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VECTOR-BORNE INFECTIOUS DISEASES

Module 3

Manual for practical training and independent work

For students of the 5th year of medical faculty

Specialty 222«General Medicine»

Master's level of training

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Introduction

Vector-borne infectious diseases, such as Malaria, Tick-borne encephalitis, Lyme disease, Epidemic typhus, of Marseilles fever, Leishmaniasis, Brucellosis, cause a significant fraction of the global infectious disease burden; indeed, nearly half of the world's population is infected with at least one type of vector-borne pathogen. Vector-borne plant and animal diseases, including several newly recognized pathogens, reduce agricultural productivity and disrupt ecosystems throughout the world. These diseases profoundly restrict socioeconomic status and development in countries with the highest rates of infection, many of which are located in the tropics and subtropics.

From the perspective of infectious diseases, vectors are the transmitters of disease-causing organisms; that is, they carry pathogens from one host to another. By common usage, vectors are normally considered to be invertebrate animals, usually arthropods, but they may also include fomites, which are defined as “any inanimate object that may be contaminated with disease-causing microorganisms and thus serves to transmit disease”, or rodents, which carry the agent from a reservoir to a susceptible host. Vectors of human disease are typically species of mosquitoes and ticks that are able to transmit viruses, bacteria, or parasites to humans and other warm-blooded hosts. For the purposes of this discussion, a disease that is transmitted to humans, plants, or animals by any agent, arthropod, or fomite is a vector-borne disease.

The considerable economic, ecological, and public health impacts of vector-borne diseases are expected to continue, given limited domestic and international capabilities for detecting, identifying, and addressing likely epidemics. Much remains to be discovered about the biology of these diseases, and in particular about the complex biological and ecological relationships that exist among pathogens, vectors, hosts, and their environments. Such knowledge is essential to the development of novel and more effective intervention and mitigation measures for vector-borne diseases.

This manual presents modern data on the etiology, epidemiology, pathogenesis, clinical manifestations, diagnosis and treatment of Malaria, Tick-borne encephalitis,

Lyme disease, Epidemic typhus, of Marseilles fever, Leishmaniasis, Brucellosis as well as the indicative amount of the scheme, the timing of examination of patients and interpretation of the results. The annex presents the algorithms of diagnostics, treatment of these diseases and diagnostic test systems permitted for use.

TICK-BORNE ENCEPHALITIS, LYME DISEASE, EPIDEMIC TYPHUS, MARSEILLES FEVER

Actuality of theme

1.1 General description of infectious diseases with the transmissible mechanism of transmission.

These are diseases which the source of infection without effective carrier usually not dangerous. Transmission of infectious need alive carrier (insect), their bodies take a place in certain cycle of the parasite. Carriers of transmissible infections are ticks, mosquitoes, gnats, blind, mokretsi, fleas, lice, bugs etc. General classification of the diseases with the transmissible mechanism of transmission:

1. arbovirus diseases:

A) *viral encephalitis (tick-borne encephalitis)*;

B) hemorrhagic fevers (Lassa, Marburg, Ebola, yellow, etc.);

C) systemic fever (denhe, panyatachi etc.);

2. rickettsial (typhus epidemic, Marseille fever etc.);

3. spirochetosis (Lyme disease, rotary etc.);

4. diseases caused by protozoa (malaria, leishmaniasis, etc.);

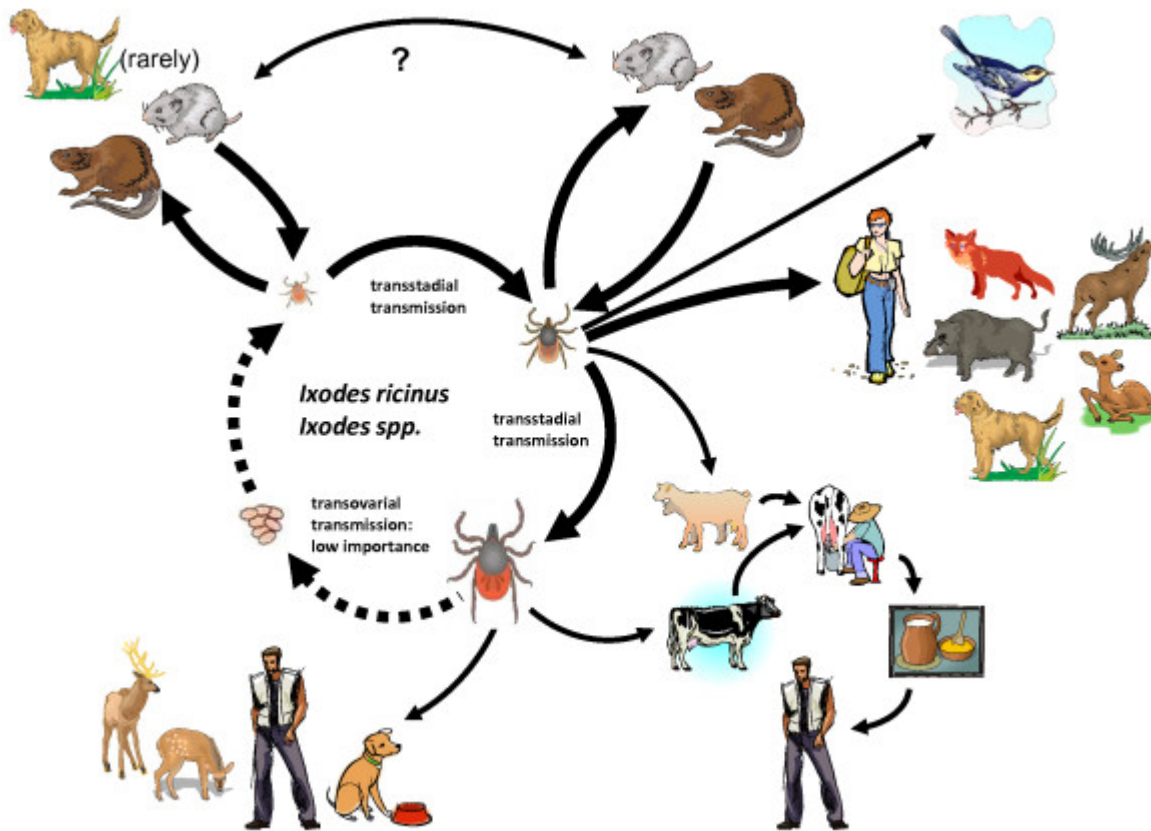
5. diseases caused by helminths (filyariozy).

1.2 Tick-borne encephalitis

Etiology The neurotropic TBEV was first described as the cause of TBE by Zilber more than 75 years ago. It is RNA virus, a member of genus Flavivirus. The mature virion is composed of 3 structural proteins-capsid (C), membrane (M), and envelope (E). Protein E is a major antigen which induces production of neutralizing antibodies. The genetic analysis shows the existence of three TBEV subtypes named as European, Siberian, and Far-Eastern subtype. They are genetically very closely related; variation between subtypes is 5%-6%. In spite of the pronounced genetic similarity of the

subtypes the illness caused by individual subtype is not completely equivalent to those due to the other subtypes.

Epidemiology TBE is endemic in Europe, Siberia, far-eastern Russia, northern China and Japan. During the past few decades endemic regions have expanded. The European TBEV subtype is predominantly found in Europe, but sometimes in west Urals, and in Siberia, whereas the Siberian TBEV subtype is found in Siberia, the Baltics, and northern Finland. The Far-Eastern TBE virus subtype is endemic in far-eastern Asia and Japan, and has been identified also in central and eastern Siberia. The primary reservoirs and hosts of TBEV in nature are small rodents; humans do not play any role in the maintenance of TBEV in nature and they are only accidental hosts. TBEV is transmitted to humans mainly by tick bites; in Europe the principal vector is *Ixodes ricinus* (*I. ricinus*), in parts of Eastern Europe, Russia and in far-east Asia the vector is *Ixodes persulcatus* (*I. persulcatus*) whereas in Japan Far-Eastern TBEV subtype has been demonstrated in *Ixodes ovatus* ticks. In Eastern Europe and the Baltic countries was registered cases of infection when people use unpasteurized milk or milk products from infected livestock, particularly goats. TBE cases usually happen in the warm months between April and November, which is also the period of the highest tick activity. In all age groups men are affected more frequently than women, as well as children have infection in 10%-20% of all reported cases. It should be pointed out that due to its unspecific clinical presentation TBE in children is often missed and is diagnosed as aseptic meningitis of unknown etiology. Because of tourism it becomes global problem in not endemic areas. It depends also on the season of travel, degree of unprotected outdoor exposure as well as on consuming unpasteurized dairy products. The risk of travel-associated TBE depends on the season of travel, degree of unprotected outdoor exposure as well as on consuming unpasteurized dairy products and availability of vaccination. Risk of infection of non-vaccinated tourist, who stay in a highly endemic region for 4 weeks during the TBEV transmission season, equivalent to the risk of contracting typhoid fever or malaria while traveling in India.



Schematic drawing of the transmission cycle of tick-borne encephalitis virus. The dog can serve as host for all three life stages of the Ixodes tick, i.e. the larvae, the nymph and the adult tick. As with humans it is rather the nymphs and even more numerous the adults that feed on dogs. The alimentary infection of humans via TBE virus-contaminated milk is also shown. Although this frequently causes clusters of infection in humans, we are not aware of such an infection route for dogs.

Classification:

1. Asymptomatic form.
2. Abortive form of TBE.
3. TBE with normal cerebrospinal fluid cell counts.
4. Encephalitis.
5. Meningitis.
6. Myelitis.

7. Chronic progressive form of TBE.

Pathogenesis

After an infected tick bite TBEV replication occurs locally. Dendritic skin cells (Langerhans cells) are assumed to be the first cells for viral replication and to transport the virus to local lymph nodes. From this initial site the TBEV then disseminate to extraneural tissues, especially spleen, liver and bone marrow, where further multiplication maintains viremia for several days. During the viremic phase (which clinically corresponds to the initial phase of TBE) the virus probably reaches the brain.

The primary targets of TBEV infection in central nervous system are neurons. According to rather limited information the neuropathological findings are nonspecific. Cerebral and spinal meninges usually show diffuse infiltration with lymphocytes and sometimes neutrophils. The most extensive meningeal inflammation is in the vicinity of the cerebellum. Pathological lesions which consist of lymphocytic perivascular infiltrations, accumulation of glial cells, nerve cells necrosis, and neuronophagia are localized in the grey matter and are most often present in the medulla oblongata, pons, cerebellum, brainstem, basal ganglia, thalamus, and spinal cord. Rarely, oligodendrocytes are infected. In the motor area of the cerebral cortex degeneration and necrosis of the pyramidal cells, lymphocytic accumulation, and glial proliferation are present.

Signs and symptoms. Infections with TBEV from 70% to 98% are asymptomatic. The incubation period of TBE ranges from 2 to 28 days and is usually 7-14 days. After alimentary TBEV transmission the incubation period is as a rule shorter, usually 3 to 4 days.

About 75% of patients with TBE due to the European TBEV subtype the disease has a typical biphasic course. The majority of patients with monophasic course of the disease has central nervous system involvement (meningitis, meningoencephalitis), while a small fraction has a febrile illness with headache but no meningitis (i.e., the initial phase

of TBE not followed by the second, meningoencephalitic phase of the disease), named abortive form of TBE or “febrile headache”.

The initial phase correlate with viremia and usually presents with non-specific symptoms such as moderate fever, headache, body pain (myalgia and arthralgia), fatigue, general malaise, anorexia, nausea, and others. This phase lasts for 2 to 7 d and is followed by amelioration or even an asymptomatic interval that usually lasts for about 1 wk (1-21 d). Then the second phase appears: in approximately 50% of adult patients it presents as meningitis, in about 40% as meningoencephalitis, and in around 10% as meningoencephalomyelitis.

Meningitis, encephalitis, myelitis.

Meningitis and encephalitis are the most frequent clinical forms of TBE. Meningitis typically manifests with high fever, headache, nausea and vomiting; many patients have photophobia, and some vertigo. Meningeal signs are present in most of patients. Encephalitis can be manifested by impaired consciousness ranging from somnolence to stupor and, in rare cases, coma. Other manifestations comprise personality changes, behavioral disorders, concentration and cognitive function disturbances, tongue fasciculations and tremor of extremities; very rarely focal or generalized seizures, delirium and psychosis develop. Flaccid pareses, that are a typical characteristic of meningoencephalomyelitis, usually arise during the febrile phase of the disease, and are occasionally preceded by severe pain in the affected muscle groups. The upper extremities are more often affected than the lower extremities and the proximal segments more frequently than the distal ones. Patients with pareses of respiratory muscles rather commonly require artificial ventilatory support. Involvement of the central portions of the brainstem and medulla oblongata are associated with poor prognosis. Myelitis usually occur with encephalitis, and only very rarely as the only manifestation of TBE. In patients with TBE the involvement of cranial nerves has been reported. Occasionally, patients with TBE have pronounced variability in heart rate or other signs of autonomic nervous system dysfunction

Abortive form of TBE.

Data on this manifestation of TBE are limited. It manifests with moderate fever, headache, fatigue, and other symptoms of initial phase of the disease that are not followed by nervous system involvement. The fever typically endures for several days, and the outcome of the disease is excellent. In Central Europe the majority of patients with the initial phase of TBE develop the second, central nervous system phase of the disease.

TBE with normal cerebrospinal fluid cell counts.

A patient with encephalitis and serologically confirmed TBEV infection but without CSF pleocytosis has been reported.

Chronic progressive form of TBE.

Cases of a chronic progressive form of TBE have been identified in Siberia and the Russian Far East. This form of TBE is believed to be caused by the Siberian TBEV subtype. Both mutation in the TBEV NS1 gene as well as an inappropriate T-cell immune response have been implicated to be associated with chronic progressive disease. Clinical presentations include Kozshevnikov's epilepsy, lateral sclerosis, progressive neuritis, progressive muscle atrophy, and a Parkinson-like disease.

Complications. *Cerebral edema* is a potential complication of acute viral encephalitis that aggravates the clinical picture and portends poor neurologic outcome.

Post-encephalitic syndrome. TBE may cause long-lasting morbidity which often has an impact on patients' quality of life and, sometimes, necessitates an alteration of lifestyle. Published data suggest that 40% to 50% of patients after acute TBE develop a post-encephalitic syndrome. The most frequently reported symptoms have been cognitive disorders, neuropsychiatric complaints (such as apathy, irritability, memory and concentration disorders, altered sleep pattern), headache, hearing loss and/or tinnitus, disturbances of vision, balance and coordination disorders, and flaccid paresis or paralysis.

Diagnosis. A case of TBE is delineated by the presence of: (1) symptoms/signs indicating meningitis or meningoencephalitis; (2) an elevated cerebrospinal fluid cell count ($> 5 \times 10^6$ cells/L); and (3) microbiologic evidence of TBEV infection (the presence of specific IgM and IgG antibodies).

Blood and cerebrospinal fluid analysis. In patients with TBE blood and cerebrospinal fluid findings are nonspecific. In the first (viremic) phase of TBE leukopenia and/or thrombocytopenia is established in approximately 70% of patients, rarely abnormal liver function test results are seen. In the second phase of the disease mildly elevated leukocyte count may be present in peripheral blood (rarely $> 15 \times 10^9$ /L); erythrocyte sedimentation rate and concentration of C-reactive protein are normal in the majority of patients but may be elevated, particularly in some long-lasting severe cases. Cerebrospinal fluid examination typically reveals elevated leukocyte counts (usually lower than 500 cells/mm³), a normal glucose concentration, and a normal to slightly elevated protein concentration. Early in the course of the disease neutrophils may predominate, while later cerebrospinal fluid profile is characterized by a predominance of lymphocytes. Elevated lymphocyte counts may last for several weeks after clinical improvement.

Microbiological investigations. At the time when neurological symptoms/signs occur TBEV has already been cleared from the blood (TBEV is present in blood in the initial but not in the meningoencephalitic phase of the disease) and is only very exceptionally present in cerebrospinal fluid. Consequently, isolation of TBEV from blood and detection of viral RNA by reverse transcriptase PCR in blood and cerebrospinal fluid of patients with TBE have a limited diagnostic yield and are as a rule not used in clinical practice. Reverse transcriptase PCR assays is mainly limited to the initial phase of the disease and could be a useful method in a diagnostic procedure of febrile illness occurring after a tick bite in areas where several tick-borne diseases are present.

The routine laboratory confirmation of the TBEV infection is based mainly on the demonstration of specific antibodies in serum (and cerebrospinal fluid), usually by

highly sensitive and specific enzyme-linked immunosorbent assay. In the majority of patients specific serum IgM and IgG antibodies are present at the beginning of the meningoencephalitic phase of the disease; rarely only IgM antibodies to TBEV are found in the first serum sample. In such cases a second serum sample has to be tested 1-2 wk later, because the demonstration of IgM antibodies alone does not suffice for the diagnosis. TBEV IgM antibodies can be detected in the serum for several months (up to 10 mo or even longer) after acute infection, whereas TBEV IgG antibodies persist for a whole life, and mediate an immunity that prevents symptomatic re-infection. In cerebrospinal fluid specific IgM and IgG antibodies are detectable several days later than in serum, and in almost all cases by day 10. However, some limitations are necessary to take into account when using and interpreting serological testing. Specific TBE IgM antibodies may be detectable for several months after acute TBEV infection (as well as in some persons after the first two doses of primary immunization) and may lead to erroneous interpretation in case of another central nervous system disease/infection within this time period.

Differential diagnosis. The differential diagnosis of TBE is extensive and includes a wide variety of central nervous system infections due to other infectious agents as well as noninfectious diseases. In the initial, viremic phase of TBE, when a patient presents with fever, headache, arthralgia, myalgia, and malaise the differential diagnosis may include various viral syndromes; if nausea, vomiting, diarrhea, and anorexia are present, gastroenteritis is a possible explanation. When signs and symptoms of central nervous system involvement develop, TBE needs to be differentiated from encephalitis or aseptic meningitis due to many other viruses. Differential diagnosis comprises also other tick-borne diseases such as Lyme borreliosis, babesiosis, human granulocytic anaplasmosis, tick-transmitted rickettsioses, and tularemia.

Treatment. There is no specific antiviral treatment for TBE. Patients as a rule need hospitalization and supportive care based on the severity of signs/symptoms, and usually encompasses administration of antipyretics, analgesics, antiemetics, maintenance of

water and electrolyte balance, and if necessary administration of anticonvulsive agents. In patients with neuromuscular paralysis leading to respiratory failure, intubation and ventilatory support are necessary.

Cerebral edema is a potential complication of acute viral encephalitis that aggravates the clinical picture and portends poor neurologic outcome. Patients who have significantly raised intracranial pressure are often treated with intravenous mannitol and/or steroids. Occasionally high dose intravenous immunoglobulins is used for patients with severe TBE.

Prophylaxis. *Nonspecific preventive measures* comprise pasteurization of milk, reduction of tick population, and personal protective procedures.

Specific preventive measures - vaccination. Historically, immunoglobulins containing gamma globulin against TBEV were used as a prophylaxis against TBE within 96 h after a tick bite in the TBE endemic regions (post-exposure prophylaxis). in a dose of 0.05 mL/kg body weight. Active immunization is the most effective way to prevent TBE. Given that TBE is a zoonosis, that the source of infection is an infected animal, and that TBEV is transmitted by a tick bite and does not spread from human to human, vaccination enables only individual protection. Consequently, high immunization rate of a population in a given environment does not protect persons who are not vaccinated.

1.3. LYME DISEASE

Etiology. The members of *Borrelia* species are spirochetes, which are motile, spiral, or wavy bacteria that are only distantly related to gram-negative and gram-positive pathogens. The genomes of *B. burgdorferi*, *B. afzelii*, and *B. garinii* comprise small linear chromosomes of approximately 1000 kb, and 17 to 21 linear and circular plasmids totaling another 400 to 500 kb.

Spirochetes have two cellular membranes like gram-negative bacteria, but their flagella, the organelles of motility, are uniquely located between in the inner and outer membrane

rather than on the surface. *B. burgdorferi* is 8 to 30 microns in length and about 0.2 microns in width. Their narrowness accounts for the inability to see unstained or Gram stained cells by standard light microscopy.

Epidemiology. Lyme disease is transmitted to humans by the bite of infected ticks of the Ixodes genus. Usually, the tick must be attached for 36 to 48 hours before the bacteria can spread. In North America, the only bacterium involved is Borrelia burgdorferi sensu stricto, while in Europe and Asia, the bacteria Borrelia afzelii and Borrelia garinii are also causes of the disease. The disease does not appear to be transmissible between people, by other animals, or through food.

Pathogenesis. Advances in the understanding of the interactions that occur between Borrelia burgdorferi and its mammalian and tick hosts have led to important insights into the pathogenic mechanisms that underlie the manifestations of human Lyme disease. With the sequencing of the B. burgdorferi genome came several surprising insights. Among these is the fact that B. burgdorferi has a very small genome compared with other bacteria. It does not encode for any toxins or lipopolysaccharides, but does encode a large number of lipoproteins relative to other bacteria. Also missing from its genome are genes that enable bacteria to synthesize such essential products as amino acids, fatty acids, enzyme cofactors, and nucleotides. As such, B. burgdorferi is dependent upon its environment to provide these nutrients and has evolved specialized mechanisms for adapting to its different environments.

The lifecycle of B. burgdorferi requires that it survive in two distinct environments — that found in a tick host and that found in a mammalian host. The challenges posed by these environments differ greatly. Because ticks do not thermoregulate, while in the tick host B. burgdorferi must survive at the extremes of ambient temperatures found in winter and summer in its areas of geographic distribution. In addition, ticks take only one blood meal every 6 to 12 months, and as a result, B. burgdorferi must be able to survive with minimal nutrition for long periods of time. In contrast, life in a mammalian host provides a stable temperature and an

abundance of nutrients. However, compared with ticks, which have rudimentary immune systems, mammals have highly sophisticated immune defenses. The ability of *B. burgdorferi* to cause long-term infection in mammalian hosts requires that it implement strategies to successfully evade and subvert host immune defenses. Optimal host immune control of *B. burgdorferi* infection requires both innate and adaptive immune systems. However, neither system, alone or in combination, is able to completely eradicate the organism in mice despite resolution of signs of infection and inflammation. In humans, it appears that the immune system can eventually eradicate the infection, since almost all patients eventually resolve their symptoms even without antibiotics. In Europe, *B. afzelii* has been cultured from skin lesions of patients in Europe with acrodermatitis atrophicans after greater than 10 years, but this genotype is not present in the United States.

Signs and symptoms.

Early Lyme Disease.

The early stage of Lyme disease is usually marked by one or more of the following symptoms and signs:

- Fatigue
- Chills and fever
- Headache
- Muscle and joint pain
- Swollen lymph nodes
- Characteristic shin rash called erythema migrans

Erythema migrans is a red circular patch that appears usually 3 days to 1 month after the bite of an infected tick at the site of the bite. The patch then expands, often to a large size. Sometimes many patches appear, varying in shape, depending on their location. Common sites are the thigh, groin, trunk, and the armpits.

The center of the rash may clear as it enlarges, resulting in a bulls-eye appearance. The rash may be warm, but it usually is not painful. Not all rashes that occur at the site of a

tick bite are due to Lyme disease, however. For example, an allergic reaction to tick saliva often occurs at the site of a tick bite. The resulting rash can be confused with the rash of Lyme disease. Allergic reactions to tick saliva usually occur within hours to a few days after the tick bite, usually do not expand, and disappear within a few days.

Late Lyme Disease.

