УЧЕБНИК

ИНФЕКЦИОННЫЕ БОЛЕЗНИ

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TEXTBOOK

INFECTIOUS DISEASES

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CONTENTS

5. MYCOSES

Mycoses are diseases caused by parasitic fungi. They are studied in the course of dermatology and venereology, however due to the HIV pandemic the spread of immunodeficiency disorders caused by environmental degradation, the widespread use of immunosuppressants and cytostatics, drug addiction, and alcoholism, mycoses are often caused by the opportunistic fungi, which infectiologists and doctors of other specialties face in their practice. This section provides basic information on opportunistic and AIDS-associated mycoses.

5.1. PNEUMOCYSTOSIS

Pneumocystosis is a zooanthroponotic mycosis with the aerosol mechanism of pathogen transmission, which develops against disturbances in the immune system and is characterized by the development of indolent pneumonia and progressive respiratory failure. It refers to AIDS-indicative diseases.

History and prevalence. The pathogen, *Pneumocystis carinii*, was isolated from the lungs of guinea pigs and humans in 1910. It is now called *P. jiroveci* and is classified as fungus according to its structure. It was further established that healthy carriage of pneumocysts in children and adults is widespread, and *P. carinii* was considered as a saprophyte for many years, but then sporadic cases of pneumonia caused by pneumocysts in debilitated children and adults with immune deficiencies began to appear. Since 1981, the incidence of pneumocystic pneumonia has increased dramatically. Pneumocystic pneumonia was described in the first AIDS-infected patients in the United States. Further studies have proven pneumocystosis to be one of the most important opportunistic infections in HIV-infected patients. In Russia, its prevalence is significantly less than in the United States due to the prevention of pneumocystosis in HIV-infected patients.

Etiology. *P. jiroveci* is found in three forms: trophozoite, sporozoite and cysts. It parasitizes in the alveoli of the lungs in humans. Cysts enter the environment with sputum, where they can persist for a long time.

Epidemiology. Pneumocysts are found in all animals and humans. The source of the pathogen can be healthy people, children, and adults, as well as the patients with pneumocystosis, who are more dangerous sources of infection. Pathogen transmission occurs by airborne and air-dust routes. Susceptibility to pneumocystosis is high, which is evidenced by the high rate of detection of IgG antibodies against the pathogen antigen in children and adults. However, a healthy carrier state develops in the vast majority of cases. Pneumocystic pneumonia develops only in the presence of immunodeficiency, which is possible as autoinfection due to the activation of pneumocysts parasitizing in the lungs or exogenous infection, which is especially characteristic of hospitals where HIV-infected individuals are focused.

Pathogenesis and pathomorphology. The life cycle of pneumocystis takes place in the pulmonary alveoli. The vegetative form of the parasite, trophozoite, is attached to the alveolocytes lining the alveoli. Sporozoites and cysts are observed in the lumen of the alveoli in the composition of the foamy exudate. Pneumocysts damage the pulmonary epithelium. Inflammatory infiltration develops in the interstitial tissue, the walls

of the alveoli thicken 5–20 times. The destruction of the surfactant violates the elasticity of the lung tissue, contributes to the development of atelectasis. These changes (accumulation of the exudate in the alveoli, thickening of the alveolar wall) lead to a sharp disturbance of gas exchange, the development of expiratory-type dyspnea, progressive hypoxemia, which is the main cause of death in the patients.

This process is possible only with a decrease in the immunological control in case of violations of cellular and humoral immunity, especially in the case of T-cell immunodeficiency. The local immunity disturbance is also of great importance. The course of the disease is complicated by the activation of concomitant bacterial and viral flora, and especially by the overlay of cytomegalovirus lesion of the lungs.

Clinical signs. In the case of exogenous infection, the incubation period lasts from 7 days to 1.5 months. The disease has a gradual onset. In young children with a burdened background (prematurity, rickets, malignant tumors, etc.), the earliest symptom is nasolabial cyanosis, as well as a slight unproductive cough. Dyspnea gradually increases, the body temperature begins to increase up to subfebrile level, and then to febrile level, cough can become productive accompanied by the release of foamy sputum often with paroxysmal character. Physical data is scarce. Shortening of percussion sound is possible, inconstant mixed wet rales are heard.

In adults, the signs of the disease are similar; the appearance of pain in the chest during breathing is possible.

