**LABORATORY DIAGNOSIS OF RESPIRATORY DISEASES.**

Gas exchange between living organisms and the environment is called respiration. The main task of the respiratory system is to supply the body with oxygen, which is essential for everyday life, and to remove carbon dioxide and water, which are formed as a result of metabolism.

The number, depth, and rhythm of breathing are regulated by the respiratory center in the medulla oblongata and in the cerebral cortex. Usually, respiratory movements are rhythmic in every person. The number of respiratory movements in adults at rest is 16-20 per minute. For women, this number is 18-22. When a person lies, the number of breaths decreases slightly (14-16 per 1 min); while standing, on the contrary, it increases (18-20 per 1 min). Deep breathing is observed in a calm state, and deep breathing is observed during physical or emotional stress.

**Classification: Distribution -**diffuse/local

**Due to ventilation problems:**

**Obstructive:**

* Chronic obstructive bronchitis (COB)
* Bronchiectasis
* Chronic obstructive pulmonary emphysema
* Chronic bronchiolitis
* Bronchial asthma

**Restrictive**:

* Pneumoconiosis
* Interstitial pneumonia, including exogenous allergic alveolitis
* Idiopathic fibrosing alveolitis
* Goodpasture's syndrome
* Sarcoidosis
* Idiopathic pulmonary hemosiderosis

**Mixed :** (almost all terminal chronic diseases)

**Assessment of the function of external respiration of the body.**

In order to characterize the function of external respiration, it is possible to correctly assess the functions of the respiratory tract (Alsoobstructive diseases, i.e., associated with obstruction: reduced airway patency) and the respiratory section of the lungs (Alsorestrictive diseases, i.e., associated with a limitation: reduction of the respiratory surface) in the study of lung function, three groups of indicators are evaluated:

- lung volume,

- expiratory flow rate,

- diffusion capacity of the lungs.

**Lung volume:**

- static indicators of lung volume reflect the elastic properties of the lungs and chest.

- dynamic indicators of lung volume characterize airway patency.

**Breathing volume**

The airflow rate depends on the volume of the lungs and the force of exhalation. The airflow begins to increase with the increasing force of exhalation. Volume velocity is also affected by lung elasticity, low airway resistance, and large airway cross-sectional area.

**Diffusion capacity of the lungs.**

The diffusion capacity (DC) of the lungs (more precisely, the aero hemic membrane) is the most effective indicator of the transition of gases from the air of the alveoli into the blood of the pulmonary capillary.

**The leading indicator characterizing pulmonary ventilation: Respiratory volume (RV).**

**Vital capacity of the lungs (VCL).**

**Increased vital capacity of the lungs (IVCL).**

**Forced expiratory volume in 1 second (FEV-1s).**

**FEV-1s / IVCL -**The ratio of FEV-1c to IVCL (Tiffno index) is expressed as a percentage (usually greater than or equal to 70%).

**Total lung volume (TLV**): The air in the lungs during maximum breathing.

**Functional residual lung capacity (FRLC)**: Volume of air remaining in the lungs at the end of a normal exhalation.

**DIAGNOSIS METHODS**

Diagnosis of respiratory system pathologies is based on laboratory and instrumental studies. Laboratory tests are divided into two groups: screening and special.

**1. Screening tests**: - General blood analysis

- General urine analysis

- Blood chemistry analysis

**2. Special analyses:**- General sputum analysis

- Sputum for Mycobacterium tuberculosis

- Sputum for atypical cells

- Sputum for bacterial culture

- Examination of the pleural fluid

**2. To instrumental research** applies to:

- Functional diagnostic methods

**-** X-ray and radiopaque research methods

- Ultrasonography

- Radioisotope method

- Endoscopic method

Screening methods of laboratory diagnostics are carried out in clinical and biochemical laboratories. At the **moment, general blood analysis shows:**

**-** Leukocytosis, the toxic granularity of neutrophils, and increased ESR are signs of inflammation of microbial origin.

**-** Eosinophilia and increased ESR are signs of allergic inflammation and parasitic diseases.

**-** Anemia and increased ESR are signs of tumor processes, bleeding, and chronic intoxication.

**-** Erythrocytosis, increased hematocrit and decreased ESR are signs of chronic respiratory failure.

**The general analysis of urine**-observed oliguria, rich yellow urine, hyperstenuria, and low or moderate proteinuria.

**A biochemical blood test** detects dysproteinemia, α2- and γ-globulins, sialic acids, seromucoid, fibrinogen, and C-reactive protein.

**STUDY OF Sputum.**

The mucous membrane of the respiratory tract consists of cylindrical ciliated epitheliocytes, that is, goblet cells that secrete mucus. The ciliated epithelium removes mucus from the body along with foreign bodies. The epithelium of the alveoli is involved in gas exchange and, during respiration, releases a surfactant that expands the alveoli. About 10-50 ml of liquid is released daily, which performs protective and cleansing functions.

Phlegm-pathological discharge is released with a cough in lung diseases. In healthy people, up to 200 ml of sputum is secreted in the respiratory tract during the day. Sputum consists of mucus, serous fluid, blood, and cellular elements of the respiratory tract. Helminths and protozoa can get into the sputum.

Sputum examination includes laboratory examination of sputum, its physical and chemical properties, and microscopic and bacteriological examination. The study of sputum allows us to determine the pathological process's origin, localization, and etiology.

**Collection and preparation of sputum for examination**:

1. After thoroughly washing the oral cavity, sputum collected early in the morning (sputum is collected only during coughing) is collected in a clean, dry glass dish.

2. Only freshly isolated sputum should be examined since its long-term storage leads to the multiplication of microbes and autolysis (dissolution).

3. If daily sputum collection is required, it should be stored in a refrigerator at 4°C.

4. It is essential to select material for microscopic examination carefully. To do so, sputum is spread with a spatula or a needle in a thin layer in a Petri dish and viewed on a black or white background. All suspicious spotting is placed on a glass slide, covered with a coverslip, and examined under a microscope.

**The amount of sputum:** It is placed in a measuring cylinder to determine the amount of sputum. The daily amount of sputum varies greatly - from 1 to 1000 ml or more. With inflammation of the respiratory tract, a small amount of sputum (25-100 ml) is released (with laryngitis, tracheitis, acute bronchitis, bronchial asthma, bronchopneumonia,etc.) with chronic bronchitis, pulmonary tuberculosis. Isolation of a large amount of sputum (0.5-2 l) is observed during bronchiectasis, lung abscess, some helminthic diseases, etc.