Some symptoms and signs of Lyme disease may not appear until weeks, months, or years after a tick bite:

- Arthritis is most likely to appear as brief bouts of pain and swelling, usually in one or more large joints, especially the knees.
- Nervous system abnormalities can include numbness, pain, Bell's palsy (paralysis of the facial muscles, usually on one side), and meningitis (fever, stiff neck, and severe headache).
- Less frequently, irregularities of the heart rhythm occur.
- In some persons the rash never forms; in some, the first and only sign of Lyme disease is arthritis, and in others, nervous system problems are the only evidence of Lyme disease.

Complications. People at highest risk for persistent symptoms are those who go the longest before treatment. Fortunately, public vigilance has significantly reduced the rates of late-stage Lyme disease. Antibiotics given at late stages will relieve symptoms in most people, although about 5% may continue to have problems. Left untreated, Lyme disease can spread (disseminate). The infection may affect almost any part of the body and cause the following complications:

- severe arthritis;
- persistent fatigue;
- mood disturbances and loss of concentration;
- neuropathy (numbness, tingling, or other odd sensations in the hands, arms, feet or legs);

- life-threatening disorders affecting the heart, lungs, or nervous system(meningitis)can occur, but are very rare;
- post-Lyme disease syndrome.

Diagnosis. Lyme disease is often difficult to diagnose because its symptoms and signs mimic those of many other diseases. The fever, muscle aches, and fatigue of Lyme disease can easily be mistaken for viral infections, such as influenza or infectious mononucleosis. Joint pain can be mistaken for other types of arthritis, such as rheumatoid arthritis, and neurologic signs can mimic those caused by other conditions, such as multiple sclerosis. At the same time, other types of arthritis or neurologic diseases can be misdiagnosed as Lyme disease. Diagnosis of Lyme disease should take into account:

- history of possible exposure to ticks, especially in areas where Lyme disease is known to occur;
- symptoms and signs;
- the results of blood tests used to determine whether the patient has antibodies to Lyme disease bacteria These tests are most useful in later stages of illness, but even then they may give inaccurate results. Laboratory tests for Lyme disease have not yet been standardized nationally.

Treatment and prognosis. Lyme disease is treated with antibiotics under the supervision of a physician. Several antibiotics are effective. Antibiotics usually are given by mouth but may be given intravenously in more severe cases. Patients treated in the early stages with antibiotics usually recover rapidly and completely. Most patients who are treated in later stages of the disease also respond well to antibiotics. In a few patients who are treated for Lyme disease, symptoms of persisting infection may continue or recur, making additional antibiotic treatment necessary. Varying degrees of permanent damage to joints or the nervous system can develop in patients with late chronic Lyme disease. Typically these are patients in whom Lyme disease was unrecognized in the early stages or for whom the initial treatment was unsuccessful.

Rare deaths from Lyme disease have been reported. Preventive Antibiotic Treatment Antibiotic treatment to prevent Lyme disease after a known tick bite may not be warranted. Physicians must determine whether the advantages of using antibiotics outweigh the disadvantages in any particular instance. If antibiotics are not used, physicians should alert patients to the symptoms of early Lyme disease and advise them to return for reevaluation if symptoms occur. Recent studies on the prophylactic value of single-dose doxycycline for the prevention of Lyme disease indicate that a 200-mg dose administered within 72 hours of tick removal can prevent disease in 87% of test subjects. However, it is worth noting that several prior controlled treatment trials found no benefit in prophylaxis.

Prophylaxis.

Prophylaxis may be considered if:

- The tick is identified as an engorged deer tick and was attached for at least 24 hours
- The patient resides in an area where the prevalence of Lyme disease in ticks is greater than 20%
- Prophylaxis can be started within 72 hours of tick removal
- There are no contraindications to doxycycline

To prescribe antibiotic prophylaxis selectively to prevent Lyme disease, health care practitioners in areas of endemicity should learn to identify *I. scapularis* ticks, including its stages , and to differentiate ticks that are at least partially engorged with blood . Testing of ticks for tick borne infectious agents is not recommended, except in research studies.

1.3. EPIDEMIC TYPHUS.

Typhus refers to a group of infectious diseases that are caused by rickettsial organisms and that result in an acute febrile illness. Arthropod vectors transmit the etiologic agents

to humans. The principle diseases of this group are epidemic or louse-borne typhus and its recrudescence form known as Brill-Zinsser disease, murine typhus, and scrub typhus.

Etiology. Louse-borne typhus is caused by *Rickettsia prowazekii*, an obligate intracellular gram-negative bacterium with a singular circular chromosome of 1.1 Mb. *R. prowazekii* belongs to the typhus group of the *Rickettsia* genus. *Rickettsia typhi*, responsible for endemic typhus, also belongs to the typhus group of the *Rickettsia* genus but is transmitted by fleas. Genomic analysis demonstrates two strains of *Rickettsia prowazekii*; one isolated only from humans and another identified in flying squirrels (*Glaucomys volans*) which is responsible only for sporadic typhus cases.

Epidemiology. Historically, large suspected outbreaks of epidemic typhus occurred worldwide especially among military troops during the Napoleonic Wars, and first and second World Wars. Epidemic typhus was widespread globally prior to the introduction of modern antibiotics. Outbreaks of louse-borne typhus occur during the colder months and have been associated with the overcrowded and unsanitary conditions that are prevalent in time of war. Epidemic typhus is rarely found among travellers. It can occur in vulnerable populations where body lice are prevalent (e.g. homeless populations in impoverished areas or refugee camps). Between the 1950s and 1980s, large epidemics of louse-borne typhus became less frequent and its geographical distribution has declined due to improvements in living standards. During this period, sporadic cases of plausible zoonotic origin (in the USA) and Brill-Zinsser disease were reported in the literature. During the 1990s, louse-borne typhus re-emerged in foci associated with poor sanitary conditions (such as in prisons and refugee camps) and a colder climate found in mountainous regions. Outbreaks were reported in the rural highlands of Central and South America (especially in Peru) and Africa (Burundi, Uganda, Ethiopia, Nigeria and Rwanda). Sporadic cases or small suspected outbreaks were identified in Northern Africa, Russia and Kazakhstan, and among homeless populations in developed countries.

Sporadic cases of epidemic typhus from a probable zoonotic origin have been reported in several states of the eastern United States in recent decades. Tick-associated reservoirs of *R. prowazekii* have been described in ticks in Ethiopia and Mexico. The importance for human epidemiology is expected to be limited. Late relapse of epidemic typhus (Brill–Zinsser disease) might be the source of a re-emerging outbreak.

Pathogenesis. Epidemic typhus is the prototypical infection of the typhus group of diseases, and the pathophysiology of this illness is representative of the entire category. The arthropod vector of epidemic typhus is the body louse (*Pediculus corporis*). This is the only vector of the typhus group in which humans are the usual host. *Rickettsia prowazekii*, which is the etiologic agent of typhus, lives in the alimentary tract of the louse. A *Rickettsia*-harboring louse bites a human to engage in a blood meal and causes a pruritic reaction on the host's skin. The louse defecates as it eats; when the host scratches the site, the lice are crushed, and the *Rickettsia*-laden excrement is inoculated into the bite wound. The *Rickettsia* travel to the bloodstream and rickettsemia develops. *R. prowazekii* is also thought to be transmitted by fleas associated with flying squirrels and their nesting material, by inhaling dried louse feces, or by rubbing *Rickettsia*-containing louse feces inadvertently into eyes, mucous membranes, or in insect bite-associated wounds.

Rickettsia parasitize the endothelial cells of the small venous, arterial, and capillary vessels. The organisms proliferate and cause endothelial cellular enlargement with resultant multiorgan vasculitis. This process may cause thrombosis, and the deposition of leukocytes, macrophages, and platelets may result in small nodules. Thrombosis of supplying blood vessels may cause gangrene of the distal portions of the extremities, nose, ear lobes, and genitalia. This vasculitic process may also result in loss of intravascular colloid with subsequent hypovolemia and decreased tissue perfusion and, possibly, organ failure. Loss of electrolytes is common.

Some people with a history of typhus may develop a recrudescent type of typhus known as Brill-Zinsser disease. After a patient with typhus is treated with antibiotics and

the disease appears to be cured, *Rickettsia* may linger in the body tissues. Months, years, or even decades after treatment, organisms may reemerge and cause a recurrence of typhus. How the *Rickettsia* organisms linger silently in a person and by what mechanism recrudescence is mediated are unknown. The presentation of Brill-Zinsser disease is less severe than epidemic typhus, and the associated mortality rate is much lower. Risk factors that may predispose to recrudescent typhus include improper or incomplete antibiotic therapy and malnutrition.

Signs and symptoms. The incubation period of epidemic louse-borne typhus is typically between 10 and 14 days. The symptoms are associated with infections of endothelial cells and the subsequent rickettsia-induced vasculitis. The onset of symptoms is usually sudden after a prodromal phase of malaise lasting a few days. Symptoms (relative frequency given in brackets) include high fever (100%), headache (91–100%), tachypnoe (97%), chills (82%) and muscle tenderness (70%), the latter being generally intense. Rash is frequent and this clinical feature is noteworthy for supporting the diagnosis. It starts in the axillae, mostly spreads over the trunk, and may extend centrifugally towards extremities (generally sparing the face, palms and soles). Lesions initially appear as non-confluent erythematous and blanching areas, but later as petechial and even purpuric lesions, and are often attributed to vasculitis (in around one third of patients).

Various central neurological system symptoms can be observed (e.g. confusion, stupor, coma and seizures). In addition, unspecific clinical manifestations (relative frequency given in brackets) might be associated with epidemic typhus such as abdominal pain (60%), nausea (32%), arthralgia (50%), cough (38%) and less frequently conjunctivitis. Splenomegaly may also be seen.

The case–fatality ratio can reach 60% among untreated patients, decreasing to below 5% with appropriate antibiotic treatment and supportive care. Common laboratory abnormalities include thrombocytopenia, increased blood urea and increased hepatic transaminase levels.

Brill–Zinsser disease is a late relapse which can occur months or years after the initial *R. prowazekii* infection. The clinical presentation is similar to louse-borne typhus but is associated with a lower mortality rate. Sporadic cases of *R. prowazekii* infection presumably acquired from a zoonotic origin present with symptoms comparable to louse-borne typhus.

Complications of systemic vasculitis can occur with multiple organ dysfunction syndrome, and peripheral and cerebral thrombosis.

Diagnosis. The laboratory diagnosis is based on serological tests such as indirect immunofluorescence assays and enzyme immunoassays. A four-fold increased titer of specific antibodies against *R. prowazekii* in acute and convalescent serum samples supports the diagnosis.

Serologic testing cannot stand alone as a means to confirm infection by *R. prowazekii* and should be interpreted in the context of the clinical presentation, immunological status of the patient and results of others supporting laboratory tests. Primary infection cannot be differentiated from Brill–Zinsser disease using IgG antibody levels. Culture can be used to isolate *R. prowazekii* from clinical samples but PCR-based genomic assays on blood and tissues can now distinguish *R. prowazekii* from *R. typhi* and other rickettsiae belonging to the spotted-fever group. Particularly, quantitative real-time PCR assays have a good specificity for species identification using species-specific probe targeting the *gltA* gene .

Differential diagnosis includes malaria, typhoid fever, viral haemorrhagic fever, leptospirosis, endemic typhus, tick-borne and louse-borne relapsing fevers, non-typhoidal salmonellosis, meningococcal septicaemia and meningitis.

Treatment. Tetracycline and chloramphenicol antibiotics are highly effective therapies for epidemic typhus. Early and empirical antibiotic administration should be prescribed when the diagnosis is suspected. Treatment failure within 48–72 hours is in favor of another etiology as a patient infected with *R. prowazekii* should improve significantly within 48 hours of initiation of therapy. Chloramphenicol treatment for five days (orally or intravenous) was proposed as first-line treatment in limited laboratory settings as this empirical treatment addresses other bacterial etiologies (notably meningococemia and typhoid fever). In outbreak situations, a single 200 mg oral dose of doxycycline has been used to limit the occurrence of relapses. Supportive care can be required in patients with a severe form of epidemic typhus.

Prognosis. The prognosis depends on what types of complications an individual patient experiences. While children usually recover well from epidemic typhus, older adults may have as much as a 60% death rate without treatment. Brillinsser, on the other hand, carries no threat of death.

Prevention. Primary prevention of louse-borne typhus relies on measures to avoid infestation with body lice. Body lice are transmitted primarily by direct contact with an infested person, transmission of the body lice also occurs through fomites, like clothes or bedding. Body lice are highly susceptible to cold and desiccation. They are found on clothing close to the human skin. Discarding infected clothes is an effective way to control the infestation. If this is not possible, clothes should be washed in temperature above 60 °C.

In outbreak situations, dusting powder with an appropriate insecticide has been applied to obtain a rapid decrease of infested persons with some lasting benefits. There have been no reports of *R. prowazekii* transmission through substances of human origin. However, transmission via blood transfusion is theoretically possible. *R. prowazekii* has been experimentally transmitted to non-human primates and other animals via infected blood and a case of transfusion-transmitted *Rickettsia rickettsii* was reported.

Furthermore, asymptomatic donation is possible by clinically recovered individuals with chronic persistent infection.

Due to possible transmission, blood collection should be avoided in refugee camps and areas where the disease is endemic. Infected individuals should be deferred from donation until signs and symptoms are gone, and a course of treatment has been completed. However, in light of the chronicity of infection (i.e. Brill–Zinsser disease), a permanent deferral should be considered for infected persons without documentation of optimal therapy. Donation of cells, tissues and organs from donors deceased after typhus is not recommended. Under specific circumstances of exposure in an epidemic environment, the need for, and potential effectiveness of specific donor screening questions should be considered.

1.4. MARSEILLES FEVER.

This disease has been designated by many geographic names: Marseilles fever, Mediterranean spotted fever, Kenya tick typhus, South African tick bite fever, Israel tick typhus and Indian tick typhus.

Etiology. The etiologic agent is *Rickettsia conori*. *R. conori* is a typical spotted fever group rickettsia, having more than 90 % DNA homology with *Rickettsia*. There are also cross-reactive protein, lipopolysaccharide antigens and cross-protection antigens, shared among *R. conori*, *R. sibirica* and *R. rickettsii*. *R. conori* is an obligate intracellular and intranuclear agent. It has both toxic and hemolytic activity.

Epidemiology. Marseilles fever is transmitted by the common dog tick, *Rhipicephalus sanguineus*. V. Durand has shown that the dog constitutes the reservoir of the *R. conori*. Dogs have been shown to be susceptible to inoculation and their blood has been proved to be infective both for man and monkeys. *R. conori* is maintained transovarially in ticks and is transmitted to humans by tick bite. Cases occur mainly in warm months with the peak incidence in July, August, and September in many Mediterranean locations.

Pathogenesis .Pathogenesis is similar to rickettsioses of the group of epidemic typhus fever, but the changes of the vessels is less expressed. The primary affect ("black spot"), regional lymphadenopathy and allergic manifestations are typical. The primary affect is local inflammation of the skin on the place of the reproduction of rickettsial with necrosis in the center. The black crust appears on the 5-8 day till rising of the temperature.

Clinical manifestations. The primary affect ("black spot") is an early sign of the disease. The crust usually falls on 4-5 day of the normal temperature. The localization of the primary affect is the strips of the skin covering by clothes. It is revealed by difficulty, because the bite of the tick is painless. After the incubation period of 7 days, fever, myalgia, and headache characterize the onset of the disease. On the 2-4 day of the disease the rash appears on the abdomen and then by the chest and alone all the body, including palms and soles. The rash is maculopapular. There is no itch. The changes from the side of the internal organs are such as other rickettsioses. Often the spleen is enlarged, the liver is enlarged rarely. The meningeal syndrome is not typical. The leukopenia, lymphocytosis, the raising ESR is temperate.

Complications. The complications occur rarely. It may be thrombophlebitis, pneumonia.

Diagnosis. The methods of the laboratory diagnostics are serological (complement fixation and indirect hemagglutination, with antigen from *Rickettsia conori*).

Differential diagnosis. The differential diagnosis need to be considered with other rickettsioses because Marseilles fever has usually nonspecific manifestations. Alternative diagnoses that may include meningococemia, measles, typhoid fever, bacterial and viral meningitis, secondary syphilis, leptospirosis etc.

Treatment. Preparations of tetracyclines - tetracyclin, metacyclin, doxycyclin are most effective. Laevomycetin, erythromycin has less expressed action. At serious course of disease infuse antibiotics in vein or in muscle. Course of treatment carry out during all period of fever and 2 days of normal body temperature.

With

desintoxication purpose in vein infuse solution of glucose, solution of Ringer-loc, donor albumin, reopoliglyc, polyvitamin, ascorutin. At psychomotor exaltation and deliriums - aminasin, fenobarbital, sodium hydroxybutyrat, sibazon (seduxen); for rising a tone of cardiovascular system and disorders of circulation - cordiamin, coffein-sodiibenzoat, sulfocamphocain, ephedrinihydrochlorid, corglykon or strophanthin are indicated. At rising of intracranial pressure and the phenomena of meningism dehydration with due to furosemid (lasix), mannitis administered, sinapismuses or pepper emplastrum on nape and thorax, gastrocnemius muscle, feet, simultaneously intensive desintoxicative therapy and correction of hydro-electrolytic structure of a blood are also effective. At serious and very serious current of typhus use glucocorticoid preparations, anticoagulants (heparin or derivatives of dicumarin).

Prophylaxis. In endemic areas prophylaxis includes obligatory registration of the dogs every year, the processing of the dogs and the places of the tick.

2. Study purpose of practical studies:

2.1. The student must have an idea (read):

α - 1

1. Have a general idea about position of tick-borne encephalitis, Lyme disease, epydemic typhus, Marseilles fever in the structure of virulent diseases, prevalence in the world; study statistic data related to case rate, case mortality, event frequency as for today .

2. Get familiar with history of scientific study of tick-borne encephalitis, Lyme disease, epydemic typhus, Marseilles fever, have an idea of scientific contribution of natives cientists, in the history of scientific research in this field.

2.2. The student should know:

α - 2

- etiology, factors pathogenicity of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- pathogenesis of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- clinical and epidemiological peculiarities of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- pathogenesis, term of arising and clinical manifestations of the complications of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- laboratory diagnosis of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- principles of treatment of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- tactics in the event of arising urgent conditions of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- prognosis of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- rules of letting go from the hospital for the convalescences;
- prophylaxis of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever.

2.3. The student should be able to:

α - 3

- know how to examine patients and reveal main symptoms and syndromes of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever
- motivate the clinical diagnosis for well-timed direction the patient to the hospital;
- carry out the differential diagnosis of visceral and dermal tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- on base of the clinical examination to recognize the possible complications

and urgent conditions by tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;

- draw up the medical documentation after determination of the primary diagnosis of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever;
- know how to form the plan of laboratory and additional examination of the patient;
- interpret the results of the laboratory examinations;
- analyze the results of the specific methods of the diagnosis depending on the material and period of the disease;
- form the individual plan of the treatment with accounting epidemiological data, stage of the disease, complications, gravity of the condition, allergic anamnesis, accompanying pathology;
- render the urgent help until the hospital treatment;
- form the plan of antiepidemic and preventive actions in the centre of the infection;
- give the recommendations in respect of regime, diets, examinations, observations at period of convalescences.

2.4. Educational goals (goals of the person):

- Develop deontological conception in the study subjects.
- To be able to observe the rules of conduct in the bedside, the principles of medical ethics.
- Master the ability to establish psychological contact with the patient and his relatives.
- Develop knowledge of the impact of socio-hygienic factors on the prevalence of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever.

- The subject materials to develop a sense of responsibility for the timeliness and accuracy of professional activities.

3. Materials for out-class self-training (before practical classes)
3.1. Basic knowledge, skills which are necessary for studying of topic (interdisciplinary integration)

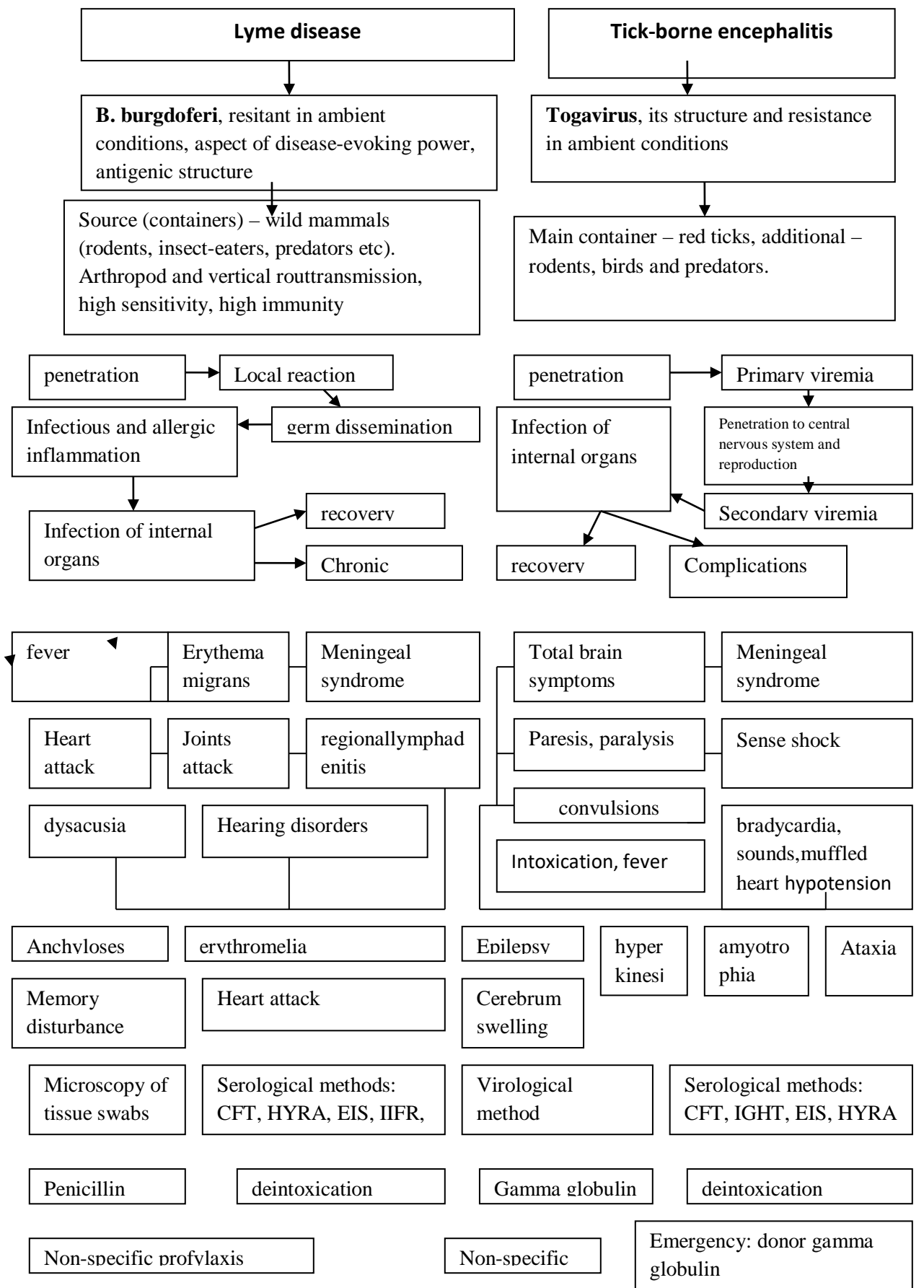
Disciplines	To know	Be able to
Microbiology	Properties of Rickettsia prowazekii and R. conorii ; B. burgdoferi and the virus of tick-borne encephalitis; rules and terms of sampling for specific diagnostics rules and time for collecting biologic material for specific diagnostics.	Interpret the results of the specific methods of the diagnosis of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever.
Physiology	Indexes of the laboratory examination in normal conditionals (the blood test, urine test, CSF).	Interpret the results of the laboratory examination.
Pathophysiology	Mechanism of function breaches of organs and systems under pathological conditions of different genesis.	Interpret pathological changes in the results of laboratory examination when functional breaches of organs and systems by different genesis are present.
	Indexes of the laboratory	Interpretation the result of