In people with AIDS, the earliest and most persistent symptom is progressive expiratory dyspnea; fever and cough are observed less frequently. Chills and sweating are possible. In some patients, the spleen and the liver are enlarged. In people with AIDS, extrapulmonary lesions are common (liver, spleen, digestive tract, lymph nodes, etc.). The course of the disease is protracted, progressive, with remissions and exacerbations.

X-ray signs of pneumocystic pneumonia are diverse and nonspecific. Radical infiltration, cloud-like decrease in transparency, increased pulmonary pattern, the appearance of focal shadows and cavities are possible. In some patients, pathology is not detected.

The blood test is characterized by elevated ESR up to 50–60 mm/h. The number of leukocytes varies considerably. As a result of respiratory failure, LDH activity increases; hypoalbuminemia develops.

Complications. Such complications as spontaneous pneumothorax and extrapulmonary lesions are to be mentioned.

Diagnosis. In HIV-infected patients due to alertness, pneumocystic pneumonia is more often clinically diagnosed. In the absence of HIV infection, the disease is usually recognized late or posthumously.

To confirm the diagnosis, it is necessary to study the sputum and (especially) the bronchial washings that are obtained during bronchoscopy. The study of biopsy specimens obtained by bronchoscopy is a reliable method, but it may result in the development of pneumothorax. Serological methods are of secondary importance, as antibodies against pneumocysts are found in the majority of the population. The increase in the activity of lactate dehydrogenase to 700–800 IU/n is of great importance. PCR has been used in recent years.

Differential diagnosis is made with pneumonia of a different etiology, in children — with pertussis.

Treatment. The patients are hospitalized in the pulmonary department when clinically indicated. Oxygen therapy is conducted. The main etiotropic agent in Russia is co-trimoxazole [sulfamethoxazole + trimethoprim] (Biseptol♠), which is prescribed at age-dependent doses for 2–3 weeks. It is combined with furazolidone or metronidazole. The prognosis significantly improves if immunodeficiency correction is carried out and if antiretroviral drugs are used in the treatment of HIV-infected patients. Pentamidine♠ is used in some countries, and dapsone, which is used to treat leprosy, is also prescribed in recent years.

Prognosis. The prognosis without treatment is severe; the mortality rate reaches 80%. Early diagnosis and treatment reduce mortality by up to 10% or less.

Prevention. The prevention of pneumocystosis is indicated to the HIV-infected patients in case of the decrease of the number of CD4+ cells to 0.2×10^9/l. Adults take co-trimoxazole (Biseptol♠) for 3 days, 2 tablets each week (primary prophylaxis), and patients undergoing pneumocystic pneumonia (secondary prophylaxis) take the drug according to the same regimen. If the amount of CD4+ is unknown and in the presence of pulmonary pathology, the HIV-infected patients at stage 4B also take co-trimoxazole (Biseptol♠). The prevention of pneumocystosis with this drug is also carried out with other immunodeficiencies.

Questions for self-control

- What is the spread of pneumocystosis? Describe pneumocystosis as an AIDS-indicating disease.
- Describe the properties and the main forms of the pathogen.
- Describe the epidemiology.
- Speak about the pathogenesis, pathology, causes of death.
- What are the clinical signs, their features on the background of HIV infection?
- How is the disease diagnosed and treated?
- Speak about the methods of prevention in HIV-infected patients.

5.2. ASPERGILLOSIS

Aspergillosis is a sapronotic opportunistic mycosis with the aspiration mechanism of pathogen transmission, characterized by a primary lesion of the lungs, toxic-allergic reactions and a severe course of the disease.

History and prevalence. The pathogen is a fungus of the genus *Aspergillus*, named for the head of the fungus resembling the holy water brush (*aspergillum*). The first description of lesions caused by *Aspergillus* appeared in the 1840s. The sporadic cases of aspergillosis are ubiquitous, usually in individuals with immune systems disturbances.

Etiology. The genus *Aspergillus* comprises more than 300 species, about 20 them can cause diseases in humans. Aspergilli are mold fungi of a complex structure, that form small spores, which are 2.5–3 μm in size. The pathogenicity factors are proteolytic enzymes that destroy tissues, a strong hepatotropic toxin, aflotoxin, formed in the process of reproduction, as well several components with allergenic properties. Fungus spores are resistant to the environment.

