DNA-TECHNOLOGY

INFECTION

DETECTION OF HERPESVIRUSES BY PCR

INTRODUCTION

According to WHO, two-thirds of the world's population under the age of 50 are infected with a herpes virus, characterized by a steady increase in incidence and rapid spread across the globe. The ***Herpesviridae*** family is widespread and represented by more than 100 species. Nine types of herpesviruses are pathogenic for humans. They mainly infect humans in early childhood, passing into a latent or persistent state and activating immunodeficiency [5]. Representatives of the ***Herpesviridae*** family are characterized by pantropism towards organs and tissues, lifelong persistence in the body, and the ability to cause various manifestations.

Human herpesviruses can be subdivided into three main subfamilies, which differ in genome structure, host tropism, spectrum of activity, and ability to establish a latent infection [37]:

a) alpha herpes viruses include herpes simplex virus type 1, herpes simplex virus type 2 and varicella-zoster virus; have the ability to rapidly destroy infected cells and establish a latent infection, primarily in the sensory ganglia;
b) beta herpesviruses include herpes simplex virus type 6, herpes simplex virus type 7, and cytomegalovirus. They are characterized by less pronounced cell cytopathicity, long replication cycle, and lifelong persistence in host cells. They also cause latent infection in cells of the monocyte-macrophage system and lymphocytes; can be the cause of generalized lesions in newborns, children, and adults with immunodeficiency states;
c) gamma herpes viruses include Epstein-Barr virus and human herpesvirus type 8; they can infect monocytes and lead to malfunctions in host cell apoptosis during latent infection.

The growth in the number of immunocompromised individuals (patients with HIV infection, organs and tissues recipients, patients with cancer), as well as the significant contribution of herpes viruses to the development of obstetric and gynecological pathologies, impose high demands for the differential diagnosis of infectious and inflammatory processes associated with this group of pathogens.

The use of molecular genetic methods in the diagnosis of herpesviral infection is reflected in guidelines:

- International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation, 2013;
- The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation, 2018;
- CDC Division of STD Prevention, 2015;
- 2017 European guidelines for the management of genital herpes;
- WHO Guidelines for the Treatment of Genital Herpes Simplex Virus. Geneva: World Health Organization, 2016.

Herpes simplex virus (HSV)

Herpes infection is a chronic recurrent viral disease. The causative agents are herpes simplex viruses of the 1st (HSV1) and 2nd (HSV2) types.

HSV belongs to the dermatoneurotropic DNA-containing intracellular pathogens of the ***Herpesviridae*** family, ***Alphaherpesvirinae*** subfamily. It has common group-specific antigenic determinants and a short reproduction cycle (8–10 hours) with a cytopathic effect in infected cells. The viral capsid has a complex structure, contains 162 capsomeres, and is surrounded by a lipid bilayer envelope. The viral DNA carries the genetic information for the viral replication, and the capsid acts as a protective cover, stabilizing the virus outside the cell and facilitating its adsorption on the cell surface [23, 32].

HSV is sensitive to drying and heat and is easily degraded by ether, alcohol, and other organic solvents. HSV persists for a day at room temperature and average humidity. It is inactivated after 30 minutes at 50–52°C. However, the virus can remain viable for 5 days at low temperatures (–70°C). On metal surfaces (coins, doorknobs, water taps), the virus survives for 2 hours in a humid environment; it persists until it dries [23].

According to WHO, herpes infection is spread worldwide: about 3.7 billion people under the age of 50 (67% of the population) are infected with the HSV1 virus, including 140 million people with genital manifestations of HSV1. In addition, about 417 million people between the age of 15 and 49 years are infected with HSV2 (11%); this type of virus is sexually transmitted [5].

A human is the only source of infection and remains a lifelong carrier of the virus, transmitting it mainly during an exacerbation. Everyone is susceptible to HSV, but the number of cases of asymptomatic carriage or low-symptom forms of the disease has increased in recent years.

HSV1 is transmitted mainly orally, causing infection of the nasolabial area, but it can also be transmitted through oral-genital contact, causing anogenital lesions. HSV2 is transmitted primarily sexually, mainly causing the clinical manifestations of genital herpes. In addition, there are frequent cases of autoinoculation of infection [5, 32].

The primary lesion is accompanied by viral replication at the site of invasion. Then the virus enters the sensory nerve endings and is transmitted to the nerve cells of the dorsal root ganglia of the spinal cord, where it persists for life in a latent state with a possibility of reactivation [32].

Latent viral infection is practically impossible to detect (it can only be detected by co-cultivation of samples of the ganglion and a sensitive culture). In immunodeficiency states, HSV begins to multiply and goes into the active stage. New viral generations appear during the host life, but they are insignificant for the development of symptoms but sufficient for producing infectious offspring that can infect other persons or the fetus during pregnancy [1].

Viral protection against the human immune system includes a range of mechanisms to suppress the immune system's cellular component. For example, herpes infection is characterized by suppressing immunocompetent cells and cells of the monocyte-macrophage system and a violation of regulatory relationships in the host organism's immune system. This leads to the impossibility of eliminating the pathogen from the body and contributes to its long-term persistence.

When immunocompetent cells are infected, there are disturbances in the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), leading to subsequent defects in the proliferation and differentiation of cells in the immune system. In chronic recurrent herpes virus infection, there is a significant decrease in natural killer cells (NK cells) activity, increasing their total number [2].

In patients with a severe course of the disease, suppression of local cellular immunity, the prevalence of mature forms of the pathogen (virions), and incompleteness of phagocytosis are observed. In addition, HSVs encode viral determinants that block or delay the onset of apoptosis in infected cells, and the viral proteins ICP10PK and UL14 prevent apoptotic processes in neurons and epithelial cells after viral infection. Taken together, this ensures the long-term persistence of the virus in the infected cells [185].

In patients with frequent recurrences of genital herpes, a decrease in the induced production of IFN-α and IFN-γ and significant changes in the level of serum IFN characteristic of chronic viral infections are revealed [2, 171].

The humoral response to herpesvirus infection has a significant diagnostic and prognostic value. During primary viral infection, IgM, low-affinity IgG, and IgA antibodies are formed. With a secondary infection, IgG antibodies with increased affinity are produced. The maximum production of IgM is observed 4–6 weeks after the primary infection and remains in the circulatory system for 6–8 weeks, which is essential for determining the time of disease [2].

One of the most famous classifications of herpesvirus infection takes into account the mechanism of infection, its course, and the localization of lesions (Table 3) (Clinical classification of herpes simplex / Ed. By V.A Isakov, 1991) [6].

Primary herpes infection develops at the first contact of a person with the virus at any age. The infection proceeds in a subclinical form in 80–90% of cases. Primary herpes simplex is most often recorded in children at the age between 6 months and 5 years. The incubation period lasts from 2 days to 4 weeks [6].

Aphthous stomatitis and acute respiratory infection are the most common forms of primary herpes in children. In addition, various lesions of the skin, conjunctiva, and cornea can be observed. Since the onset of sexual activity, genital herpes has been a common manifestation of the primary infection. Manifestations of primary herpes are characterized by a pronounced intoxication syndrome: fever, general weakness, headache, muscle and joint pain [6].

Recurrent (secondary) herpes infection is associated with the reactivation of a virus that was in a latent state. Relapses of the disease can occur with varying frequency: from once a year to several times a month. The localization of lesions in recurrent and primary herpes simplex is usually the same. Cutaneous and genital herpes is the most common forms of recurrent herpes. With a relapse of the disease, the general intoxication syndrome and inflammatory changes in the lesion are generally less pronounced [6, 23].

Table 1. Classification of herpes infection

Depending on the duration of the presence of the virus in the body	Depending on the distribution of skin lesions
• short term persistence of HSV in the body: a) acute form; b) inapparent (asymptomatic) form. • long term persistence of HSV in the body: a) latent form; b) chronic form (with relapses); c) slow infection.	• localized; • widespread; • generalized.
Depending on the mechanism of infection	**Depending on the clinic and localization of the pathological process**
• congenital; • acquired: a) primary; b) secondary (recurrent).	• typical forms: a) herpetic lesions of the gastrointestinal mucosa (stomatitis, gingivitis, pharyngitis, etc.); b) herpes eye disease – ophthalmic herpes (conjunctivitis, keratitis, iridocyclitis, etc.); c) herpes skin lesions (herpes of the lips, wings of the nose, face, hands, buttocks, etc.); d) genital herpes (mucous membranes of the penis, vulva, vagina, cervical canal, perineum, etc.); e) herpetic lesions of the nervous system (meningitis, encephalitis, meningoencephalitis, neuritis, etc.); f) generalized herpes simplex (pneumonia, hepatitis, esophagitis, sepsis); • atypical forms: a) edematous; b) zosteriform herpes simplex; c) eczema herpeticum Kaposi (Kaposi varicelliform eruption); d) necrotizing ulcerative; e) hemorrhagic; f) hemorrhagic necrosis.

Localized herpes simplex infection, both primary and recurrent, is located in a specific region. The widespread form is characterized by the deepening of the lesion, its spread to nearby tissues, and the appearance of new foci in distant areas of the skin and mucous membranes. This form of herpes develops in immunocompromised patients [6, 23].

With generalized herpes infection, there are visceral and disseminated forms. Meningitis and meningoencephalitis are the most frequent diseases; hepatitis and pneumonia are less common. The disseminated form is characterized by the involvement of many organs and systems, fever, severe intoxication, hemorrhagic syndrome. This form of herpes develops in immunocompromised children with HIV infection under 1 month of age [79, 164].

The clinical picture of herpes infection in pregnant women corresponds to the clinical manifestations in non-pregnant women. Primary herpes infection often causes a more severe course of the disease than an exacerbation of chronic genital herpes, increasing the risk of spontaneous abortion, premature birth, secondary infertility, missed abortion, and intrauterine infection of the fetus. The infection affects fetal development in the first trimester. Not only does herpes infection with clinical manifestations and inapparent infection poses a threat to the pregnant woman, fetus, and newborn [35, 61, 167, 168].

There are four clinical types of neonatal herpes: congenital herpes, disseminated form (generalized congenital herpes infection), cerebral (herpetic encephalitis), and localized congenital herpes infection with lesions of the skin, oral mucosa, and eyes.

Congenital herpes is the result of antenatal transplacental infection. It causes stillbirth, premature birth, intrauterine growth retardation, CNS damage (microcephaly, hydrocephalus, calcifications in the brain), skin scars, microphthalmia, and hepatosplenomegaly. In addition, there may be extremity hypoplasia (cortical dwarfism), thrombocytopenia, and early neonatal bacterial sepsis [61, 102].

Disseminated neonatal herpes (intrapartum infection) involves many organs in the infectious process. Severe course of the disease: the clinical picture may resemble bacterial sepsis with the development of DIC syndrome. The onset of symptoms is on the 4–5th day of life, with the most prominent manifestations on the 9–11th day: increased excitability, high-frequency cry, convulsions, alternating with CNS depression (manifestation of encephalitis), jaundice (a symptom of severe hepatitis), diffuse interstitial pneumonia, myocarditis with arrhythmias and heart failure. Herpetic vesicular skin rash, aphthous stomatitis, keratoconjunctivitis are typical symptoms, but they may be absent in 20–30% of patients. This form accounts for 25–50% of all cases of neonatal herpes. There have been cases of generalized herpes infection in premature infants complicated by massive epidermolysis [44, 66, 95, 110].