After the dissolution of sputum, the division into layers is determined within an hour. In bronchitis, lung gangrene, and bronchiectasis, sputum is usually divided into three layers: the upper one is a foamy-mucous layer, the middle one is serous, cloudy yellowish plasma and the lower layer is purulent, complex, yellowish-green colors. With a lung abscess, sputum is often divided into two parts: the upper layer consists of serous fluid, and the lower layer consists of a greenish-yellow purulent mass. The reason for dividing sputum into layers is that the relative density of its constituents is different. General clinical sputum analysis includes a macroscopic and microscopic examination. The main components of sputum are mucus, pus, blood, and rarely serous fluid.

**Macroscopic determination of sputum.** The study of sputum begins with its macroscopic examination, first examined in a transparent glass, then in a Petri dish, placed alternately on a black and white background. Its quantity is noted, then the nature, color, smell, texture, and sputum layering are also noted.

**Sputum color -** depends on the number of leukocytes and erythrocytes. Depending on the change in hemosiderin, the mixture of red blood cells may be colored red, brown, or rusty. Spots of sputum may be spotted with blood or slightly reddish (brown). With autolysis, cancer, or malignant lung tumors, the sputum becomes purple and yellow with jaundice. The black color of sputum is due to the admixture of coal dust. Brown (chocolate) sputum is released with abscesses and bronchiectasis of the lung. Rust-colored sputum is more often observed with lobar pneumonia and is associated with the release of hematin during the breakdown of red blood cells. The color of sputum can change under the influence of wine, coffee, drugs, etc.

**By nature**, sputum is distinguished as serous, mucous, purulent-mucous, mucopurulent, serous-purulent, bloody, and asthmatic. Its nature is determined based on microscopic examination.

**Mucous sputum** is usually colorless or slightly whitish. We excluded acute bronchitis, inflammation of the upper respiratory tract, and bronchial asthma attacks.

**Serous sputum** - colorless, frothy, is observed in acute pulmonary edema.

**Mucopurulent sputum** is yellow or greenish and occurs in chronic bronchitis, tracheitis, and bronchopneumonia.

**Clear purulent sputum** - greenish-yellow sputum, which is characteristic of a lung abscess.

**Bloody sputum** can be purebred (for tuberculosis, cancer, or actinomycosis) or mixed. For example, mucopurulent sputum with blood clots is observed with bronchiectasis, serous-bloody with pulmonary edema, muco-bloody with pulmonary infarction, and purulent-bloody with gangrene and abscess. If the minor is allocated blood, its hemoglobin turns into hemosiderin and gives the sputum a rusty color (with croupous pneumonia). With asthma, the sputum is yellowish and contains many eosinophilic granulocytes and Charcot-Leiden crystals.

The following pathological elements and parasites can be found in sputum:

• **Charcot-Leiden crystals** are thin, elongated crystals formed by an enzyme called eosinophils found mainly in the sputum of asthma patients.

• **Kurshman's spirals** are tiny, tightly coiled whitish threads (for obstructive diseases).

• **Fibrin clots** - whitish-reddish in color, resembling a tree branch (with fibrinous bronchitis, rarely with croupous pneumonia);

• **Rice grains (lentils)** - dense balls containing mycobacterium tuberculosis, consisting of tiny elastic fibers of a greenish-yellow color, cholesterol crystals, and soap.

• **Dietrich's corks** - similar in appearance and composition to lentils, but do not contain Mycobacterium tuberculosis and have an odor when crushed (gangrene, chronic abscess, purulent bronchitis, with bronchiectasis detected);

• **Lime grains**- as a result of the collapse of old foci of tuberculosis;

• **Actinomycetes** - yellowish grains, similar to cereals;

• **Fragments of the chitinous membrane of the echinococcal sac;**

**• Necrotic decomposition products lung tissue and tumors.**

**Characteristics of sputum in various pathological conditions**

|  |  |
| --- | --- |
| Disease | The nature of sputum |
| Bronchitis | Mucopurulent or purulent-mucous. There are few leukocytes, few erythrocytes, and enough epitheliocytes. |
| Bronchial asthma | A small amount, slimy, solid, colorless. Many eosinophils, single erythrocytes, epithelial cells, different numbers of leukocytes, Charcot-Leiden crystals, Kurshman spirals |
| Lung abscess | Lots of sputum. Microscopically, leukocytes, erythrocytes, fibrin, elastic fibers (a sign of lung tissue destruction), hematoid crystals, microbial flora |
| Pulmonary gangrene | Lots of putrid sputum. Microscopy reveals a large number of leukocytes in the stage of degradation, elastic fibers, and hematoid crystals. |
| Bronchiectasis | Copious sputum early in the morning (when going from lying to standing), more often purulent, sometimes with a bad smell. There are few leukocytes, single erythrocytes, Dietrich's plugs, and no elastic fibers. |
| Tuberculosis | Sputum at the initial stage is small - mucous, thick, mixed with various purulent nodules. Leukocytes and alveolar epithelium are not numerous. Mycobacteria may be absent. In the late stage - calcified elastic fibers, signs of caseous decay, cholesterol crystals, mycobacteria |
| Lungs' cancer | The most common is squamous (45-60%), undifferentiated (20-40%), and adenocarcinomas (9-12%). In the sputum - mucous, purulent, bloody cellular elements, atypical cellular complexes with signs of malignant tumors. |

**Microscopic examination of sputum**.

Sputum is almost always contagious, so it is crucial to be careful. Particular attention should be paid to the cleaning of used laboratory glasses. That is, Mycobacterium tuberculosis is difficult to kill; therefore, if the laboratory vials used are poorly washed, they can be found in the sputum of people who do not have tuberculosis and can also be a source of infection. Mucopurulent sputum is characteristic of nonspecific diseases of the bronchi and lungs. Sputum may be reddish or yellowish with an admixture of blood and its decay products. Among the cellular elements of sputum, neutrophils predominate (in mucous sputum - singly, purulent sputum - more). There may be other cellular elements - eosinophils (especially in malignant tumors of the lungs), lymphocytes, and basophils (in allergic processes),

**Examination of the pleural fluid.**

Serous cells normally secrete a small amount of fluid. (into the pericardial cavity - 1-2 ml, into the pleural cavity - 10 ml, into the abdominal cavity - 50 ml). Thanks to this fluid, the serous layers glide more easily. The fluid increases in various pathological processes, and this fluid is used for laboratory diagnostics. The fluid that accumulates in the serous cavity may be of different origins. In this regard, they are divided into two groups: transudate and exudate.