Epidemiology. *Aspergillus* is widespread. It reproduces in moist soil, rotting plants, food. Aspergillus spores can be found in the air, dust, on various objects. A sick person

presents no danger. The contamination of a human occurs through the air-dust route. Contamination by the alimentary route is possible when using products contaminated with fungus, as well as by contact route if spores enter the damaged skin or mucous membranes, during medical manipulations with spore-infected instruments. More often, people working at production facilities where *Aspergillus* is used as producers of enzymes (production of ethyl alcohol, organic acids) or contacting with infected raw materials (workers at breweries, ginning plants, weaving factories, granaries) are infected. The risk group includes people with immune system disturbances (congenital and acquired immunodeficiency disorders, use of glucocorticoids and immunosuppressants, neutropenia of various genesis, blood disease, diabetes, and lung disease). Risk factors also include intravenous drug administration, marijuana smoking, long-term antibiotic therapy. In HIV-infected patients, aspergillosis can develop on the background of other infections, such as pneumocystosis, tuberculosis, cryptococcosis, during chemotherapy of Kaposi's sarcoma, treatment with ganciclovir. Autoinfection is possible.

Pathogenesis. *Aspergillus* spores enter the body with the inhaled air and reach the alveoli due to their small size. There they germinate and form mycelium. A healthy body is rapidly released from fungi due to phagocytosis by pulmonary macrophages and neutrophils. When the functions of these cells are disturbed, aspergilli rapidly multiply, exerting a necrotic effect on the surrounding tissues, penetrate the blood vessels and thrombose them, this also contributes to the tissue damage as a result of circulatory disorders. They can disseminate to other organs and tissues, spreading hematogenously, as well as by contact. The allergic effect of fungi can lead to the development of anaphylaxis, which is manifested by bronchospasm, an increase in the amount of IgE in the blood, and eosinophilia. Bacterial flora often joins *Aspergillus*, contributing to the suppurative processes. The clinical signs depend on the location of the lesion and the state of the body's protective resources. Death is possible as a result of respiratory failure, damage to the CNS, severe intoxication during septic disease.

Clinical signs. The clinical signs are determined by the localization of the process. In most cases, pulmonary aspergillosis appear which can be exogenous and endogenous. The exogenous form is rare. It is possible for individuals with a non-burdened premorbid background. It develops as a result of the aspiration of a large number of spores. The incubation period lasts from 15–20 minutes to 3 days. At first bitterness in the mouth, sore throat, unproductive cough is noted. Then the chills join, the body temperature rises to 38–39 °C, pain in the muscles and joints, shortness of breath appear, dry and moist rales are heard in the lungs. Eosinophilia is found in the blood. If the treatment is rational, recovery occurs within 7–10 days, but the process can be chronized.

Pulmonary aspergillosis and aspergillosis of other sites develop as autoinfection in individuals with impaired immune systems. It can develop acutely (later it becomes chronic) or gradually, imperceptibly. In the case of acute onset, irregular fever, intoxication, chills, sweating, cough with purulent mucous, often with streaks of blood, sputum appears. There are greenish-gray sticks, the mycelium of the fungus, in the sputum. Frequent symptoms are shortness of breath, pain in the chest during breathing. Weakness and weight loss are increasing. Blood test shows leukocytosis, eosinophilia, elevated ESR. X-ray examination reveals infiltrates, especially in the middle and lower parts of the lungs, the formation of cavities of disintegration is possible.

Chronic forms more often overlay previous pulmonary destructive processes (bronchiectasis, cavities, abscesses). They are characterized by increased cough, low-grade fever, the appearance of moldy smell from the mouth, detection of fungi in the sputum. The radiographic examination helps to observe the filling of the cavities with gradually growing spherical shadow, aspergilloma, which is capable of reaching 3–5 cm in diameter and more. The course of chronic aspergillosis is undulating, progressive, with periods of exacerbations and remissions. The development of the disease with bilateral lesions is especially severe.

In the case of pronounced immunodeficiency, in particular with AIDS, aspergillosis takes a generalized course. In that case, hematogenous spread of the pathogen from the primary focus (usually the lungs) with the formation of metastatic foci in other organs, most often in the central nervous system, with the formation of brain abscesses or the development of meningitis occurs. Digestive tract and skin are also affected. Aspergillosis of ENT-organs is possible.

Diagnosis. The clinical diagnosis is very difficult. An important, yet inconstant symptom is the presence of greenish-gray lumps in the sputum (clusters of mycelium and fungal spores). Eosinophilia of blood and the presence of eosinophils in the sputum are of a certain value. Microscopic evaluation and microbiological examination of the sputum, bronchial washings, blood, CSF, as well as a histological examination of the biopsy specimens of the affected organs are used for confirmation of the diagnosis. Serological diagnostic methods (CFT, etc.) are used.