Cerebral neonatal herpes (a local form with lesions of the central nervous system - herpetic encephalitis) accounts for 30–35% of all cases of neonatal herpes and can clinically manifest itself at 2–4 weeks of a child's life with typical signs of encephalitis: fever, symptoms of CNS depression (lethargy, stupor, coma) or hyperexcitability (convulsions, high-frequency cry, etc.). Hyperthermia is characteristic of full-term newborns; in premature infants, herpetic encephalitis often develops against a background of average temperature or is accompanied by hypothermia. Seizures develop in 60–80% of newborns, more often generalized. Epilepsy with seizure polymorphism in the form of generalized or local myoclonus of the facial and extremities muscles, adversive seizures, atonic absences with resistance to anticonvulsant therapy is formed. In severe cases, signs of decortication or decerebration are registered from the 10th day of disease [102, 162, 163].

Localized congenital herpes infection with lesions of the skin and mucous membranes occurs in 20–40% of patients with neonatal herpes and is characterized, along with typical vesicular skin rashes, by lesions of the oral mucosa (aphthous stomatitis in 10%), eyes (in 40% of children – conjunctivitis, keratitis, chorioretinitis). A frequent recurrent infection characterizes the localized form in the 1st year of life. Corneal ulcers, optic atrophy, and blindness are complications of herpes eye infection. In the absence of etiotropic therapy in 50–70% of newborns, the localized form can generalize the process or damage to the central nervous system; therefore, neonatal herpetic vesicular skin lesions are an indication for specific antiherpetic therapy [7, 32].

Laboratory diagnosis of herpesvirus infections

The diagnosis of herpesvirus infection with typical clinical symptoms does not cause difficulties; however, in some cases (pregnant women, immunocompromised persons, etc.), the clinical picture may be asymptomatic or atypical.

In guidelines for managing patients with herpesvirus infection, the detection of HSV-1,2 DNA is the "gold standard" of diagnosis. Compared to the culture method, this approach is more specific and sensitive, does not require compliance with strict conditions for storage and transportation of the sample, and is also characterized by a low risk of contamination. Real-time PCR is the choice criterion for diagnosing herpesvirus infection of the nervous system and in the generalized infection. The culture method is advisable when it is necessary to determine the sensitivity of the antiviral drug [92, 144].

When examining asymptomatic patients, patients with a recurrent herpesvirus infection, or atypical forms of infection, the culture method and PCR may be harmful. In this case, serological tests for specific IgG and IgM can be practical. This method is also recommended when examining a sexual partner for genital herpes [92, 161].

Direct immunofluorescence techniques and cytological studies for detecting viral antigens are not recommended due to their low specificity and sensitivity [92, 161].

By clinical guidelines, laboratory techniques are recommended to clarify the etiology of the disease, in atypical forms of the disease, and differentiate from other conditions. Therefore, the diagnosis of herpesvirus infection should be established by a combination of anamnestic, epidemiological, clinical data and available laboratory techniques: cytomorphological analysis of smears to detect multinucleated giant cells and intracellular inclusions, virus isolation in cell culture, enzyme-linked immunosorbent assay (ELISA) to determine the titer of viral antibodies, detection of viral DNA using polymerase chain reaction (PCR) [51].

In diagnosing herpesvirus infection, two PCR options are possible: qualitative PCR, which allows detecting or not detecting the herpes virus in the sample, and quantitative real-time PCR, determining the viral load [51].

Quantitative analysis is advisable for mild or asymptomatic infection and severe clinical manifestations since a high viral load correlate with the infectious process's severity. The determination of the initial viral load makes it possible to determine the treatment duration, and dynamic observations allow monitoring drug therapy and assessing its effectiveness. With adequate treatment, the viral load decreases, up to its complete disappearance in the samples. In the absence of positive dynamics or an increase in viral load, it is necessary to correct drug therapy.

The content of vesicles or cracks (atypical infection), washings from tissues and organs, impression smears, urethral, vaginal, and cervical scrapings (discharge), body fluids and secretions (mucus, lacrimal fluid, saliva, urine, prostatic fluid, blood), placental biopsy specimen, amniotic fluid, umbilical cord blood can be collected for analysis. It is vital that the specimens for PCR tests were collected from the site of infection (a prerequisite for direct laboratory diagnostic methods).

Detection of viral DNA indicates the acute phase of herpesvirus infection. In the latency period, viruses are found in the nerve ganglia, hepatocytes, endotheliocytes and are not detected by PCR. Therefore, it is possible to confirm or refute the herpesvirus infection using serological diagnostic methods in such cases.

When examining pregnant women, it is recommended to take smears from the cervical canal and erosive and ulcerative surfaces for PCR tests and a serological diagnostic test to detect IgG and IgM and determine the IgG avidity index. In addition, it is recommended to take a smear from the cervical canal to detect the herpes simplex virus by PCR in the hospital.

Pregnancy risks are higher for HSV seronegative women with negative IgM and IgG. In such cases, the most dangerous is the primary infection because it is often severe. In immunodeficiency states (during pregnancy, neonatal period with immature immunity), serological diagnostic methods can give false-negative results due to the low ability of the immune system to produce a sufficient amount of immunoglobulins.

In pregnant women, primary herpesvirus infection is confirmed by specific IgM antibodies in the blood serum in an amount 2 or more times higher than the immune threshold in two studies performed with an interval of 14 days in the same laboratory by the same method (immunofluorescence assay (IFA), chemiluminescent immunoassay (CLIA)), provided that specific IgG is detected in the second study that exceeds the sensitivity threshold with an avidity below 40%. In addition, the reactivation of latent herpesvirus infection is confirmed by at least one detection of specific IgM antibodies in the blood serum in an amount 2 or more times higher than the sensitivity threshold (IFA, CLIA), or an increase in the specific IgG with high avidity (more than 50%) 4 or more times within 4 weeks.

Antenatal diagnosis of congenital herpesvirus infection is based on detecting primary infection or reactivation of latent herpesvirus infection in pregnant women. There is a typical rash on a pregnant woman's mucous membranes and skin, the etiology of which is confirmed by detection of the virus by PCR, viral antigens by immunocytochemistry, or immunofluorescence staining impression smears.

The diagnosis of congenital herpesvirus infection is established in a newborn in the presence of clinical manifestations of the disease and etiological verification in one of the following ways:

- positive PCR test results (impression smears of skin lesions, blood (leucoconcentrate), cerebrospinal fluid), or the detection of herpesvirus antigens by immunocytochemistry (ICC) in impression smears, blood, cerebrospinal fluid in the first two weeks of life;
- detection of specific IgM in an amount 2 or more times higher than the sensitivity threshold (detected twice with an interval of 5–7 days by IFA or CLIA methods);
- detection of herpesvirus in sterile samples by a virological method in the first two weeks of life;
- the level of specific IgG does not decrease in the child's blood serum at 6 weeks of age (in comparison with the initial level, the level decreases by less than 40%);
- seroconversion (the appearance and elevation of specific IgM or IgG), provided that the assay is performed using the same method and reagent kits from the same manufacturer (B).

The diagnosis of congenital herpesvirus infection (congenital herpes, localized form with lesions of the skin and mucous membranes, disseminated neonatal herpes, cerebral herpes-isolated herpes encephalitis) is made based on clinical signs.

Treatment of herpesvirus infection

Herpesvirus infection treatment regimens are recommended by clinical guidelines, taking into account the stage of the infectious process (Table 2).

Table 2. Treatment regimens for herpesvirus infection according to clinical guidelines

European guidelines for the management of genital herpes (2017)	Sexually Transmitted Diseases Treatment Guidelines (CDC, 2015)
First Clinical Episode	
• acyclovir 400 mg orally 3 times/day for 5–10 days • acyclovir 200 mg orally 5 times/day for 5–10 days • valacyclovir 500 mg orally 2 times/day for 7–10 days •famciclovir 250 mg orally 3 times/day for 7–10 days	• acyclovir 400 mg orally 3 times/day for 7–10 days • acyclovir 200 mg orally 5 times/day for 7–10 days • valacyclovir 1 g orally 2 times/day for 7–10 days • famciclovir 250 mg orally 2 times/day for 7–10 days
Recurrent herpes	
• acyclovir 800 mg orally 3 times/day for 2 days • valacyclovir 500 mg orally 2 times/day for 3 days • famciclovir 250 mg orally 3 times/day for 7–10 days *Alternative regimen* • acyclovir 400 mg orally 3 times/day for 3–5 days • acyclovir 200 mg orally 5 times/day for 5 days • valacyclovir 500 mg orally 2 times/day for 5 days • famciclovir 125 mg orally 2 times/day for 5 days	• acyclovir 400 mg orally 3 times/day for 5 days • acyclovir 800 mg orally 2 times/day for 5 days • acyclovir 800 mg orally 3 times/day for 2 days • valacyclovir 500 mg orally 2 times/day for 3 days • valacyclovir 1 g orally once a day for 5 days • famciclovir 125 mg orally 2 times/day for 5 days • famciclovir 1 g orally 2 times/day for 1 day
Management of pregnant women (from the 36th week)	
• acyclovir 400 mg orally 3 times/day	• acyclovir 400 mg orally 3 times/day • valacyclovir 500 mg orally 2 times/day
Management of neonatal herpes	
	• cyclovir 20 mg/kg body weight IV every 8 hours for 14–21 days

Topical treatment for herpes [51]:

- acyclovir ointment;
- aniline dye solutions, antiseptics for lesions (1% brilliant green dye solution, 5–10% potassium permanganate solution).

Varicella-zoster virus (VZV)

Varicella-zoster virus (herpesvirus type 3) is the cause of two clinically dissimilar diseases: varicella – chickenpox, which occurs mainly in childhood, and zoster – herpes zoster (shingles), the clinical manifestations of which are usually observed in people of mature age.

VZV belongs to DNA-containing viruses, genus *Varicellavirus*, subfamily *Alphaherpesvirinae* of the *Herpesviridae* family. The virion consists of a nucleoid located in the central part, a capsid covering the nucleoid, and supercapsid shell [24].

The virus is volatile, capable of persisting for a long time with subsequent reactivation, dermato, and neurotropic. It is unstable in the environment, inactivated at a temperature of 50–52°C for 30 minutes, sensitive to ultraviolet radiation; it tolerates low temperatures, repeated freezing, and thawing [24].

The only source of infection is a person with chickenpox or shingles. VZV is transmitted by air dust and contact [34].

After infection, the virus first enters the skin and mucous membranes, replicating; sometimes, the virus invades the lymph nodes, causing primary viremia. With shingles, the virus may multiply outside the skin, for example, in the parenchymal organs (lungs, liver, spleen, and pancreas). Further spread of the virus in the host can be hematogenous, lymphogenous, and neurogenic (along with the axons of the sensory nerves) [24].

With the neurogenic spread, VZV enters the sensory spinal ganglia and dorsal roots of the spinal cord. In severe cases, the process involves the anterior and posterior horns, the white matter of the spinal cord, and the brain. When the virus enters the motor cells and roots, a picture of amyotrophic radiculoplexus neuropathy occurs; in the gray matter of the spinal cord – myelitis; in the cerebrospinal fluid – meningoradiculoneuritis or serous meningitis [24].

The virus remains latent mainly in the trigeminal ganglia and dorsal root ganglia. With a decline of immune function in the elderly, those with impaired immunity, or patients receiving immunosuppressive therapy, as well as in the presence of some other factors, the virus can reactivate in neurons, causing shingles [115].

