast to leptospirosis, infectious mononucleosis has less pronounced symptoms of intoxication, no myalgia, and no hemorrhagic syndrome. For a final diagnosis, it is necessary to examine the blood in the dynamics of the disease, but it should be borne in mind that the number of mononuclears can increase sharply only in the 2nd week of the disease. It should be remembered that in the jaundice form of infectious mononucleosis, the activity of transaminase increases very early and the thymol test in a high titer turns out to be positive.

In some cases, there is a need for a differential diagnosis of leptospirosis with typhoid-paratyphoid diseases, trichinellosis, sepsis, malaria, and toxic hepatitis.

Diagnostics

In the early stages of the disease, leptospirosis can be suspected based on clinical and epidemiological data. To do this it is necessary to take into account the following clinical manifestations in patients:

- acute onset of the disease (sometimes gradual in about 3% of cases);
- severe intoxication and high body temperature from the 1st day of the disease; fever of the remitting type, a tendency to repeat waves;
- the presence of muscle pain (independent or palpation);
- characteristic appearance of the patients (hyperemia of the facial skin, "diver's eyes"); injection of blood vessels and jaundice of the sclera or the appearance of a pronounced jaundice syndrome (after a short pre-jaundice period), exanthema (large-spotted, erythematous, and less often roseolous and hemorrhagic);
- an increase in the liver, small and short-lived in the non-jaundice form and more pronounced and prolonged in the jaundice form. Less often-a small increase in the spleen;
- the possibility of early complications: serous or purulent meningitis, meningoencephalitis, pneumonia, various bleeding, and starting from the 2nd week of the disease-the development of kidney failure, anemia and other complications;
- hematological changes-neutrophilic leukocytosis with a shift of the leukocyte formula to the left, eosinopenia or complete absence of eosinophils with a slight decrease in lymphocytes and increased ESR to 50-70 mm/h; a decrease in the number of red blood cells, platelets and hemoglobin in the later stages of the disease;
- albuminuria and the presence of white blood cells, red blood cells and cylinders in the urine sediment.

It should also be taken into account that even with a pronounced jaundice form of leptospirosis with significant bilirubinemia, there is usually no stool discoloration, and the activity of transaminase is characterized by a very small increase.

Especially typical is the combination of signs of kidney and liver damage with hemorrhagic and menigeal syndrome.

At the same time when making a diagnosis it is necessary to take into account the data of the epidemiological history:

- stay of the patient in leptospirosis-endemic areas. Bathing in natural reservoirs and drinking raw water from them, participation in agricultural work.
- professional nature of infection of workers of the meat processing industry, livestock farms, animal farms and kennels for animals, agricultural workers or other persons performing various

field work, especially related to harvesting, veterinarians, deratizers, laboratory assistants, preparators and doctors working with laboratory animals, workers serving sanitary facilities, miners;

- possibility of contact with rodents, dogs, other animals at home, taking care of them in personal subsidiary farms (cows, pigs, sheep, rabbits, etc.);

- severe summer seasonality when infected through water (swimming, hunting, fishing, agricultural work in wetlands);

- lack of seasonality in cases of contact-professional infection, as well as in cases of alimentary infection (consumption of raw milk from infected cows, raw meat or products infected with rodent secretions);

- the lack of transmission from person to person.

Biochemical parameters of blood in the jaundice form of leptospirosis include an increase in bilirubin (with a predominance of bound), an increase in aminotransferases, hypocholesterolemia, increased activity of alkaline phosphatase.

It is possible to detect live motile Leptospira in the blood by microscopy of a crushed drop in a dark field, as well as their isolation when sowing blood, urine or liquor on nutrient media (at the 1st week of the disease). 3-5 ml of fresh biological material taken directly from the patient's bed is sown in each of 3-5 Petri dishes with a nutrient medium. Leptospira are classified as slow-growing microorganisms, so the isolation of culture is important only for retrospective confirmation of the diagnosis and a more detailed explanation of the etiology of the case or outbreak.

Serological methods are popular in clinical practice. The diagnosis is confirmed by microagglutination (MMA) and agglutination-lysis reactions, as well as RSC and rnga. Reactions are put in paired serums taken during the height of the disease and in the stage of reconvalescence. For the minimum diagnostic titer, take a dilution of blood serum 1: 100. RMA is characterized by high sensitivity and specificity, but it is not a method of early diagnosis, since antibodies to Leptospira in the titer of 1: 100 are detected in the blood serum no earlier than 8-10 days of the disease, and the maximum titers are most often on the 14th-17th day. It is necessary to examine paired serums (the first on the 5th-7th day of the disease and again after 7-14 days). The diagnosis is confirmed by a 4-fold increase in the antibody titer. It should be taken into account that in the severe course of the disease, antibodies are produced at an even later time and in low titres.