Differential diagnosis is performed with other mycoses (histoplasmosis, candidiasis), tuberculosis, lung abscesses, pneumonia, and chronic bronchitis.

Treatment. The treatment of aspergillosis should be comprehensive. Antifungal drugs, immunomodulators, treatment of the underlying disease, the surgical methods are used. As for the antifungal drugs, amphotericin B is the most effective, which is administered intravenously in a 5% dextrose solution (Glucose♠) at a dose of 250 U/kg 2–3 times a week for 4–12 weeks. In the case of the CNS damage, the intravenous administration of medication is combined with endolumbal. Itraconazole (Orungal♠) is effective against many types of *Aspergillus*, it is used in capsules of 100 mg, 2 capsules are prescribed t.i.d. for 4 days, then 2 capsules b.i.d. for a year or longer. In acute cases, if there are signs of anaphylaxis, glucocorticoids and antihistamines are prescribed. In a localized process, the surgical treatment, which is combined with chemotherapy, is the most effective.

Prognosis. In the case of localized lesions, the possibility of radical surgical treatment, acute aspergillosis in people with the intact immune system, the prognosis is favorable. In the case of generalized forms, the mortality reaches 20–40%. In the case of a generalized course of the disease in HIV-infected patients, the prognosis is unfavorable.

Prevention. The prevention is aimed at dust control at the place of production, the respirators are used. In hospitals, where the patients with immunodeficiency disorders are focused, the cleaning of incoming air with filters is used. Early diagnosis and treatment of the diseases involving pulmonary destruction are of great importance.

Questions for self-control

- Describe the prevalence of the disease.
- Describe the properties of the pathogen.
- Describe epidemiology (the environment as a reservoir of the pathogen).

- What are the features of pathogenesis? How does lung damage occur?
- Describe the clinical signs of pulmonary aspergillosis.
- Describe the course of aspergillosis in the case of immunodeficiency.
- List the principles of diagnosis.
- How is the disease treated, what is the prognosis?

5.3. CANDIDIASIS

Candidiasis is mycosis with predominant damage to the mucous membranes, as well as the dissemination of the pathogen against immune system disturbances and the development of dysbiosis (dysbacteriosis).

History and prevalence. Fungi, subsequently attributed to the genus *Candida*, were first isolated from a patient by B. Langebeck in 1839. In 1939, yeast-like fungi were attributed to the genus *Candida*. Among other mycoses, candidiasis is one of the most widespread diseases. The increase in the incidence is associated with the start in the consumption of antibiotics in the 1940s, and the later use of glucocorticoids and cytostatics. An increase in immunodeficiency disorders contributes to its incidence growth.

Etiology. Fungi of the genus *Candida* include more than 150 species, at least 20 of them are found in humans, the development of candidiasis in 90% of cases is caused by *C. albicans*, less frequently by *C. tropicalis*, *C. krusei*, *C. lusitanie*, and others. *Candida* can exist in two forms: yeast — in the form of large rounded cells, which are found in the culture and on the surface of the mucous membranes, as well as in the form of pseudomycelium — in the tissues. *Candida* is conditionally pathogenic microorganisms. Pathogenicity factors include adhesins, which determine the fixation of *Candida* on the surface of the endothelium, cell membrane oligosaccharides, which suppress cellular immune reactions, as well as on enzymes, phospholipases and acid proteases, which inhibit phagocytosis and the penetration of the fungus into the tissues. *Candida* has complex antigenic structure. Their antigens cause the formation of hypersensitivity of the delayed-type and the formation of specific antibodies. In culture, they are resistant to the low temperatures, drying. They die quickly when boiling, as well as due to the action of disinfectants and organic dyes.

Epidemiology. *Candidae* is the part of the normal microflora of the mucous membranes of mouth and vagina, and the detection rate of *Candidae* on the mucous membrane of the vagina of pregnant women reaches 80%. Primary contamination often occurs during childbirth. Exogenous infection occurs by contact, in particular at workplaces, and sexually. Natural susceptibility is high but clinically expressed forms of candidiasis develop only when the protective mechanisms are violated, therefore candidiasis is usually autoinfection.

Pathogenesis and pathology. Candidiasis develops only due to the unfavorable background. Typical background conditions include the following:

- mucosa microecology disturbance (dysbacteriosis) when using broad-spectrum antibiotics;
- immune system disorders when taking glucocorticoids and cytostatics, severe oncological (hematological) diseases, endocrinological diseases, especially diabetes mellitus, immunodeficiencies of an infectious nature (HIV infection, other

chronic infections), environmental factors (radiation), eating disorders (hypovitaminosis), age-related disorders (newborns, especially premature infants, people of older age groups), during pregnancy;
- damage to the skin (injuries, medical manipulations).