When reactivated, the virus moves centrifugally through the nerve to the skin, where its replication and the appearance of characteristic skin lesions – unilateral vesicular rash – are noted. These clinical signs reflect the viral "escape" from the innate and adaptive immune mechanisms [24].

VZV has several unique ways to evade the host immune system. When the virus enters the skin, it suppresses the synthesis of IFN-α by epidermal cells, which enhances the local replication of VZV. In addition, VZV inhibits the induction of intercellular adhesion molecule-1 (ICAM-1) synthesis by proinflammatory cytokines (IL-1β and TNF-α). Disruption of cell adhesion molecules allows the virus to avoid the early recruitment of inflammatory cells to the site of infection. Lack of ICAM-1 expression can also impair the ability of keratinocytes to present the virus to host T-cells. In the presence of VZV, there is interference in the expression of genes of the major histocompatibility complex class I and class II (HLA I and II), which are involved in the presentation of virus antigens to CD4 + and CD8 + T lymphocytes [14, 166].

Recognition of the virus by cells of the innate immunity is carried out through pattern recognition receptors on their surface, particularly Toll-like receptors (TLR). The participation of TLR2 – cytomegalovirus in the triggering of inflammatory reactions and the immune response in herpesvirus infection was established by inducing IL-6 synthesis through TLR2-dependent activation of the nuclear factor NF-kB. Conversely, VZV can suppress this activation mechanism, causing the sequestration of proteins of the NF-kB family in the cytoplasm of infected cells (fibroblasts or epidermal cells) [14].

In recent years, an increased frequency of severe forms of chickenpox, accompanied by damage to the central nervous system (CNS), often in the form of encephalitis, has been recorded. Clinical observations have shown that the course of chickenpox depends on the early T-cell immune response but not on the antibody production: the severe course of primary VZV infection is associated with a reduced T-cell count and suppression of the proinflammatory antiviral cytokines production [181, 182].

Thus, an increase in the blood levels of IL-1β, IL-8, IFN-α, IFN-γ, and IL-10 3–9 times compared with uninfected people characterizes an adequate immune response to VZV infection resolution without the development of neurological complications. At the same time, suppression of cytokine production in the first days of the disease can predict a severe course of chickenpox with the risk of central nervous system involvement. The determination of IL-6 blood levels, the elevation of which can be a diagnostic sign of neurological complications of chickenpox [14, 45, 182].

The modern epidemic process is characterized by an increase in the incidence of chickenpox in both children and adults. According to the literature, the incidence rate of chickenpox among adults is up to 800 per 100 000 cases, the absolute incidence is from 500 000 to 1 150 000 issues per year, and the mortality rate is 1 per 60 000 cases. The incidence rate among children is 7 000 per 100 000 cases; children between the age of 3 and 7 years are more likely to get sick. In addition, chickenpox affects up to 1% of pregnant women [45].

During chickenpox, 4 periods are distinguished: incubation, prodromal, periods of rash and crusting. The incubation period is 10–21 days. Prodromal phenomena can be observed within 1–2 days before the onset of the rash. In this case, the patient may feel feverish and have a sore throat, nausea, headache, loss of appetite, and sometimes vomiting. If the prodromal period is absent, then the disease begins with the appearance of a rash. Fever coincides with the

period of generalized rash, while in adults, it reaches significant numbers. The rash appears gradually, so the fever is typically undulant, rising and falling like a wave [45, 54, 55].

The rash is polymorphic; there are elements at different stages of development due to its wave-like appearance with an interval of several days. However, in the first days of the disease, the rash may be accompanied by severe itching [55].

According to the course of the disease and its severity, the following clinical variants are usually distinguished:

I. Typical forms:

- mild;
- moderate;
- severe.

II. Atypical forms:

- inapparent (asymptomatic) form;
- bullous form;
- hemorrhagic form;
- gangrenous form;
- generalized form (with internal organ damage – visceral).

In children, chickenpox is often mild, with rare complications. However, in adults, the course of the disease is more severe, and complications are more common.

Complications develop in adult patients with aggravated comorbid pathology and immunodeficiency states with the cellular component of immunity (HIV infection, diabetes mellitus, autoimmune diseases, bronchial asthma, acute leukemia, etc.). An increase follows the acute onset of the disease in body temperature to 38.5 °C and the appearance of a maculopapular rash, new elements of which appear with an interval of 24–48 h [45].

Secondary streptococcal infection of ruptured vesicles can lead to erysipelas, sepsis, acute hemorrhagic nephritis, and skin gangrene. In the case of staphylococcal infection, pyoderma or bullous impetigo may develop. Chickenpox in adults with a weakened immune system can be complicated by pneumonia, encephalitis, myocarditis, transient arthritis, hepatitis, Guillain-Barré syndrome. Acute postinfectious cerebellar ataxia is one of the most common neurological complications [8, 78, 158].

In pregnant women, chickenpox is not more common and is not more severe than in non-pregnant women; however, primary infection with VZV can lead to pathologies in the fetus and newborn – congenital chickenpox. Therefore, cases of neonatal varicella before 11 days of age should be considered congenital VZV infection [31, 43].

Congenital forms of chickenpox include:

- congenital varicella syndrome;
- neonatal varicella.

Intrauterine transplacental infection with VZV in the first 20 weeks of gestation can lead to spontaneous abortion, intrauterine fetal death, or the birth of a child with congenital varicella syndrome in 2–5% of cases. Pregnancy ends in an intrauterine fetal death in more than 60% of cases. A newborn baby with congenital varicella syndrome is not a source of infection [32, 43].

The congenital varicella syndrome is characterized by disseminated skin lesions with dermatomal distribution, neurological disorders (cortical atrophy of the brain, spinal atrophy, paresis of the extremities, seizures, microcephaly, Horner's syndrome, encephalitis, dysphagia), eye diseases (microphthalmia, chorioretinitis, cataract, nystagmus, anisocoria, optic nerve atrophy), muscular hypoplasia and skeletal abnormalities. In addition, it is accompanied by anemia, thrombocytopenia, changes in the leukocyte count, and metabolic disorders [84, 127].

In addition, autonomic system denervation is observed, resulting in bulbar palsy, Ramsey Hunt syndrome, diaphragmatic palsy, intestinal atresia, esophageal dilatation, and reflux. Gastroesophageal reflux or diaphragmatic palsy can lead to respiratory failure, which can be fatal. Other abnormalities are intrauterine growth retardation, thrombocytopenia, erythroblastosis, and multiple organ microcalcification with focal necrosis [31, 43, 127].

Neonatal (congenital) varicella develops in infected pregnant woman if a pregnant woman becomes infected less than 10 days before delivery.

The timing of the infection determines the severity of neonatal varicella. Chickenpox that occurs in a pregnant woman less than 5 days before or 2–3 days after delivery, due to the lack of transplacental transmission of maternal antibodies in 20% of cases leads to the disseminated fulminant varicella infection in the newborn. There are often cases of generalized infection with internal organs damage: lungs, myocardium, kidneys, intestines. Mortality can reach 61% [31, 43, 49].

When a pregnant woman 5-10 days before delivery, the first clinical signs in a newborn appear immediately after birth, the course of the disease in these cases is milder, and death does not usually occur. If a pregnant woman becomes infected 16 or fewer days before delivery, a newborn with chickenpox is a source of infection [31, 43].

In general, if a woman becomes infected in the second half of pregnancy, a baby can acquire a latent infection, as a result of which herpes zoster develops in the first years of life. Late complications of congenital varicella include developmental delay, encephalopathy, blindness, diabetes mellitus, a higher incidence of malignant tumors, leukemia because the virus can cause chromosomal aberrations. However, in a mother with herpes zoster, congenital varicella syndrome occurs in the fetus relatively rarely since the fetus is protected by antibodies obtained from the mother [31, 43].

Shingles (herpes zoster) is an infectious disease that occurs due to the reactivation of latent VZV: people who have previously had chickenpox fall ill [24].

The disease occurs among people of all age groups. In children under 15 years of age, the incidence of herpes zoster does not exceed 5%, while in people between 60 and 80 years of age, it rises to 50–70% against the background of age-related decrease in immune protection. Shingles often occurs in immunocompromised people (patients with organ and tissue transplants, leukemia, lymphogranulomatosis, neoplasms, acquired immunodeficiency syndrome, patients receiving chemotherapy, corticosteroids, and immunosuppressants). In HIV-infected patients, the incidence of shingles is 25%, which is 8 times higher than the average incidence in people between 20 and 50 years of age. Among the patients of transplantation and oncology departments, up to 25–50% of patients with a mortality rate up to 3–5% develop herpes zoster [24, 136].

Skin manifestations and neurological disorders characterize the clinical presentation of herpes zoster. In typical cases, shingles begins as an infectious process – with symptoms of general intoxication, malaise, weakness, fatigue, fever, nausea, vomiting, lymphadenopathy, changes in the cerebrospinal fluid (lymphocytosis and monocytosis). Next, there are pronounced neuralgic pains in the affected dermatome, then the rashes appear. In adult patients, this period (preherpetic neuralgia) occurs 2 times more often (in 85% of cases) than in children and lasts up to 7 or more days; in rare cases, this period can last for 1–3 days [24].

Typical forms of herpes zoster include shingles involving nerve ganglia and skin lesions; shingles with mucous membranes; oticus and ocular (ophthalmic herpes) lesions; shingles with lesions damage to the autonomic ganglia; meningoencephalitis [91, 112].

By clinical guidelines, depending on the severity of the clinical manifestations of herpes zoster, there are:

- mild form: a temperature exceeds 37.5–38.5 °C within 2–3 days, intoxication is absent or moderate intoxication. The rash is localized; it disappears without a trace;
- moderate form: body temperature exceeds 38.6–39.5 °C for –5 days, moderate intoxication. The rash is abundant, including the rash on the mucous membranes, after its disappearance, temporary pigmentation may remain;
- severe form: temperature is above 39.6 °C for 7–10 days, development of meningoencephalitis is possible. The rash is profuse, enormous, “frozen” in one stage of development, both on the skin and the mucous membranes (including the upper respiratory tract and urinary tract). After the rash disappears, along with pigmentation, scars may remain.

In some patients, an atypical course of herpes zoster may be observed, manifested either by the absence of vesicles (abortive form) or by the appearance of vesicles in the form of bullae (bullous form) with hemorrhagic content (hemorrhagic form) or with the formation of a dark scab after the rapture (gangrenous, necrotic form), etc.

The complications of herpes zoster include acute and chronic encephalitis, myelitis, retinitis, rapidly progressive herpetic necrosis of the retina, leading to blindness in 75-80% of cases; Herpes zoster ophthalmicus with contralateral hemiparesis, lesions of the gastrointestinal tract and cardiovascular system, etc.

The most common complication of herpes zoster is postherpetic neuralgia. It is defined as pain syndrome that persists for more than 120 days after the onset of the rash (differs from acute herpetic neuralgia – pain lasts up to 30 days from the onset of the rash, and subacute herpetic neuralgia – pain lasts for 30–120 days after the onset of the rash) [39, 111].

Postherpetic neuralgia combines three subtypes of sensory disorders, depending on the nature of neuronal damage, which influences the choice of a therapeutic regimen [34, 39, 85]:

- nociceptive irritation, including such manifestations as mechanical allodynia, normal or increased temperature sensitivity;
- central reorganization with mechanical allodynia and temperature sensitivity disorder;
- deafferentation pain syndrome, without allodynia and loss of deep sensitivity.