The causes of **transudate** formation include general circulatory disorders (cardiovascular, renal failure, portal hypertension, etc.), a decrease in oncotic pressure in the vessels (with hypoproteinemia), and electrolyte metabolism disorders.

**Exudate** is formed due to damage to the serous membranes (against the background of primary disease of the serous membranes or secondary diseases of the lungs and abdominal organs - pneumonia, rheumatism, tuberculosis, etc.).

**The purpose of the study of liquids:**

1. Definition of transudate or exudate. If it is a transudate, no further investigation is required.

2. Determination of the nature and etiology of the process (in the presence of exudate)

The liquid is removed through a puncture, collected in a clean container with heparin or sodium citrate (at the rate of 1 g / l), and immediately sent to the laboratory for analysis. If the amount of liquid received is more than 1 liter, either the liquid at the bottom of the container or the last received liquid in the amount of 1 liter is sent for examination. If necessary, the liquid is collected in a separate sterile container for bacteriological examination. The analysis includes the physicochemical properties of the liquid and sediment microscopy.

***Table.*****Laboratory signs of transudate and exudate**

|  |  |  |
| --- | --- | --- |
| Research | transudate | Exudate |
| Relative density | Usually below 1.015; in rare cases (compression of large vessels by a tumor), above 1.013–1.025 | Not less than 1.015  Usually 1018 |
| Coagulation | It does not roll up | Curled up |
| R Color and transparency | Transparent, lemon yellow, or light yellow | Serous exudate does not differ from transudate; other types of exudate are cloudy and differ in color. |
| Opponent's reaction | Negative | Positive |
| Protein content, g/l | 5–25 | 30–50 (up to 80 g/l with pus) |
| Protein concentration ratio | Less than 0.5 | More than 0.5 |
| LDH (lactate dehydrogenase) | Less than 200 IU/l | More than 200 IU/l |
| LDH ratio | Less than 0.6 | More than 0.6 |
| Cytological examination | Cellular elements are few, usually mesothelial cells, erythrocytes, sometimes lymphocytes, and eosinophils after a repeated puncture. | Lots of cells. The number of cellular elements, their types, and their condition depends on the etiology and stage of inflammation. |

**Functional research methods:**

* Spirography is a method for assessing the condition of the lungs by measuring the volume and speed of exhaled air.
* Peakflowmetry is a test for the maximum airflow rate during breathing.
* Ergospirometry is a modern method that allows simultaneous assessment of the lungs and heart condition during exercise.
* Spirometry is a functional test that determines the movement of the breath. This test (method) is an entirely safe and highly informative examination method, which is carried out to determine the appropriate vitality and lung volumes based on specific respiratory movements, and allows you to diagnose respiratory diseases in general: the choice of treatment tactics and monitoring the effectiveness of treatment (organs of the pulmonary and extrapulmonary respiratory system - bronchi, diaphragm, respiratory center, musculoskeletal elements of the respiratory system, etc.). It helps diagnose asthma, cystic fibrosis, and COPD (chronic obstructive pulmonary disease) and is performed using a spirometer. Spirometry checks the respiratory tract's patency, limiting the airflow's speed. In a short time, a non-invasive, painless, easy-to-use method was performed by a simple inhalation and exhalation. Physiological values ​​(sex, age, height) are considered in many parameters of the spirogram.

**Indications for spirometry:**

* When diagnosing and determining the severity of bronchial asthma, chronic obstructive pulmonary disease, sarcoidosis, and other lung diseases.
* Evaluation of the effectiveness of treatment and the choice of different treatment tactics.
* Assessment of the prognosis of the disease.
* Assessment of lung function in smokers.
* Evaluation of respiratory function in patients before and after surgery.
* Differentiation of obstructive, restrictive diseases.

**BRONCHIAL ASTHMA** - a disease characterized by chronic inflammation of the airways, manifested by symptoms such as expiratory dyspnea, heaviness in the chest, cough, wheezing, and suffocation, observed with airway obstruction. These symptoms are usually caused by various triggers (allergens, weather, viral infections, etc.). Both airway obstruction and disease symptoms vary over time. The most common clinical phenotypes of asthma are:

- Allergic asthma: the most common phenotype, usually onset in childhood, is associated with other allergic diseases (eczema, allergic rhinitis, food allergies, etc.) that the patient or his relatives have. Before treatment, sputum examination of such patients reveals changes characteristic of eosinophilic inflammation of the respiratory tract.

- Non-allergic asthma: occurs in some patients and is not associated with allergies. In the study of the sputum of these patients, neutrophils, eosinophils, and cells of macro granulocytic or mixed type are detected.

- Late asthma: some patients (especially women) develop asthma for the first time in adulthood. In such patients, bronchial asthma is usually non-allergic.

- Asthma with persistent airway obstruction: occurs in patients with long-term asthma who develop persistent or irreversible obstruction due to airway remodeling.

- Asthma in obese individuals: symptoms are more pronounced, but eosinophilic airway inflammation is less significant.

**Etiology and pathogenesis of bronchial asthma**

Various factors influence the development of bronchial asthma:

***Internal factors***: a hereditary tendency to atopy, the hereditary tendency to bronchial hyperreactivity, obesity, sex

***External factors***: Allergens (house dust mites, plant pollen, pet allergens, cockroaches, molds, fungal allergens, etc.), infectious agents (viruses), food products, occupational factors, ozone, sulfur and nitrogen dioxide, diesel combustion products, tobacco smoke (active and passive smoking), etc.

The pathogenesis of bronchial asthma is based on the inflammatory process. According to the mechanism of pathogenetic development, atopic and non-atopic bronchial asthma are distinguished:

***Atopic asthma.*** This is the most common type of asthma. Occurs in patients sensitive to allergens. The pathogenesis of atopic asthma is based on the type I hypersensitivity reaction. Sensitization of the body to allergens leads to the activation of Th2-lymphocytes, the synthesis of cytokines IL-4, IL-5, and IL-13, and the synthesis of Ig E from B-lymphocytes. When the allergen re-enters the body, mast cells degranulate and release mediators. Due to the action of free mediators, bronchospasm, obstruction, and swelling of the bronchial wall occur, and mucus secretion increases.