Biochemistry	examination (blood and liquor glucose, liquor protein, electrolytes)	the laboratory examination.
Immunology	Role of the immunity system in infectious process.	Value the data of the immunological examinations
Propedeutics of internal diseases	Main stages and methods of the clinical examination.	Ask the case history, conduct the clinical examination the patient, reveal the pathological symptoms, form the syndromes. Analyse the data you have got.
Epidemiology	Source of the infection, mechanism of the transmission, factors of the transmission by the tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever	Ask the epidemic anamnesis. Give the recommendations on preventive given disease.
Neurology	Pathogenesis, clinical signs in patients with tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever.	To conduct the clinical examinations the sick with defeat of the nervous system.
Dermatology	Clinical feature of exanthema.	To recognize and describe correctly the eruption in

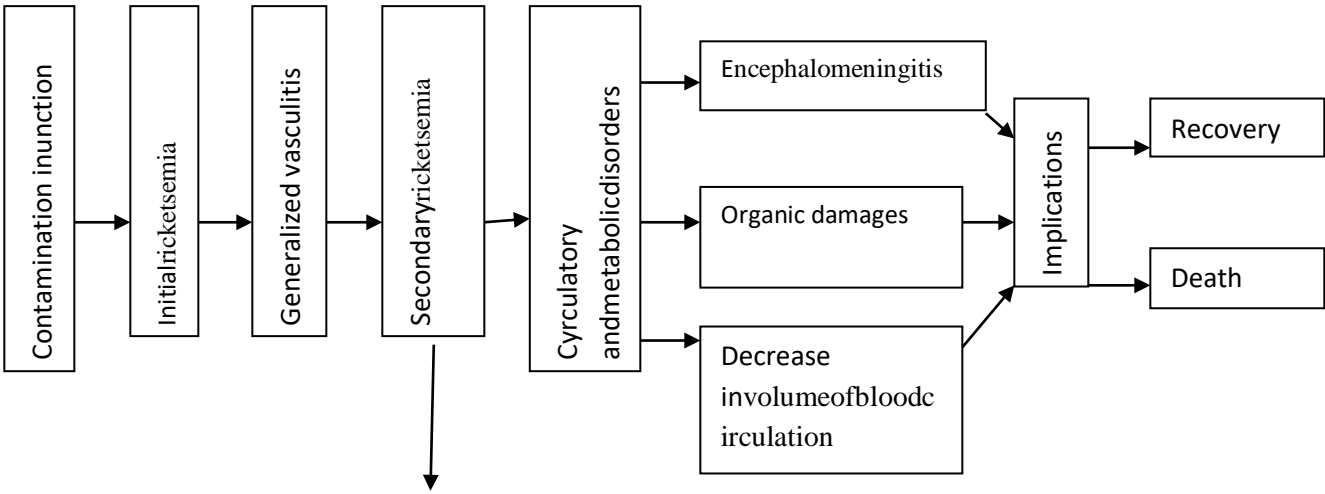
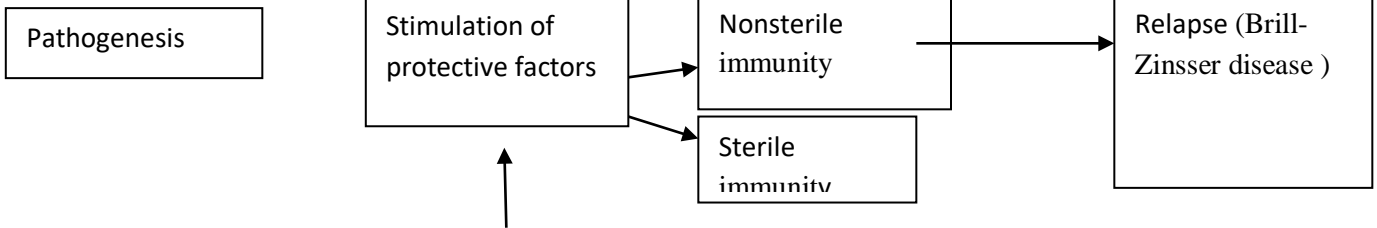
		patient with tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever.
Resuscitation and intensive therapy	Urgent conditions: expressed anemia, hemorrhagic diathesis, edema of larynx	Diagnose in good time and render urgent help under urgent conditions.
Clinical pharmacology	Pharmacodynamics and pharmacokinetics of drugs used in the treatment.	Choose optimum doses of drugs depending on forms of the disease.
Other disciplines		
Family practice	Pathogenesis, epidemiology, intensiveness of clinical signs, possible complications of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever. Principles of prophylactics and treatment.	Perform differential diagnostics of diseases with various genes at tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever . Find out tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever and possible complications; analyze results of laboratory examination. Admit the patient to contagious isolation ward in due

		time. Fill in the emergency notice. Provide rescue emergency care if required
Integration between subjects		
Virulent diseases	Features of infectious diseases. Methods of diagnostics, treatment and prophylactics of infectious diseases. Pathogenesis, epidemiology, intensiveness of clinical signs, laboratory diagnostics, possible complications specific features of clinical progress of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever. Prophylactics and treatment methods	Perform differential diagnostics of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever with other infectious diseases, their complications; analyze results of laboratory examination. Prescribe treatment. Provide rescue emergency care in pre-hospital stage.

3.2. Theme contents.



Epidemiology
 Anthroponosis; source – ill person, carrier; Transmission mechanism – transmissible (lice); routes – air and dust, blood transfusion; seasonality – January-March; susceptibility – general; immunity – sterile/nonsterile, prolonged



Clinics

Initial stage (before exanthema):
 Intoxication, agitation, hyperesthesia, dermahemia, enanthema

Main phase of disease (to normalization of body temperature):
 Govorov-Godeliersyndrome, exanthema, tachycardia,

Convalescent period:
 thrombosis, embolism (pulmonary embolism), infarcts, cerebrovascularaccidents

Implications

Specific: hemorrhagia, thromb detachment, embolism, endomyocarditis, psychosis, endarteritis

Nonspecific: pneumonia, otitis, parotitis, glomerulonephritis

Specific diagnostics

Bacteriologic

Serologic: complement fixation test, Rickettsia agglutination test, indirect immunofluorescence test

Treatment

Antibiotics **Detoxication** **Anticoagulant** **Disaggregant**

Preventive measures

Nonspecific (measures directed against pediculosis) **Vaccination indications**

3.4. Self-control materials

3.4.1. Questions for self-control

a - 1

1. Which group of infectious diseases with regard to source of infection and transmission mechanism does Lyme disease and tick-borne encephalitis refer to? 2. Routes of transmission of Lyme disease and tick-borne encephalitis.
3. Carriers of Lyme disease and tick-borne encephalitis.
4. Clinical classification of Lyme disease and tick-borne encephalitis.
5. Key symptoms in early period of Lyme disease.
6. Characteristics and main period of local modifications of Lyme disease.
7. Clinical signs of tick-borne encephalitis.
8. Complications of borreliosis.
9. Hemogram at Lyme disease and tick-borne encephalitis.
10. Specific diagnostic methods of Lyme disease and tick-borne encephalitis.
11. Modifications in cerebrospinal fluid at tick-borne encephalitis and Lyme disease.
12. Etiotropic therapy of Lyme disease.
13. Prophylactics of Lyme disease and tick-borne encephalitis.
14. Tick-borne encephalitis therapy.
15. Main pathogenic factors of rickettsia.
16. Describe the center of infection and infection carrier in the case of Brill-Zinsser disease.
17. Transmission mechanism of epidemic typhus.
18. Phases (chains) of pathogenesis of epidemic typhus.
19. Explain the concept of thrombovasculitis in the case of epidemic typhus.
20. Identify stages of the disease in the case of epidemic typhus.

21. Describe syndrome of encephalitis in the case of epidemic typhus.
22. Give implications of epidemic typhus.
23. What is the basis for early diagnostics of epidemic typhus?
24. Specific laboratory diagnostics of epidemic typhus.
25. Principles of casual treatment of epidemic typhus.
26. Describe epidemiology of Marseilles fever.
27. Describe primary affect in the case of Marseilles fever.
28. Duration of the disease phases in the case of Marseilles fever.
29. Complications of Marseilles fever.
30. Principles of diagnostics of Marseilles fever.
31. Principles of treatment of Marseilles fever.
32. Principles of preventive measures of Marseilles fever.
33. Principles of preventive measures of epidemic typhus.

3.4.2. Tests for self-control

Choose correct answers:

$\alpha=2$

1. Carriers of tick-borne encephalitis:
 - A. Red ticks
 - B. Mosquitoes
 - C. Fleas
 - D. Lice
 - E. Harvest mites.
2. Germs of Lyme diseases are:
 - A. *Borellia burgdoferi*
 - B. *Yerseniapestis*
 - C. *Salmonellatyphi*
 - D. *Leptospira interrogans*
 - E. *Yersenia pseudotuberculosis*.

3. Clinical forms of tick-borne encephalitis:

- A. Meningeal
- B. Bulbar
- C. Polyradiculoneuritic
- D. Encephalitic
- E. Fever

4. Clinical signs of nervous breakdown in the case of epidemic typhus is:

- A. insomnia;
- B. irritation
- C. hypesthesia;
- D. impairment of consciousness, psychoses;
- E. psychic inhibition;

5. For the main phase of epidemic typhus the following symptoms are typical:

- A. hypothyria;
- B. dysarthria;
- C. Deviation of tongue;
- D. Normal ingestion;
- E. nystagmus;

6. For Marseilles fever the following statements are correct:

- A. sporadic morbidity;
- B. Epidemic morbidity;
- C. Summer seasonality in the temperate zone;
- D. Absence of seasonality in the tropical zone;
- E. Low susceptibility of the disease;

Standards of correct answers

1. a	3. a,b,c,d	5.a,b,c,e
2. a	4. a,b,d	6. a,c,d

3.4.3. Situational tasks of the second level learning

α -3

Task 1

Patient C, 30 years old, came to infectious inpatient clinic on the third day of the disease, complaining of general weakness, temperature increase up to 38,7 °C, headache, sore throat and pain in major joints, nausea. A week and a half ago the patient went to the forest to have a rest. After coming back home he found out a tick in right inguinal zone and removed it himself. Obviously: body temperature 38.2°C, arterial tension 120/60 mm of mercury column, beat 90/min. Conscious, active. No scleritis or conjunctivitis. Erythematous attack of skin in right inguinal zone, with a clarification inside. Roseolas on the skin of the arms. Muffled heart sounds, rhythmic. Definite vesicular resonance in lungs. Palpatory tenderness. Palpation of liver edge and spleen. Negative Kernig's symptom. Stiffness of occipital muscles not specified.

1. The preliminary diagnosis.
2. The plan of the examination.
3. The treatment.

Task2

Patient, 35 years old, female, was hospitalized to infectious disease ward in the state of psychomotor agitation. From the patient history it was established that onset of disease was acute, body temperature was 39C, headache, dizziness, nausea, insomnia. From the first days euphoria was observed. Provisional diagnosis was influenza, symptomatic therapy was not efficacious. The patient was excited, rude. Physical examination: body temperature 39.5oC, heart rate 126 /min, blood pressure 100/70 mm Hg, respiration frequency 22/minute. The patient did not wish to communicate, negativism was manifested. Her face was hyperemic and edematous; catarrhal conjunctivitis, roseolous-petechial rash on the breast, body, bends of extremities. Hemorrhagic enanthema on posterior veil of soft palate. Harsh respiration, muffled heart sounds, cardiac borders

somewhat extended. Abdomen soft, did not hurt, hepatolienomegaly. Hyperacusia, photophobia, deviation of tongue to the left, dysarthria are observed. Minor rigidity of postcranial muscles.

1. The preliminary diagnosis.
2. The plan of the examination.
3. The treatment.

4. Materials for the class of independent work

4.1. List of practical training tasks to be done during the practical class:

- Study the method of examination of patient with Lyme disease and tick-borne encephalitis.
- Examine the patient with Lyme disease and tick-borne encephalitis.
- Perform differential diagnostics of Lyme disease
- Make up a plan of laboratory examination of patient for Lyme disease and tick-borne encephalitis.
- Make up a treatment plan for the patient with Lyme disease.
- Define medical approach in case of complications.
- Arrange medical documentation based on diagnosis “Lyme disease”.

4.2. List of practical training tasks to be done during the practical class:

- To master the method for examination of patients with epidemic typhus, Marseilles fever.
 - To carry out curation of the patient with epidemic typhus, Marseilles fever.
 - To carry out differential diagnostics of epidemic typhus, Marseilles fever.
 - To prepare a plan for laboratory investigation of the patient
 - To interpret the results of specific examination of the patient with epidemic typhus, Marseilles fever.
 - To define implications of epidemic typhus, Marseilles fever.
 - To prepare a plan for define medical tactics in the case of arising of emergencies.

- To prepare clinical documentation upon the diagnosed “Epidemic typhus”, “Marseilles fever”.

1. Materials of after-work

α -4

Proposed topics for essays on the most pressing issues, such as:

"Prospects for early diagnosis of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever »

"Clinical and epidemiological characteristics of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever "

"Differential diagnosis of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever "

“Pathogenesis of complication of tick-borne encephalitis, Lyme disease, epidemic typhus, Marseilles fever "

MALARIA. SEPSIS.

Urgency of the issue:

Malaria - a group of vector-borne diseases are endemic protozoal etiology. It is characterized by recurrent bouts of fever, anemia, hepatosplenomegaly. From the parasitic disease malaria is now according to the WHO's disease is the most common, besides giving a large number of severe and high mortality. The overall proportion of malaria is 2.6% of all diseases in the world. Mortality from malaria varies from 1.5 million people annually, with 85% of this index is the death rate from malaria in Africa. The percentage of deaths from malaria reaches 4-5% of the total mortality in the world.

Etiology. Malaria parasites - protozoa Protozoa, belong to the genus Plasmodium. There are more than 60 species of parasites. In humans, the disease can cause 4 types of parasites: Pl.vivax - pathogen vivax, Pl.ovale - the causative agent of a special form of vivax (now recovered his two subspecies curtizi and wallikeri), Pl.falciparum - the causative agent of malaria tropica, Pl.malariae - a four-day malaria pathogen.

The life cycle of malaria parasites consists of two phases of development: sexual and asexual. The sexual phase of development occurs in the body of female mosquitoes of the genus Anopheles, sexless - in the human body.

Epidemiology.

The source of infection for malaria is a person sick or parasite in the peripheral blood that are mature gametocytes. The main natural mechanism for the transmission of malaria - transmissible. Carriers of malaria are various types (over 50) of mosquitoes of the genus Anopheles. A man attacked only the female mosquito: her blood is needed for the normal development of her offspring. At the same time, in her stomach with blood enters the male and female sex cells. During sporogony from germ cells formed invasive stage parasites - sporozoites, which with the current hemolymph penetrate the mosquito's salivary glands.

Potentially infected mosquitoes depends on the adaptation of this strain of the parasite to mosquitoes certain type. For example, in Ukraine local species of Anopheles are not capable of infecting gamont *Pl.falciparum*.

Features of the sexual cycle of the malaria parasite in the mosquito, its duration depends on the type of parasites and the air temperature. Thus, at temperatures below T 16°C sporogony *Pl.vivax*, and if T air is below 19°C sporogony *Pl.falciparum* occurs. Sporogony *Pl.vivax* air at T 16°C is complete only after 45 days at T of 30°C - after 6,5 days. Sporogony *Pl.falciparum* at T temperature of 20°C will be completed in 26 days at T 30°C - 8 days. Once infected, the female malaria mosquito are contagious before wintering. The mosquitoes are wintering, the sporozoites are killed. To infect enough introduction into the bloodstream of 10 sporozoites.

Further development of malaria parasites in the human body occurs where sporozoites penetrate the saliva of a mosquito when bloodsucking. Sporozoites in the liver cells are tissue (exo-erythrocytic) schizogony. Transmission of malaria can occur from an infected pregnant woman to the fetus transplacentally or intrapartum.

In addition to the natural ways of malaria is possible, and the artificial: the transfusion of blood during medical procedures by insufficiently treated syringes, catheters, etc. The probability of infection by blood transfusion depends on the initial number of parasites in the blood and the survival of preservatives. In the case of the introduction of a small number of recipients clinical malaria parasites appearance may be delayed up to three months. For parenteral infection in humans occurs only erythrocytic schizogony in the absence of tissue (pre-erythrocytic).

Pathogenesis.

When an infected mosquito bite sporozoites with the saliva into the blood and then into the cells of the liver, where the tissue (exo-erythrocytic) schizogony. For all types of malaria parasites are tissue schizogony. As a result of repeated division of a single sporozoite is formed merozoites huge amount - up to 50 thousand. Hepatocytes

die merozoites into the bloodstream. Tissue schizogony corresponds to the incubation period of the disease, clinically, it does not manifest itself. This is due to the relatively small number of infected hepatocytes and liver huge compensatory abilities.

At the end of the incubation period, the resulting tissue merozoites leave the blood and all clinical manifestations of the disease are caused by erythrocyte schizogony. Merozoite, penetrated into the bloodstream, attaches to the receptor erythrocyte erythrocyte membranes at the point of attachment invaginated and absorbs merozoite. The penetration merozoites in erythrocytes occurs in 0.5 minutes. The erythrocyte merozoite passes a cycle of development. After the annular trophozoites formed trophozoite young, semi-mature, adult trophozoite. Trophozoite - a growing parasite feeds on hemoglobin absorbs oxygen, puts food in the digestive process in the form gemomelanina eritorotsite. Then formed schizonts - immature schizonts are divided into small (young), medium (amoeboid) and the large (mature). After maturing schizonts comes the stage of division of the nucleus formed morula.

For parenteral infection of malaria parasites (blood transfusions, non-sterile instrument) in humans occurs only erythrocytic schizogony.

Immunity in malaria non-sterile, species-specific. It is supported by reinfection. To develop sufficient immunity tensions need to be subjected to constant reinfection for about 7 years. Individuals with high immunity living in endemic foci, clinical manifestations of malaria are mild or absent. Moving people from the focus of intense malaria-free areas from it for 1-2 years and reduces the disappearance of immunity.

Clinic.

Accordingly, 4 types of malaria parasites are distinguished: a 3-day, four-tropical and malaria. **3-day malaria (Pl.vivax, Pl. Ovale)**. It is characterized by intermittent bouts of fever with most every other day, anemia, hepatosplenomegaly and a tendency to recurrent course with repeated attacks occurring after a latent period lasting several months 3.6.14.

The incubation period for vivax malaria by 10-20 days, ovale malaria - 11-16 days. Malaria vivax and ovale malaria in individuals begin with prodromal period: the patient has malaise, chilliness, headache, general aches, low-grade fever. However, most prodrome is absent and the disease begins acutely with the typical malaria paroxysms occurring with alternate phase-change - chills, fever, sweats. Between bouts of malarial chills accompanied by generalized contraction (spasm) of the peripheral vessels, during the heat - cutting their expansion (vasodilation). The attack begins shaking chills. The patient lies in bed, hiding his head, but could not get warm. Chills amplified and appears a typical shaking syndrome when, as they say, "teeth were chattering." The skin is pale, with cyanotic tint, cold, shivering, "goose bumps." Patients concerned about headache, back pain, nausea and sometimes vomiting. Fever lasts from 10-15 minutes. 2-3 hours and is accompanied by a rapid rise in temperature. There comes a second phase. The phenomena of intoxication is increasing, the temperature rises to 39-40 ° C, increasing headache, myalgia, there is a feeling of anxiety, craving, sometimes disturbed consciousness, delirium. The face becomes congested, the skin is dry, hot to the touch, shortness of breath, tachycardia, decreased blood pressure. A few hours later the heat is replaced by profuse sweating, the temperature decreases critically. Improving the health of patients, they experience general weakness and quickly fall asleep. In general, the malarial paroxysm lasts 6-12 hours. After the attack, a period apyrexia. Home malarial paroxysm - chills - coincides with the end of the cycle of erythrocytic schizogony. In the presence of lead in the blood of a generation of parasites intermittent fever has the right character with the onset of paroxysms in 48 hours. At the same time, after several bouts of ill at a certain time already expected next paroxysm. Anemia. Skin and visible mucous membranes become characteristic pale yellow color on the lips and nose wings appear herpes, the number of paroxysms in the untreated malaria can be - 10-14. Hepatosplenomegaly. Subsequently, the condition of patients improves, but insufficient treatment after 2-3 months may be early, but after 8-14 months late relapses. Vivax malaria relapses may occur for up to 4 years.

The most common complication of the 3-day malaria is hypochromic anemia. At 0,7% (3 million people) able to finish splenic rupture. The immediate causes of the gap greatly enlarged spleen may even be bruised stomach, vomiting. When you break the spleen appears acute severe abdominal pain, symptoms of peritoneal irritation and internal bleeding, shock. Displaying an emergency surgery. Ovale malaria is endemic in West Africa. At the clinic similar to malaria vivax. A distinctive feature - the beginning of the attacks most often in the evening and night hours. It is characterized by benign course.

4-day malaria. Proceeds benign. The incubation period of 21 to 42 days. For intravenous infection schizont - from several days to several months. Start of acute intermittent fever is characterized by the development of seizures in 2 days, moderate anemia, splenomegaly, relatively low parasitaemia.

A distinctive feature of the 4-day malaria is a long-lasting after undergoing primary attack erythrocytic schizogony at submicroscopic level without clinical manifestations. Insufficiently active treatment in the primary attack may subsequently cause a relapse (more than 30 years). Relapses often develop after diseases, operations, colds, with a change of residence, pregnancy and so on. D. This probably leads to abuse Create immunological equilibrium between parasite and host.

Tropical malaria. In falciparum malaria falls somewhere 50% of the incidence of malaria in the world, it is the cause of death in 98% of all malaria deaths. The incubation period of 8 to 16 days. Disease begins acutely, appear typical malarial paroxysms, but because mostly in tropical malaria in the blood circulate more than simultaneously developing generations, there is layering attacks smoothed apyrexia periods. Fever is permanent or laxative character when during the day the temperature may rise 2-3 to 41 ° C. Fever accompanied by chills, sharp pains in the kidneys, muscle pain, back pain, epigastric, nausea, vomiting, sleep disorders, at the height of the fever - delusions, hallucinations. Characteristic tachycardia, a significant decrease in blood pressure - 90 / 50-80 / 40 mm Hg, shortness of breath. Quickly increases the size of the

spleen. Often develop chronic hepatitis (ALT activity is increased by 2-3 times). Most often it occurs in pregnant women treated with quinine. Quickly develop anemia - anisocytosis, poikilocytosis, reticulocytosis. On day 10 of the disease reduced hemoglobin to 70 g/l Number of red blood cells - up to $2.5-3.0 \times 10^6/l$. The degree of anemia at a frenetic period can only be determined in terms of hematocrit, reaching 30-25% (normal 36-40%), as fever leads to blood clots. Identify signs of kidney damage: decreased urine specific gravity, there cylindruria, protenuriya, azotemia, increases in serum residual nitrogen, urea, creatinine (more than 265mmol / l). May develop acute renal failure. Already in the first days of the disease tropical malaria can develop malarial coma, pulmonary edema.