It was found that almost 50% of patients have the 2nd subtype of pain, and the 1st and 3rd subtypes are equally distributed.

VZV diagnosis

Chickenpox is diagnosed by anamnesis, physical examination, additional examination methods. These methods are aimed at determining the severity of the condition and indications for treatment and identifying the factors that can affect treatment.

Recommended approaches to the laboratory diagnosis of chickenpox include:

- analysis of the fluid and/or discharge from vesicles, erosions, and ulcers on the skin and mucous membranes, impression smears, body fluids, and secretions (blood) by molecular biology methods;
- analysis of the fluid and/or discharge from vesicles, erosions, and ulcers on the skin and mucous membranes, body fluids and secretions (blood, cerebrospinal fluid) using sensitive cell cultures;
- analysis of the body fluids and secretions (blood, cerebrospinal fluid) to detect circulating specific antibodies (IgM, IgG) by enzyme-linked immunosorbent assay (ELISA).

Laboratory criteria confirming the diagnosis of chickenpox and shingles are:

- detection of VZV DNA by polymerase chain reaction (PCR) in different clinical specimens (vesicular fluid, nasopharyngeal washings, cerebrospinal fluid);
- isolation of VZV in cell culture from vesicular fluid, skin scrapings, saliva, cerebrospinal fluid;
- direct immunofluorescence (DIF) can be used to detect the virus quickly, but with less sensitivity than PCR;
- detection of VZV-specific serum IgM is significantly less sensitive than PCR and is not the method of choice for confirming chickenpox;
- positive Tsank test – detection of multinucleated giant cells in scrapings from the base of the vesicle, placed on a glass slide, fixed with 95% alcohol, and stained with Giemsa;
- serum IgG screening can be used to assess immunity or susceptibility to chickenpox in unvaccinated individuals.

The diagnosis of herpes zoster is based on typical complaints (manifestations of neurological symptoms), the course of the disease (prodromal period and skin manifestations), and the peculiarities of skin manifestations [24].

To verify the diagnosis, the detection of Varicella-zoster DNA in specimens from lesions on the skin and/or mucous membranes is recommended [24].

Treatment of VZV infection

By the clinical guidelines, the treatment of patients with chickenpox depends on the clinical signs (on the form, period, severity of the disease), symptoms manifestation, the presence of complications, concomitant diseases, patient age.

Treatment regimen [177]:

- etiotropic therapy;
- pathogenetic therapy;
- symptomatic therapy;
- immunotherapy and immunocorrection.

General recommendations for patients with chickenpox during pregnancy and lactation: bed rest, drinking plenty of fluids, care of the skin and mucous membranes during the period of rashes. Treatment is usually pathogenetic and symptomatic (antiseptics for skin and mucous membranes, antipyretic drugs – according to indications, etc.).

List of medicines may include:

- recombinant human interferon alpha-2b (rectally) – 1 suppository (500 000 IU) 2 times/day for 5 days, possibly from the 28th week of gestation (risk/benefit ratio);
- pyridoxal phosphate 0.02 g 3 times/day;
- cocarboxylase 100 mg IV in 40% glucose solution;
- riboflavin 1 tablet 3 times/day;
- Riboxin 0.2 g 3 times/day;
- lipoic acid 0.0025 g 3 times/day;
- folic acid 1 tablet 3 times/day;
- potassium orotate 1 tablet 3 times/day;
- calcium pantothenate 0.2 g 3 times/day;
- vitamin E orally 100 mg per day;
- troxevasin 1 capsule 2 times/day.

Treatment for patients with herpes zoster depends on the clinical signs (on the form, period, severity of the disease), symptoms manifestation, the presence of complications, concomitant diseases, patient age. The treatment regimen in HIV-positive patients also depends on the degree of immunosuppression (severe – <200 cells/μl, advanced – 200–350 cells/μl, mild – 350–500 cells/μl, no significant immunosuppression – > 500 cells/μl), use of antiretroviral agents (ART), sensitivity to acyclovir.

Antiviral therapy: the reduced sensitivity of VZV to acyclovir compared to HSV and a high level of antiviral activity determine the preferred treatment of herpes zoster – with famciclovir or valacyclovir. Prescription of antiviral drugs is most effective in the first 72 hours of clinical manifestations of the disease. Essential therapy includes the following medicines:

- acyclovir 800 mg orally 5 times/day for 7 days;
- famciclovir 500 mg orally 3 times/day for 7 days;
- valacyclovir 1000 mg orally 3 times/day for 7 days.

Treatment regimens for shingles in adults take into account the form and severity of clinical manifestations of the disease (Table 3).

Table 3. Treatment of shingles in adults

With a limited typical form (within the dermatome) without immunosuppression or with mild to advanced immunosuppression (drugs of choice)	
Acyclovir	800 mg orally 5 times/day for 7–10 days
Valacyclovir	1 g orally 3 times/day for 7–10 days
Famciclovir	500 mg orally 3 times/day for 7–10 days
With a limited typical form (within the dermatome) with severe immunosuppression (drugs of choice)	
Acyclovir	800 mg orally 5 times/day for 10 days
Valacyclovir	1 g orally 3 times/day for 10 days
Famciclovir	500 mg orally 3 times/day for 10 days
With disseminated form with lesions of the skin, eyes, internal organs (drugs of choice)	
Acyclovir	10 mg/kg IV 3 times/day (every 8 hours) for 7–10 days
Valacyclovir	1 g orally 3 times/day for 7–10 days
Famciclovir	500 mg orally 3 times/day for 10 days
Phosphonoformic acid (2nd line drug)	40 mg/kg, 60 mg/kg, or 90 mg/kg IV 3 times/day for 7–10 days

For the treatment of children, acyclovir is recommended: 20 mg/kg orally 4 times/day for 5 days. Antiviral drugs of other groups acceptable for shingles therapy:

- by the Russian "Federal clinical guidelines for the management of patients with herpes zoster" (2015), interferon-gamma 500,000 IU subcutaneously once a day every other day, for a course of 5 injections can be prescribed;
- by the "Draft clinical guidelines (treatment regimen) for the provision of medical care to adults with shingles" (2016), it is recommended:
  - inosine pranobex – prescribed for shingles, including recurrent shingles in patients with immunosuppression, ophthalmic herpes, meningoencephalitis; 2 tablets (500 mg) orally after meals 3–4 times a day for 10 days;
  - human interferon 10,000,000 IU intramuscularly daily for 5 days. Recommended also for ophthalmic herpes.
- It is allowed to prescribe non-steroidal anti-inflammatory drugs, and in severe cases, add glucocorticosteroids to antiviral drugs: prednisolone 60 mg per day orally in 2 doses for 7 days. If glucocorticosteroid drugs do not improve the condition, medications with a central analgesic activity and neural blockade (sympathetic and epidural) can be used after a neurology consultation.

  The anti-inflammatory and analgesic regimen includes three main stages:
  1st stage: acetylsalicylic acid, paracetamol, metamizole + triacetonamine 4-toluene sulfonate, ibuprofen, per os and by injection; ibuprofen 400 mg orally 3 times/day for 10 days; and/or
  2nd stage: opioid analgesics, including tramadol;
  3rd stage: drugs with central analgesic effect (tricyclic antidepressants, anticonvulsants).

- Topical treatment: to provide local anti-inflammatory action and prevent bacterial superinfection, 1–2% alcohol aniline dye solutions (methylene blue, brilliant green), fucorcin solution are prescribed.

In the presence of bullous eruptions, the blisters are opened (cut with sterile scissors) and treated with aniline dye or antiseptic solutions (0.5% solution of chlorhexidine bigluconate, etc.).

EPSTEIN-BARR VIRUS (EBV)

Epstein-Barr virus infection (herpesvirus type 4) is an acute or chronic human infection caused by the Epstein-Barr virus from the ***Herpesviridae family***, the ***Gammaherpesvirinae subfamily***, the ***Lymphocryptovirus genus***, the Human herpesvirus 4 species. The EBV genome is a double-helical DNA molecule. In infected cells, viral DNA is not integrated into the cellular genome; it is located in the nucleus extrachromosomally in the form of a closed ring (episome) [9].

Currently, there are two types of Epstein-Barr virus (EBV) – EBV-1 and EBV-2 (also known as type A and type B). These virus strains have differences in gene expression during latent infection and different abilities to transform Blymphocytes but do not differ in clinical symptoms and course of the disease. Both types are ubiquitous and can simultaneously infect a patient [17, 86].

According to the WHO and the International Agency for Research on Cancer, about 90% of the world's population is infected with EBV. The virus is ubiquitous; it persists for the lifetime of the host.

EBV is relatively stable in the environment, quickly dies upon drying, exposure to high temperatures, and the action of disinfectants [11].

Human is the only natural host for EBV. Route of transmission: airborne, sexual, contact. The priority route is airborne transmission: the virus spreads most commonly through saliva ("kissing" virus), and objects contaminated with saliva; can be found in cervical discharge [9].

Like other viruses of the Herpesviridae family, EBV is characterized by unproductive (latent) and productive (lytic) types of infection. In this case, a prerequisite for malignant transformation is the expression of genes encoding latent membrane (LMP1, LMP2A, LMP2B) and latent nuclear (EBNA-1, EBNA-2, EBNA-3A, EBNA-3C, EBNA-LP) viral proteins, as well as the expression of two viral RNAs (EBER-1 and EBER-2) that do not encode a protein. In infected individuals, EBV persists in long-lived memory B cells [117].

Like other herpes viruses, EBV can "escape" from the immune response of an infected host. The mechanisms of EBV-induced immunosuppression are due to the production of several cytokines that inhibit the production of interferon-γ, decrease the concentration of colony-stimulating factor (CSF), and inhibit the mobilization of stem cells from the depot.

Viral-expressed immunosuppressive proteins, including a protein that has 70% homology with anti-inflammatory interleukin-10 (IL-10), a protein similar in structure and function to the receptor antagonist of IL-1, and a protein (BI3) that suppresses the production of IL-12, play an essential role in the suppression of the cellular immunity.

Infected tonsillar epithelial cells intensively synthesize IL-1β, IL-6 and TNF-α. In the acute phase of the disease, the blood levels of cytokines IL-1β, IL-2, IL-6, IL-8, and IFN-γ increase, and the level of interferon-α decreases. The intensive production of proinflammatory cytokines in the acute period of the disease leads to the cellular immune response and the relapsing course of the illness with recovery [65, 141].

With an active form of EBV infection, the level of circulating immune complexes (CICs) increases, and the phagocytic activity of leukocytes decreases. Immune complexes circulating in the blood can cause adverse immunopathological reactions. The immediate and long-term prognosis for a patient with acute infection depends on the presence and severity of immune dysfunction. The chronic disease and its relapses are caused by an imbalance between the populations of clones of CD4+ T-helper lymphocytes of the 1st (Th1) and 2nd (Th2) types against the background of changes in the production of various cytokines [69, 89, 141].

During the viral replication, its antigens can be detected. They are classified into early antigenic complex (EA), viral capsid antigens (VCA), nuclear antigen (EBNA), and membrane antigens (LMP). Features of humoral immunity in EBV infection are due to the formation of neutralizing IgM antibodies to VCA, later - IgG to early antigens (EA) in primary infection. On the other hand, IgG antibodies to nuclear antigens (EBNA) persist for life, do not have a virusneutralizing effect, and are serological markers of latent EBV infection [107, 113, 173].