Under these conditions, the fungi begin to multiply rapidly, penetrate through the mucous membranes, skin, turning into a mycelial form; then enter into the submucosal layer, into the blood-forming secondary foci in various organs and tissues or developing the generalized infection, fungal sepsis. The foci are characterized by the necrotic changes followed by suppuration caused by bacterial flora. Under the influence of *Candida* antigens, the sensitization of the organism occurs with the development of allergic lesions of the skin, mucous membranes, and respiratory organs, where fungi are not detected. In the case of the restoration of immunological homeostasis, the composition of the normal flora, due to the action of the antibodies, phagocytosis, the organism is released from the pathogen or *Candida* takes the form of yeast again.

Clinical signs. There are the following types of candidiasis:
- mucosal candidiasis of the oral cavity (cheilitis, gingivitis, glossitis, stomatitis), oropharynx (tonsillitis, pharyngitis), genital organs (vulvovaginitis, balanoposthitis);
- visceral candidiasis of the digestive system (esophagitis, gastritis, enterocolitis, hepatitis), respiratory organs (laryngitis, sinusitis, tracheitis, bronchitis, pneumonia), urinary system (urethritis, cystitis, pyelonephritis), cardiovascular system (endocarditis), CNS (meningitis, meningoencephalitis), musculoskeletal system (arthritis, osteomyelitis);
- disseminated candidiasis (candida sepsis).

Allergic damages to the skin, mucous membranes, digestive tract and respiratory organs are also possible.

In most cases, lesions of the mucous membrane of the mouth and oropharynx — thrush, are detected. Dryness and hyperemia of the mucous membrane are noted at first. Then white or creamy caseous patches on the mucous membrane of the cheeks, gums, hard and soft palate, the inner surface of the lips appear. They are easily removed with a spatula. In the case of progression of the process, the patches become more indurated, when they are removed, the mucous membrane bleeds, erosions are formed on it. In the case of gingivitis, gums become swollen, ulcers can form on them. In the case of glossitis, there are lengthwise and transverse striation of the tongue, papilla atrophy, and sometimes hyperkeratosis and papilla hypertrophy in addition to the patches. At the same time, the tongue is coated with dark fur, acquiring the specific appearance of a black hairy tongue. Erosions in the corners of the mouth may appear. Candidal angina is characterized by the appearance of caseous patches on the tonsils against mild hyperemia. The general condition of health is not disturbed much. The patients may complain of small pain when swallowing.

In the case of cutaneous candidiasis, the clearly defined lesions are formed in the skin folds, covered with crusts, localized over the erosions. The patients suffer from itching and burning sensation. Lesions of the nail bed and of nails also occur. Candidal vulvovaginitis is characterized by itching, burning sensation in the genital area, the appearance of white discharge. There are typical caseous white patches on the mucous membrane.

Visceral lesions can be local (one organ) or generalized; they are usually combined with the lesions of oropharyngeal mucosa and skin.

Esophagitis, which develops gradually, is especially specific. Pain behind the sternum when swallowing food, dysphagia appear at first. Esophagoscopy reveals hyperemia of the mucous membrane, erosion, white patches. In HIV-infected patients, esophagitis may be asymptomatic. Colitis and enterocolitis are accompanied by abdominal pain, diarrhea with an admixture of mucus and blood in the feces. Intoxication, fever, weight loss and dehydration (in children) are possible. Endoscopy detects catarrhal, erosive and even ulcerative lesions.

A common manifestation of candidiasis is a lesion of the respiratory organs, it is especially typical of the elderly and young children against antibiotic therapy. The mucous membranes of the nose and its paranasal sinuses, larynx and bronchi suffer. The basal areas of the lungs are often affected. Fever, dry cough and scratchy pain in chest appears on the background of general malaise. Then the cough becomes productive, the sputum is scarce at first, grayish in color, sometimes with the smell of yeast, it becomes more abundant later. Lung injury is usually preceded by candidiasis of the mucous membranes and skin.

Candidiasis of the urinary tract (cystitis, urethritis), candidal endocarditis, candidal meningitis is also possible.