Laboratory diagnosis. The main method of diagnosis of malaria - parasite-microscopic, based on the detection of red blood cell parasites and gametocyte forms in stained blood (thick film, smear) under the microscope. Blood for parasite-microscopic research for all types of malaria should be taken until the appointment of a specific treatment, with three- and four-day malaria blood examined both during the attack and during the normal temperature at a tropical malaria blood tests are repeated at least 3-4 times at intervals of 4 -6 hours.

In endemic areas, where a large number of cases, you can use rapid methods - based immunnohromatografic reaction with 2-NRR antigen carried by the *Pl.falciparum*, *falciparum* malaria can be diagnosed.

Serologic methods based on the determination of antibodies, even the most modern methods (ELISA, immunoassay, and others), Can be used only for the retrospective diagnosis verification and screening of donated blood.

Treatment. There are several directions in the treatment of patients with: 1- mild asthma malaria; 2 - the prevention of later relapse in vivax and ovale malaria; 3 - elimination of germ cells at a tropical malaria.

For cupping used gematoshizotropnye malaria drugs acting on erythrocytic stage of the parasite. These include: 4 aminoquinolines: chloroquine (synonyms - delagil,

hingamin) Plaquenil; quinine; artemisinin and its derivatives (artesunate, artemotil, artemether); amodiaquine; antifolievym drugs: pyrimethamine (daraprim, tindurin), proguanil; mefloquine; halofantrine; clindamycin; doxycycline and a combination of drugs - Fansidar, metakelfin.

To influence tissue forms *Pl.vivax* and *Pl.ovale* gistoshizotropnye used drugs: primaquine, hinotsid.

For effects on germ cells using drugs gamontotropnye: primaquine, quinine, hinotsid, pyrimethamine, gidrooksihlorohin. Appointment advisable only if their *falciparum* malaria since gamonts other malaria parasites quickly die if you do not get into the mosquito.

For the four-day malaria treatment prescribed hingamin. In the first day and 0,5 grams. within the next 3-5 days. Appointment primaquine inappropriate.

Treatment of *falciparum* malaria depends on the area where the infection occurred. At present, in many regions of the spread of *falciparum* malaria has become resistant to the pathogen hingamin (table 1).

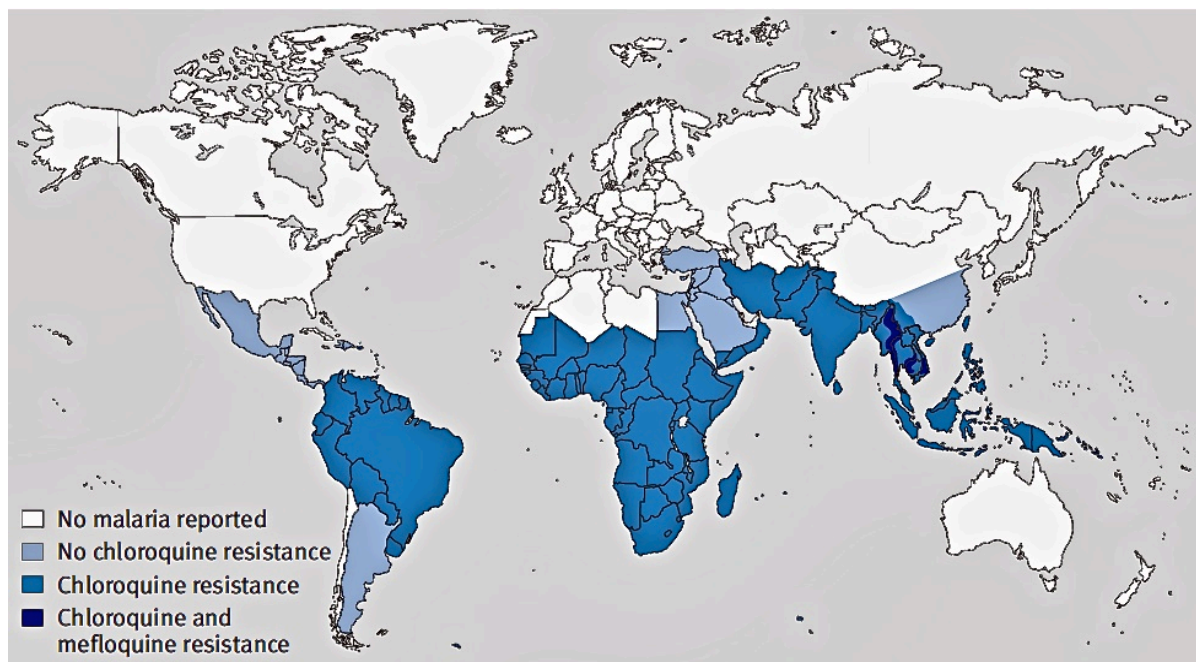


Table 1. The prevalence of malaria in tropical countries, depending on the resistance hignamin

For the treatment of falciparum malaria resistant hignamino (parasitaemia ++, 1 ml of blood), oral use one of the combinations:

- Artesunate + amodiaquine 2 table a day for 3 days, orally;
- Artesunate + mefloquine 1 table 3 days orally;
- Metakelfin 1 table 3 consecutive days orally;
- Table 3 Fansidar simultaneously orally.

When tropical malaria, more severe (+++ parasitaemia in 1 ml of blood) is used:

- Artesunate - water-soluble artemisinin derivative of 2 mg / kg 1 time a day plus Clindamycin 10 mg / kg two times a day for 7 days;
- Quinine 10 mg / kg every 12 o'clock (no more than 2 g. Per day) + doxycycline intravenously 5 mg / kg, 1 time per day for 7 days.

In the presence of germ cells in the blood to affect the gametocytes appointed for 3 consecutive days primaquine 15 mg. Can be used for this purpose instead of pyrimethamine, primaquine 50 mg (2 tab.) At the reception once or daraprim (England), tindurin (Hungary). The use of quinine at a tropical malaria causes rapid death of gametocytes.

Sepsis - a serious infectious disease caused by microorganisms, and generalization is accompanied by significant pathophysiological changes in the organs and systems of the body.

Etiology. Sepsis can cause virtually all microorganisms belonging to both pathogenic and conditionally pathogenic to. First of all, sepsis can be caused by bacteria as Gram-positive (staphylococci, streptococci, pneumococci, and others.) And Gram (meningococcus, Salmonella, Klebsiella, Pseudomonas aeruginosa, Yersinia, Escherichia), fungi (Candida sepsis). In recent years, it becomes less likely to stand out most gram-positive and gram-negative bacteria, particularly Pseudomonas aeruginosa, Klebsiella, and anaerobes.

Pathogenesis. The occurrence of sepsis is caused not so much by the properties of the pathogen, as the state of the microorganism, in particular its inability to localize the pathogen and the immune deficiency of various factors. Factors depressing resistant microorganism can include any disease (diabetes, cancer, hematological, and others), malnutrition (low levels of protein, vitamins), radiation, stress, long-term use of immunosuppressive drugs, corticosteroids, cytostatics.

Apart from sepsis caused by community-acquired strains in recent years has recorded and hospital sepsis, which is more common in intensive care units, surgical, burn. At the same time, sources of infection may be even objects of the environment. Proven high of contamination of environmental objects in septic chambers and dressing. When nosocomial infection contamination is possible during catheterization of blood vessels, the urinary tract, endoscopy, bronchoscopy and other studies. Pathogens can get into the joint cavity, pleural cavity, that is, they fall into the cavity, which in the evolutionary development due to the lack of biological need not purchased opportunities to local resistance and virtually defenseless.

Gram-positive bacteria are the cause of septic reactions from exposure exotoxins, cell wall components such as peptidoglycan and teichoic acid, staphylococcal protein A and streptococcus protein M. Starting cascade reactions Gram-negative bacteria occurs via a potent endotoxin.

Clinic. The clinical course distinguish:

- Acute (lightning), sepsis, proceeds rapidly with the development of septic shock and leads to death within 1-2 days;
- Severe sepsis, which lasts up to 4 weeks;
- Subacute, lasting 3-4 months .;
- Recurrent sepsis, occurs in the form of exacerbations and remissions, lasting up to 6 months .;
- Chronic sepsis can last up to a year or more.

Sepsis, unlike other infectious diseases, has cycled within.

The clinical picture of sepsis varied. It consists of the symptoms of intoxication and symptoms of the disease caused by primary and metastatic foci.

In the course of sepsis impose definite imprint pathogenetic features separate clinical entities. So, the island (lightning) staphylococcal sepsis occurs extremely hard, with shaking chills, high fever, severe intoxication, cyanosis, rapid drop in blood pressure. At the same time, in this form of metastases is detected. In acute staphylococcal sepsis often a hemorrhagic rash with necrosis in the distal extremities (palm or fingers), numerous septic metastases in the kidney in endocarditis, osteomyelitis possible, arthritis. Staphylococcal sepsis often takes relapsing course, when relapses associated with the formation of new lesions are replaced by remissions.

In anaerobic sepsis for secondary foci characterized by rapid abscesses. Develop brain abscesses (85% of abscesses due to anaerobic infection), liver abscess, lung. Most often associated with sepsis *B.fragilis*, having a capsular polysaccharide, whereby *B.fragilis* can cause abscess formation without the participation of other microbes. The mortality rate for sepsis reaches 50%.

Differential diagnosis and laboratory diagnosis. Recognition of sepsis often causes difficulties. A crucial role in the diagnosis belongs to the careful analysis of clinical symptoms. Differentiate sepsis from typhoid, paratyphoid diseases, acute brucellosis, chlamydia, tuberculosis and other diseases that occur with prolonged fever or hectic incorrect type. When typhoid fever, as well as in sepsis, fever may be prolonged, there is an enlarged liver and spleen, pallor, anemia. However, the characteristics of the course of sepsis is largely determined by the location of the primary septic focus, reactivity.

Acute brucellosis, as well as sepsis, can occur with prolonged, sometimes for several months with fever, recurrent chills, sweating, enlarged liver and spleen. Acute brucellosis distinguish sepsis from satisfactory state of health of patients, not corresponding to the height and duration of fever (T - 39°S above the patient can read books, play chess, watch TV, etc.), no focal changes (metastases). The differential

diagnosis is important severity of the disease, the progressive deterioration of the development of septic shock, the appearance of new lesions.

The basic method of specific laboratory testing for diseases caused by bacteria - bacterial, aimed at the identification of the causative agent.

Treatment of sepsis should be timely, comprehensive. The first is carried out reorganization of primary septic focus (opening and drainage of abscess, removal of bad teeth). If necessary, a reorganization and secondary septic foci. Causal treatment should be administered as soon as possible. For sufficient serum concentrations and metastatic foci, large doses of antibiotics are used for a long time. The correct choice of antibiotics is one of the most important aspects of the treatment of patients with sepsis. In the treatment of sepsis with established primary focus or identifiable pathogen with the determination of its sensitivity to antibiotics prescribed appropriate antibiotics. For Pseudomonas sepsis patients can use drugs carbenicillin 2-3 grams every 4 hours, erythromycin 0.5 4-6 hours, cephalosporins III - IV generations. Patients with staphylococcal sepsis can be administered by intravenous vancomycin 1 g. 2 times a day, linezolid 600 mg 2 times a day, 2 g oxacillin every 4 hours. In the first 48 to 72 hours oxacillin added gentamicin (1 mg / kg) every 8 hours with allowance renal function. The course of treatment for at least 2 weeks. When treating patients with the anaerobic sepsis administered intravenously klindomitsin 600 -900 mg 3 times a day, lincomycin 600 mg 3 times a day, metronidazole, 500 mg 3-4 times a day, which also penetrates well into the cerebrospinal fluid. Fungal sepsis fluconazole administered intravenously at 6-12 mg / kg per day, or caspofungin, amphotericin B.

In the treatment of sepsis with unknown primary site and do not take into account the conditions identified causative agent of infection: community-acquired or hospital. Community-acquired sepsis drugs of choice are fluoroquinolones (levofloxacin, moxifloxacin, ofloxacin, pefloxacin, ciprofloxacin intravenously at 400 mg 2 times a day) and cephalosporins III-IV generation (cefepime, ceftazidime, ceftazidime 2g intravenously. - 2-3 times a day) .

Currently, the structure of the causative agents of nosocomial infections is dominated by Gram-negative bacteria. The drugs of choice in the hospital sepsis are the carbapenems (ertapenem, meropenem, imipenem 1 gr. 3 times a day). Causal treatment is carried out to achieve a stable positive dynamics of the patient's condition and the disappearance of the main symptoms of the disease.

To correct the deficiency of circulating blood volume effectively administered to patients alternately crystalloid and colloid (albumin) solutions. The most favorable ratio between crystalloid and colloid solutions is 3 to 1 (3: 1) or 2: 1 (2: 1). To prevent absorption of toxic metabolites from the intestine into the bloodstream using chelators. With the stabilization of hemodynamic parameters can be used the methods of extracorporeal detoxification (hemosorption, plasmapheresis). In the case of severe renal insufficiency is shown hemodialysis.

2. Tasks of the training course (indicating expected level of learning):

2.1. The student should have an idea (get familiar with): ***a – 1***

- have general idea about position of malaria in the structure of virulent diseases, prevalence in different areas of the world and different age groups; study statistic data related to case rate, case mortality, event frequency, long-term effects of;
- get familiar with history of scientific study of malaria, have an idea of scientific contribution of native scientists in the history of scientific research in this field.
- incidence of sepsis;
- consequences of sepsis;
- differential diagnostics of sepsis.

2.2. The student should know: ***a – 2***

1. Causation aspects leading to malaria, sepsis and prevalence of malaria germs in different regions of the world
2. Epidemiology of malaria, sepsis
3. Malaria, sepsis pathogenesis

4. Clinical signs of malaria, sepsis in standard progress
5. Specific features of clinical progress with regard to type of germ that caused the diseases
6. Pathogenesis, genesis term and clinical aspects of malaria complications
7. Malaria, sepsis laboratory diagnostics
8. Methods of malaria, sepsis treatment
9. Rules of discharge of patients with malaria, sepsis
10. Ways of individual malaria prophylactics
11. Septoprognosis of malaria with regard to type of germ that caused the disease

2.3. The student should be able to:

a – 3

1. Follow the main rules of behavior by sickbed.
2. Make up medical history estimating epidemiological data
3. Examine the patient and find out the main symptoms and syndromes of malaria and justify the clinical diagnosis.
4. Based on clinical examination define possible complications of malaria, emergencies.
5. Fill in medical documentation based on previously stated diagnosis “malaria” (emergency call to regional epidemiological department).
6. Make up a plan of patient’s laboratory and instrumental examination.
7. Analyze the results of laboratory examination
8. Analyze the results of specific methods of diagnostics.
9. Make up an individual treatment plan taking into account epidemiological data, stage of disease, available complications, severity of the condition, allergic anamnesis, comorbidity, provide rescue emergency care at pre-hospital stage
10. Provide recommendations related to mode of treatment, diet, examination and medical supervision during recovery period.

3. Reference materials for pre-classroom independent activities:

3.1. Basic knowledge and skills required to master the subject.

Interdisciplinary integration:

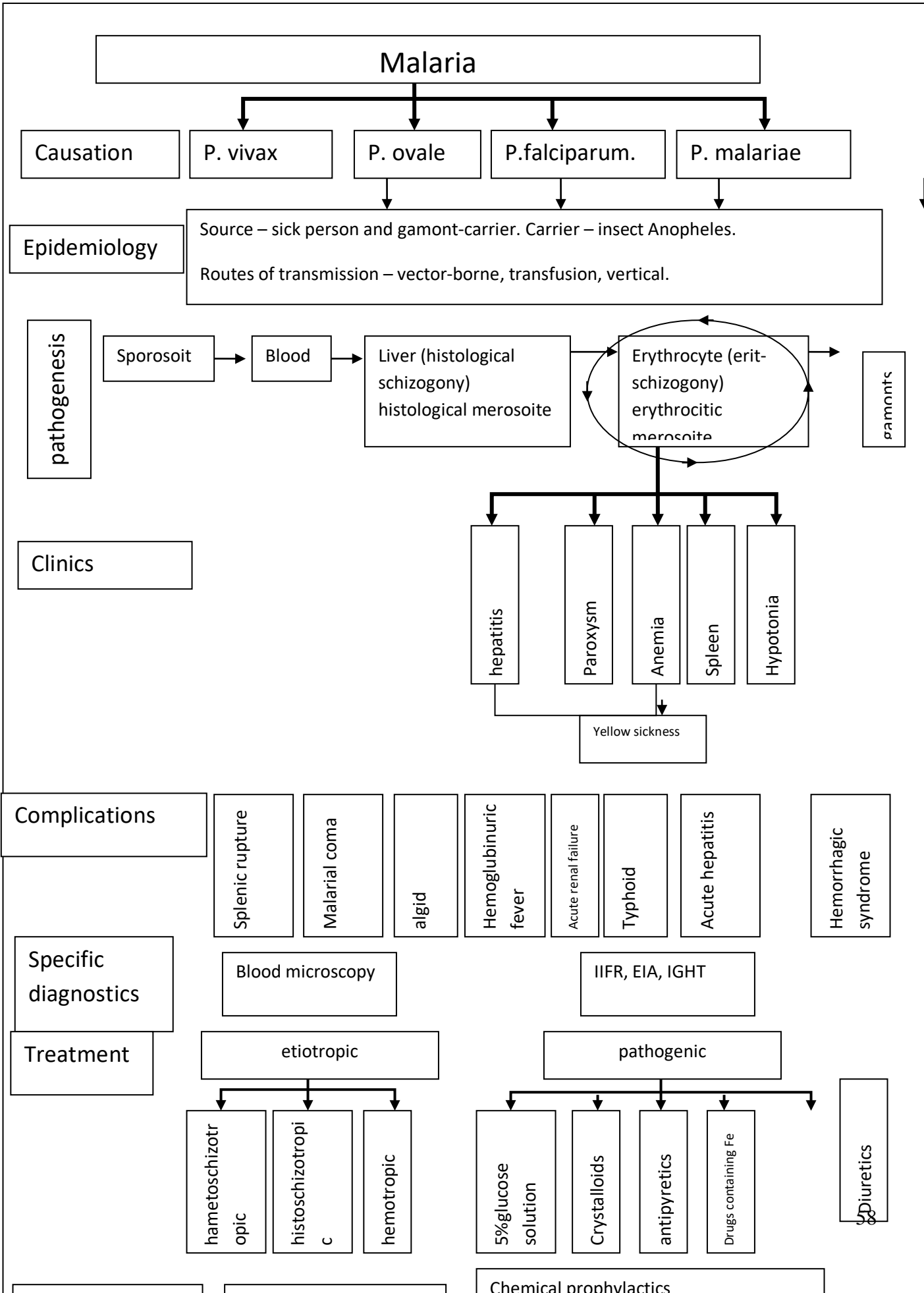
Discipline	To know:	To be able to:
Microbiology	Features of germs of malaria, serological response based on disease period, rules and terms for sampling for specific diagnostics	Take samples of material for parasitological testing (spot and thick-blood film), analyze the results
Biology	Structure and life cycle of Anopheles mosquitoes	
Propedeutics of medical diseases	Main stages and methods of patient clinical examination	Make up medical history, perform clinical examination of the patient by different organs and systems, define clinical symptoms of pathology. Analyze obtained data
Epidemiology	Epidemiological process (source, mechanism of infection, routes of transmission) at malaria, prevalence of such pathologies in Ukraine and worldwide. WHO's strategy towards liquidation of this infection.	Make up an epidemiological history, perform antiepidemic and preventive measures in the centre of infection

Immunology and allergology	Key terms of the discipline, role of immunity system in infectious process, influence on the term of germ elimination from human organism. Immunological aspects of complications	Analyze data of immunological examinations
Physiology	Aspects of physiological standards of human organs and systems; aspects of laboratory examination in standard condition (general blood and urine analysis, spinal fluid, biochemical blood analysis, features of acid-base balance, electrolytes etc).	Estimate data of laboratory examination
Neurology	Clinical, laboratory and instrumental signs of meningitis, encephalitis and toxic encephalopathy	Perform clinical examination of the patient with affected nervous system. Perform lumbar puncture
Clinical pharmacology	Pharmacokinetics and pharmacodynamics, adverse effects of antivirals and means of pathogenic therapy	Prescribe treatment with regard to age, individual symptoms of the patient, chose an optimum mode of drug intake and dosage, provide

		prescriptions
Reanimation and intensive care	<p>Emergencies:</p> <p>Cerebral edema (malarial coma)</p> <p>Acute respiratory failure</p> <p>Acute renal failure</p> <p>Hemoglobinuric fever</p>	<p>Make diagnosis of and provide rescue care in cases of emergency at:</p> <p>Cerebral edema (malarial coma)</p> <p>Acute respiratory failure</p> <p>Acute renal failure</p> <p>Hemoglobinuric fever</p>

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3.3 Materials for self-control

3.3.1. Questions for self-control

1. Source of infection and route of transmission of malaria.
2. Pathogenic characteristics of malaria germs.
3. Malaria pathogenesis.
4. Life cycles of malaria germ at histological and erythrocytic stages.
5. Stages of cyclic clinical progress of malaria.
6. Key symptoms of malaria at height of the disease.
7. Clinical signs of nervous system disorders at malaria.
8. Type of fever curve at malaria.
9. Sequences of malaria.
10. Route causes of mortality at malaria.
11. Specific complications of malaria.
12. Terms of early and late recidives at malaria.
13. Haemogram of the patient with malaria at the height of the disease.
14. Plan of patient's examination with suspicion for malaria.
15. Methods of malaria specific diagnostics.
16. Malaria etiologic therapy. Dosing, routes of administration and duration of treatment.
17. Rules of discharge of the patient with malaria from indoor hospital.
18. Drugs for malaria treatment.
19. Rescue emergency care at malaria coma.
20. Clinics of hemoglobinuric fever, possible causes.
21. Source of infection and route of transmission of sepsis.
22. Pathogenic characteristics of sepsis germs.
23. Sepsis pathogenesis.
24. Stages of cyclic clinical progress of sepsis.

25. Key symptoms of sepsis at height of the disease.
26. Type of fever curve at sepsis.
27. Sequences of sepsis.
28. Route causes of mortality at sepsis.
29. Specific complications of sepsis.
30. Terms of early and late recidives at sepsis.
31. Haemogram of the patient with sepsis at the height of the disease.
32. Plan of patient's examination with suspicion for sepsis.
33. Methods of sepsis specific diagnostics.
34. Sepsis etiologic therapy. Dosing, routes of administration and duration of treatment.
35. Drugs for sepsis treatment.

3.3.2. Tests for self-control

$\alpha=2$

Choose correct answers

Tests to the topic of "Malaria"

1. Malaria refers to:

- A - fungi;
- B - spirochaetes;
- C - rickettsiae;
- D - the simplest;
- E - bacteria.

2. Malaria is a disease:

- A - endemic;
- B - natural focal;
- C - quarantine;
- D - saprophytic;
- E - zoonotic.

3. The source of infection for malaria:

A- persons;

B - the animals;

C - mosquitoes;

D - mites;

E - all right.

4. The main natural mechanism for the transmission of malaria vivax:

A - transmissible;

B - by blood transfusion;

C - contact;

D - percutaneous;

E - all right.

5. Plasmodium malaria occur in the sexual cycle:

A - human hepatocytes;

B - erythrocytes;

C - lymphocytes;

D - mosquitoes;

E - all right.

6. The female mosquitoes of the genus Anopheles, sucked the blood of a patient with malaria vivax, it becomes contagious:

A - 5 hours;

B - 5 days at ambient temperature 10 ° C;

C - 45 days at a temperature 16°S;

D - in the presence of the pathogen in the ring stage;

E - in the presence of the pathogen in the trophozoite stage.