Highly sensitive and specific test systems for detecting the DNA of pathogenic Leptospira have been developed on the basis of PCR. This method should be used for early rapid diagnosis of leptospirosis (blood serum is examined starting from the first and up to 10 days of the disease), as well as to control the course of infection and the effectiveness of treatment.

Also put a biological sample: 3-5 ml of blood, urine or liquor of the patient is administered to Guinea pigs intravenously, intraperitoneal or subcutaneous; after the death of animals, Leptospira is detected in various organs after coloring the sections with silver nitric acid.

Treatment

All leptospirosis patients (or suspected leptospirosis patients) are subject to hospitalization. During the height of the disease, it is necessary to observe bed rest. The choice of diet depends on the severity of kidney and liver damage.

Etiotropic therapy is performed with penicillin or tetracycline preparations. In a non-severe (mainly non-jaundiced) form, benzylpenicillin can be prescribed for intravenous administration at a daily dose of 4-6 million UNITS or ampicillin-4 g; either doxicillin (0.2 g per day) or amoxicillin (0.5 g 3 times a day) per os. In severe cases, antibiotics are administered only parenterally (IV or V / m – - benzylpeicillin-6-12 million UNITS/day (with meningitis up to 20-24 million UNITS/day) or ampicillin in a daily dose of 4 g.

Reserve drugs – Amoxiclav (50 mg/(kg * day) in 3 administration or ampicillin (75 – 100 mg/(kg * day) in 4 administration.

If you are intolerant to penicillin, you can use antibiotics of the tetracycline group, cephalosporins and levomycetin, although they are inferior in effectiveness to penicillin. Antibiotic therapy should be carried out throughout the entire febrile period and for another 2 – 3 days at normal body

temperature. The most effective treatment is started in the initial period of the disease, i.e. no later than 3 days of the disease.

In case of relapses, it is advisable to use an antibiotic that was not used during the first wave; cephalosporins (Ceftriaxone) or erythromycin may be recommended.

The use of tetracycline is undesirable, especially in patients with jaundice and / or hemorrhagic syndrome.

The effectiveness of a specific immunoglobulin used in the past has not been confirmed. The goal of pathogenetic therapy is to eliminate intoxication, prevent the progression of renal failure and hemorrhagic syndrome, and combat ITS, if it has developed. The volume and method of detoxification therapy depends on the severity of intoxication.

In the light and medium-heavy course of the disease, the appointment of enterosorbents and the conduct of infusion therapy in a small volume may be sufficient. In severe cases, signs of ITSH require intensive infusion therapy with glucose-salt and colloidal solutions, the introduction of dopamine, corticosteroids (prednisone up to 10 mg/kg), correction of hemostasis disorders (heparin, curantil, trental). In cases of severe DIC-syndrome, freshly frozen plasma and protease inhibitors are used.

To prevent acute kidney injury and in its initial phase, the administration of osmodiuretics (mannitol, 20% glucose solution) is indicated. When acute renal failure worsens, it is advisable to administer intravenous lasix (40-80 mg or more) against the background of stable hemodynamics. Carry out washing of the stomach and intestines with slightly alkaline solutions. With persistent 2-3 days of anuria, an increase in the content of urea and creatinine in the blood, acidosis, hemodialysis, plasma ultrafiltration are indicated.

When OPN alternate sessions of hemodialysis and hemosorption, and use other methods of extracorporeal detoxification, including hemofiltration.

Patients are discharged from the hospital only after a complete clinical recovery, not earlier than 10 days, under the control of a clinical blood and urine test, and in meningitis, a control spinal puncture is mandatory. Before discharge, an examination by an optometrist and neurologist is desirable.

Medical examination of convalescents is carried out for six months with monthly examination by an infectious disease specialist and, if necessary, by a nephrologist, oculist, neuropathologist, and therapist. Control tests of blood (General – all, biochemical-transferred jaundice) and urine are also necessary. After 6 months, patients can be removed from the register, provided that they have a clinical recovery and normalize the results of laboratory tests. With persistent residual phenomena, reconvalescence is observed in a specialist of the appropriate profile for at least 2 years.

Prevention

It is carried out jointly by the health authorities and the veterinary service. It is necessary to identify and treat farm animals that carry leptospir, regularly deratize, protect reservoirs from contamination with animal secretions, ban bathing in non-flowing reservoirs and use raw water from open water sources. Measures should be taken to limit the number of grey rats and stray dogs; owners ' dogs should be vaccinated against leptospirosis.