The reason for the development of non-atopic bronchial asthma is a hyperallergic inflammatory reaction to viral infections, cold and toxic substances in the air, resulting in bronchial obstruction and bronchospasm.

**Diagnosis of bronchial asthma.**

A bronchial asthma diagnosis is based on the patient's complaints, anamnesis, the results of functional examination methods, laboratory parameters, specific allergological studies, and the denial of other diseases. Typical asthma symptoms are wheezing, shortness of breath, chest tightness, choking, and coughing.

► Most of these symptoms are commonly seen in people with asthma;

► Symptoms usually worsen at night and early in the morning

► Symptoms and their intensity change over time;

► Viral infections (including during colds), physical activity, exposure to allergens, laughter, cold weather, changing seasons, and motor fuel fumes, smoke, or strong odors cause or worsen symptoms.

**METHODS OF EXAMINATION OF PATIENTS WITH BRONCHIAL ASTHMA**

- Complete blood count (CBC - possibility of eosinophilia).

- General and cytological examination of sputum (eosinophils, Kurshman spirals, Charcot-Leiden crystals)

- Scarification, subcutaneous test, and puncture test (prick test).

- Allegro test (determination of specific Ig E-antibodies in blood serum).

**Methods for assessing the function of external respiration**:

- Spirometry (VC, Tiffno index, etc.).

- Peak flowmetry (PFM) - checking the speed of airflow during exhalation

**For differential diagnosis:** Bronchoscopy is the study of the bronchi. A flexible endoscope with a video camera and a lighting system is inserted through the mouth. The screen displays an image of the inner surface of the bronchial passages.

- Irritation test with methacholine.

- X-rays of light.

- EKG.

- CT (if indicated)

**GENERAL BLOOD ANALYSIS**

A general blood test determines the concentration of hemoglobin, the number of erythrocytes, leukocytes and platelets, hematocrit and erythrocyte indices, erythrocyte sedimentation rate (ESR), and the calculation of the leukocyte formula. The latter is calculated taking into account the number of eosinophils in patients with bronchial asthma and chronic obstructive pulmonary disease. Average reference values ​​range from 50 to 250 cells per 1 µl. The critical level is 450 cells per 1 µl, which indicates a pathological process associated with the possible influence of eosinophils on the inflammatory process. At the same time, hypereosinophilia may not correlate with bronchoalveolar and tissue eosinophilia. In addition, the level of eosinophils in the peripheral blood is an essential indicator in patients with chronic obstructive pulmonary disease.

**Acute phase proteins.**

BOF is directly involved in eliminating damaging factors and contributes to the localization of the focus of damage, the restoration of the damaged structure of cells and organs, and their functions. Fibrinogen is more associated with vascular reactions during inflammation, while other markers are polyfunctional and involved in implementing numerous immune processes.

**C-reactive protein (CRP**) is a stimulant of immune reactions, including phagocytosis. Participates in T- and B-immune reactions and activates the classical complement system. As a rule, except for some physiological processes, a healthy person's serum does not contain CRP or is in a small amount (less than 5 mg / l). The CRP test is directly related to the ESR. Both indicators rise sharply at the onset of the disease, but the C-reactive protein reacts before changes in ESR. In laboratory diagnostics, this test is used to monitor the course of the disease and the effectiveness of therapy. In addition, the concentration of CRP in the blood is associated with the disease's activity and the process's stage.

An increase in the concentration of this protein in the blood is not characteristic of any particular type of disease; however, in all acute inflammatory processes, the level of C-reactive protein in the blood gives grounds to judge the degree of activity of the process.

Usually, C-reactive protein concentration increases rapidly during pathological processes such as tissue damage, inflammation, and necrosis. However, some drugs (steroids, salicylates, etc.) can reduce the amount of this protein.

**Fibrinogen -**its level tends to increase in various inflammatory reactions.

It is the main plasma protein, directly affects ESR, and is a sensitive indicator of inflammation and tissue necrosis. With an increase in the concentration of fibrinogen, the ESR also increases.

**Procalcitonin (PCT)** is a more specific marker of bacterial infection than CRP and is synthesized by several cell types in different organs under the influence of pro-inflammatory agents (bacteria). A PCT level above two ng/ml indicates an infectious nature of the inflammation.

**Natriuretic peptides -** 60% of patients over 65 years of age have along with cardiovascular diseases and chronic respiratory diseases. At this stage, the differential diagnosis of dyspnea is critical since it is the most noticeable symptom in comorbidities. For this purpose, natriuretic peptide C is determined. To exclude chronic deficiency, this figure is less than 125 pg/ml up to 75 years and less than 450 pg/ml over 75 years; less than 300 pg/ml to rule out the acute deficiency.

**Immunoglobulin E.** Synthesis of IgE begins in the liver and lungs in the second week of embryonic development. The molecular weight of this type of immunoglobulin is relatively small, and its ability to penetrate tissues and biological activity is high compared to other immunoglobulins. Therefore, IgE is highly active even in small amounts in the blood serum. 50% of the total mass of IgE in the body is collected in the serum; IgE is also found in nasal mucus, sputum, and mucous membranes of the respiratory and digestive systems. Blood serum is used to determine IgE. Standard value: 0–380 V/ml. Its diagnostic role should be considered when determining IgE, and the allergy diagnosis should not be solely based on this indicator. Identification of allergen-specific IgE is not 100% pathognomonic. At the same time, the absence of specific IgE or its low concentration in peripheral blood serum does not exclude the involvement of an IgE-dependent mechanism. High concentrations of total IgE may give false positive results in some patients, such as those with atopic dermatitis. The Fadiatop test (ImmunoCAP) is used to determine sensitivity to respiratory allergens and assess the possibility of an allergic nature of the pathology in patients with upper respiratory tract diseases. It aims to detect IgE against the most common inhalant allergens (tree pollen, grass pollen, pet dander). This study was designed as a preliminary analysiscrosssensitization to various allergens, which are usually the basis for the development of atopy.