7. Mosquito genus Anopheles, sucked the blood of a patient with malaria falciparum, is dangerous:

A - after 8 hours from the blood-sucking;

B - after 48 hours;

C - 72 hours;

D - by 7.5 days at ambient temperature 30°C;

E - after 6.5 days at ambient temperature 22°S.

8. Plasmodium vivax malaria are asexual development cycle:

A - mosquito stomach;

B - the saliva of the mosquito;

C - standing water;

D - the human body;

E - all right.

9. Exo-erythrocytic schizogony Pl.ovale place in

A - mosquito stomach;

B - the saliva of the mosquito;

C - human hepatocytes;

D - human erythrocytes;

E - all right.

10. The clinical examination of patients who have had malaria vivax, ovale, malariae, should be performed:

A - there is no need;

B - 1 month;

C - 2 months;

D - 6 months;

E - 2 years.

11. Tachy and bradisporozoity are:

A - Pl.malariae;

B - Pl.vivax;

C. Pl.ovale;

D - Pl.vivax and Pl.ovale;

E - Pl.falciparum.

12. Antibodies against malaria appear:

A - sporozoites;

B - merozoites;

C - gametocyte;

D - sporozoites and merozoites;

E - all of the above is true.

13. The duration of the erythrocyte schizogony at *P. vivax* is:

A - 24 hours;

B - 48 hours;

C - 72 hours;

D - 9 days;

E - 10 months.

14. Duration of erythrocyte schizogony at *P. malariae* is:

A - 24 hours;

B - 48 hours;

C - 72 hours;

D - 9 days;

E - 10 months.

15. Duration of erythrocyte schizogony *P. falciparum* is:

A - 24 hours;

B - 48 hours;

C - 72 hours;

D - 9 days;

E - 10 months.

16. Patient A., returned from Tajikistan. In the morning 1.09 to 39,5°C fever with chills, change of heat, but in the evening the temperature was normalized. Temperature rise repeated three times every 2 days. Splenomegaly. Diagnosis:

A - sepsis;

- B - 4-day malaria;
- C- 3-day malaria;
- D - leptospirosis;
- E - typhoid.

17. A. The patient returned 1.03 from Uzbekistan. Acutely ill: 3.03, 5.03, 7.03 in the morning the temperature rise to 39°S with chills, fever. 4.03, 6.03 - temperature normal. Pale skin. Hepatosplenomegaly. Diagnosis:

- A - sepsis;
- B - 4-day malaria;
- C- 3-day malaria;
- D - leptospirosis;
- E - typhoid.

18. The main complication of the 3-day malaria is:

- A - malarial coma;
- B - brain edema;
- C - rupture of the spleen;
- D - acute kidney failure;
- E - hemoglobinuric fever.

19. The main method of laboratory diagnosis of malaria is:

- A - a microscopic;
- B - bacterial;
- C - the reaction of passive hemagglutination (PHA);
- D - complement fixation test;
- E - allergic.

20. Determination of the intensity of parasitaemia is necessary in the treatment of malaria patients:

- A - vivax;
- B - ovale;

C - falciparum;

D - malariae;

E - this is not necessary.

21. Effects on tissue forms *P. vivax* used:

A - hingamin;

B - primaquine;

C - quinine;

D - artemisinin;

E - all right.

22. Gamontotropy drugs include:

A - primaquine;

B - quinine;

C - hinotsid;

D - pyrimethamine;

E - all right.

23. In order to control attacks of malaria, you can use all, except

A - hingamin;

B - delagil;

C - artemisinin;

D - primaquine;

E - amodiaquine.

24. In order to control attacks of fever in patients with *vivax* used:

A - hinotsid;

B - primaquine;

C - hingamin;

D - quinine;

E - all right.

25. For cupping fever in early relapse of malaria *vivax* must be assigned

- A - primaquine;
- B - hingamin;
- C - mefloquine;
- D - Fansidar;
- E - doxycycline.

26. To prevent late recurrence of malaria ovale must be assigned

- A - primaquine;
- B - hingamin;
- C - Fansidar;
- D - artemether;
- E - all right.

27. In order to control a four late relapses of malaria must be assigned

- A - primaquine;
- B - hinotsid;
- C - Fansidar;
- D - hingamin;
- E' all right.

28. In order to determine the method of administration etiotropic drugs in falciparum malaria must be:

- A - to identify the causative agent;
- B - to determine the amount of pathogens in 1 ml of blood;
- C - have an enzyme-labeled antibody response data (REMA);
- D - to determine creatinine and urea;
- E - all right.

29. Patients infected with malaria in the tropical central Africa, causal treatment should be carried out:

- A - hingaminom / O;
- B - primaquine;

C - quinine in combination with doxycycline;

D - delagilom;

E - tetracycline.

30. The drug of choice for the prevention of falciparum malaria after brief trip to Central Africa are:

A delagil 1 tab. 1 time a week before departure, and all the days of your stay;

B - delagil 1 tab. before departure and 1 tab. every 2 weeks stay in the country;

C - mefloquine 250 mg 1 time a week prior to departure, all the days of stay in the country and 1 month. After returning.

D - chloroquine phosphate, 0.1 g. every day all days of stay in the country;

E - all of the above is true.

Tests to the theme of "Sepsis"

1. Sepsis can be caused

A - iersiniya;

B - Escherichia;

C - Candida;

D - clostridia;

E - All right.

2. Gram-negative bacteria causing septicemia include everything except:

A - meningococcus;

B the - pneumococci;

C - Salmonella;

D - klebsiela;

E - Pseudomonas aeruginosa.

3. Agents of anaerobic sepsis are:

A - negative staphylococci;

B - streptococci;

C - clostridia;

D - Candida;

E - all right.

4. The agents of sepsis can not be:

A - negative staphylococci;

B - meningococcus;

C - pneumococci;

D - plasmodium;

E - Candida.

5. The occurrence of sepsis caused by:

A - high virulence of the pathogen;

B - the presence of the pathogen the R-factor;

C - L- forms of the pathogen;

D - the inability of the microorganism to the localization of the pathogen;

E - all right.

6. To develop sepsis requires:

A - center associated with the blood or lymphatic vessels;

B - entry of the pathogen from the source of the blood;

C - deficiency of factors of the immune system;

D - dissemination of infection;

E - all right.

7. clinical course of acute sepsis may continue:

A - 1-3 days;

B - up to 4 weeks;

C - up to 4 months;

D - up to 6 months;

E - up to a year.

8. clinical course of acute sepsis may continue:

A - 1-3 days;

B - up to 4 weeks;

C - up to 4 months;

D - up to 6 months;

E - up to a year.

9. In the clinical course of chronic sepsis can proceed:

A - 1-3 days;

B - up to 4 weeks;

C - up to 4 months;

D - up to 6 months;

E - up to a year.

10. The temperature curve in sepsis can be:

A - of intermittent;

B - hectic;

C - constant type;

D - remitting;

E - all right.

11. Pathogens nosokomial infections can be transmitted through:

A - air;

B - catheters;

C - infected hands of the medical staff;

D - dressing;

E - all right.

12. Gate infection in staphylococcal sepsis often are:

A - loss of skin and subcutaneous tissue;

B - pneumonia;

C - endocarditis;

D - meningitis;

E all right.

13. Pseudomonas sepsis may occur with:

A - wounds;

B - burns of grade III-IV;

C - available abscesses;

D - peritonitis;

E - all right.

14. Infection atrioms anaerobic sepsis can be:

A - necrotizing gingivitis;

B - ear infections;

C - criminal abortion;

D-operation on the abdomen;

E - all right.

15. For acute sepsis is characterized by everything except

A - cycling course;

B - acyclic flow;

C - prolonged high fever;

D - severe intoxication;

E - multiple organ failure.

16. In a patient with septic shock, blood pressure is 80/40 mm Hg, pulse 120 beats per minute. Shock index is:

A - 0.5;

B 1,0;

C - 1.5;

D 2;

E - 2.5.

17. The patient, 32 years old. During labor, uterine rupture occurred, it operated. On the third day after the operation T - 41°S, chills, headache, weakness, anorexia. On the 4th day T-36,8°S, sick inhibited. Extremities cold. Administrative 60/30 mm Hg, pulse 110 beats per minute. Diagnosis:

A - septic shock;

B - Stevenson-Johnson syndrome;

C - bacterial endocarditis;

D - peritonitis;

E - all right.

18. Complications of sepsis can be:

A - toxic shock;

B - acute adrenal insufficiency;

C - acute respiratory failure;

D - acute kidney failure;

E - all of the above is true.

19. compensated stage of endotoxin shock when meningococcal disease is characterized by all except:

A - C-40 ° C;

B - headache, myalgia;

C - shock index 1.3;

D - pale skin, cold hands and feet;

E - hemorrhagic rash.

20. subcompensated stage of endotoxin shock when meningococcal disease is characterized by all except:

A - C-40 ° C;

B - lethargy, apathy;

C - acrocyanosis;

D - shock index 1.2;

E - hemorrhagic rash.

21. For the decompensated stage of endotoxin shock is characterized by everything except

A - skin cold, earthy shades;

B - purpura large with necrosis;

C - somnolence;

D - shock index 1.1;

E - respiratory failure.

22. acute renal failure in sepsis patients can speak with the

A - systolic blood pressure of 90 mm Hg .;

B - systolic blood pressure of 70 mm Hg

C - diuresis 1000 ml / day;

D - relative density of urine in 1020;

E - Creatinine - 120 mmol / L.

23. The main method of specific laboratory research in sepsis:

A - bacterioscopic;

B - bacterial;

C - serum;

D - biology;

E - all equally valid.

24. The ratio of blood and blood cultures in the environment at the bacteriological examination is as follows:

A - 1: 1;

B - 1:10;

C - 1:20;

D - 1:50;

E - ratio does not matter.

25. For effective bacteriological examination is sufficient to take in the amount of blood:

A - 0.5 ml;

B - 1 ml;

C 3 ml;

D - 10 ml;

E - the number does not matter.

26. The drug of choice for the etiological treatment for Pseudomonas sepsis is:

A - metronidazole;

B - fluconazole;

C - penicillin;

D - cephalosporins III-IV generation;

E - all are equally effective.

27. The drug of choice for treatment of anaerobic sepsis is:

A - metronidazole;

B - fluconazole;

C - amphotericin B;

D - ampicillin;

E - all are equally effective.

28.The drug of choice in the treatment of fungal sepsis is:

A - metronidazole;

B - fluconazole;

C - cephalosporins III-IV generation;

D - clindamycin;

E - lincomycin.

29.The drug of choice for the treatment of community-acquired sepsis with unknown primary site and did not identify the causative agent are as follows:

A - levofloxacin;

B - ciprofloxacin;

C - ceftazidin;

D - cefepime;

E - all are equally effective.

30.The drug of choice for hospital sepsis with unknown primary site and did not identify the causative agent are as follows:

A - fluoroquinolones;

B - carbapenems;

C - cephalosporins;

D - aminoglycoside;

E - all right.

Standards of answers to section "Malaria"

1.D	11.B	21.E
2.A	12.B	22.D
3.A	13.C	23.C

4.A	14.B	24.B
5.D	15.B	25. A
6.C	16.C	26. D
7.D	17.C	27. B
8.D	18.A	28.C
9.C	19.C	29.E
10.D	20.B	30.C

Standards of answers to Section 2 "Sepsis"

1.E	11.E	21.D
2.B	12.A	22.B
3.C	13.E	23.B
4.D	14.A	24.B
5.D	15.A	25. D
6.E	16.C	26. D
7.B	17.A	27. A
8.A	18.E	28.B
9.E	19.C	29.E
10.E	20.A	30.B

3.3.4. Problems for self-control

Problem No.1

Patient, 52 years old, had an acute form of the disease; rigor was followed by body temperature increase up to 39.8°C, headache and non-repeated vomiting. During the next days, despite of aspirin intake, constant fever remained, and increasing drowsiness. On the 6th day she felt unconscious. 10 days ago she came back from Africa where she stayed for a month.

Obviously: T-40.1°C. Unconscious, clear psychomotor agitation. Miotic pupil, poor light reaction. Increased patellar reflexes, positive Babinski and Oppenheim's symptoms. Pale skin with lemon hint, lips cyanosis. Bile-stained scleras. Beat 112 per minute, low strength. Arterial tension - 90/60 mm of mercury column. Muffled heart sounds. Large palpatory spleen mass. Moderate increase of liver mass. Low hemoglobin level in general blood analysis.

1.Previous diagnosis

2.Examination plan

3.Treatment plan

4. Materials for auditory individual work.

4.1 List of practical tasks to be done during the practical class:

- Study the method of examination of patient with malaria.
- Examine the patient with malaria.
- Perform differential diagnostics of malaria.
- Make up a plan of laboratory examination.
- Analyze results of specific examination of patients with malaria.

- Define complications of malaria.
- Make up a treatment plan for the patient with malaria.
- Define medical approach in case of emergencies.

Professional algorithm of gaining knowledge and skills about malaria diagnostics

#	Task	Sequence of actions	Remarks and cautions for self-control
1.	Study the methods of examination of patient with malaria	1. Define the complaints of the patient. 2. Medical history 3. Patient's life history 4. Epidemic history	Divide complaints attributable to syndromes of: - total toxicosis - organs attack - additional attacks Sequence and period of development of - fever - algor - sweat - other syndromes (nausea, vomiting, diarrhea and etc) - previous diseases Define: - stay in epidemic malaria region - individual chemical prophylactics
2.	Examine the patient	1. General examination Skin	- Estimate the state of the patient, condition - yellow sickness, its color

		Eyes	- scleritis, conjunctivitis
		Oral pharynx	- hyperemia, oropharynx mucosa edema
	2. Palpation		- size, stiffness and tenderness of , lymphnodes
		Lymphatic system	- voice tremor
		Lungs	- size and characteristics of liver and spleen
		Stomach	- stomach palpatory tenderness
			- meningeal syndrome (yes/no)
		Muscles	- percussion cardiac borders
	3. Percussion		- comparative pulmonary topographic percussion (presence or absence of percussion signs of pulmonary tissue induration)
		Heart	
		Lungs	
	4. Auscultation		- rhythm, loudness of cardiac sounds
		Heart	- breathing pattern – vesicular, hard, bronchial; weak, increased
		Lungs	- pathologic respiratory events – crepitation, rhonchi and their nature, location, changes in the course of breathing and coughing
			- bronchophony

3.	Perform laboratory testing	<p>1. General blood analysis</p> <p>2. General urine analysis</p> <p>3. ECG</p> <p>4. X-ray of thoracic organs</p> <p>5. Biochemical blood examination</p> <p>6. Parasitological examination</p> <p>7. Serological examination</p>	<p>- level of leucocytes, neutrophils, lymphocytes and blood sedimentation rate</p> <p>- presence of leucocytes, erythrocytes and protein</p> <p>- signs of infectious toxic myocarditis (yes/no)</p> <p>- diffusion or focal herd attack of pulmonary tissue</p> <p>- level of bilirubine and its fractions, alanine aminotransferase, ACT, BUN, creatinine</p> <p>- acid-base balance, electrolytes</p> <p>- coagulogram</p> <p>- blood glucose</p> <p>- spot and thick-blood tape (sampling to be taken at the height of the fever)</p> <p>- in paired serums titer increase by 4 times and more</p>
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LEISHMANIASIS, BRUCELLOSIS

Actuality of theme

1.1 Leishmaniasis

Leishmaniasis is a disease caused by an intracellular protozoan parasite (genus *Leishmania*) transmitted by the bite of a sandfly. The clinical spectrum of leishmaniasis ranges from a self-resolving cutaneous ulcer to a mutilating mucocutaneous disease and even to a lethal systemic illness. Therapy has long been a challenge in the more severe forms of the disease, and it is made more difficult by the emergence of drug resistance.

Etiology. Poverty and malnutrition play a major role in the increased susceptibility to leishmaniasis. Extracting timber, mining, building dams, widening areas under cultivation, creating new irrigation schemes, expanding road construction in primary forests such as the Amazon, continuing widespread migration from rural to urban areas, and continuing fast urbanization worldwide are among the primary causes for increased exposure to the sandfly.

Distribution of cutaneous leishmaniasis

Old World spread of *cutaneous disease* includes the following *Leishmania* species:

L donovani - China, India, Bangladesh, Sudan

L tropica - Middle East, China, India, Mediterranean

L aethiopica - Ethiopia, Kenya, Namibia

L major - Middle East, Africa, India, Asia

L infantum - Asia, Africa, Europe

New World spread of cutaneous disease includes the following *Leishmania* species:

L mexicana - Central, South, and North America

L amazonensis - Dominican Republic, Central and South America

L donovani chagasi - Texas, Caribbean, Central and South America

A relatively uncommon clinical variant of leishmaniasis, leishmaniasis recidivans appears as a recurrence of lesions at the site of apparently healed disease years after the original infection.

Post-kala-azar dermal leishmaniasis (PKDL) is a syndrome characterized by skin lesions that develop at variable intervals after (or during) therapy for visceral leishmaniasis. This condition is best described in cases of *L donovani* infection in South Asia and East Africa. In general, post-kala-azar dermal leishmaniasis is more common, develops earlier, and is less chronic in patients in East Africa.

Old World spread of *mucocutaneous leishmaniasis* is via *L aethiopica* in Ethiopia, Kenya, and Namibia.

New World spread of mucocutaneous leishmaniasis includes the following *Leishmania* species:

L braziliensis - Central and South America

L panamensis - Central and South America

L guyanensis - Guyana, French Guyana, Surinam, and Brazil

Less often seen with *L mexicana* - Central, South, and North America

Less often seen with *L amazonensis* - Brazil and Panama

Old World spread of *visceral leishmaniasis* is via the following:

L donovani - China, India, Bangladesh, Sudan, and Kenya

L infantum - Asia, North Africa, and South Europe

L tropica - Iran and Kenya

New World spread of visceral leishmaniasis is via *L donovani chagasi* in Central and South America.

Classification

The taxonomy of *Leishmania* organisms is complex, and no single categorization is generally accepted. The 2 simplest and most widely used systems for categorizing leishmaniasis are as follows:

Categorization by clinical disease: In this system, leishmaniasis is divided into 3 primary clinical forms: cutaneous (localized, diffuse (disseminated), leishmaniasis recidivans, post-kala-azar dermal leishmaniasis), mucocutaneous, visceral (kala-azar), and viscerotropic

Categorization by geographic occurrence: In this system, disease is divided into (1) Old World leishmaniasis (caused by *Leishmania* species found in Africa, Asia, the Middle East, the Mediterranean, and India), which produces cutaneous or visceral disease, and (2) New World leishmaniasis (caused by *Leishmania* species found in Central and South America), which produces cutaneous, mucocutaneous, and visceral disease

Epidemiology

In leishmaniasis, the obligatory intracellular protozoa are transmitted to mammals via the bite of the tiny 2- to 3-mm female sandfly of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World.

The sandfly is usually one half to one third the size of a mosquito. Leishmaniasis infections are considered zoonotic diseases, because for most species of *Leishmania*, an animal reservoir is required for endemic conditions to persist. Humans are generally considered incidental hosts. Infections in wild animals are usually not pathogenic, with the exception of dogs, which may be severely affected.

The bite of one infected sandfly is sufficient to cause the disease, because a sandfly can egest more than 1000 parasites per bite. Traditionally divided between Old World and New World parasites, more than 20 pathogenic species of *Leishmania* have been identified ; about 30 of the 500 known phlebotomine sandfly species have been positively identified as vectors of the disease.

Common Old World hosts are domestic and feral dogs, rodents, foxes, jackals, wolves, raccoon-dogs, and hyraxes. Common New World hosts include sloths, anteaters, opossums, and rodents. The reservoir of infection for Indian kala-azar is humans, whereas it is rodents for African kala-azar, foxes in Brazil and Central Asia, and canines

for the Mediterranean and Chinese kala-azar. Other mammalian reservoirs for the *Leishmania* parasite include equines and monkeys.

Uncommon modes of transmission include congenital transmission, contaminated needle sticks, blood transfusion, sexual intercourse, and, rarely, inoculation of cultures. Although, clear documentation of the potential of transfusion-associated leishmaniasis exists, there is less certainty of clear documentation of the actual occurrence of transfusion-related disease, because most cases in the literature occur in endemic areas of the world.

In India, visceral leishmaniasis caused by *L. donovani* does not appear to have an animal reservoir and is thought to be transmitted via human-sandfly-human interaction.

Co-infection with human immunodeficiency virus (HIV) has also led to the spread of leishmaniasis, typically a rural disease, into urban areas. In patients infected with HIV, leishmaniasis accelerates the onset of acquired immunodeficiency syndrome (AIDS) by cumulative immunosuppression and by stimulating the replication of the virus. It may also change asymptomatic *Leishmania* infections into symptomatic infections. Sharing of needles by intravenous drug users can spread not only HIV but also leishmaniasis.

Leishmania life cycle

The parasites exist in the flagellated promastigote stage in sandflies and in artificial culture and then transform into the nonflagellated amastigote form in animal and human hosts (see the following image).

Only the female sandfly transmits the protozoan, infecting itself with the *Leishmania* parasites contained in the blood it sucks from its human or mammalian host. Over 4-25 days, the parasite continues its development inside the sandfly, where it undergoes a major transformation into the promastigote form. A large number of flagellate forms (promastigotes) are produced by binary fission. Multiplication proceeds in the mid gut of the sandfly, and the flagellates tend to migrate to the pharynx and buccal cavity of the sandfly. A heavy pharyngeal infection is observed between days 6

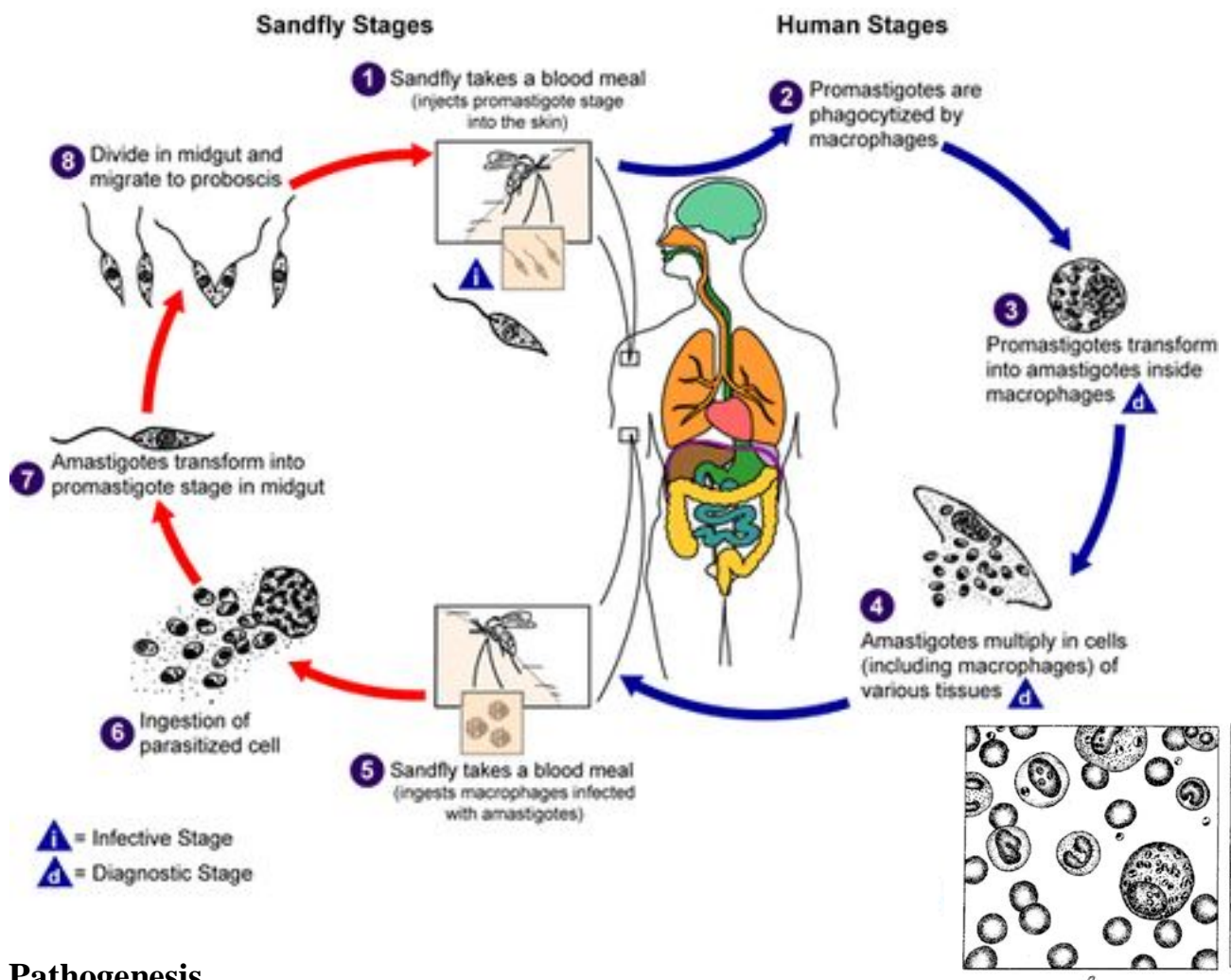
and 9 of an infected blood meal. The promastigotes are regurgitated via a bite during this period, resulting in the spread of leishmaniasis.