At the same time, in patients infected with EBV, antibody class switching from IgM to IgA, IgG or IgE occurs. Therefore, in some cases, excessive production of IgG and IgA is possible, which leads to the development of autoimmune diseases or excessive synthesis of IgE, which predisposes to atopy [141].

Among pregnant women, antibody titers to EBV decrease towards the end of pregnancy (compared to the beginning of pregnancy), which may be associated with changes in the function of cellular and humoral immunity during pregnancy and/or antibody transmission to the fetus at the end of pregnancy. In addition, African American women showed higher titers of IgG VCA antibodies compared to white women.

Primary infection occurs in early childhood without pronounced clinical manifestations. EBV invades the oropharyngeal epithelial cells and infects B-lymphocytes of the pharyngeal lymphoid ring after initial replication, entering the bloodstream. At the entry site, a "primary focus" is formed – catarrh, difficulty breathing occurs. Further, the virus is introduced into various tissues and organs with predominant damage to the liver, spleen, lymph nodes, etc. During this period, atypical mononuclear cells appear in the blood against the background of a moderate lymphocytosis [41, 50, 56].

A productive replicative (lytic) pathological process is characteristic of acute infectious mononucleosis (IM). There is a replication of viral DNA and the production of viral glycoproteins. While the virus particles mature and are released from the cell, the cell dies. Clinically, this is manifested by the recurrence of infectious mononucleosis [21].

The age-related changes in immune function determine the inadequate protection against EBV infection in children in the first years of life due to the immature mechanisms of innate and adaptive immunity and adolescents due to the influence of hormonal changes on the immune system. This contributes to the more development of chronic infectious mononucleosis in them.

Infectious mononucleosis during pregnancy is manifested by intermittent fever, malaise, headache, sore throat, enlargement and soreness of the cervical and axillary lymph nodes. In 75% of cases, splenomegaly is observed, in 17% – hepatomegaly. Jaundice develops in 11% of patients. Primary EBV infection during pregnancy is rare, but acute mononucleosis in pregnant women can present with symptoms similar to preeclampsia. EBV, like other herpesviruses, can penetrate transplacentally; in some cases, stillbirths, spontaneous abortions, fetal pathologies (chorioretinitis, microphthalmos, damage to the heart, and nervous system) have been described [124, 132, 147, 165].

The classification of infectious mononucleosis considers the features of the course and clinical manifestations of the disease (Table 4).

Table 4. The classification of infectious mononucleosis (Clinical guidelines «Infectious mononucleosis in adults» (National Scientific Society of contagious diseases, 2014))

Type	Course of the disease
• typical; • atypical: а) asymptomatic; б) inapparent; в) visceral.	• smooth; • uneven: a) with complications; b) with a secondary infection; c) with exacerbation of chronic diseases; d) with relapses.
Severity	**Duration of the disease**
• mild disease; • moderate disease; • severe disease.	• acute (up to 3 months); • protracted (3–6 months); • chronic (more than 6 months).

By the clinical guidelines “Infectious mononucleosis in adults” (NNOI, 2014), a typical course of acute infectious mononucleosis is characterized by a benign cyclical course and the presence of clinical signs characteristic of this disease, as well as hematological changes in the peripheral blood (lymphomonocytosis with leukocytosis and atypical mononuclears ≥10%).

Atypical forms of infectious mononucleosis include:

- inapparent form: proceeds with mild and quickly passing symptoms or simulates acute respiratory diseases. It is diagnosed mainly in epidemic focus;
- asymptomatic form: proceeds without any clinical symptoms, is diagnosed based on hematological, serological, and epidemiological methods;
- visceral form: characterized by a severe course with multiple organ lesions involving the cardiovascular, central, and peripheral nervous system, kidneys, adrenal glands, and other organs.

The atypical course of mononucleosis in children is accompanied by the development of acute dacryocystitis, viral myocarditis, atherosclerosis, hematological complications (aplastic anemia, thrombocytopenia, secondary hemophagocytic syndrome, and agranulocytosis), hematuria or proteinuria, cholestatic hepatitis or acalculous cholecystitis, neurological disorders (Alice in Wonderland syndrome (AIWS), Guillain-Barré syndrome, encephalitis), and autoimmune disorders [73].

In an unproductive pathological process, the virus invades a host cell and inserts its genes into that cell’s DNA, which allows it to escape the immune control and creates optimal conditions for the chronic course of EBV infection. Protecting infected B-lymphocytes from apoptosis, EBV simultaneously enhances apoptosis of T-lymphocytes and neutrophils, creating conditions for progressive lymphoproliferation of B-cells and, in severe cases, malignancy of lymphoid tissue due to suppression of T-cell immunological control. Furthermore, the immortalized B-lymphocyte with integrated EBV DNA replicates uncontrollably and becomes a strong focus of the virus latency [21].

According to the WHO and the International Agency for Research on Cancer, three forms of latent EBV infection are determined by the expression of viral proteins. In type 1, only EBNA1 is expressed (characteristic of Burkitt’s lymphoma). With type 2 latency, EBNA1 and three latent membrane proteins (LMP1, LMP2a, and LMP2D) are described (part of nasopharyngeal carcinoma and Hodgkin’s disease). Finally, with type 3 latency, six latent antigens and three membrane proteins are expressed (an aspect of EBV-associated lymphoproliferative disorders). Almost all EBV genes are described in the productive infection, which blocks tumor suppressors p53 and pRb [10].

It is now known that EBV can cause a wide range of B-cell lymphoproliferative diseases such as Burkitt lymphoma, Hodgkin’s lymphoma, and EBV-associated lymphomas in immunocompromised patients. By the classification, posttransplant lymphoproliferative disorders (PTLD) are divided into early (EBV-associated polyclonal lymphoid proliferation) and accurate (monoclonal) diseases, including polymorphic and monomorphic PTLD, which can subsequently differentiate into Burkitt lymphoma, Burkitt-like lymphoma, diffuse large B-cell lymphoma, and Hodgkin’s lymphoma. Although at the same time, PTLD diagnosed at the early stages after hematopoietic stem cell transplantation is usually EBV-associated, late PTLS is often not associated with EBV infection [10, 118, 138, 170, 176].

Laboratory diagnosis of EBV infection

By the “Clinical guidelines for the provision of medical care to children with infectious mononucleosis” (2013) and the clinical guidelines “Infectious mononucleosis in adults” (2014), the recommended laboratory diagnostic methods are the following (Table 5).

Table 5. Recommended methods for laboratory diagnosis of EBV infection

Method	Indications
Hematological	Patients with clinical symptoms of infectious mononucleosis to confirm the diagnosis and determine the severity.
Biochemical	Patients with clinical symptoms of infectious mononucleosis to determine the severity.
Paul Bunnell test, Hoff-Bauer rapid test	Patients with clinical symptoms of infectious mononucleosis to confirm the diagnosis.
Molecular genetic (PCR)	Patients with clinical symptoms of infectious mononucleosis for diagnosis
Immunohistochemistry	Patients with clinical symptoms of infectious mononucleosis for diagnosis
Serological (IFA)	Patients with clinical symptoms of infectious mononucleosis

The results of serological tests are interpreted in the context of the stage of development of the infectious process (Table 6).

Acute period:

- IgM VCA from the onset of clinical symptoms and the next 4–6 weeks are present and decreasing;
- IgG EA from the first week of disease increase to several years after it and persist at a low level;
- IgG VCA are detected several weeks after the appearance of IgM VCA, increase, and persist for life at a low level;
- IgG-EBNA-1, -2 are absent or present in small quantities.

Reconvalescence:

- IgM VCA absent or in small quantities;
- IgG EA persist for life at a low level; IgG VCA persist for life;
- IgG EBNA is detectable several weeks after the onset of clinical symptoms and persists for life at a low level.

Table 6. Interpretation of serological test results

IgM VCA	IgG VCA	IgM VCA	IgG EBNA-1	Interpretation
+/–	+	+	–	Acute infection
–	+	–	+	EBV infection, signs of previous acute infection
+/–	+	–	–	More tests are needed. (IgG VCA avidity test, immunoblotting or PCR)
–	+	+	+	
–	–	+	–	
–	–	–	+	

The avidity index (AI) of IgG to VCAn is an additional marker that makes it possible to distinguish between the primary infection and reinfection or reactivation and establish the approximate timing of EBV infection [33, 48].

If the serological indicators do not allow assessing the stage of the infectious process, there is a need for additional tests. In this case, PCR helps to detect the DNA of the pathogen in the blood or other biological material (saliva, oropharyngeal swabs, a biopsy of the liver, lymph nodes, intestinal mucosa, etc.).

Qualitative PCR allows confirming the diagnosis of EBV infection, collecting epidemiological data on its prevalence among the population. Furthermore, to assess the dynamics of EBV-associated diseases, it is advisable to use quantitative PCR [33].

By the Russian clinical guidelines "Infectious mononucleosis in adults" (2014), a load of more than $10^{2.5}$ copies of the EBV genome/μg DNA when using the real-time PCR is clinically significant. Although there is an approximately constant number of infected B-lymphocytes with latent EBV infection - 1–50 infected cells per 1 000 000 Blymphocytes in the blood of clinically healthy individuals, the viral load is less than 100 copies of DNA per 10^5 cells.

The detection of 10–100 copies of EBV DNA in the sample (1000 GE/ml in 1 ml of the sample) by quantitative PCR characterizes the "healthy carriage," and the detection of 100 or more copies (10 000 GE/ml in 1 ml of the sample) allows to diagnose the active phase of the EBV infection. PCR is especially effective for detecting EBV in newborns when the serological indicators are not informative due to the immature immune system and in complex and doubtful cases of EBV infection in adults [12, 13].

By the recommendations of the 6th European Conference on Infections in Leukemia (ECIL-6) «Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation (2016)», when diagnosing EBV-PTLD, it is advisable to detect EBV DNA in whole blood, plasma, serum, and biopsy material. Thus, viral load determination is essential in assessing the risks of post-transplant complications. At the same time, there is no unambiguous opinion regarding the clinically significant threshold value of viral load: some authors use the threshold of 1000 copies/ml, 10 000 copies/ml, or 40 000 copies/ml when detecting EBV DNA in whole blood, plasma, or blood serum; other authors consider 1000 copies per 10^5 mononuclear cells to be critical. In this regard, it is recommended to use one's own experience in combining laboratory parameters with the clinical picture when determining the clinically significant viral load for therapy administration.

Quantitative analysis of EBV DNA is used to identify residual (clinically occult) tumors after radiation therapy and to predict the effectiveness of treatment [106, 179].

Several researchers note that the risk of recurrence increases with an increase in the number of copies of viral DNA during dynamic observations from the time of diagnosis. Analysis of the EBV DNA levels in the plasma of patients with lymphoid tumors is also informative: the high level of EBV DNA found in the plasma of patients before treatment indicates the need for more intensive therapy (based on prospective studies EBV-associated extranodal NK/T-cell lymphomas). When studying a small series of EBV-associated lymphomas, EBV DNA levels correlated with the clinical course: in patients in remission, EBV DNA in plasma was not detected, and in patients with a resistant system of the tumor remained at a detectable level [63, 116, 125, 179, 180].