**Eosinophilic cationic protein** (ECP) The level of ECP in most cases is associated with the severity of bronchial asthma clinical symptoms, reflecting the severity of the eosinophilic component of the inflammatory process and, with certain limitations, can serve as a marker for determining the severity of bronchial asthma. In patients with atopy, even with an average number of eosinophils in the peripheral blood, the concentration of ECP is high.

Eosinophils are derived from myeloblasts in the bone marrow. Newly formed eosinophils remain in the bone marrow for 3-4 days and then move to the tissues with blood. Most of them accumulate in the intercellular zone of the intestine, liver, and skin. Eosinophils comprise 0.5-5% of all blood leukocytes (200-400 IU per 1 µl of blood). More than 400 eosinophils in 1 µl of blood are called eosinophilia. Corticosteroids reduce the number of eosinophils in the peripheral blood. Therefore, since the number of eosinophils in blood taken at different times of the day is different, the result of the analysis carried out in the morning is considered correct.

**Instrumental examination.** Spirometry is recommended for all individuals with suspected asthma to confirm the diagnosis and assess the severity of airway obstruction. A repeat lung function test is sometimes more informative than the first test. Normal spirometry (or peak flow) does not rule out a diagnosis of asthma.

**Evaluation of the allergic condition.**

Allergy testing: The presence of atopy increases the likelihood of allergic asthma in patients with respiratory symptoms, but this is not specific to asthma and does not occur in all asthma phenotypes. Atopic status is determined by skin allergic (prik- or scarification) tests or the level of specific immunoglobulin E (IgE) in the blood serum. Skin prick testing with household and environmental allergens is a simple and fast testing method with high sensitivity.

**Other examinations** are recommended to check the fraction of nitric oxide in exhaled air (FeNO) and the level of eosinophils in sputum as markers of allergic inflammation in bronchial asthma. FeNO is usually elevated in eosinophilic asthma. An increase in FeNO is observed in eosinophilic bronchitis, allergic rhinitis, and other atopic conditions. FeNO is low in some asthma phenotypes (e.g., neutrophilic asthma), in the early phase of allergic reactions, in bronchospasm, and smokers.

**EMPHYSEMA OF THE LUNG.** The term ocular emphysema is a pathological change characterized by an increase in the air due to excessive expansion of the alveoli in one or both sections of the lungs and the gradual collapse of the partitions between them. Factors that increase interalveolar pressure and age-related changes in lung tissue elasticity also play an essential role in the development of the disease. Sometimes in newborns, there is an acute, congenital form of pulmonary emphysema (associated with malformations of the bronchi).

Emphysema of the lungs occurs after 40-45 years. Inflammation of the bronchi (bronchitis), bronchial asthma, and other lung diseases cause emphysema formation. In other cases, it occurs on its own. At this time, under the influence of internal (congenital propensity) and external factors (environmental pollution), the walls of the alveoli become thinner and crack, significant gaps form in them, the total surface decreases, and the elasticity of the lungs decreases. At the same time, ventilation of the lungs and blood circulation is also disturbed. The patient first complains of shortness of breath during physical work and then during rest in a calm state, while breathing first becomes problematic. In many cases, slight sputum is challenging to separate; the cough does not comfort the patient.

**Pathogenesis.**

The mechanism of development of pulmonary emphysema is an imbalance between elastase and anti-elastase (enzymes and inhibitors). In primary emphysema, the leading cause of the disease is a congenital deficiency of antielastase, and in secondary emphysema, an increase in the activity of elastase and other proteases.

**Clinic and diagnostics.**

**Complaints:**

• Shortness of breath, shortness of breath of the expiratory type (the patient breathes heavily), increased shortness of breath when the weather changes, especially when leaving a warm room in a cold one, the influence of irritating odors

• weakness

• the type of inflammation determines cough and sputum, the nature of sputum in the bronchi (catarrhal or purulent).

On an objective examination:

•"pink face," puffiness of the face, absence of cyanosis for a long time;

•barrel-shaped chest, increasing its volume;

•complete or partial lack of mobility of the lower edge of the lung

•weakening of voice vibration and bronchophony;

•on auscultation in patients with primary emphysema observed shortness of breath.

**CLINICAL AND LABORATORY SIGNS OF EMPHYSEMA AND CHRONIC BRONCHITIS**

|  |  |  |
| --- | --- | --- |
|  | **Emphysema** | **Chronic bronchitis** |
| Age of diagnosis, year | 60+ | 50+ |
| Appearance | Poor nutrition  pink skin  cold feet | Too much food  Diffuse cyanosis  Warm feet |
| First symptoms | Dyspnea | Cough |
| Sputum | Lightweight, slimy | Very, purulent |
| Bronchial infections | Rarely | Often |
| Pulmonary heart | At the terminal stage | Often |
| X-rays of light | Hyperinflation,  bullous changes,  Dripping heart | Strengthening the shape of the lungs,  > at the bottom  Enlargement of the heart |
| Hematocrit, % | 35–45 | 50–55 |
| PaO2, mm arb. St. | 65–75 | 45–60 |
| PaCO2, mm arb. St. | 35–40 | 50–60 |
| Elastic rejection | Significantly decreased | Norm |
| Diffusion ability | Decreased | A regular or slight decrease |

**Laboratory diagnostics:**

General clinical blood test (detailed analysis, ESR, leukocyte formula (microscopy of a blood smear with pathological changes)

* If necessary, biochemical blood tests
* determination of C-reactive protein;
* Determination of the acid-base composition of the blood;

**Instrumental diagnostics:**

* Computed tomography of the chest organs with the determination of the optical density of the lung tissue;

**Functional diagnostics:**

* a comprehensive study of the function of external respiration;
* spirometry;
* test with a bronchodilator drug;
* body plethysmography (bodyplethysmographylung volume measurement) is a method for assessing lung function (breathing function).
* diffuse test (a method for studying lung function, which allows measuring the process of diffusion of gases through the alveolar-capillary membrane);
* pulse oximetry;
* 6-minute walk test;

**Diagnostic result:**

**Clinical blood test.** During an exacerbation of the disease, both anemia and polycythemia can be detected with an increase in neutrophilic leukocytosis and ESR.

**Hematocrit:** Chronic hypoxia can cause polycythemia. This condition is indicated by a hematocrit of more than 52% in men and 47% in women. Secondary polycythemia should be suspected in patients who have quit smoking.