Following the bite, some of the flagellates that enter the new host's circulation are destroyed, whereas others enter the intracellular lysosomal organelles of macrophages of the reticuloendothelial system, where they lose their flagella and change into the amastigote form. The amastigote forms also multiply by binary fission, with multiplication continuing until the host cell is packed with the parasites and ruptures, liberating the amastigotes into the circulation. The free amastigotes then invade fresh cells, thus repeating the cycle and, in the process, infecting the entire reticuloendothelial system. Some of the free amastigotes are drawn by the sandfly during its blood meal, thus completing the cycle.

Depending on the species of parasite and the host's immune status, the parasites may incubate for weeks to months before presenting as skin lesions or as a disseminated systemic infection involving the liver, spleen, and bone marrow. Temperature is an important factor that helps determine the localization of leishmanial lesions. Species causing visceral leishmaniasis are able to grow at core temperatures, whereas those responsible for cutaneous leishmaniasis grow best at lower temperatures. Pathogenesis appears related to T-cell cytotoxicity.

Cutaneous leishmaniasis is caused by *L. tropica*; an animal reservoir for leishmaniasis caused by this organism has not been identified, although it has been found in some dogs in endemic areas. Morphologically, it is indistinguishable from *L. donovani*. The life cycle is exactly the same as that of *L. donovani* except that the amastigote form resides in the large mononuclear cells of the skin.

Picture 1. *Leishmania* life cycle



Pathogenesis

After inoculation by sandflies, the flagellated promastigotes bind to macrophages in the skin. Two of the parasite surface molecules appear to play a prominent role in parasite-phagocyte interactions. The extent and presentation of disease depend on several factors, including the humoral and cell-mediated immune response of the host, the virulence of the infecting species, and the parasite burden. Infections may heal spontaneously or may progress to chronic disease, often resulting in death from secondary infection.

Promastigotes activate complement through the alternate pathway and are opsonized. The most important immunologic feature is a marked suppression of the cell-mediated immunity to leishmanial antigens. In persons with asymptomatic self-resolving infection, T-helper (Th1) cells predominate, with interleukin 2 (IL-2), interferon-gamma, and IL-12 as the prominent cytokines that induce disease resolution, although

immune suppression years later can result in disease. An overproduction of both specific immunoglobulins and nonspecific immunoglobulins also occurs. The increase in gamma globulin leads to a reversal of the albumin-globulin ratio commonly associated with this disease.

As noted earlier, leishmaniasis involves the reticuloendothelial system. Parasitized macrophages disseminate infection to all parts of the body but more so to the spleen, liver, and bone marrow. The spleen is enlarged, with a thickening of the capsule, and is soft and fragile; its vascular spaces are dilated and engorged with blood. The reticular cells of Billroth are markedly increased and packed with the amastigote forms of the parasite. However, no evidence of fibrosis is present. In the liver, the Kupffer cells are increased in size and number and infected with amastigote forms of *Leishmania*. Bone marrow turns hyperplastic, and parasitized macrophages replace the normal hemopoietic tissue.

With visceral or diffuse (disseminated) cutaneous disease, patients exhibit relative anergy to the *Leishmania* organism and have a prominent Th2 cytokine profile. Typically, visceral leishmaniasis incubates for weeks to months before becoming clinically apparent. The disease can be subacute, acute, or chronic, and can manifest in patients who are immunocompromised years after they have left endemic regions.

Signs and symptoms

Cutaneous leishmaniasis includes the following features:

Localized *cutaneous leishmaniasis*: crusted papules or ulcers on exposed skin; lesions may be associated with sporotrichotic spread

Diffuse (disseminated) cutaneous leishmaniasis: multiple, widespread nontender, nonulcerating cutaneous papules and nodules; analogous to lepromatous leprosy lesions

Leishmaniasis recidivans: presents as a recurrence of lesions at the site of apparently healed disease years after the original infection, typically on the face and often involving the cheek; manifests as an enlarging papule, plaque, or coalescence of papules that heals with central scarring (ie, lesions in the center or periphery of an old

healed leishmaniasis scar); relentless expansion at the periphery may cause significant facial destruction similar to the lupus vulgaris variant of cutaneous tuberculosis

Post–kala-azar dermal leishmaniasis: Develops months to years after the patient's recovery from visceral leishmaniasis, with cutaneous lesions ranging from hypopigmented macules to erythematous papules and from nodules to plaques; the lesions may be numerous and persist for decades

Mucocutaneous leishmaniasis consists of the relentless destruction of the oropharynx and nose, resulting in extensive midfacial destruction. Specific signs and symptoms include the following:

- Excessive tissue obstructing the nares, septal granulation, and perforation; nose cartilage may be involved, giving rise to external changes known as parrot's beak or camel's nose
- Possible presence of granulation, erosion, and ulceration of the palate, uvula, lips, pharynx, and larynx, with sparing of the bony structures; hoarseness may be a sign of laryngeal involvement
- Gingivitis, periodontitis
- Localized lymphadenopathy
- Optical and genital mucosal involvement in severe cases

Visceral and viscerotropic leishmaniasis include the following features:

Visceral leishmaniasis (kala-azar): potentially lethal widespread systemic disease characterized by darkening of the skin as well as the pentad of fever, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia

Viscerotropic leishmaniasis: nonspecific abdominal tenderness; fever, rigors, fatigue, malaise, nonproductive cough, intermittent diarrhea, headache, arthralgias, myalgias, nausea, adenopathy, transient hepatosplenomegaly

Complications

Complications of leishmaniasis occur as a consequence of anemia, leukopenia, and thrombocytopenia. They may include the following:

- Secondary bacterial infection, including pneumonia and tuberculosis
- Septicemia
- Disfigurement of nose, lips, and palate (eg, cancrum oris)
- Uncontrolled bleeding
- Splenic rupture
- Late stages: Edema, cachexia, and hyperpigmentation
- Metastatic lesions in the nasopharynx with tissue destruction

Co-infection with human immunodeficiency virus (HIV) can also complicate cases of visceral leishmaniasis. A well-described and feared interaction is kala-azar in combination with HIV infection, which leads to more severe and rapidly progressive fatal outcomes from both diseases acting synergistically.

Diagnosis

Laboratory diagnosis of leishmaniasis can include the following:

- Isolation, visualization, and culturing of the parasite from infected tissue
- Serologic detection of antibodies to recombinant K39 antigen
- Polymerase chain reaction (PCR) assay for sensitive, rapid diagnosis of *Leishmania* species

Other tests that may be considered include the following:

- CBC count, coagulation studies, liver function tests, peripheral blood smear
- Measurements of lipase, amylase, gamma globulin, and albumin
- Leishmanin (Montenegro) skin testing (LST)

Cutaneous and mucocutaneous leishmaniasis generally display normal laboratory values in Routine Laboratory Studies.

For confirmation of cutaneous disease, procedures consist principally with performing biopsies, obtaining dermal scrapings, and/or needle aspirates. The smears are stained in Leishman, Giemsa, or Wright stains and examined under oil immersion microscope.

Localized cutaneous leishmaniasis is characterized by irregular acanthosis, with or without epidermal ulceration, and dense dermal infiltrate of mixed inflammatory cells, particularly plasma cells, lymphocytes, and histiocytes. Early in the course of localized disease, organisms may be numerous and found readily in the cytoplasm of macrophages. As the lesion ages and as delayed-type immunity is upregulated, the infiltrate is replaced by noncaseating granulomata in which few or no organisms can be seen.

Ulcerated lesions are often secondarily infected by bacteria, in which case histologic changes may be nonspecific. Results with biopsy specimens obtained from old (>6 mo), partially treated, or low-burden infections are frequently nondiagnostic. Diffuse cutaneous leishmaniasis occurs in individuals with poor cellular immunity to *Leishmania* parasites. Histologic diagnosis is straightforward in these cases. The dermis contains sheets of macrophages containing great numbers of amastigotes, with few lymphocytes or plasma cells. *Leishmaniasis recidivans* is usually difficult to confirm because of the rarity of organisms and because of its histologic similarity to lupus vulgaris. Post-kala-azar dermal leishmaniasis has a variable histology that is determined by the degree of host immunity and the parasite load. Granulomatous histology is seen with low numbers of organisms, whereas diffuse histiocytic or xanthomatous infiltrates may be seen with numerous organisms.

In both the localized cutaneous and mucocutaneous forms of leishmaniasis, cell-mediated immunity to the parasite is vigorous and organism density in the skin and/or mucosa is low, especially in long-standing disease (although very early in the disease large numbers of the parasites are frequently found). Therefore, growing organisms in culture can be difficult, as can finding them in pathologic specimens.

In more than 70% of cutaneous leishmaniasis cases, microscopy of the parasite in Giemsa stains or histologic section can reveal the parasite and should be attempted first. Culture of the organisms is an option but is unreliable (approximately 40% sensitivity), because the organisms are difficult to isolate from the lesion, especially as the lesion

becomes older. Consequently, the diagnosis often is epidemiologic (travel to endemic area, clinical picture, coupled with laboratory data). The organism grows on liquid media with fetal calf serum (eg, Schneider Drosophila medium) (positive results in 1 wk) and Novy-MacNeal-Nicolle (NNN) medium (media available from the CDC), or a biphasic medium. Cultures can produce positive results in 1-3 weeks.

Biopsy and/or Aspiration. For cutaneous leishmaniasis, take a 3-mm punch or wedge biopsy sample from a cutaneous sore from the raised edge of an active lesion where parasites are present. Avoid samples from the necrotic center. Additional tissue can be obtained through saline aspiration, tissue scrapings, or slit incisions. Once tissue is obtained, send touch preparations, tissue impression slides, and formalin-fixed paraffin sections for hematoxylin and eosin staining. Send touch preparations and aspirations for Giemsa staining, as well. Direct visualization of amastigotes with their red rodlike cytoplasmic kinetoplast is diagnostic and helps distinguish them from other parasites (see the image below). Brown-Hopps staining has a higher sensitivity than other staining techniques. Finding an organism in a tissue sample depends on the parasitic burden, the efficacy of the host's immune response, any coexisting bacterial contamination of the ulcer, and the age of the lesion (findings in older lesions are frequently nondiagnostic).

For mucocutaneous leishmaniasis, tissue can be obtained through dental scrapings or mucosal granuloma biopsy, although parasites may be difficult to isolate. A nonspecific granulomatous reaction often is observed. Giemsa stain may show the organisms.

Tissue Culture. In vitro cultures of tissue are regularly obtained to aid in leishmaniasis diagnosis and to help identify difficult *Leishmania* species. This technique has approximately the same diagnostic sensitivity as that of pathologic evaluation, but special laboratory capabilities and technical skills are required.

Specimens may be cultured on Novy-MacNeal-Nicolle (NNN) medium (rabbit-blood agar that has an overlay of Locke solution with added antibiotics), rabbit blood

agar, Schneider Drosophila medium, or a multitude of specialized media to induce promastigote growth. Cultures usually take a few days to 2 weeks to demonstrate growth. Positive culture results occur approximately 75% of the time.

Additional cultures can be performed by inoculating tissue into the footpad and nose of hamsters or certain highly susceptible mouse strains (ie, in vivo cultures via animal inoculation). This is a sensitive method, especially in difficult cases, but results can take several weeks to months.

Routine Laboratory Studies for *visceral disease*.

- Complete blood cell (CBC) count. In patients with visceral leishmaniasis, the presence of (1) normocytic normochromic anemia, (2) leukopenia with decreased neutrophils and a relative monocytosis and lymphocytosis, and (3) thrombocytopenia may occur due to parasitic bone-marrow infiltration. The severity of pancytopenia may vary with only 1 or 2 cell lines decreased.

- Peripheral blood smear. Amastigotes are revealed inside the circulating monocytes and neutrophils. However, these are often difficult to locate because of their small numbers.

L. donovani is best detected by either (1) creating thick film by producing a single straight leukocyte edge when making a peripheral smear or (2) centrifuging citrated blood and withdrawing the sediment, which is then smeared, dried, and stained. See the image below.

Parasitologic diagnosis using peripheral blood smear and buffy coat smear is easier in patients with human immunodeficiency virus (HIV) coinfection, because parasites are more commonly found in the circulating monocytes of these patients.

- Liver function tests (LFTs). Patients with visceral leishmaniasis may exhibit mild elevations in alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels.

- Other tests. Hypogammaglobinemia, circulating immune complexes, and rheumatoid factors are present in sera of most patients with visceral leishmaniasis.

Rarely, immunocomplex deposition in the kidneys may lead to mild glomerulonephritis. However, renal failure is not a feature of visceral leishmaniasis.

For visceral disease, the parasite can be detected through direct evidence (amastigotes in tissue) from peripheral blood, bone marrow, liver, or splenic aspirates. The most sensitive method is splenic puncture, although iatrogenic complications can be serious, including potentially life-threatening hemorrhage. In current practice, the high sensitivity and specificity of the recombinant K39 assay has generally made such invasive procedures unnecessary. Considerable experience has been gained and success achieved with using bone marrow aspirates (and especially a small piece of the spiculated core tissue) for cultivating the parasite or for looking for macrophages filled with amastigotes in the stained bone marrow aspirate smears.

A variety of immunodiagnostic serologic tests have been developed to aid in the diagnosis of systemic leishmaniasis. However, the only successfully deployed serologic tests are limited to species of *Leishmania* that cause visceral disease. Limitations include false-negative serologic results due to inadequate titers of antibodies late in the course of the disease and false-positive results in the setting of other infectious or autoimmune diseases.

Serologic testing is useful with the indirect fluorescent antibody (IFA) test, which is 80-100% sensitive in patients with visceral leishmaniasis who are not infected with human immunodeficiency virus (HIV). However, IFA may cross-react in patients who have leprosy, tuberculosis, malaria, schistosomiasis, Chagas disease, and African trypanosomiasis. Serologic tests such as isoenzyme or monoclonal antibody analysis are not well established.

An enzyme-linked immunosorbent assay (ELISA) can be combined with IFA and/or Western blot to increase sensitivity and specificity. Polymerase chain reaction (PCR) is being used more frequently; it is more accurate in determining new-onset leishmaniasis than serum tests (92-99% sensitivity; 100% specificity).

Biopsy and/or Aspiration for visceral leishmaniasis. Historically, bone marrow, liver, or splenic aspirates were the key to the laboratory diagnosis of visceral disease, but in current practice the high sensitivity and specificity of the recombinant K39 assay has generally made such invasive unnecessary.

The safest and most common way to obtain tissue is through bone-marrow aspiration obtained from the sternum or the iliac crest, although splenic aspiration may be used in cases that are difficult to diagnose. Amastigote forms are revealed in plain film, and the promastigote forms are revealed in culture. Although safer than splenic puncture, the parasites are scant and may give a false-negative test result. Positivity rates of 54-86% have been obtained using bone marrow.

Splenic aspiration has a higher sensitivity than bone-marrow aspiration—as many as 98% of positive results have been obtained using splenic aspiration—but this procedure should be attempted only by experienced physicians. Splenic puncture is associated with the risk of uncontrolled hemorrhage and, therefore, should be carried out only when bone marrow examination findings are inconclusive. Contraindications include low platelet count, abnormal prothrombin time, and a spleen that is palpable 4 cm or less below the costophrenic angle.

Additional tissue can be obtained through liver biopsy and lymph node dissection. Leishmaniasis is a disease that involves the reticuloendothelial system. The parasitized macrophages disseminate infection to all parts of the body, especially to the spleen, liver, and bone marrow. Direct visualization of the *Leishmania* organism is diagnostic, but this can be difficult in tissue sections because of its small size (2-4 μ m) and because of subtle distinguishing characteristics on routine hematoxylin and eosin (H&E) stains. Diagnosis is usually much easier using Giemsa-stained touch preparations.

Hepatosplenic features in visceral disease. The spleen is enlarged, with a thickening of the capsule, it is soft and fragile, its vascular spaces are dilated and engorged with blood, and the reticular cells of Billroth are markedly increased and packed with amastigote forms of the parasite. However, no evidence of fibrosis is present. In the

liver, the Kupffer cells are increased in size and number and infected with amastigote forms of *Leishmania*. The bone marrow is hyperplastic, and parasitized macrophages replace the normal hemopoietic tissue.

Definitive diagnosis of visceral disease is made by observing the parasite (more specifically, amastigotes in tissue) on stained Giemsa smears or by observing the culture of bone marrow, splenic, hepatic, or lymph node aspirates.

Serologic Studies. Recombinant K39 reactivity is absent in cutaneous and mucocutaneous infections. DAT detects the specific immunoglobulin M (IgM) antibody at an early stage and has been found to be useful in the detection of both clinical and subclinical leishmaniasis infections. Because this test is easy to perform and the results are available in 24 hours, it can be used as a rapid test in primary care settings. **Polymerase Chain Reaction.** Over the past several years, significant advances in polymerase chain reaction (PCR) techniques have allowed for the highly sensitive and rapid diagnosis of specific *Leishmania* species. PCR can identify parasite DNA using sequences from the variable region of kinetoplast DNA. However, a negative serologic test result does not exclude the possibility of a leishmanial infection.

Treatment is tailored to the individual, because leishmaniasis is caused by many species or subspecies of *Leishmania*.

Pharmacologic therapies include the following:

- Pentavalent antimony (sodium stibogluconate or meglumine antimonate): Used in cutaneous leishmaniasis.
- Liposomal amphotericin B (AmBisome): Effective against pentavalent antimony-resistant mucocutaneous disease and visceral leishmaniasis
- Oral miltefosine (Impavido): Approved for visceral leishmaniasis due to *L. donovani*; cutaneous leishmaniasis due to *L. braziliensis*, *L. guyanensis*, and *L. panamensis*; and mucosal leishmaniasis due to *L. braziliensis*
- Intramuscular pentamidine: Effective against visceral leishmaniasis but associated with persistent diabetes mellitus and disease recurrence

- Orally administered ketoconazole, itraconazole, fluconazole, allopurinol, and dapsons: None is as effective as the pentavalent antimony compounds, but they may be useful in accelerating cure in patients with cutaneous leishmaniasis that does not progress to mucosal disease and tends to self-resolve

- Topical paromomycin: Shown to be effective against cutaneous leishmaniasis caused by *L major* and *L mexicana*

- Local therapies for some forms of cutaneous leishmaniasis include the following: cryotherapy, local heat therapy at 40-42°C

Other important issues are as follows: correction of malnutrition, treatment of concurrent systemic illness (eg, HIV disease or tuberculosis), control of local infection

Although treatment was previously recommended for every case of leishmaniasis, this is no longer the conventional practice. The decision to treat leishmaniasis medically depends on various factors and must be a balance of risk versus benefit.

Given the associated morbidity, always treat visceral, mucocutaneous, and severe forms of cutaneous leishmaniasis. Patients should receive treatment at facilities experienced with the use of pentavalent antimony compounds.

In New World leishmaniasis, estimates of recurrence range from less than 5% to as many as 10% of untreated individuals experiencing chronic ulcers, recidivans lesions, or mucocutaneous involvement. Because of this, treatment is very often the standard of care, and parenteral therapy is usually the treatment of choice.

New World cutaneous leishmaniasis due to *L mexicana* is not associated with mucocutaneous leishmaniasis and may not require systemic treatment. Cutaneous leishmaniasis acquired in the Old World tends to resolve spontaneously (eg, *L major* from Iraq), but patients with this infection should receive treatment if the lesions are disfiguring, painful, infected, over joints, or slow to heal.

Multiple medical treatment options are used throughout the world for cutaneous disease. In addition to parenteral and oral medications, local therapies for some forms of cutaneous leishmaniasis include cryotherapy, infiltration of sodium stibogluconate at

0.3-0.8 mL, local heat therapy at 40-42°C, and various topical paromomycin preparations, typically 15% with 10% urea.

Of primary importance in dealing with leishmaniasis is the treatment of malnutrition, concurrent systemic illness (eg, human immunodeficiency virus [HIV] infection, tuberculosis), or local infection (secondary bacterial). Malnourished individuals are at greater risk of acquiring leishmaniasis, have increase morbidity and mortality in mucocutaneous and visceral disease, and respond less well to treatment than those with adequate nutrition.

The earliest sign of improvement is an improvement in symptoms; regression of splenomegaly takes a few months

Despite successful clinical outcomes, the question of whether the parasites are completely eradicated is unclear, because reactivation of leishmaniasis with immunosuppression has been reported.

The treatment mainstays of leishmaniasis are the pentavalent antimony compounds first introduced in the 1930s. The 2 available preparations, sodium stibogluconate (Pentostam), produced in Great Britain, and meglumine antimonate (Glucantime), produced in France, have similar efficacy. Depending on the species and region, cure rates of 80-100% have generally been reported.

Combination of intravenous (IV) stibogluconate and allopurinol showed improved efficacy against cutaneous *L. (Viannia) panamensis* infections compared with stibogluconate alone. However, this effect was not reproduced in the treatment of mucosal leishmaniasis. In many regions of the world, direct intralesional injection of pentavalent antimony is used to treat cutaneous disease, although this can be painful and is technically difficult.

Unfortunately, resistance to this agent is on the rise. In the Bihar province of India, where visceral leishmaniasis is endemic, resistance is as high as 43%.

Amphotericin B is effective against pentavalent antimony-resistant mucocutaneous disease and visceral leishmaniasis. Its use is limited because of its toxic adverse effect

profile. The newer lipid preparations (amphotericin B lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion) are more active, better tolerated, and are being used as first-line therapy against visceral leishmaniasis, but the response with cutaneous disease has been mixed, and treatment is costly.

Amphotericin B deoxycholate is the drug of choice in India, whereas the lipid formulation liposomal amphotericin is used in Europe. A single-dose treatment with liposomal amphotericin B has shown a 91% cure rate in India, but it is still considered too expensive for general treatment. In endemic areas of north India, liposomal amphotericin is used in combination with miltefosine. A short-course regimen consisting of a single dose of liposomal amphotericin followed by 7-14 days of miltefosine has resulted in cure rates of over 90%.

Response to liposomal amphotericin B may be suboptimal in patients infected with human immunodeficiency virus (HIV).