Disseminated candidiasis is characterized by fever, intoxication, chills, sweating, shortness of breath, tachycardia. General symptoms are accompanied by the damage to the skin, mucous membranes and internal organs. The disease becomes progressive without treatment.

The course of all forms of candidiasis may be complicated by the development of candidoallergy, which is manifested by the development of dermatitis, urticaria, stomatitis, conjunctivitis, rhinitis, bronchial asthma, and enterocolitis. Unlike candidiasis, fungi are not found in the lesions in the case of candida allergy. In the case of generalized candidiasis, the accession of bacterial flora (staphylococcus) and the development of sepsis of mixed etiology are possible.

Candidiasis can be acute, lingering and chronic. It depends on the cause of the disease and the therapy.

Diagnosis. A preliminary diagnosis of candidiasis of the mucous membranes and skin is established on the basis of the specific candida lesions. The diagnosis is confirmed by mycological studies: the detection of mycelium or pseudomycelium in swabs from mucous membranes, skin, nails, tissue biopsies, isolation of fungal culture from normal sterile substrates (blood, CSF).

The **differential diagnosis** depends on the localization of the process. The disease is to be differentiated from viral aphthous stomatitis, Filatov–Koplik spots in measles, diphtheria, and various types of dermatitis.

Treatment. The treatment of localized lesions of the mucous membranes and skin is carried out at home; in case of damage of the internal organs and disseminated forms of the disease, hospitalization is indicated. Depending on the clinical form of the disease, antifungal agents are administered topically, orally or parenterally. The lesions of the skin and mucous membranes are treated with the following drugs: methylthioninium chloride (Methylene blue♠), Fucorcin♠, undecylenic acid + undecylenate zinc (Mycoceptin♠), levorin (Levorin ointment 500 KU/g), nystatin (Nystatin oint-

ment 100 KU/g). The oral cavity is irrigated with boric acid (boric acid solution in glycerin 10%), Iodolipol♠.

In the case of disseminated forms, fluconazole (Diflucan♠) at a dose of 50–100 mg/day, ketoconazole (Nizora♠l) at a dose 200–400 mg/day, and clotrimazole, itraconazole, amphotericin B are used. Mandatory conditions for the effectiveness of therapy are good nutrition, treatment of background diseases, the normalization of the composition of the intestinal flora with the help of eubiotics, the use of immunomodulators according to indications, such as Imunofan♠, azoxymere bromide (Polyoxidonium♠), etc.

Prognosis. In the case of localized forms, the prognosis is favorable; in the case of disseminated forms, it is serious. To a greater extent, the prognosis depends on the timeliness of treatment of candidiasis and background diseases.

Prevention. The prevention is aimed at eliminating the factors, which contribute to the development of candidiasis. Following the rules of personal hygiene, careful care of children, especially premature babies, good nutrition, early treatment of immunodeficiency disorder and dysbacteriosis are significantly important. In the case of HIV infection, chemoprophylaxis of fungal infections using nystatin, ketoconazole, and fluconazole depending on the number of CD4+ lymphocytes is performed.

Questions for self-control

- Give a definition of the disease.
- What is the prevalence of candidiasis?
- Describe the pathogen, its properties, forms of existence.
- Specify the epidemiology of candidiasis.
- Describe candidiasis as autoinfection.
- Identify the factors contributing to the development of the disease.
- Describe mucosal candidiasis.
- Specify the forms of visceral candidiasis.
- List antimycotic drugs for local and systemic use.
- What are the main directions of the prevention of candidiasis?

5.4. COCCIDIOIDOSIS

Coccidioidosis is a sapronotic mycosis with the aspiration mechanism of transmission characterized by a predominant lesion of lungs and dissemination of the pathological process in people with immune system disturbances.

History and prevalence. The disease was firstly described in 1892, the pathogen was found in the soil in 1900. Coccidioidosis is endemic in the Western Hemisphere, in the western and southwestern states of the USA, in Central and South America.

In the USA, about 100 thousand cases of the disease are reported annually. In endemic areas, the antibodies against the pathogen (*Coccidioides immitis*) are found in 60–90% of the population. Imported cases are described in Europe. About 50 cases are known in Russia. In endemic regions, the incidence of coccidioidosis has increased due to the spread of HIV infection, and coccidioidosis is considered as an AIDS-associated disease.

Etiology. *Coccidioides immitis* is a dimorphic fungus that lives in the soil in micellar form forming arthrospores. When entering the human body, arthrospores are

transformed into spherules where endospores are formed. When the coat ruptures, the spherules of the endospores spread throughout the human body.