**Arterial blood gas analysis**: As the disease progresses, further changes in gas content change and both hypoxemia and hypercapnia develop. Patients should be examined for hypoxemia during rest, exercise, or sleep. In the absence of changes in blood gases, bicarbonate levels may help assess disease progression.

**Determination of α1-antitrypsin (AAT).** In the inflammatory process of the lung tissue, α1-antitrypsin inhibits the function of elastase released from neutrophils and prevents the breakdown of connective tissue protein (elastin) in the walls of the alveoli and the development of pulmonary emphysema. It modulates the local immune response, has antioxidant and antimicrobial effects, and inhibits the proteolytic enzymes of apoptosis. The concentration of α1-antitrypsin is significantly increased in acute inflammation of various etiologies, infectious, rheumatic diseases, malignant processes, estrogen replacement therapy, oral contraceptives, increased estrogen levels during pregnancy, and inflammatory processes in hepatocytes. α1-antitrypsin deficiency is associated with a high risk of pulmonary pathology. The diagnosis of acute α1-antitrypsin deficiency is confirmed when the serum level exceeds the protective threshold (i.e., 3-7 mmol/l) decreases. A genetic study is carried out on patients whose serum α1-antitrypsin level is 7-11 mmol/l.

**Sputum examination:** The sputum becomes purulent with an exacerbation of COPD (chronic obstructive pulmonary disease). According to the Gram method, a mixture of many neutrophils and microorganisms is determined. Pneumococci and Haemophilus influenza are the most commonly cultured pathogens during exacerbations. Cytological examination of sputum provides information about the nature of the inflammatory process and its severity. Determination of atypical cells increases oncological alertness and requires additional examination methods.

**PNEUMONIA** - inflammation of the lower respiratory tract of various etiologies, develops against the background of intraalveolar exudation and is accompanied by characteristic clinical and radiological signs. The alveoli in a healthy person are clean. During breathing, they are filled with oxygen-rich air, and oxygen enters the bloodstream through a network of microvessels. In pneumonia, the alveoli become filled with pus and fluid. In this case, the oxygen supply is limited, and breathing causes pain and coughing fit. Typical pneumonia is caused by bacterial flora.

**Etiology** - Streptococcus pneumonia (S. pneumonia) is the most common cause and accounts for 50% of cases. The following risk factors play a role in the development of resistance to Streptococcus pneumonia:

- Alcoholism, smoking

- Immunosuppressive state

- Cooling

- Stress

- Age (up to 5 years old, over 60 years old)

- Viruses (e.g. influenza A, B, parainfluenza, adenovirus, coronavirus)

Concomitant conditions: asthma, lung cancer, obstructive pulmonary disease (COPD), diabetes mellitus, alcoholism, liver and kidney failure, congestive heart failure, long-term use of corticosteroids, malnutrition or sudden weight loss (> 5%), infection with HIV.

- Use of antibiotics within the last three months

**Pathogenesis.** A common pathogenetic mechanism is the fixation of microorganisms to the epithelium of the upper respiratory tract, followed by an inflammatory reaction and cell necrosis. When the process spreads to the alveoli, as a rule, interstitial inflammation begins, and inflammatory exudate accumulate in the alveolar spaces. Such changes on a chest x-ray can be mistakenly regarded as bacterial pneumonia. Damage and desquamation of the airway epithelium disrupt the mucociliary apparatus's function and create a tendency for secondary bacterial infections.

**Diagnostics.** The diagnosis of pneumonia is based on the patient's medical history, physical examination, and chest x-ray. With increasing age, the symptoms of the disease weaken, and the results of the physical examination decrease. Fever in this group of patients is less common, and the symptoms of delirium are more pronounced.

**Anamnesis**► Fever +/- chills

► Cough (may be productive or non-productive)

► Presence of pleural pain in the chest

► Fatigue, headache, nausea, abdominal pain, myalgia

**Detected based on a physical examination:**

► Temperature above 37.8°C

► Increased respiratory rate(≥25/min) (number of breaths should be counted in full minutes)

► Signs of sclerosis of the lung parenchyma: decreased mobility of the chest, increased voice vibration, muffled percussion sound, reduced air intake, presence of bronchial breathing, moist rales with tiny local bubbles, crepitus, pleural friction noise

**Laboratory and instrumental research**:

► X-ray of the chest organs 2 times: 1st: no later than the 2nd day of illness, 2nd: on the 14-16th day, the location and origin of the infiltrate should be determined. Mandatory x-ray examination of the chest (in 2 projections - direct and lateral) and CT - allow you to clarify the localization of the process in the lungs, the volume, the dynamics of the development of changes, and distinguish different types of pneumonia.

► Complete blood count (detailed) 2 times: 1st: no later than the 2nd day of illness, 2nd: on the 14-16th day (in hospitalized patients).

► During cough, Gram stain, and sputum culture

► Blood cultures in patients with high fever and chills (recommended before antibiotic treatment).

► Biochemical blood test: glucose, electrolytes, creatinine, C-reactive protein

► Pulse oximetry

► Determination of arterial blood gases, Sat O2 < 90%, chronic obstructive pulmonary disease, if the patient receives oxygen for a long time (taking into account baseline O2 values)

► Thoracocentesis should be considered in patients with large volumes of pleural exudate

► Serological tests are not usually recommended

The most important laboratory tests are blood tests (general and biochemical) and sputum analysis. In patients with bacterial pneumonia, in the general blood test, the level of leukocytes, changes in the leukocyte formula (an increase in the number of neutrophils, a decrease in the number of lymphocytes), and acceleration of ESR are determined. The appearance in the leukocyte formula of young forms of leukocytes (pro- and metamyelocytes) indicates a severe course of the disease.

**Clinical blood test for pneumonia:** individual indicators of a blood test indicate the presence of an inflammatory process in the lungs:

• A mild form of pneumonia is manifested by leukocytosis and a tendency to the left of the leukoformula. The average severity of the disease is characterized by a more pronounced leukocytosis and a tendency to the left. The severe stage of pneumonia is characterized by a very high leukocytosis, a shift of the leukocyte formula to the left towards myelocytes. The absence of leukocytosis indicates a decrease in the patient's immunity, is more common in elderly and debilitated people and is associated with an unfavorable disease prognosis.

• Red blood cells. The study takes into account the erythrocyte sedimentation rate.