The discovery of an affordable, orally administered, well-tolerated therapy for visceral leishmaniasis has made mass treatment of the disease in the developing world a reality. Miltefosine is the sole oral agent that has been shown to be effective against leishmaniasis. This drug is a phosphocholine analogue that was originally developed as an antineoplastic agent; it interacts with membrane synthesis and signal production.

Monotherapy with oral miltefosine (2.5 mg/kg/d) for 28 days effective in the treatment of visceral leishmaniasis in children and adults. This medication is approved in India for visceral leishmaniasis.

Orally administered ketoconazole, itraconazole, fluconazole, allopurinol, and dapsone have been examined internationally, but none is as effective as the pentavalent antimony compounds. However, given their minimal adverse effect profile, these agents may be useful in accelerating the cure in patients with cutaneous leishmaniasis that does not progress to mucosal disease and tends to self-resolve.

Patients with leishmaniasis may have concurrent systemic illness or local infection. Visceral leishmaniasis is an important opportunistic infection associated with acquired

immunodeficiency syndrome (AIDS), and patients co-infected with human immunodeficiency virus (HIV) can develop unusual manifestations of leishmaniasis. Guidelines for prevention and treatment of opportunistic diseases in patients with HIV infection have been established.

Pentamidine is a first-line medication in cutaneous leishmaniasis except for *L. mexicana* (ketoconazole 600 mg PO qd for 28 days). It is a treatment alternative in visceral leishmaniasis. Available antibiotic preparations include pentamidine isethionate (Pentam) and pentamidine dimethanesulfonate (Lomidine). Pentamidine dimethane sulphonate administered in the same dose schedule is more effective than pentamidine isethionate.

Surgical excision to manage leishmaniasis is not usually recommended because of the following risks: relapse (exacerbation of quiescent disease), recurrence at the excision site, cosmetic disfigurement. Surgical intervention may be necessary for adjunctive splenectomy in patients with treatment-resistant disease. Patients with severe mucocutaneous leishmaniasis may require orofacial surgery.

Prognosis

Generally, the prognosis depends on the nutritional and overall immune status of the host, the precise species of infection, as well as appropriate therapy.

Localized *cutaneous leishmaniasis* often spontaneously resolves in 3-6 months without therapy, although some infections persist indefinitely. Most individuals respond exceedingly well to therapy: Rapid, complete resolution of the lesion(s), with decreased potential for secondary bacterial infections and diminished scarring, is the rule. This is not to say that the disease is without morbidity, especially in areas where even minimal facial disfiguring can condemn young girls to life without the prospect of marriage or acceptance in society.

Most cases of diffuse cutaneous leishmaniasis, post-kala-azar dermal leishmaniasis, and leishmaniasis recidivans are chronic and resistant to treatment. These

forms can be exceedingly disfiguring cosmetically because of the degree of persistent involvement; however, they are associated with low mortality rates.

Mucocutaneous leishmaniasis is chronic and progressive. This form of the disease affects the mucous membranes of the mouth, nose, and soft palate, and it is especially debilitating and destructive, resulting in extensive midfacial mutilation. Death can occur from secondary infection and after respiratory tract mucosal invasion. Respiratory compromise and dysphagia may lead to malnutrition and pneumonia.

The general consensus is that less than 5% of individuals infected by *L. brasiliensis*, and a smaller percentage of individuals infected by *L. panamensis* and *L. guyanensis*, develop mucosal metastases several months to years after the apparent resolution of cutaneous disease. However, no rigorous studies prove this commonly accepted rate.

Visceral leishmaniasis is a serious, progressive, and potentially lethal systemic disease. It tends to affect individuals in poor states of health, with poor nutritional status, and with even the most minor decreased immune status much more severely than individuals with good health, good nutritional status, and intact immune systems.

In well-nourished individuals with intact immune systems, full recovery from visceral disease is expected after treatment with the appropriate medication. With early therapy and supportive care, mortality in patients with visceral disease is reduced to approximately 5%; without therapy, most patients with visceral disease (kala-azar) (75-95%) die within 2 years, often from malnutrition and secondary infection, such as bacterial pneumonia, septicemia, dysentery, tuberculosis, cancrum oris, and uncontrolled hemorrhage or its sequelae.

In some endemic regions, pentavalent antimonial resistance is causing increased mortality rates.

Prophylaxis. Educate patients about the possibility of recurrent disease, and instruct them to schedule follow-ups as needed; the transmission of leishmaniasis; and the risk factors of leishmaniasis, including the following:

- Exposure to sandfly habitat

- Age (depending on the infecting species and geographic area)
- Male sex
- Adults who are immunologically naïve and entering an endemic area
- Patients who are immunosuppressed (eg, transplant recipients, chronic steroid users, those with malignancies)
- Malnutrition
- Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS)
- Intravenous drug use in endemic areas

Behavior modification to avoid vector contact, combined with insect control measures, significantly diminishes the risk of acquiring infection.

Immunization. In some areas of the world (eg, Russia, Middle East), live-attenuated L major promastigotes have been used preemptively to immunize against Old World cutaneous leishmaniasis. This practice produces a modified form of the disease and results in a scar at the injection site. Immunity to subsequent L major infections is usually good; however, as with natural infection, cross-reactive immunity to other Leishmania species does not occur.

Many more universally useful and cosmetically acceptable Leishmania vaccine formulations are under investigation. To date, no vaccines are commercially available.

1.2 Brucellosis

Brucellosis is a zoonotic infection caused by the bacterial genus Brucella. The disease is an old one that has been known by various names, including Mediterranean fever, Malta fever, gastric remittent fever, and undulant fever. Humans are accidental hosts, but brucellosis continues to be a major public health concern worldwide and is the most common zoonotic infection. Interest in brucellosis has been increasing because of the growing phenomena of international tourism and migration, in addition to the potential use of Brucella as a biologic weapon.

Etiology. Brucella organisms, which are small aerobic intracellular coccobacilli, localize in the reproductive organs of host animals, causing abortions and sterility. They are shed in large numbers in the animal's urine, milk, placental fluid, and other fluids. To date, 8 species have been identified, named primarily for the source animal or features of infection. Of these, the following 4 have moderate-to-significant human pathogenicity:

Brucella melitensis (from sheep; highest pathogenicity)

Brucella suis (from pigs; high pathogenicity)

Brucella abortus (from cattle; moderate pathogenicity)

Brucella canis (from dogs; moderate pathogenicity)

Of the 4 Brucella species known to cause disease in humans B. melitensis is thought to be the most virulent and causes the most severe and acute cases of brucellosis; it is also the most prevalent worldwide. B. melitensis may be acquired via exposure to animals or animal products or, in the case of laboratory technicians, to specimens from animals (including humans) whose tissues are operated upon or submitted for culture or pathologic analysis.

B. abortus is more widely distributed throughout the world than B. melitensis is, but it is less pathogenic for both animals and humans. This species gives rise to mild-to-moderate sporadic disease that rarely causes complications.

Infection with B. suis gives rise to a prolonged course of illness, often associated with suppurative destructive lesions.

B. canis infection has a disease course that is indistinguishable from that of B. abortus infection. Its infection has an insidious onset, causes frequent relapses, and does not commonly cause chronic brucellosis.

Although B. pinnipediae and B. cetaceae typically affect marine animals, they are now known to be capable of causing disease in humans (mainly neurobrucellosis).

Ingestion of unpasteurized goat milk and related dairy products is the main route by which B. melitensis is transmitted to humans.

Slaughterhouse workers, primarily those in the kill areas, become inoculated with brucellae through aerosolization of fluids, contamination of skin abrasions, and splashing of mucous membranes. Farmers and shepherds have similar exposure risks, and they also have exposure to aborted animals. Veterinarians are usually infected by inadvertent inoculation of animal vaccines against *B abortus* and *B melitensis*. Laboratory workers (microbiologists) are exposed by processing specimens (aerosols) without special precautions.

Epidemiology. Brucellosis causes more than 500,000 infections per year worldwide. Its geographic distribution is limited by effective public and animal health programs, and the prevalence of the disease varies widely from country to country. Overall, the frequency of brucellosis is higher in more agrarian societies and in places where handling of animal products and dairy products is less stringent.

The bacteria are transmitted from animals to humans by ingestion through infected food products, direct contact with an infected animal, or inhalation of aerosols.

Although brucellosis is still a reportable disease, it has become rare as a result of the institution of veterinary control measures (eg, routine screening of domestic livestock and vaccination programs). Occupational exposures tend to be isolated. A large-scale outbreak of the infection should raise suspicion that a biologic weapon has been released, most likely via an infectious aerosol.

Pathogenesis. Brucellae are aerobic gram-negative coccobacilli that possess a unique ability to invade both phagocytic and nonphagocytic cells and to survive in the intracellular environment by finding ways to avoid the immune system. This ability helps explain why brucellosis is a systemic disease and can involve almost every organ system.

Brucella can gain entry into the human body through breaks in the skin, mucous membranes, conjunctivae, and respiratory and gastrointestinal (GI) tracts. Sexual transmission has not been convincingly documented. Ingestion usually occurs by way of unpasteurized milk; meat products often have a low bacterial load.

Once within the bloodstream, the organisms quickly become intracellular pathogens contained within circulating polymorphonuclear cells (PMNs) and macrophages, making use of numerous mechanisms to avoid or suppress bactericidal responses.

In addition, *Brucella* species have relatively low virulence, toxicity, and pyrogenicity, making them poor inducers of some inflammatory cytokines, such as tumor necrosis factor (TNF) and interferons. Furthermore, the bacteria do not activate the alternative complement system. Finally, they are thought to inhibit programmed cell death.

After ingestion by phagocytes, about 15-30% of brucellae survive. Susceptibility to intracellular killing differs among species, with *B abortus* readily killed and *B melitensis* rarely affected; these differences might explain the differences in pathogenicity and clinical manifestations in human cases of brucellosis.

Brucellae that survive are transported into the lymphatic system and may replicate there locally; they also may replicate in the kidney, liver, spleen, breast tissue, or joints, causing both localized and systemic infection. Any organ system can be involved (eg, central nervous system [CNS], heart, joints, genitourinary system, pulmonary system, and skin); localization of the process may cause focal symptoms or findings. After replication in the endoplasmic reticulum, the brucellae are released with the help of hemolysins and induced cell necrosis.

Development of cell-mediated immunity is the principal mechanism of recovery. The host response to infection with *B abortus* is characterized by the development of tissue granulomas indistinguishable from those of sarcoidosis. In contrast, infection with the more virulent species (*B melitensis* and *B suis*) more commonly results in visceral microabscesses.

Although *Brucella* infection is primarily controlled through cell-mediated immunity rather than antibody activity, some immunity to reinfection is provided by serum immunoglobulin (Ig). Initially, IgM levels rise, followed by IgG titers. IgM may

remain in the serum in low levels for several months, whereas IgG eventually declines. Persistently elevated IgG titers or second rises in IgG usually indicate chronic or relapsed infection.

Classification of disease

Traditionally, brucellosis has been classified as subclinical, acute, subacute, or chronic; localized and relapsing forms have also been described. This classification system, though commonly used, is subjective and of limited clinical utility.

Clinical symptoms

Symptoms of brucellosis are protean in nature, and none is specific enough to support the diagnosis. Generally, physical examination findings are normal or only minimally abnormal (see below), and the diagnosis is made on the basis of the history and serologic studies.

Fever is the most common symptom and sign of brucellosis, occurring in 80-100% of cases. It is intermittent in 60% of patients with acute and chronic brucellosis and undulant in 60% of patients with subacute brucellosis. Fever can be associated with a relative bradycardia.

Constitutional symptoms of brucellosis include anorexia, asthenia, fatigue, weakness, and malaise, and weight loss and are very common (> 90% of cases).

Bone and joint symptoms include arthralgias, low back pain, spine and joint pain, and, rarely, joint swelling. These symptoms affect as many as 55-80% of patients. Arthralgias may be diffuse or localized, with a predilection for bone ends and the sacroiliac joint. Acute monoarticular arthritis is uncommon but may be part of the presentation.

Neuropsychiatric symptoms of brucellosis are common despite the rare involvement of the nervous system. Headache, depression, and fatigue are the most frequently reported neuropsychiatric symptoms. In patients with advanced disease who have meningoencephalitis, these complaints may include changes in mental status, coma, neurologic deficit, nuchal rigidity, or seizures.

A significant percentage (approximately 50%) of patients have gastrointestinal (GI) complaints, primarily dyspepsia, though abdominal pain from hepatic abscesses may occur. Hepatic abscesses should be suspected in patients with signs of systemic toxicity and persistently elevated liver enzymes. The abscess can serve as a source of bacteremic seeding. Spontaneous bacterial peritonitis secondary to brucellosis infection has been reported. Constipation, diarrhea, and vomiting may occur.

Genitourinary infections with brucellae have been reported and include orchitis, urinary tract infection (UTI), and glomerulonephritis. Frank renal failure or sepsis is rare.

Neurologic symptoms of brucellosis can include weakness, dizziness, unsteadiness of gait, and urinary retention. Symptoms associated with cranial nerve dysfunction may affect persons with chronic central nervous system (CNS) involvement.

Cough and dyspnea develop in up to 19% of persons with brucellosis; however, these symptoms are rarely associated with active pulmonary involvement. Endocarditis from brucellae is reported, with septic embolization a common complication of this form of brucellosis. Brucella endocarditis is the form most commonly associated with fatalities.

With the chronic form of brucellosis, in which the illness has lasted longer than 1 year (undiagnosed and untreated brucellosis), an afebrile pattern is typical, with a history of myalgia, fatigue, depression, and arthralgias (chronic fatigue syndrome is the most important disease in the differential diagnosis). The chronic form is primarily caused by *B melitensis* and usually affects adults older than 30 years.

Laboratory Studies. Given that symptoms and signs of brucellosis are nonspecific, cultures and serology are usually necessary for diagnosis. Some general laboratory findings might suggest the diagnosis (eg, leukopenia, relative lymphocytosis, or pancytopenia). A slight elevation in liver enzyme levels is a very common finding. These elevated levels may reflect the severity of hepatic involvement and correlate clinically with hepatomegaly. The standard test for diagnosis of brucellosis is the

isolation of the organism from blood or tissues (eg, through bone marrow biopsy or liver aspiration). Urinalysis, urine culture may be indicated in the presence of symptoms of urinary tract infection (UTI).

Definitive diagnosis of brucellosis is based on culture, serologic techniques, or both. Clinically, identification to the genus level is sufficient to warrant initiation of therapy. The particular *Brucella* species involved does not affect the choice of therapeutic agents; however, speciation is necessary for epidemiologic surveillance and requires more detailed biochemical, metabolic, and immunologic testing.

Serologic testing is the most commonly used method of diagnosing brucellosis. Repeated serologic testing is recommended if the initial titer is low. The tube agglutination test, developed by Bruce, measures antibodies against smooth lipopolysaccharide (LPS); it remains the most popular test tool for the diagnosis of brucellosis. The 2-mercaptoethanol test detects immunoglobulin G (IgG), and titers higher than 1:80 define active infection. A high IgG antibody titer or a titer that is higher after treatment suggests persistent infection or relapse. Enzyme-linked immunosorbent assay (ELISA) typically uses the cytoplasmic proteins as antigens and measures IgM, IgG, and IgA, allowing better interpretation, especially in cases of brucellosis relapse. This is because antibodies against LPS, which are used in agglutination tests, might persist for longer periods and are believed to yield higher sensitivity and specificity. ELISA of CSF also helps diagnose neurobrucellosis. Because levels should decrease with effective treatment, ELISA is also helpful in follow-up.

Polymerase chain reaction (PCR) tests have been developed for the detection and rapid diagnosis of *Brucella* species in human blood specimens. Possible applications would include evaluating cases of relapse and monitoring response to therapy.

Treatment. The goal of medical therapy in brucellosis is to control symptoms as quickly as possible in order to prevent complications and relapses.

No special diet is required for the treatment of brucellosis. Discuss with patients the importance of consuming pasteurized milk and milk products and avoiding other

possible sources of infection. Obviously, the impact of such education will have the greatest effect on family and friends who may be at risk for infection.

Restriction of activity with bed rest appears to confer benefit in the acute phase of brucellosis, increasing the rate of recovery.

Although multiple antibiotics display *in vitro* activity against *Brucella* species, clinical response has been demonstrated with only a limited number of agents. Drugs that display clinical activity with low relapse rates include the following: Doxycycline, Gentamicin, Streptomycin, Rifampin, Trimethoprim-sulfamethoxazole (TMP-SMZ), other agents with potential roles (Chloramphenicol, Imipenem-cilastatin, Tigecycline, Fluoroquinolones).

In those cases where relapse has occurred, the development of antibiotic resistance does not appear to be the underlying cause.

Optimal antibiotic therapy for brucellosis has been studied to some degree; however, recommendations may differ.

For simple infection, doxycycline (100 mg PO twice daily for 6 weeks) may be the most appropriate monotherapy; however, relapse rates with such monotherapy approach 40% and as a result, rifampin (600-900 mg/day) is usually added. Fluoroquinolones (eg, ciprofloxacin) have been used as monotherapy as well but also carry a high relapse rate; adding these agents to doxycycline offers no specific advantages over other combination regimens but may be preferred in areas where resistance to rifampin is high.

For acute brucellosis in adults and children older than 8 years, the World Health Organization (WHO) guidelines recommend the following:

Doxycycline 100 mg PO twice daily plus rifampin 600-900 mg/day PO – Both drugs are to be given for 6 weeks; this regimen is more convenient but probably increases the risk of relapse

Doxycycline 100 mg PO twice daily for 6 weeks and streptomycin 1 g/day IM for 2-3 weeks – This regimen is believed to be more effective, mainly in preventing relapse; gentamicin can be used as a substitute for streptomycin and has shown equal efficacy

Ciprofloxacin-based regimens have shown efficacy equal to that of doxycycline-based regimens.

Chronic brucellosis is treated with triple-antibiotic therapy. The combination of rifampin, doxycycline, and streptomycin often is used.

Prognosis. The prognosis is generally excellent. Although initial symptoms of brucellosis may be debilitating, if they are treated appropriately and within the first few months of onset, the disease is easily curable, with a low risk of relapse or chronic disease. However, the prognosis is poor in persons who present with congestive heart failure due to endocarditis, in whom mortality approaches 85%. In some patients, brucellosis can cause chronic debilitating illness with extensive morbidity.

In uncomplicated cases of acute brucellosis, fever, malaise, and many other manifestations improve rapidly with bed rest, whereas sustained physical activity may prolong or worsen the degree of illness. Considerable improvement from the symptoms of the acute phase of illness typically occurs within a few weeks, with or without treatment. In many cases, this is followed by complete remission within 2-6 months. Recovery tends to be more rapid with *B abortus* infection than with *B melitensis* or *B suis* infection.

Recurrence of symptoms of acute brucellosis is not uncommon. The recurrent disease may be systemic or localized. In some of these patients, the condition evolves into chronic brucellosis, which may be progressive if untreated. Chronic brucellosis includes systemic and specific localized forms (including various types of neurobrucellosis). These various forms are due to continued infectious disease, for which additional treatment is indicated and effective. The likelihood of recurrence is greater in individuals who are not treated or who are inadequately treated for acute brucellosis. However, recurrence is possible even in properly treated patients who have had acute brucellosis. Addition of oral rifampicin to oral tetracycline may reduce the recurrence risk for patients who are treated with that combined therapy for acute brucellosis.

Chronic brucellosis may continue to trouble patients for as long as 25 years, but such cases are quite rare.

Prophylaxis. Prevention of brucellosis in humans depends on eradication or control of the disease in animals and on avoiding potential sources of infection. Better handling of infected animals or animal products is paramount. Public awareness and education play major roles in prevention.

Consumption of unpasteurized milk and milk products, as well as of raw or undercooked meats, should be avoided. Education may be provided to the patient and family concerning risks and should emphasize avoiding anything identified as a specific cause in the case at hand. Should the identified source be a live animal, the herd or flock from which it came should be investigated. In endemic areas, investigation is warranted for all animals.

Scrupulous hygiene may prevent infection, especially when practiced by individuals likely to have close contact with goats, sheep, cows, camels, pigs, reindeer, rabbits, or hares. Obviously, this contact is of greatest importance in areas of endemic disease.

At present, immunization is not an option for patients; the vaccine is attenuated for animals but not for humans and may cause disease in humans. However, immunization of at-risk animals reduces the number of infected animals and therefore the reservoir of infection. Results from a study of the planned brucellosis control program in Egypt showed that removal of infected animals under the actual implementation of the program would likely permit brucellosis to remain endemic in the goat and sheep population.

All persons with an occupational risk for brucellosis should be informed about the use of protective devices (eg, goggles, masks, and gloves) to avoid exposure to aerosols, body fluids, or the brucellosis vaccine. In particular, laboratory personnel should be advised of the potential diagnosis so they will use biosafety level-3 precautions when in contact with suspicious specimens.

Serious concerns have been expressed concerning the utilization of *Brucella* species in biologic weapons. Airborne transmission of these bacteria is readily achieved via the mucous membranes of the conjunctivae, nasal passages, oropharynx, and respiratory tract. Infection may occur as the result of lodging of organisms in cuts or abrasions. As few as 10-100 organisms may produce infection via aerosol exposure. The resulting disease may exhibit any of the various manifestations of which *Brucella* species are capable.

Patient education should include efforts to address the following issues:

The nature of the disease and the routes by which it can be transmitted

The symptoms, complications, and treatment of the disease, as well as the risk of relapse if it is not adequately treated

The potential adverse effects of the medications administered

The need for strict compliance with the antibiotic regimen

The need to avoid potential sources of infection – This may involve avoiding infected animals, using stricter precautions (eg, gloves and mask) when dealing with a potentially infected animal, or avoiding potentially contaminated foods

For farmers and ranchers, immunization of their cattle against the disease as necessary

For laboratory workers, maintenance of the appropriate level of containment

The development of an effective *Brucella* vaccine for use in humans would be an important step to controlling and probably eradicating brucellosis. However, the vaccine strategy is currently applicable only in control of livestock disease.

2. Study purpose of practical studies:

2.1. The student must have an idea (read):

***α* -1**

1. have a general idea about position of leishmaniasis, brucellosis in the structure of virulent diseases, prevalence in the world; study statistic data related to case rate, case mortality, event frequency as for today.
2. get familiar with history of scientific study of leishmaniasis, brucellosis, have an idea of scientific contribution of native scientists, in the history of scientific research in this field.

2.2. The student is should know:

$\alpha - 2$

- etiology, factors pathogenicity of leishmaniasis (dermal, mucocutaneous visceral), brucellosis;
- epydemiology of leishmaniasis, brucellosis;
- pathogenesis of leishmaniasis, brucellosis;
- clinical and epidemiological peculiarities of leishmaniasis, brucellosis;
- pathogenesis, term of arising and clinical manifestations of the complications of leishmaniasis, brucellosis;
- laboratory diagnosis of leishmaniasis, brucellosis;
- principles of treatment of leishmaniasis, brucellosis;
- tactics in the event of arising urgent conditions of leishmaniasis, brucellosis;
- prognosis of leishmaniasis, brucellosis;
- rules of letting go from the hospital for the convalescences;
- prophylaxis of leishmaniasis, brucellosis.