Treatment of EBV infection

According to the "Clinical guidelines for the provision of medical care to children with infectious mononucleosis" (2013) and the clinical guidelines "Infectious mononucleosis in adults" (2014), the treatment of patients with infectious mononucleosis is determined by the following factors:

- period of the disease;
- severity of the disease;
- patient's age;
- complications;
- the availability and possibility of performing the treatment by the required type of medical care.

Treatment of infectious mononucleosis includes:

- regimen;
- diet;
- medications (Table 7):
  – etiotropic therapy;
  – symptomatic therapy;
  – immunotherapy and immunocorrection;
- non-drug treatment.

Table 7. Basic requirements for drug care for mononucleosis in an outpatient care setting

Name of the medicinal product	The average frequency of pharmaceutical care provision		Average daily dose (ADD)*	Average course dose (ACD)
	adults	children		
Ibuprofen	0.3	0.3	600 mg	1800 mg
Interferon alpha	0.5	0.5	1 000 000 IU	5 000 000 IU
Recombinant human interferon alpha-2	0.5	–	9000 IU	9000 IU
Meglumine Acridone Acetate	0.5	1	300 mg	3000 mg
Tiloron	0.5	1	125 mg	1250 mg
Antibodies to human interferon-gamma affinity purified	0.5	1	5 tablets	50 tablets
Paracetamol	0.5	0.5	1000 mg	3000 mg
Xylometazoline (drops)	0.9	0.9	12	72

* Average drug doses are calculated per kg when the weight of the child is ≥40 kg. In cases where the drug is prescribed to children at the age when their weight is less than 40 kg, the calculation should be made for 20 kg.

General recommendations for the treatment of patients with infectious mononucleosis during pregnancy and lactation include:

- recombinant human interferon alpha-2b – 1 suppository 2 times/day rectally for 5 days from 28 to 34 weeks of gestation;
- pyridoxal phosphate 0.02 g 3 times/day;
- cocarboxylase 100 mg IV on 40% glucose solution 20.0 ml;
- riboflavin 1 tab. 3 times/day;
- riboxin 0.2 g 3 times/day;
- lipoic acid 0.0025 g 3 times/day;
- folic acid 1 tab. 3 times/day;
- potassium orotate 1 tab. 3 times/day;
- calcium pantothenate 0.2 g 3 times/day;
- vitamin E orally 100 mg per day;
- troxevasin 1 capsule 2 times/day.

With a mild course of EBV mononucleosis, treatment of patients is limited to supportive therapy, including adequate hydration, rinsing the oropharynx with an antiseptic solution (with the addition of 2% solution of lidocaine (xylocaine) for severe pharyngeal pain), non-steroidal anti-inflammatory drugs such as paracetamol. In addition, antibacterial medications are prescribed according to strict indications [48, 104].

Until now, the practical use of glucocorticosteroids in patients with EBV infection has been preserved. Glucocorticosteroids (prednisone, prednisolone, hydrocortisone, and dexamethasone) are recommended for patients with severe EBV mononucleosis, with airway obstruction, neurological and hematological complications (severe thrombocytopenia, hemolytic anemia) [104, 152].

The most controversial issue is the prescription of acyclic nucleosides – acyclovir, valacyclovir, and others – for patients with EBV mononucleosis. It should be remembered that these drugs are effective only in the acute period of the disease or during the reactivation of the infection when there is an active replication of viral particles. In these cases, the synthesis of viral enzymes that activate medicines occurs, which, in turn, suppresses the synthesis of viral DNA. With the latent course of infection, this does not happen, and the use of these drugs is ineffective [58, 59, 143].

CYTOMEGALOVIRUS (CMV)

Cytomegalovirus (CMV) infection is an infection caused by Cytomegalovirus. It is characterized by multiple organ involvement and, accordingly, polymorphic clinical symptoms, and specific morphological changes with cytomegalic cells and lymphohistiocytic infiltrates [29].

The causative agent of CMV infection is ***Cytomegalovirus hominis*** of the ***Herpesviridae family***, the ***Betaherpesvirinae subfamily***, the ***Cytomegalovirus genus***. The virus has a large DNA genome (nucleocapsid diameter – 100–120 nm), slow replication, relatively low virulence against the background of significant suppression of cellular immunity. It replicates without cell damage and exhibits low cytopathogenicity in tissue culture [25].

The virus is thermolabile, inactivated at 56 °C, persists for a long time at room temperature; its optimum pH is 7.2–8.0. CMV quickly loses its virulence when frozen to –20 °C. It has a relative insensitivity to the interferon; the virus is resistant to the action of antibiotics. It is much less sensitive than HSV to antiherpetic drugs - acyclovir and its analogs [25].

Cytomegalovirus replicates in macrophages and dendritic cells. In addition, it was shown that in latently infected healthy people without viremia, genes of the viral lytic cycle are expressed in alveolar macrophages, and virions are created. This confirms the viral replication even in the latent and asymptomatic course of CMV infection.

New viral particles infect the surrounding tissue-resident macrophages, epithelial cells, and myeloid progenitor cells of the bone marrow, in which the virus enters a latent phase. Virus reactivation in myeloid progenitor cells and monocytes occurs during their differentiation into macrophages and dendritic cells.

CMV has a different life cycle from other herpesviruses and the unique ability to modulate the immune system response to infection, affecting the distribution of natural killer cells and T cell subpopulations and modulating macrophage functions.

In infected monocytes, due to the interaction of the virus with surface receptors (epidermal growth factor receptor and integrins), migration into organs and tissues is enhanced, followed by differentiation into macrophages.

This contributes to the constant replication of the virus after the initial infection (in children, the process is observed up to 23 weeks from the moment of disease).

Usually, during differentiation into macrophages, monocytes lose CD14 antigen and toll-like receptors 4 and 5. However, during the differentiation of infected monocytes, the expression of CD14, TLR4, and TLR5 continues, which increases the proinflammatory properties of such macrophages. In addition, the activation of the transcription factors IκBα and NF-κB in macrophages infected with the virus is enhanced, increasing the production of inflammatory cytokines and chemokines. Therefore, it is assumed that the enhancement of the proinflammatory properties of macrophages under the action of CMV contributes to the pathological development of inflammation in tissues, especially when they are infected with bacteria, and an increase in chronic inflammatory processes with age [101, 130].

The inflammatory response is an essential factor for the reactivation of latent CMV. For example, proinflammatory cytokines are produced when the T-cell immunity is activated during an allogeneic response or an inflammatory response, primarily IFNγ and TNFα. Both cytokines play a vital role in the induction of monocyte differentiation into macrophages, which is necessary for the progression of infection. However, CMV is resistant to the antiviral effects of these cytokines. Moreover, a homologue of cellular IL-10 was found in the CMV genome (IL-10 belongs to immunosuppressive lymphokines). It suppresses the cell response to IFNα and IFNγ, which plays a vital role in the control of expression of IFN genes and antigens of the major histocompatibility complex (HLA) and inhibits the proliferation of lymphocytes and monocytes and their production of proinflammatory cytokines (TNFα, IL-1, IL-6) [46].

CMV has a significant effect on the functioning of natural killer cells (NK), which form the first line of defense against viral expansion until a specific immune response is initiated. The virus suppresses the recognition of infected cells by natural killer cells, blocking the surface expression of antigen-presenting MHC class I molecules, which leads to impaired processing of viral antigens and their presentation to CD8+ cells. In addition, CMV also affects CD4+ lymphocytes, suppressing their activity by degrading MHC class II proteins [3].

Latent CMV infection significantly affects T-cell immunity: an accumulation of differentiated memory T-cells specific to Cytomegalovirus and exhaustion of undifferentiated T-cells. Moreover, with the patients' age, these signs increase. This phenomenon is called memory inflation [121].

It is assumed that memory inflation occurs due to the constant reactivation of Cytomegalovirus during the differentiation of hematopoietic cells into macrophages. Reactivation proceeds without clinical symptoms, but constant antigenic stimulation leads to the expansion of memory T cells. In addition, the cells are characterized by a high production of proinflammatory cytokines: IL-6 and TNFa [119, 174].

The presence of a large genome allows the virus to change the structure of its antigenic determinants, which makes it "invisible" for the humoral immune response. Moreover, in infected cells, the expression of FcR molecules (Ig Fc receptor) significantly increases, which leads to the elimination of virus-specific antibodies [6].

A specific interaction between CMV and the immune system of its host contributes to the almost constant production of viral particles and the maintenance of a chronic inflammatory reaction.

CMV infection is ubiquitous and non-seasonal. Once in the human body, the virus persists for life. The presence of specific antibodies in the blood (seropositivity) in most cases means the presence of CMV in the body. However, the seropositivity rate varies widely in different populations: in developed countries, CMV seropositivity rates in women of childbearing age range from 50 to 85%, while in developing countries, seropositivity rates reach 100% [70, 80, 129].

Sources of infection: virus carrier, a patient with an acute form (in the case of primary infection) or during an exacerbation of the disease. Routes of transmission: airborne, sexual, contact, oral, parenteral, enteral, and vertical. The virus can be transmitted through all body fluids and secretions (saliva, blood, urine, etc.). CMV is not highly contagious; its transmission requires close or intimate contact between people with infected secretions. According to American and Russian studies, CMV was isolated from the cervix of 3.5–20.0% of practically healthy women and the sperm of 30% of healthy men [47, 183, 184].

Blood transfusions and parenteral manipulations can lead to CMV infection. For example, transfusion of whole blood and its components containing leukocytes leads to the transmission of the virus at a frequency of 0.14–10 per 100 doses. Thus, with each blood transfusion, the risk of CMV infection increases by 5–12% [25, 159].

Mucous membranes of the respiratory and genital tract, respiratory system, gastrointestinal tract are the entrance door of the infection. The virus replicates there and enters the systemic circulation (viremia phase). Monocytes and lymphocytes carry the virus to various organs, where it mainly affects epithelial cells. CMV exhibits a particular tropism for the salivary glands, where it slowly multiplies without cell damage; therefore, it is trans-

mitted by kissing ("kissing disease"). CMV can also infect nerve cells, smooth muscle cells, and bone marrow stromal cells.

Despite the cellular and humoral response, CMV induces chronic latent infection. Monocytes, lymphocytes, endothelial and epithelial cells serve as a reservoir of viral particles. In addition, physiological immune deficiency in young children, immunodeficiency caused by pregnancy, anthropogenic impact on the environment, iatrogenic interventions, and HIV infection cause the reactivation of CMV infection and its clinical manifestations [1, 25].

Latent CMV infection persists for life in the absence of clinical manifestations. However, under the influence of factors affecting resistance to disease (oncology, radiation sickness, severe burn injuries, organ transplantation, use of cytostatic, immunosuppressive, corticosteroid drugs, HIV infection, and other immunodeficiency states), the infection becomes active and manifest (clinically expressed) [68, 77, 93, 126, 157].

Acquired infection in adults and children is not accompanied by damage to the central nervous system (characteristic of the congenital form). Instead, it often proceeds as infectious mononucleosis, accompanied by fever, catarrhal symptoms, enlargement of the cervical and submandibular lymph nodes, edema, and soreness of the parotid salivary glands. In addition, the course of the disease with isolated damage to internal organs is possible [25].

CMV infection is classified depending on the timing and mechanisms of infection (congenital and acquired infection, prenatal, intranatal, and postnatal CMV infection), the virus activity (latent, persistent, and reactivated infection), primary or reinfection (acute infection, virus reactivation, and reinfection) [25]:

I. Congenital CMV infection:

a) asymptomatic form;

b) CMV disease (manifest CMV infection).