• Neutrophils. In the severe stage of the disease, a toxic granularity of cells is noted;

• Eosinophils. A decrease in the number of eosinophils is observed in the severe stage of pneumonia. Before the disease worsens increase in the number of eosinophils indicates a favorable prognosis for pneumonia;

• Lymphocytes. A decrease in the number of lymphocytes characterizes the severe stage of the disease;

• ESR. An increase in ESR is observed with mild and moderate inflammation of the lungs. A sharp increase in the erythrocyte sedimentation rate (in the absence of concomitant pathology) indicates the development of pneumonia; A very high ESR characterizes the severe stage of the disease. ESR norms for men and women differ: for men 1-10 mm/h, for women 2-15 mm/h.

**Blood chemistry**. The primary indicator that allows us to assess the severity of pneumonia is C-reactive protein (CRP). It is necessary to know the level of potassium, sodium, urea, creatinine, ALAT, ASAT, total bilirubin, and fibrinogen to assess the functioning of organs and systems and select adequate therapy based on a biochemical blood test.

**When examining sputum** basically, it is possible to determine the causative agent of the infection and determine its sensitivity to antibacterial drugs.

**COVID-19 infection.**

Coronaviruses (Coronaviridae) are a large family of RNA viruses with proven pathogenic properties that spread between humans and animals. Discovered in December 2019, the COVID-19 coronavirus (CoronaVirus Disease, 2019) is an acute respiratory disease caused by the SARS-CoV-2 virus and a new strain of this virus. The disease is more dangerous for people with weak immune systems, especially newborns, children, the elderly, and people with hypertension, diabetes, and chronic respiratory diseases.

Coronaviruses can cause a variety of illnesses in humans (from mild acute respiratory infection to severe acute respiratory syndrome (SARS)). It is currently known that four coronaviruses (HcoV-229E, OC43, NL63, and HKU1) circulate among the population. They are part of the ARVI structure, causing mild to moderate upper respiratory tract damage. According to serological and phylogenetic analysis results, coronaviruses are divided into three genera: Alphacoronavirus, Betacoronavirus, and Gammacoronavirus. Currently, most of the known coronaviruses are carried by mammals. In late 2001, SARS-CoV, the causative agent of SARS that causes severe acute respiratory syndrome in humans, was discovered, and belonged to the genus Betacoronavirus. In 2012, the new MERS coronavirus (MERS-CoV) was discovered worldwide, the causative agent of the Middle East respiratory syndrome (belongs to the genus Betacoronavirus).

MERS-CoV is currently circulating in nature and is causing a new disease. COVID-2019 is a new coronavirus single-stranded RNA virus belonging to the Coronaviridae family, Beta-CoV line, pathogenicity group 2, like other members of this family (SARS-CoV, MERS-CoV). The novel coronavirus COVID-2019 is believed to be a recombinant virus between a bat coronavirus and a coronavirus of unknown origin. The genetic sequence of the novel coronavirus COVID-2019 is 70% similar to that of SARS-CoV. The beta-CoV line, like other members of this family (SARS-CoV, MERS-CoV), belongs to the 2nd pathogenicity group. Counts, that the novel coronavirus COVID-2019 is a recombinant virus between a bat coronavirus and a coronavirus of unknown origin. The genetic sequence of the novel coronavirus COVID-2019 is 70% similar to that of SARS-CoV. Like other members of this family (SARS-CoV, MERS-CoV), the Beta-Cov line belongs to the second pathogenicity group.

SARS is an epidemic similar in nature to the 2019 coronavirus infection. The two digits in the name of the pandemic refer to the second type of coronavirus for the associated type of disease.

SARS-CoV - coronavirus associated with SARS:

• SARS - atypical pneumonia;

• CoV - coronavirus.

**Etiology and pathogenesis.** Currently, the primary source of infection is the patient and a person in the incubation period of the disease. Ways of transmission of infection are airborne (when coughing, sneezing, talking), airborne, and contact. Transmission factors are air, food, and household items. Health workers can also be the cause of the spread of COVID-2019.

SARS-CoV-2 mainly affects the lower respiratory tract; its main target is the lungs. This virus enters the human body through the respiratory tract. After the virus enters the body, it begins to multiply in the epithelium of the upper and lower respiratory organs. At the initial stage, symptoms of a cold appear. If the virus is neutralized and eliminated by the body's defense mechanisms, patients do not suspect they are infected with COVID-19. If the process continues, the pulmonary phase begins. As a result, diffuse lesions of alveocytes (cells located in the lungs) and pneumonia are observed. This virus binds to cells expressing the ACE-2 receptor (angiotensin-converting enzyme 2, an integral cell membrane protein) and damages cells with these receptors on its surface. In this case, the virus penetrates the lungs, the permeability of cell membranes increases, interstitial and alveolar edema develops, and the alveoli collapse.

According to the literature, in the lungs of patients with COVID-19, diffuse alveolar damage, perivascular T-cell infiltration, alveolar cell necrosis, type II pneumocyte hyperplasia, and fibrin deposition in the intraalveolar zone are observed. The presence of fibrin thrombi in the alveolar capillaries has been established, which causes damage to the alveoli and disrupts their function. There is no hypoxemia in the initial period of the pulmonary phase. Nevertheless, damage to the lungs and shortness of breath can cause hypoxemia. If the development of the disease is not prevented, the next stage - Type II pneumocyte hyperplasia and fibrin deposition in the intraalveolar zone are observed. The presence of fibrin thrombi in the alveolar capillaries has been established, which causes damage to the alveoli and disrupts their function. There is no hypoxemia in the initial period of the pulmonary phase. However, lung damage and shortness of breath can cause hypoxemia. If the development of the disease is not prevented, the next stage begins - the stage of hyperinflamation. In this case, acute respiratory distress syndrome (difficulty breathing) may develop as the standard gas exchange process is disrupted. It becomes difficult for such patients to breathe without the help of a special respiratory apparatus, the body is deprived of oxygen and multiple organ failure occurs.

**Clinical features of coronavirus infection**.

The incubation period is from 2 to 14 days. The presence of clinical symptoms of an acute respiratory viral infection caused by COVID-2019 is typical:

• fever;

• Cough (dry or with phlegm) in 80% of cases;

• shortness of breath (55%);

• myalgia and fatigue (44%);

• feeling of congestion in the chest (>20%).