2.3. The student should be able to:

$\alpha-3$

- know how to examine patients and reveal main symptoms and syndromes of leishmaniosis, brucellosis motivate the clinical diagnosis for well-timed direction the patient to the hospital;
- carry out the differential diagnosis of visceral and dermal leishmaniasis, brucellosis;

- on base of the clinical examination to recognize the possible complications and urgent conditions by visceral leishmaniasis, brucellosis;
- draw up the medical documentation after determination of the primary diagnosis of leishmaniasis, brucellosis;
- know how to form the plan of laboratory and additional examination of the patient;
- interpret the results of the laboratory examinations;
- analyze the results of the specific methods of the diagnosis depending on the material and period of the disease;
- form the individual plan of the treatment with accounting epidemiological data, stage of the disease, complications, gravity of the condition, allergic anamnesis, accompanying pathology;
- render the urgent help until the hospital treatment;
- form the plan of antiepidemic and preventive actions in the centre of the infection;
- give the recommendations in respect of regime, diets, examinations, observations at period of convalescences.

2.4. Educational goals (goals of the person):

- Develop deontological conception in the study subjects.
- To be able to observe the rules of conduct in the bedside, the principles of medical ethics.
- Master the ability to establish psychological contact with the patient and his relatives.
- Develop knowledge of the impact of socio-hygienic factors on the prevalence of leishmaniasis, brucellosis.

- The subject materials to develop a sense of responsibility for the timeliness and accuracy of professional activities.

3. Materials for out-class self-training (before practical classes)

3.1. Basic knowledge, skills which are necessary for studying of topic (interdisciplinary integration)

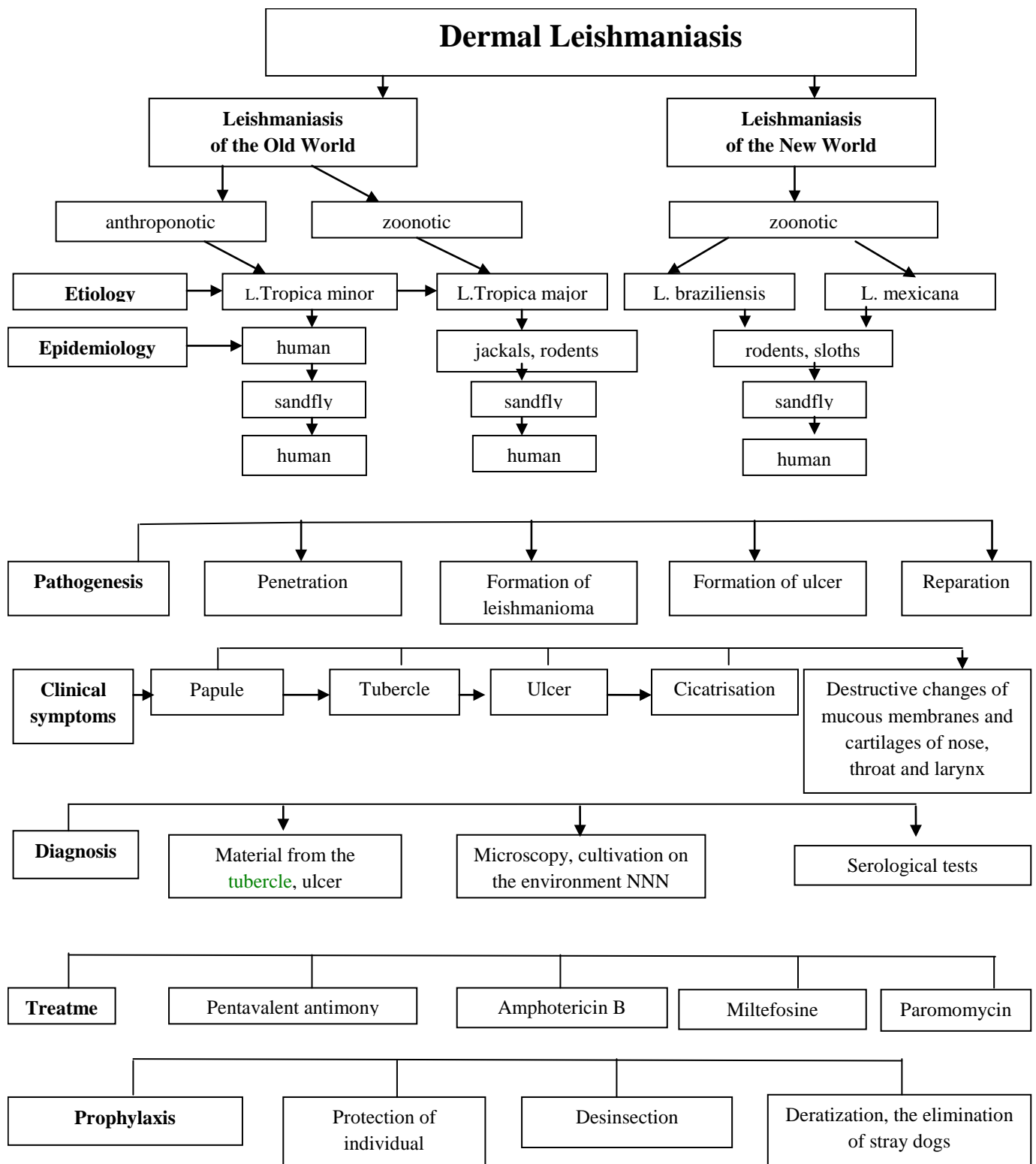
Disciplines	To know	Be able to
Microbiology	Peculiarities of the incitant <i>L.donovani</i> infantus, <i>L.d.donovani</i> , <i>L.d.chagasi</i> , <i>L.tropica</i> minor, <i>L.tropica</i> major, <i>L.braziliensis</i> , <i>L.mexicana</i> ; <i>Br. melitensis</i> , <i>Br. suis</i> , <i>Br. abortus</i> , <i>Br. canis</i> . The methods of the specific diagnosis.	Interpret the results of the specific methods of the diagnosis of leishmaniasis, brucellosis.
Physiology	Indexes of the laboratory examination in normal conditionals (the blood test, urine test, CSF).	Interpret the results of the laboratory examination.
Pathophysiology	Mechanism of function breaches of organs and systems under pathological conditions of different genesis.	Interpret pathological changes in the results of laboratory examination when functional breaches of organs and systems by different genesis are present.

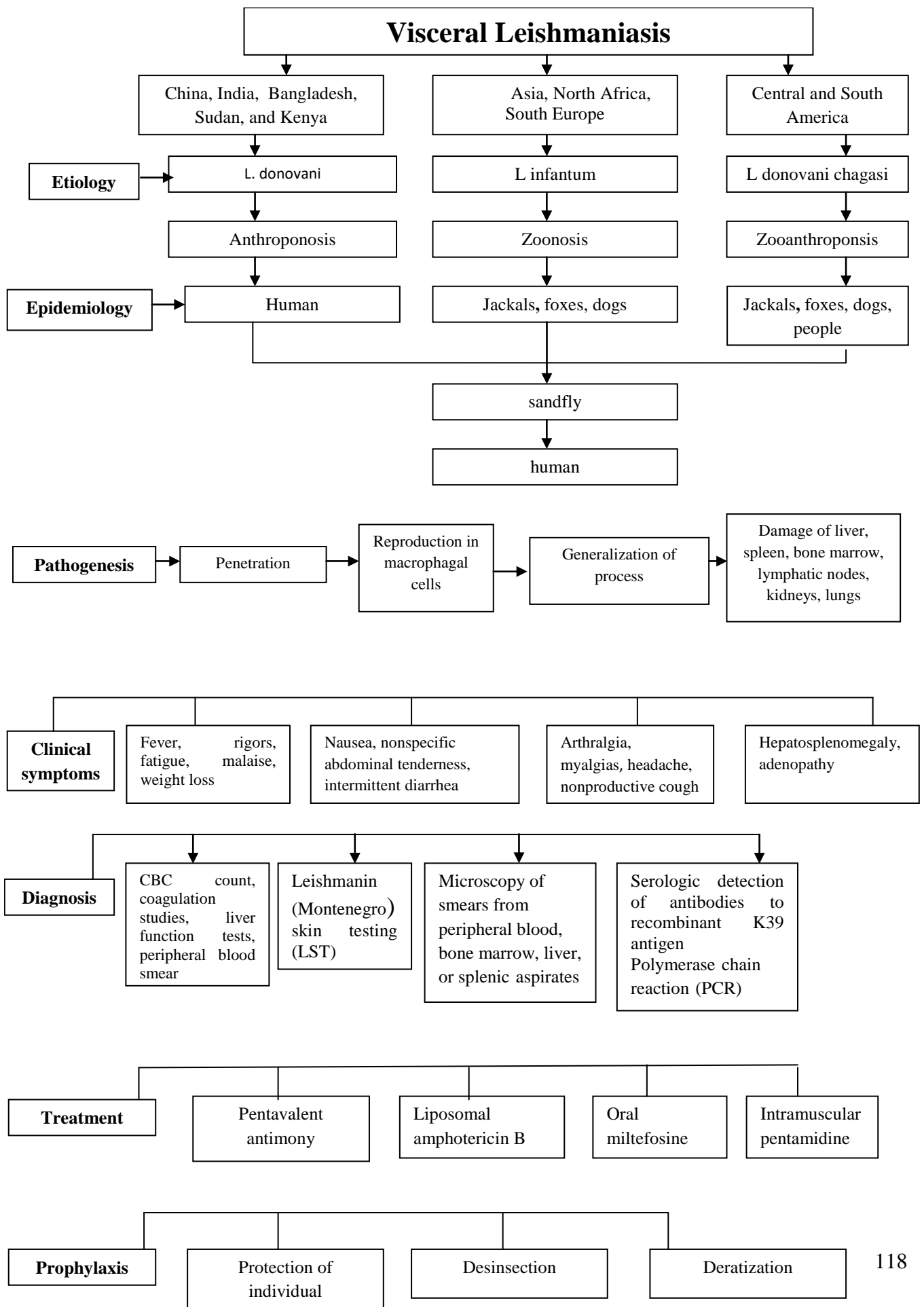
Biochemistry	Indexes of the laboratory examination (blood and liquor glucose, liquor protein, electrolytes)	Interpretation the result of the laboratory examination.
Immunology	Role of the immunity system in infectious process.	Value the data of the immunological examinations
Propedeutics of internal diseases	Main stages and methods of the clinical examination.	Ask the case history, conduct the clinical examination the patient, reveal the pathological symptoms, form the syndromes. Analyse the data you have got.
Epidemiology	Source of the infection, mechanism of the transmission, factors of the transmission by the visceral and dermal leishmaniasis, brucellosis.	Ask the epidemic anamnesis. Give the recommendations on preventive given disease.
Neurology	Pathogenesis, clinical signs of the toxic encephalopathy in patients with visceral leishmaniasis, brucellosis.	To conduct the clinical examinations the sick with defeat of the nervous system.
Dermatology	Clinical feature of exanthems.	To recognize and describe correctly the eruption in patient with

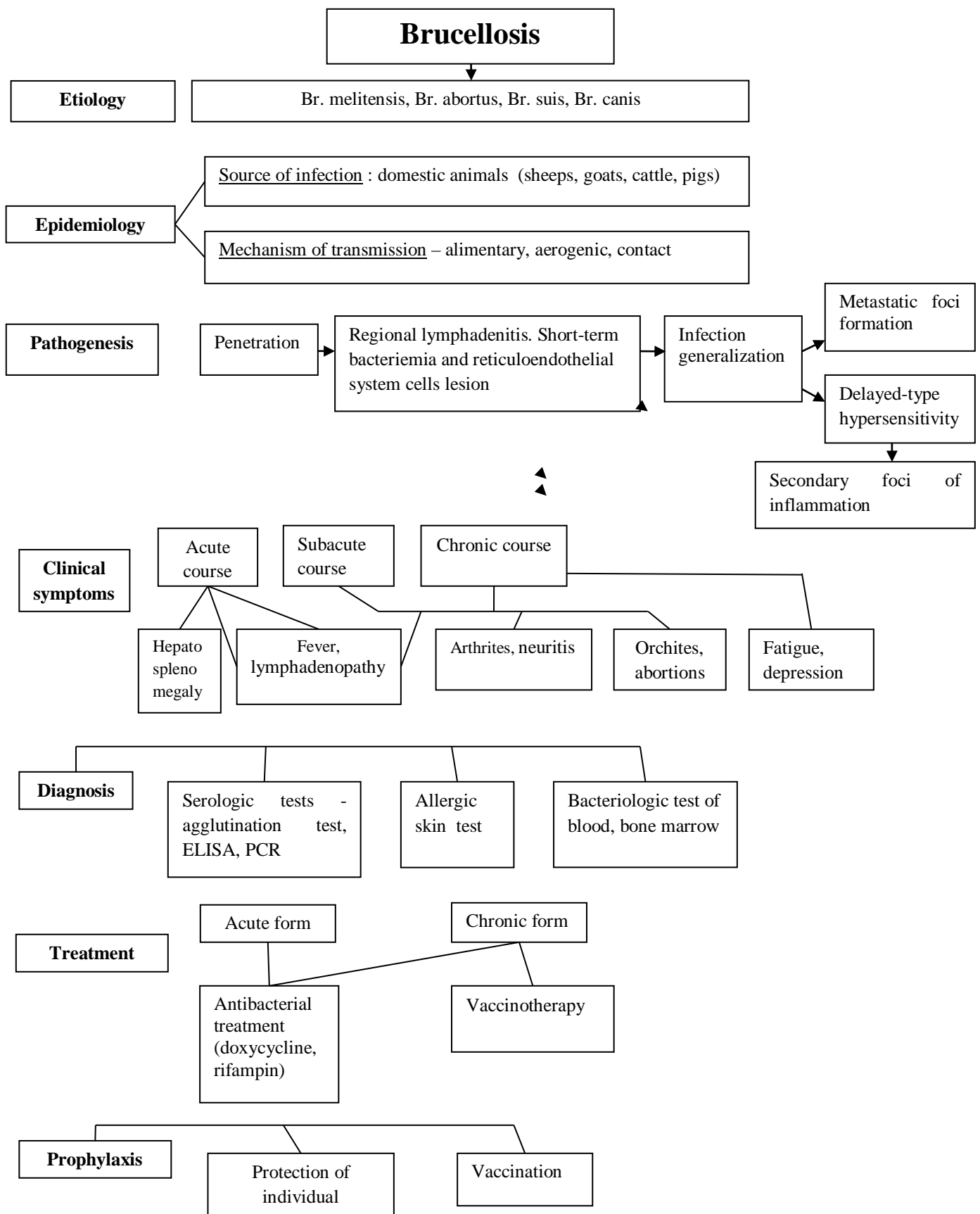
		leishmaniasis.
Resuscitation and intensive therapy	Urgent conditions: expressed anemia, hemorrhagic diathesis, edema of larynx	Diagnose in good time and render urgent help under urgent conditions.
Clinical pharmacology	Pharmacodynamics and pharmacokinetics of drugs used in the treatment.	Choose optimum doses of drugs depending on forms of the disease.
Other disciplines		
Family practice	Pathogenesis, epidemiology, intensiveness of clinical signs, possible complications of leishmaniasis, brucellosis. Principles of prophylactics and treatment.	Perform differential diagnostics of diseases with various geneses at leishmaniasis. Find out leishmaniasis and possible complications; analyze results of laboratory examination. Admit the patient to contagious isolation ward in due time. Fill in the emergency notice. Provide rescue emergency care if required
Integration between subjects		
Virulent diseases	Features of infectious diseases. Methods of diagnostics, treatment and prophylactics of infectious diseases.	Perform differential diagnostics of leishmaniasis, brucellosis with other infectious

	Pathogenesis, epidemiology, intensiveness of clinical signs, laboratory diagnostics, possible complications specific features of clinical progress of leishmaniasis, brucellosis. Prophylactics and treatment methods	diseases. Define leishmaniasis, brucellosis their complications; analyze results of laboratory examination. Prescribe treatment. Provide rescue emergency care in pre-hospital stage.
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3.2 Theme contents.







3.4. Self-control materials

3.4.1. Questions for self-control

1. The ways of the transmission of dermal, visceral and of the New World leishmaniasis, brucellosis.
2. The stages of pathogenesis of dermal and visceral leishmaniasis, brucellosis.
3. Morphological changes in dermal leishmaniasis.
4. Stages of the clinical current of visceral leishmaniasis, brucellosis.
5. Main symptoms of dermal and visceral leishmaniasis at initial period disease.
6. Main symptoms of dermal and visceral leishmaniasis in peak of the disease.
7. The feature, periods of the arising the ulcer in dermal forms of leishmaniasis.
8. The peculiarities of the current of the Old and New World dermal leishmaniasis.
9. Specific complications of the dermal leishmaniasis, brucellosis.
10. Hemogram of the patient with visceral leishmaniasis.
11. The plan of the examination the patients with dermal and visceral leishmaniasis.
12. The methods of the specific diagnosis of leishmaniasis, brucellosis. Interpretation the results in dependence from periods of the disease and material for the examination.
13. Etiotropic therapy of dermal and visceral leishmaniasis, brucellosis: doses, ways of the introduction, duration of the treatment.
14. The principles of the pathogenetic therapy of visceral leishmaniasis.
15. The treatment of the complications of dermal and visceral leishmaniasis.
16. Rules for letting go from the hospital for the convalescences.

3.4.2. Tests for self-control

Choose correct answers:

$\alpha=2$

Variant 1

1. Patient V., a shepherd. During the year, the pain in the knee joints, low-grade fever, profuse sweating concerned him. Knee joints swollen, movement in them is painful. Hepatosplenomegaly. Impotence. Diagnosis:
 - A. pseudotuberculosis,
 - B. skin leishmaniasis,
 - C. Lyme borreliosis,
 - D. brucellosis,
 - E. visceral leishmaniasis.

2. While what form of leishmaniasis characteristic changes in hemogram are observed: anemia, leukopenia, thrombocytopenia, a sharp increase of speed of erythrocyte sedimentation, hypergammaglobulinemia?:
 - A. visceral leishmaniasis,
 - B. urban type of skin leishmaniasis,
 - C. rural type of skin leishmaniasis,
 - D. skin leishmaniasis of the New World,
 - E. everything is right.

3. For the diagnosis of skin leishmaniasis should be used all except:
 - A. parasitological method (punctate nodule or infiltrate, scraping the edges of the ulcer),
 - B. parasitological method (of the bone marrow, lymph nodes),
 - C. reaction of erythrocyte fixation, ELISA,
 - D. skin tests with allergen,
 - E. there isn't correct answer.

4. While what form of leishmaniasis the medicines of 5-valent antimony are used for treatment?:
 - A. visceral leishmaniasis,
 - B. urban type of skin leishmaniasis,
 - C. rural type of skin leishmaniasis,
 - D. skin leishmaniasis of the New World,

E. everything is right.

5. While what form of leishmaniasis lesions of the nasal mucosa, pharynx, larynx are observed?:

A. visceral leishmaniasis,

B. urban type of skin leishmaniasis,

C. rural type of skin leishmaniasis,

D. skin leishmaniasis of the New World,

E. everything is right.

6. The patient 46 years old, animal technician, complains about fever 39 ° C during 2 weeks, chills, a significant pain in muscles and joints. Hepatosplenomegaly, enlarged lymph nodes, the result of Byurine test is 6,5 cm. Make the diagnosis:

A. pseudotuberculosis,

B. skin leishmaniasis,

C. lymphogranulomatosis,

D. brucellosis,

E. visceral leishmaniasis.

7. The causative agent of visceral leishmaniasis is:

A. *Leishmania donovani*,

B. *Leishmania infantum*,

C. *Leishmania archibaldi*,

D. *Leishmania chagasi*,

E. everything is right.

8. The causative agent of urban type of skin leishmaniasis is:

A. *Leishmania donovani*,

B. *Leishmania infantum*,

C. *Leishmania archibaldi*,

D. *Leishmania chagasi*,

E. *Leishmania tropica*.

9. The carriers of leishmaniasis are:

- A. ticks,
- B. lice,
- C. cockroaches,
- D. mosquitoes,
- E. horseflies.

10. The source of infection of visceral leishmaniasis are:

- A. dog,
- B. monkey,
- C. sick man,
- D. rodents,
- E. A and C are true.

Standards of correct answers

1. D	3. B	5. D	7. E	9. D
2. A	4. E	6. D	8. E	10. E

Variant 2

1. The main carriers of Brucella melitensis are:

- A. cattle,
- B. pigs,
- C. dogs,
- D. rats,
- E. sheep.

2. The source of rural type of skin leishmaniasis are:

- A. dog,
- B. monkey,
- C. sick man,
- D. rodents,
- E. A and C are true.

3. What serological tests are used for diagnosis of brucellosis:

- A. Weil-Felix's,
- B. Ericksen's,
- C. Lovrik's,
- D. Wright's, Heddison's,
- E. Provachek's.

4. What allergic test is used for diagnosis of brucellosis:

- A. with tulyarin,
- B. with malein,
- C. Byurne's test,
- D. Larrey's,
- E. John -Ber's .

5. What treatment is necessary for patients with brucellosis?:

- A. when acute form of disease - antibiotic, when chronic form - vaccinothrapy,
- B. in the acute form - vaccinothrapy, when chronic form - antibiotics,
- C. only antibiotic in each form of disease,
- D. only vaccinothrapy in each form of disease,
- E. antiviral therapy.

6. The causative agent of visceral leishmaniasis in human's body harms such organs as:

- A. bone marrow,
- B. lymph nodes,
- C. liver, spleen,
- D. adrenals,

- E. everything is right.
7. What is the way of infection of human by brucellosis?:
- A. contact,
 - B. nutritional,
 - C. aerogenic,
 - D. transmissible,
 - E. everything is right, except for D.
8. The main factor in the pathogenesis of brucellosis is:
- A. toxic damage of internal organs,
 - B. allergic defeat,
 - C. immune-indirect defeat,
 - D. necrotic processes in the internal organs,
 - E. everything is right.
9. What system is affected more frequently in patients with chronic brucellosis:
- A. nervous,
 - B. endocrine,
 - C. locomotive system,
 - D. cardiovascular,
 - E. respiratory.
10. When patients with acute brucellosis are contagious:
- A. at the end of the incubation period,
 - B. during the first week of clinical manifestations,
 - C. Whole feverish period,
 - D. only if there is pulmonary form of the disease,
 - E. not contagious at all.

Standards of correct answers

1. E	3. D	5. A	7. E	9. C
2. D	4. C	6. E	8. B	10. E

3.4.3. Situational tasks of the second level learning

α -3

Task 1

The patient 46 years old, animal technician, complains about fever 39 ° C during 2 weeks, chills, a significant pain in muscles and joints, profuse sweating, impotence. He has hepatosplenomegaly, enlarged lymph nodes. His knee joints are swollen, painful.

1. The preliminary diagnosis.
2. The plan of the examination.
3. The treatment.

Task 2

Patient, 20 years old, has arrived from India. He has already been 2 weeks in a hospital with clinic of prolonged fever, expressed splenomegaly and hepatomegaly, anemia, thrombocytopenia, leucopenia, significant lymphocytes and monocytes increase. And now in his oral cavity there are symptoms of necrotizing gingivitis development.

1. The preliminary diagnosis.
2. The plan of the examination.
3. The treatment.

4. Materials for the class of independent work

- Study methods of examination of patient with leishmaniasis, brucellosis.
- Perform differential diagnostics of leishmaniasis, brucellosis.
- Make up a plan of laboratory examination
- Study the results of specific examination of patients with leishmaniasis, brucellosis.
- State the complications of leishmaniasis, brucellosis.
- Make up a treatment plan for the patient with leishmaniasis, brucellosis.
- Define medical approach in different complications of leishmaniasis,

brucellosis.

5. Materials of after-work

α -4

Proposed topics for essays on the most pressing issues, such as:

"Prospects for early diagnosis of leishmaniasis, brucellosis »

"Clinical and epidemiological characteristics of leishmaniasis, brucellosis "

"Differential diagnosis of leishmaniasis, brucellosis "

“Pathogenesis of complication of leishmaniasis, brucellosis ”.

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