Epidemiology. Artrospores easily fall into the air, especially in the dry season, and are aerially dispersed. Contamination of a human occurs through the air-dust route. The penetration of *Coccidia* through the skin and the digestive tract is possible. The susceptibility is high, it is enough to stay in an endemic focus for several hours, but in the normal condition of the T-cell immune system, the infection is asymptomatic or has a benign form. People of the Negroid race, pregnant women, individuals who are taking glucocorticoids are more susceptible.

Pathogenesis. When penetrating the alveoli with inhaled air, arthrospores transform into spherules, which are subject to phagocytosis by leukocytes, macrophages, and giant cells, however, phagocytosis may be incomplete. The formation of an inflammatory granuloma occurs, which undergoes necrosis and subsequent scarring. In the case of the normal functioning of the T-cell immune system, the pathogen is eliminated from the body. Immunity is formed. The delayed hyperresponsiveness is preserved for a long time, it can be detected by the intracutaneous test with coccidioidin. Infection in most cases is asymptomatic, less frequently proceeds in the form of pneumonia. In the case of T-cell immunodeficiency, the process in the lungs progresses, large infiltrates, which are necrotized, are formed. After that caverns and abscesses appear. In the case of immunodeficiency disorders, hematogenous dissemination of the pathogen is also possible. At the same time, the secondary foci are found in the skin, muscles, bones, liver, CNS. The disease becomes septic.

Clinical signs. There are four main forms of the disease: acute pulmonary, chronic pulmonary, chronic with extrapulmonary manifestations, disseminated.

Acute pulmonary form. The incubation period lasts for 10–20 days. The disease develops acutely, accompanied by fever, chills, catarrhal symptoms, cough with sputum, sometimes hemoptysis, pain in the chest. X-ray examination detects pneumonia, enlarged lymph nodes of the roots of the lungs; pleurisy is possible. Some patients have toxic-allergic reactions, such as pain in the joints, urticaria, erythema nodosum. Most patients recover in a few weeks. In some patients, necrosis of pneumonic foci develops, thin-walled caverns are formed. The disease takes a chronic course. Granulomas, in which viable spherules preserve, are formed in the lung tissue.

Extrapulmonary manifestations, such as ulcerative-necrotic skin lesions, abscesses in soft tissues, osteomyelitis, arthritis, polyadenitis, are observed in some patients with chronic pulmonary process several months after the contamination. The most severe complication of chronic coccidioidosis with extrapulmonary manifestations is the development of sluggish meningitis, which is fatal.

In patients with AIDS and other immunodeficiencies, severe disseminated infection develops, which is characterised by high fever with chills and sweating, weight loss, bilateral lesion of the lungs, hemoptysis, lung fulguration, pleurisy, damage to lymph nodes, skin, soft tissues, kidneys, CNS, with progressive course and adverse outcome of the disease.

Diagnosis. The clinical diagnosis is difficult. Mycological examination of the sputum, purulent discharge from abscesses, biopsy specimens stained by Romanowsky–Giemsa, where spherules and fungal endospores are found, is used for confirmation of the diagnosis. It is also possible to obtain the culture of the fungus in specialized

laboratories with a high degree of bacteriological protection. An intracutaneous allergy test with coccidioidin is used.

Differential diagnosis is carried out with other deep mycoses, tuberculosis, syphilis, osteomyelitis.

Treatment. The treatment is carried out with amphotericin B at a dose of 0.5–1.0 mg/kg b.i.d. or with fluconazole (Diflucan®) at a dose of 200–400 mg/day. The duration of treatment is at least 2 months. Maintenance therapy is carried out with the same drugs for the prevention of recurrence. In the case of localized lung lesions, the surgical treatments are indicated.

Prognosis. In individuals without immune system disorders, the prognosis for the acute pulmonary form is favorable. When the process is chronized, the prognosis is serious. In patients with AIDS, the prognosis is unfavorable.

Prevention. No specific prevention has been developed. It is not advisable to stay in endemic regions for immunocompromised individuals. In endemic regions, the HIV-infected patients are examined for early detection of coccidioidosis.

Questions for self-control

- What is the prevalence of the disease?
- Describe the etiology. What are the forms of existence of the pathogen?
- Describe coccidioidosis as a sapronosis mycosis.
- Describe the pathogenesis.
- Describe the clinical signs. Indicate the main forms of the disease.
- Describe the diagnosis principles (specific therapy, prognosis).