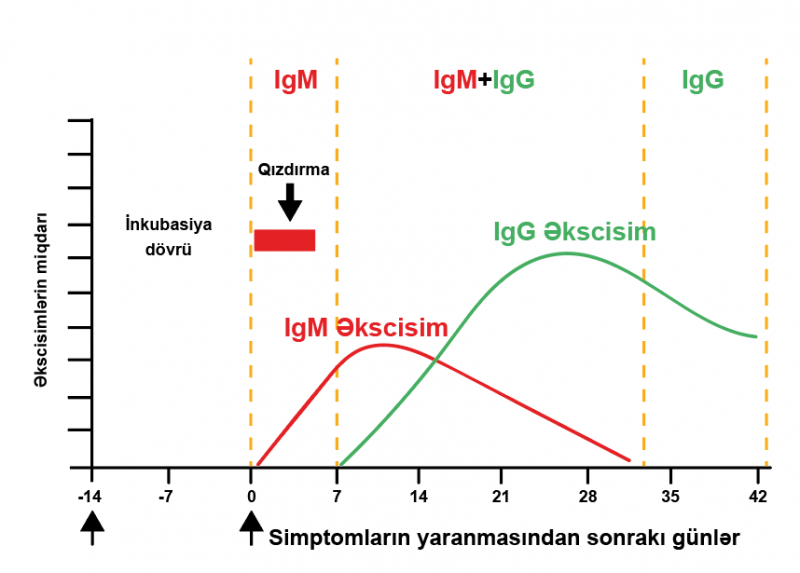
The most severe shortness of breath develops on the 6-8th day of infection. It was also found that the first symptoms include headache (8%), bloody cough (5%), diarrhea (3%), nausea, vomiting, and palpitations. When these symptoms appear, body temperature may not rise. Other symptoms include a runny nose, loss of smell, loss of taste, headache, weakness, etc.

**Schedule for the production of antibodies against COVID-19 by day**

**IgM antibodies** formed on the 5-7th day after the onset of the disease. The presence of these antibodies in the blood reflects the current infection. As one recovers, the levels of these antibodies also decrease.

**IgG antibod**y synthesis starts later and reaches its maximum level 10-14 days after infection. The detection of IgG to COVID-19 indicates that a person infected with the virus is in recovery or has previously been infected with a coronavirus infection.

If both IgM and IgG antibodies are detected in a person at the same time, then the asymptomatic course of the disease is noted, and infection is likely to have occurred 10-14 days ago. During this period, the risk of transmission of infection to others is high.



**Diagnosis of coronavirus infection**

The diagnosis is based on clinical signs, epidemiological history, and positive laboratory results.

1. Detailed assessment of all complaints, patient history, and epidemiological history.

2. Physical examination necessarily includes:

• examination of the visible mucous membranes of the upper respiratory tract

• auscultation, percussion of the lungs

• palpation of the lymph nodes

• examination of the abdominal organs with the determination of the size of the liver and spleen

• thermometry

• determination of the severity of the patient's condition.

3. General laboratory diagnostics:

**• General (clinical) blood test**- determination of the level of erythrocytes, hematocrit, leukocytes, platelets, and leukocyte formula;

**• Biochemical blood test -** urea, creatinine, electrolytes, liver enzymes, bilirubin, glucose, albumin. This analysis does not provide any specific information, but the identified changes indicate organ dysfunction, decompensation of concomitant diseases, and the development of complications. This has a certain prognostic value and plays a role in the choice and dosage of drugs.

• Study of the level of C-reactive protein in the blood (CRP) • The level of CRP correlates with the spread of inflammatory infiltrate in pneumonia, the severity of the course, and prognosis;

**• Pulse oximetry**- SpO2 measurement is an assessment of respiratory failure and hypoxemia. This is the simplest and most reliable screening method to identify hypoxic patients in need of respiratory support;

**Acute respiratory failure (ARF)**

• Patients with (according to pulse oximetry SpO2 less than 90%) an examination of arterial blood with the determination of PaO2, PaCO2, pH, bicarbonates, lactate;

• Coagulogram with the determination of prothrombin time, international normalized ratio, activated partial thromboplastin time is recommended for patients with symptoms of ARF.

• Specific laboratory diagnostics:

• Detection of COVID-2019 RNA by PCR.

**Comprehensive lab tests for COVID-19 include:**

1. Investigation of the virus by RNA-PCR (PCR)

2. Determination of specific antibodies to coronavirus in the blood - IgM, IgG.

**Polymerase chain reaction (PCR)** - This method is based on the presence of genetically specific virus fragments in the material. The diagnosis is confirmed based on a positive laboratory result for SARS-CoV-2 RNA. The virus's genetic material is detected in the human body a few days after infection by PCR. This situation allows us to determine both the disease and the asymptomatic course of the disease.

**Instrumental diagnostics**:

**• Chest x-ray** - recommended for all patients with suspected pneumonia (in case of unknown localization of the inflammatory process, the picture should be taken in the proper lateral projection) in frontal and lateral projections. An X-ray revealed bilateral diffuse infiltrative spots. More pronounced changes are localized in the basal sections of the lungs.

• **CT-scan of the lungs** is the most sensitive method in diagnosing viral pneumonia; in pneumonia, bilateral infiltrates are detected in the form of "ground glasses" or seals located in the lower and middle sections of the lungs.

• **ECG** - recommended for all hospitalized patients. This study does not contain specific information, but it is currently known that viral infection and pneumonia, in addition to decompensation of concomitant chronic diseases, increase the risk of developing arrhythmias and acute coronary syndrome, and their timely detection affects the prognosis.

**ELISA (enzyme linked immunosorbemt assay) in the diagnosis of coronavirus:**

IgM < 1, IgG < 10 - no antibodies to the virus in humans. Additional measures should be taken.

IgM from 1 to 2, IgG < 10 - the result is doubtful, infection and asymptomatic course of the disease are possible, it is recommended to limit contact with others and re-analyze after seven days.

IgM > 2, IgG < 10 - the body is infected, and the person poses a risk of infecting others, must be in self-isolation, and under medical supervision.

IgM> 2, IgG> 10 - there are antibodies to the virus in the body, but the infection can continue in a latent form. It is important to limit contact with others; a re-test should be taken within a week.

IgM < 2, IgG > 10 - antibodies to the virus have been developed. The person is infected with the coronavirus.