II. Acquired CMV infection:

• Acute CMV infection:

a) asymptomatic form;

b) mononucleosis-like syndrome;

c) CMV disease (manifest CMV infection).

• Latent CMV infection.

• Active CMV infection (reinfection or virus reactivation):

a) asymptomatic form;

b) CMV-associated syndrome.

• CMV disease (manifest CMV infection).

Primary CMV infection in immunocompetent individuals is usually asymptomatic or with the mild mononucleosislike syndrome. It is characterized by high fever lasting more than two weeks, general malaise, severe fatigue, lymphadenopathy, headache, myalgia, arthralgia, hepatosplenomegaly, and increased aminotransferases and alkaline phosphatase. Acute tonsillitis and enlargement of the posterior and occipital lymph nodes are rare. Development of hepatitis and pneumonia is possible. Specific changes in the salivary glands (sialoadenitis) are not typical for adults. Relative lymphocytosis is revealed, and more than 10% of lymphocytes are atypical. Most patients recover completely, although asthenic syndrome persists for a long time. The acquired CMV infection incubation period ranges from 15 to 90 days, the active stage of the primary disease – from 2 to 8 months [25, 74].

Giant cells in tissues, saliva, sputum, urine sediment, and cerebrospinal fluid are characteristic pathomorphological signs of CMV infection. Cells have intranuclear and cytoplasmic inclusions with an "owl's-eye" appearance and contain a multiplying virus. Giant cells are localized mainly in the epithelium of the excretory ducts of the salivary glands, distal nephron in the kidneys, bile ducts in the liver, and the ependyma of the cerebral ventricles [25, 74].

In response to CMV, lymphohistiocytic infiltrates appear in the surrounding interstitial tissue, sometimes in the form of nodules. In the generalized form, damage to the lungs, kidneys, and intestines is more often observed, less often – liver and other organs. Along with giant cells and lymphohistiocytic infiltrate, a picture of interstitial pneumonia is found in the lungs, interstitial nephritis in the kidneys, ulcerative enterocolitis in the intestine, and cholestatic hepatitis in the liver [25, 74].

By the clinical guidelines "Cytomegalovirus infection in adults after solid organ transplantation" (2014), there are three main epidemiological variants of CMV infection in patients with organ transplants:

- primary infection in CMV-seronegative patients who received a transplant from seropositive donors – D+R– (frequency of CMV disease is up to 60%);
- reactivation of a latent endogenous virus, when the donor is CMV-seronegative, and the recipient is seropositive – D–R+ (the frequency of CMV disease is 10–15%);
- superinfection, when both the donor and the recipient are seropositive and active CMV has a donor origin – D+R+ (25–30% of patients develop CMV disease).

The highest risk of developing CMV infection and CMV disease is in the first 6 months after transplantation. However, episodes of late CMV infection are possible – 6–12 months and even several years after surgery, especially after the end of anti-CMV prophylaxis, against the background of other severe infectious complications and treatment of transplant rejection.

CMV causes not only severe organ damage (direct effect of the virus) in immunocompromised patients but also has several "indirect" effects – general (increased risk of bacterial, fungal, and viral infections; post-transplant lymphoproliferative diseases; cardiovascular complications; post-transplant diabetes mellitus, etc.) and graftspecific (acute graft rejection; chronic allograft nephropathy and/or loss of renal graft; recurrence of hepatitis C after liver transplantation; hepatic artery thrombosis after liver transplantation; graft vasculopathy after liver transplantation; obliterative bronchiolitis after lung transplantation) [128].

The indirect effects of CMV can be realized with a long-term low viral load, which is usually not accompanied by direct effects.

The clinical picture in pregnant women does not differ from the clinical picture in non-pregnant women. In most cases (>90%), clinical manifestations are absent. However, some patients may develop symptoms of infectious mononucleosis. The probability of transmission of CMV to the fetus during primary infection is 30–35%, while with latent infection, the incidence of transmission is significantly reduced, amounting to 1.1–1.7% [27, 38, 149].

By the "Clinical recommendations for the diagnosis, treatment, and prevention of congenital cytomegalovirus infection of the Russian Association of Perinatal Medicine Specialists (RAPMS)," the most significant risk to the fetus is the primary infection of the mother in early pregnancy. On average, 2% (0.7–4%) of women have the primary infection during pregnancy, while approximately 40% (24–75%) of cases transmit the infection to the fetus. With the development of acute CMV infection, the risk of mother-to-child transmission depends on gestational age. It is about 30% in the first trimester, 40% in the second trimester, and 70% in the third trimester [72, 108, 109, 178].

Reinfection or reactivation of CMV in the mother causes infection of the fetus less frequently (0.2–2.2% of cases). At the same time, secondary infection (primarily reinfection) also plays a significant role in the condition of the child, and a substantial proportion of infants with congenital CMV infection are born by mothers who have IgG antibodies to CMV by the time of pregnancy (Table 8) [27].

Table 8. Risk of fetal infection in different variants of the course of CMV infection during pregnancy ("Clinical guidelines for the diagnosis, treatment, and prevention of congenital cytomegalovirus infection", RAPMS)

The course of CMV infection	The presence of viremia	CMV antigens	Anti-CMV antibodies	Risk of fetal infection
Latent	No	Not detected	IgG	Extremely low
Persistent	No	Detected	IgG	Less than 2%
Reactivated	Yes	Detected	IgG increase, IgM may appear	Less than 8 %
Primary	Yes	Detected	IgM, gradual increase in lowavidity IgG in «paired serum»	30–50 %

Congenital cytomegalovirus infection is an infectious disease that develops because of antenatal transplacental infection of the fetus with a virus. Initially, the placental tissue is infected, and then the fetus is infected; subsequently, the fetus also becomes infected by swallowing the infected amniotic fluid [22].

Congenital cytomegalovirus infection, unlike acquired, often leads to serious long-term consequences, such as sensorineural hearing loss in combination with balance disorders (most often), intellectual disability, behavioral disorders, cerebral palsy, epilepsy, visual impairment, microcephaly. The most common clinical signs are hepatosplenomegaly (60%); microcephaly (53%); jaundice (67%); petechiae (76%); at least one neurological abnormality (68%) [15, 22, 103].

Almost 50% of newborns with clinical symptoms and 10% of asymptomatic newborns develop hearing loss, which determines the leading role of congenital CMV infection in non-genetic hearing loss in children. Therefore, it is vital that all infants with congenital CMV infection, regardless of clinical manifestations at birth, undergo regular screening during the first years of life for early detection of signs of CMV infection [97, 135].

Congenital CMV infection must be distinguished from the acquired form in newborns and infants, which occurs because of intrapartum or postnatal infection of the child and manifests itself after the 3rd week of life. Intrapartum CMV infection develops because of infection of a child with an infected cervicovaginal mucus during natural childbirth. After birth, CMV infection most often occurs through breast milk, but it is also possible because of blood transfusion and contact with infected body fluids [74].

In most cases, infection of older children and adults leads to the formation of asymptomatic virus carriers or subclinical, an inapparent form of chronic CMV infection. Generalized forms of acquired CMV infection are rare; they usually occur against a background of diseases associated with immunosuppression and are characterized by a severe course [25, 29].

Laboratory diagnosis of CMV infection

By the clinical guidelines “Cytomegalovirus infection in adults (excluding HIV patients)” (2014):

- laboratory tests for a pregnant woman with suspicion of acute CMV infection or active CMV infection due to reactivation (reinfection) of the virus are carried out to establish the fact of disease, to identify the risk of disease of the fetus, or to establish the presence of its infection;
- laboratory tests for an adult patient with suspected active CMV infection or CMV disease are not to establish the presence of the virus in the body, but to prove the presence of active CMV replication and its etiological role in the existing organ pathology;
- laboratory tests for patients with suspected manifest CMV infection include tests aimed at confirming the etiological cause of the disease, establishing the clinical form of CMV, and determining the virus activity.

Laboratory methods are mandatory for diagnosing CMV infection and are recommended if necessary (Table 9).

Table 9. CMV infection laboratory testing

Laboratory tests for CMV infection and differential diagnosis	The need for research
Serological markers of CMV infection – detection of IgG and IgM antibodies in blood serum, as well as determination of the IgG avidity index (IFA, immunoblotting, IHC)	mandatory
Detection of CMV antigens in biological material (immunofluorescence reaction, immunocytochemistry, NASBA)	if necessary
Molecular biological markers of CMV infection – detection of CMV DNA in blood, bronchoalveolar lavage, CSF, pleural fluid, urine, saliva, amniotic fluid, umbilical cord blood; determination of the CMV DNA concentration in blood, CSF, amniotic fluid	mandatory
Detection of cytomegalovirus-infected cells in biopsy and autopsy specimens (histological method)	if necessary
Laboratory markers of other infections (markers of viral hepatitis, testing for herpetic and opportunistic infections (pneumocystosis, toxoplasmosis, fungal infections, etc.), testing for HIV infection)	if necessary
Clinical laboratory tests	
General blood test	
Clinical urine test	

According to the "Draft Clinical Guideline for the Diagnosis, Treatment, and Prevention of Congenital Cytomegalovirus Infection" (CMPV), the diagnosis of congenital CMV infection includes tests to identify markers of disease in the antenatal period and children of the first year of life.

Antenatal diagnosis of congenital CMV infection is based on the detection of primary CMV infection in a pregnant woman, latent reactivation, or the fact of superinfection with a new CMV strain.

Routine tests during pregnancy include the detection of specific IgM and IgG antibodies, the IgG avidity in the blood serum by IFA or CLIA methods, performed primarily when the pregnancy is confirmed.

Primary CMV infection in a pregnant woman is diagnosed based on the detection of seroconversion (the appearance and increase of specific IgG) by IFA or CLIA methods during the dynamic testing or the detection of specific IgM in 2 samples (in a pregnant woman IgM persists for up to 5 weeks) and/or in combination with low-avidity (less than 30%) IgG [74].

Reactivation of latent CMV infection or superinfection with a new CMV strain is diagnosed if a 4-fold increase in the value of specific IgG with the avidity of more than 60% is detected, regardless of the presence/absence of specific IgM by IFA/CLIA methods in dynamic testing with an interval of 4–6 weeks, performed in the same laboratory.

In the presence of laboratory, clinical and instrumental signs of primary (exacerbation of latent infection or superinfection) CMV infection, it is recommended to analyze the amniotic fluid obtained during amniocentesis (performed no earlier than 7 weeks from the expected time of the onset of the disease/exacerbation/ superinfection and not earlier than 21 weeks of gestation) by PCR or by virological method (CMV cultivation).

When diagnosing CMV infection at the outpatient stage, it is recommended to study blood and urine by PCR, perform serological tests to detect antibodies to Cytomegalovirus (IgG, IgM), and determine the IgG avidity index.

Indications for laboratory diagnosis of CMV infection in the antenatal period are ("Clinical guidelines (draft) for the diagnosis, treatment, and prevention of congenital cytomegalovirus infection", RAPMS):

- the age of the pregnant woman is under 20 years old;
- pregnant women who have undergone (especially in the first half of pregnancy) an acute respiratory infection with minor catarrhal manifestations, in combination with lymphadenopathy and hepatosplenomegaly syndrome;
- pregnant women with atypical mononuclear cells in the blood;
- pregnant women are working with children (kindergarten, school) and pregnant women whose children attend kindergarten or school.