5.5. CRYPTOCOCCOSIS

Cryptococcosis is an opportunistic deep mycosis characterized by multisystemic lesions and a severe course of the disease in case of the CNS damage.

Prevalence. Cryptococcosis is a widespread disease, but it is more common in countries with a subtropical and tropical climate.

Etiology. The pathogen of cryptococcosis is Cryptococcus neoformans. It has 4 serovars A, B, C, D. In culture it forms round yeast-like budding cells 4–8 μm in size, covered with a capsule. The main pathogenicity factor is the mucopolysaccharide capsule, which prevents phagocytosis and the synthesis of proinflammatory cytokines; the phenoloxidase enzyme is a pathogenicity factor as well.

Epidemiology. The source of cryptococcus is a soil containing organic matter (pigeon droppings), less often rotting fruit, vegetables, plants. Rodents, cats, dogs, livestock may suffer from the disease. Infection occurs through the air-dust route by inhalation of the capsule-free cells and cysts, less often through the damaged skin and mucous membranes. HIV-infected individuals are susceptible to the disease in the case of immunodeficiency, as well as in the presence of immunodeficiency of a different etiology. Cryptococcosis is an AIDS-defining disease.

Pathogenesis. The pathogen multiplies primarily in the lung tissue, causing pneumonia, which proceeds benignly in the absence of immunodeficiency. In the case of immunodeficiency, pneumonia takes a chronic progressive course, the pathogen spreads hematogenously, penetrates the various organs, causing a disseminated infec-

tion with lesions of bones, skin, and CNS. The CNS damage leads to the development of meningoencephalitis, occurring with signs of progressive CE, leading to the dislocation of the brain and the death of the patient.

Clinical signs. The incubation period is not established. The pulmonary damage is asymptomatic. A productive cough is possible. In HIV-infected patients fever, shortness of breath, the development of pleurisy are noted. Sputum may be mixed with blood; the formation of cavities and pleural effusion are possible. Respiratory failure, which is the cause of death, is increasing.

As an independent form of the disease, the manifestation of disseminated cryptococcosis is a skin lesion. The elements of a rash are represented by papules at first, which transform into flat plaques, then ulcerate. The elements of a rash are located on the scalp and face; if there is no treatment, they persist for a long time, without a tendency to healing. Bone lesions are characterized by osteolysis with the formation of foci of osteoporosis. Damage to the organs of vision and prostate gland is possible.

The most frequent form of the disease is cryptococcal meningoencephalitis. The disease develops subacutely, because the pathogen does not cause a primary inflammatory reaction. Fever, persistent headaches appear, they are accompanied by nausea, less often by vomiting. The examination reveals mild or moderate meningeal syndrome, which is usually not fully apparent. During puncture the CSF is squirting, its pressure is increased up to 300–500 mm H_2O and higher. When a smear is examined, a mixed or lymphocytic 2–3-digit pleocytosis is detected, and pathogen cells are often found. The protein level is elevated, the glucose level is low. The disease is characterized by the increased level of lactate up to 5 mmol/l and over. The disease has a progressive course, but the patients remain active for a long time, then a sudden acute deterioration occurs due to brain dislocation, accompanied by convulsions, loss of consciousness, respiratory failure, leading to the development of apnea and death of the patient. Brain dislocation is possible within 10–12 days in the course of the treatment.

A blood test is not very characteristic, an increase in the level of LDH in blood and CSF is often observed.

Diagnosis. The clinical signs are not very typical. The diagnosis is confirmed by the detection of yeast cells surrounded by a capsule in the CSF, sputum, smears from skin elements, sometimes in blood. The genetic material of the pathogen is detected in blood and CSF by PCR, and when the pathogen is inoculated on Saburo medium, the pathogen culture is isolated; its sensitivity to antimycotic drugs is studied.

The **differential diagnosis** is carried out with viral, tuberculous and other bacterial meningitis.

The treatment is carried out with voriconazole, fluconizole, amphotericin B (in the case of CNS damage) and other antimycotic drugs. In the case of the CNS damage, they are injected intravenously at the maximum doses. According to the resistance of the pathogen to antimycotic agents, two medications are used before determining the sensitivity. The effectiveness of treatment is studied by the method of quantitative PCR to reduce the microbial load, microscopy of CSF and other substrates, the rehabilitation of CSF. The pathogenetic therapy is used in the case of CE; ART is used in HIV-infected patients.

Prevention. No prevention methods have been developed. In HIV-infected patients with the CNS damage, a CSF test for cryptococcosis is required.