Persons who are at an increased risk of Leptospira infection due to their occupation are subject to routine vaccination: employees of livestock and forest-Park farms, zoos, pet stores, dog kennels, enterprises processing raw materials of animal origin, etc., as well as employees of laboratories working with Leptospira. Vaccination is carried out with leptospirosis concentrated inactivated liquid vaccine starting from 7 years. The vaccine is administered subcutaneously in a dose of 0.5 ml, once. Revaccination is carried out after 1 year.

Measures in the epidemic center

All patients with an obvious disease or suspected of leptospirosis are necessarily subject to immediate hospitalization. Separation of persons who were in contact with the sick is not carried out. The quarantine is not established. Individuals who have leptospirosis are subject to medical supervision for 6 months with mandatory clinical examination by an optometrist, neuropathologist and therapist in the first month after the disease. In the following months, dispensary observations

are carried out monthly by district doctors with the involvement of specialists in the profile of clinical manifestations. De-registration is carried out in full clinical recovery. For emergency antibiotic prophylaxis of leptospirosis, persons at risk of infection are prescribed doxycycline (vibramycin) according to the scheme: 1 capsule (0.1 g) once a day with a course of 5 days. The decision to conduct emergency chemoprophylaxis is made by the territorial Centers of state sanitary and epidemiological supervision. In the epidemic center, measures for the extermination of rats, disinfection are carried out.

Questions for self-monitoring

1. Etiology and epidemiology of leptospirosis.
2. The mechanism of development of hemorrhagic syndrome, lesions of the kidneys, liver, Central nervous system in leptospirosis.
3. The main clinical symptoms of leptospirosis.
4. The most common clinical forms of leptospirosis.
5. The main complications of leptospirosis.
6. Methods of laboratory diagnostics of leptospirosis.
7. Basic principles of treatment of leptospirosis.
8. Prevention of leptospirosis.

Task

Patient A. 19 years old called the doctor of the polyclinic on 25.08. Complained of a severe headache, pain in the entire body, a feeling of heat. I fell ill 5 days ago; the temperature suddenly increased to 39.0° C, my head ached, I had difficulty moving because of severe pain in my legs. I took antipyretics, but it didn't get any better: weakness, fever, and pain in the calf muscles persisted. Upon examination, facial hyperemia, conjunctivitis, pulse 102 BPM, blood PRESSURE 95/70 mm Hg were detected. the Tongue is densely overlaid at the root, the liver is enlarged, the edge is sensitive on palpation, the spleen edge is palpated. The muscles, especially the calves, are painful on palpation, the urine is darker than usual, and the amount of it is reduced. There are no meningeal symptoms. His disease is associated with hypothermia (he worked in a dacha, built a shed, washed his hands in a pit with water). Sent for hospitalization with the diagnosis of "flu".

1. Do You agree with the diagnosis of the clinic's doctor? Is there any reason to suspect leptospirosis?
2. What should I do to confirm the diagnosis?
3. Tactics of conducting the patient.

Answer

1. There is no data for the flu. Given the severe intoxication within 5 days, the absence of catarrhal symptoms, hyperemia of person, scleritis, pronounced pain in the muscles, especially in calf, enlarged liver and spleen, reducing the amount of urine, as well as data of anamnesis (washed my hands standing in the AOD), we can assume leptospirosis.
2. To confirm the diagnosis, a clinical blood test should be performed (neutrophilic leukocytosis is characteristic, ESR increases), when examining the urine, albuminuria, microhematuria, cylindruria are detected, the diagnosis is confirmed by a positive reaction of microagglutination with Leptospira (positive from the second week of the disease).
3. The patient should be hospitalized in an infectious hospital, shown detoxification therapy, the appointment of antibiotics, symptomatic agents.

Literature

1. E. P. Shuvalova, E. S. Belozerov, T. V. Belyaeva, E. I. Zmushko. Infectious disease. Textbook for Universities. 2001.
2. V. I. Pokrovsky, S. G. Pak, N. I. Briko, and B. K. Danilkin. Infectious diseases and epidemiology. Textbook for Universities. Moscow. 2003.

3. N. D. Yushchuk, Yu. Ya. Vengerov. Lectures on infectious diseases. Moscow. 2007.
4. Yu. V. Lobzin. Selected questions of therapy of infectious patients. Saint Petersburg, 2005.
5. A. L. Lesnikov, K. N. Tokarevich. Leptospirosis. L-d, Medicine. 1982.