Indications for testing, determined by the results of instrumental studies (ultrasound signs of fetal CMV infection), include:

- intrauterine growth retardation;
- cerebral ventriculomegaly;
- microcephaly;
- intracranial calcifications;
- ascites, hydrothorax;
- "non-immune dropsy" of the fetus;
- low amniotic fluid or polyhydramnios;
- hyperechogenic fetal bowel;
- calcifications in the liver;
- thickening and calcifications in the placenta.

The indications for laboratory and instrumental testing to exclude or verify congenital CMV infection in children of the first year of life are ("Clinical guidelines (draft) for the diagnosis, treatment, and prevention of congenital cytomegalovirus infection", RAPMS):

- the presence of clinical signs of congenital infection in a newborn, regardless of the possible etiology;
- confirmed primary CMV infection, reactivation of the latent infection, superinfection with a new CMV strain in the mother during pregnancy, regardless of the presence/absence of clinical manifestations in the child;
- signs of damage to the placenta during a pathomorphological examination, as well as the detection of CMV antigens in the placenta by the IHC or ICC method, the study of the genetic material of the pathogen by PCR (if such studies were carried out);
- signs of intrauterine infection detected antenatally.

The risk of CMV infection and the development of clinically pronounced congenital CMV infection is associated with the concentration of CMV DNA in the amniotic fluid. When CMV DNA is $<10^3$ copies/ml, the child will remain uninfected in 83% of cases. If the amount of CMV DNA is 10^3 copies/ml or more, the child is infected in 100% of cases. The level of CMV DNA $<10^5$ copies/ml indicates the absence of manifestation of infection in the fetus and newborn with a probability of 92%. The concentration of CMV DNA in the amniotic fluid of 10^5 copies/ml or more means the development of a clinically expressed CMV disease in a child. Cordocentesis and examination of umbilical cord blood for the presence of CMV DNA and specific IgM antibodies are performed from the 20th week of pregnancy. The sensitivity of detecting IgM antibodies is more minor than detecting CMV DNA [25, 75, 76].

The required minimum number of tests for the etiological verification in case of suspected congenital CMV infection in newborns includes:

- study of blood serum (saliva, urine, cerebrospinal fluid) of a newborn (and mother, substrate – blood serum) with quantitative measurement of cytomegalovirus-specific IgM and IgG by IFA (or CLIA), indicating the threshold sensitivity values for this test (for IgG – in IU/ml, for IgM – in arbitrary units, in the form of a positivity coefficient or optical density values of the sample and positive control serum);

- PCR (blood, urine, saliva, cerebrospinal fluid) – qualitative and quantitative analysis with quantification of the number of copies of the virus;
- rapid culture method – RCM [28].

Other laboratories and instrumental studies are performed according to clinical indications.

There are special requirements for the diagnosis of CMV infection in transplantation (clinical guideline "Cytomegalovirus infection in adults after solid organ transplantation", 2014):

- before transplantation, to assess the risk of the recipient's disease in the post-transplant period, the determination of antibodies to CMV IgG in the donor and recipient should be performed. If the pre-transplant assessment of the recipient is negative, it must be repeated at the time of transplantation. In adult patients with questionable serological test results, the donor result should be considered positive, and the potential recipient's development should be carefully interpreted to identify the group of patients with the highest risk of CMV infection;
- quantitative PCR is the preferred method for the diagnosis of CMV infection after organ transplantation, deciding on preventive therapy and monitoring the response to treatment due to the possibility of standardizing this method;
- for PCR, plasma, and whole blood can be used, but the differences in viral load and viral kinetics must be taken into account. During monitoring, the type of biological specimens should not be changed in one patient (blood or plasma);
- commercial and laboratory-developed PCR tests must comply with WHO standards; the results must be expressed in IU/ml;
- at present, it is impossible to establish a universal level of CMV load (trigger point) for all laboratories, at which it is necessary to start therapy. At the same time, knowledge of the trigger point is essential for implementing a preventive therapy protocol. Laboratories themselves must set their cut-off points with clinicians and track clinical results to select a trigger point for starting a therapy;
- viral culture of blood or urine plays a minimal role in the diagnosis of CMV disease. The histological or immunohistochemical examination is the preferred method for diagnosing tissue-invasive CMV disease. Tissue culture methods and PCR of tissue specimens are not crucial in diagnosing tissue-invasive disease. Still, they can be helpful in gastrointestinal tract lesions with negative PCR blood tests. A positive culture of bronchoalveolar lavage fluid (BALF) does not always correlate with disease.

IMPORTANT! These recommendations for diagnosing CMV infection are given in strict accordance with the International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation, 2013 (updated in 2018: The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation). The document indicates that the definition of viral load in dynamics is more significant from the point of view of predicting the development of the disease than the determination of absolute values. This is fundamental for low viral loads, which may nevertheless be clinically significant in specific patient populations. Therefore, establishing uniform requirements for the limit of quantitative detection of CMV DNA may be incorrect [122, 123].

For example, two lower detection limits are most commonly cited: 1000 IU/ml (samples: whole blood or plasma) and 10 IU/ml. The indicator is of little use in the first case for patients with a low but clinically significant viral load. In the second case, there is a high probability of detecting a latent virus, which casts doubt on the clinical significance of the results (increased risk of overdiagnosis).

It is noted that kits for the detection and quantification of CMV DNA must be calibrated according to the WHO's International Standard for Human Cytomegalovirus for Nucleic

Acid Amplification Techniques NIBSC code: 09/162 Instructions for use (Version 6.0, Dated 09/10/2014) (similar requirements apply to reagent kits for quantitative detection of EBV DNA: WHO's International Standard for Epstein-Barr Virus for Nucleic Acid Amplification Techniques NIBSC code: 09/260 Instructions for use (Version 4.0, Dated 09/10/2014).

As for the qualitative PCR, clinical guidelines note its importance for confirming the CMV nature of an infection. It is essential that in the case of primary infection, at the stage of the "serological window" before the start of antibody synthesis, detection of CMV DNA in the blood is the only marker of active viral replication. The CMV DNA detection rate is 80–100% in the first month of developing acute CMV infection, but it significantly decreases 30 days after its detection [25].

Treatment of CMV infection

Treatment of patients with CMV infection includes etiotropic drugs, symptomatic agents, and post-syndrome therapy in developing complications. The method of choice for treatment of CMV disease is carried out differentially, depending on the clinical picture, the severity of clinical manifestations, the presence of complications, concomitant diseases, pregnancy, the patient's age, and laboratory markers CMV activity.

Medicines with proven anti-cytomegalovirus activity and approved for use are ganciclovir and valganciclovir. Unfortunately, the drugs suppress the replicative activity of CMV and are toxic [22, 120].

The use of specific anti-cytomegalovirus immunoglobulin for intravenous administration as monotherapy in patients suffering from manifest, life-threatening, or severe consequences of CMV infection is not indicated.

Antiherpetic drugs (acyclovir, valacyclovir, famciclovir) are not very practical for CMV infection; their use for the treatment of CMV disease is impractical.

The use of interferons and immunocorrectors with active CMV infection and the manifestation of the disease is inappropriate.

Treatment for adult patients with a manifestation of CMV infection [25]

- Treatment course – 21 days or more until symptoms and CMV DNA disappear from the blood disappear: ganciclovir 5 mg/kg 2 times a day or valganciclovir 900 mg 2 times a day (CMV retinitis).
- Maintenance therapy – at least 1 month to prevent relapse of the disease in the presence of immunosuppression: valganciclovir 900 mg per day.

In case of relapse of the disease, a repeated treatment course is carried out.

Preventive therapy for acute or active CMV infection during pregnancy (to prevent vertical fetal infection) [25]

The treatment of choice for acute or reactivated CMV infection during pregnancy to prevent congenital CMV infection depends on the risk of fetal infection and the timing of possible conditions. When choosing a drug, it is necessary to take into account the risk category for the fetus.

- With active CMV infection in pregnant women: specific anti-cytomegalovirus immunoglobulin 1 ml/kg per day IV: 3 injections with an interval of 2 weeks
- In the case of a high concentration of CMV DNA in the blood of a pregnant woman, a high concentration of CMV DNA in the amniotic fluid, or the absence of elimination of the virus from the blood after a course of specific anticytomegalovirus immunoglobulin for IV administration: valgancyclovir at a dose of 900 mg per day for 14 days in the third trimester of pregnancy.

IMPORTANT! The therapy is prescribed after the conclusion of the medical commission and obtaining informed consent from the pregnant woman.

Therapy of congenital CMV infection ["Clinical guidelines for the diagnosis, treatment, and prevention of congenital cytomegalovirus infection", RAMSP]

- Therapy in the manifestation of CMV infection: valganciclovir orally 16 mg/kg 2 times a day; the duration of therapy is up to 6 months or (if it is impossible to prescribe the drug orally) ganciclovir: 5–7.5 mg/kg per day by two intravenous infusions for 14–21 days (until the disappearance of clinical symptoms).

Additionally can be used:
Pentaglobin (for the prevention of severe bacterial infections against the background of CMV infection);
Viferon (antiviral and immunomodulating effect):
>34 weeks, 150 000 IU 2 times a day for 5 days. Recommended 2-5 courses with an interval between periods of 5 days;
<34 weeks, 150 000 IU 3 times a day for 5 days. Recommended 2-5 courses with a gap between courses of 5 days.

- Monotherapy for subclinical infection: NeoCytotect (1 ml/kg IV every 48 hours), 6 injections in total. The criterion of effectiveness is a negative PCR one month after the end of treatment.

Prevention and preventive therapy of CMV infection after organ transplantation [Clinical guidelines "Cytomegalovirus infection in adults after solid organ transplantation", 2014]

- Primary prevention of CMV infection after organ transplantation: valganciclovir 900 mg orally once a day or ganciclovir 5 mg/kg IV once a day. The main side effect is leukopenia.

ATTENTION! Doses of ganciclovir and valganciclovir require mandatory correction by a particular patient's GFR (glomerular filtration rate).

The optimal duration of valganciclovir prophylaxis in patients with kidney transplants is at least 6 months. However, in thoracic transplant patients (lungs, heart-lung complex), prophylaxis is usually carried out longer than with transplantation of a kidney, pancreas, and liver. In 50% of D+/R– lung transplants, prophylaxis is generally carried out. Recipients who received valganciclovir for 6 months develop a late CMV infection.

- Secondary prophylaxis of CMV infection is necessary to treat acute rejection, especially when using antilymphocytic drugs: valganciclovir 900 mg per day with a GFR≥60 ml/min or ganciclovir 5 mg/kg per day IV.
  Duration of prophylaxis: 4–12 weeks.

Treatment of CMV infection in solid organ transplant recipients is determined by the clinical guidelines "Cytomegalovirus infection in adults after solid organ transplantation", 2014 (Table 10).

Table 10. Treatment of CMV infection in solid organ transplant recipients

Indications	Drugs*	Recommendations
Asymptomatic CMV infection/viremia**	• Valganciclovir – 900 mg orally 2 times/day. • Alternatively, ganciclovir 5 mg/kg IV every 12 hours.	• Reduce the level of immunosuppression. • Viral load monitoring or antigenemia once a week. • The duration of treatment is individual. Preferably within 2 weeks after the end of the period of viremia.
Cytomegalovirus syndrome	• Valganciclovir 900 mg orally 2 times/day or ganciclovir 5 mg/kg IV every 12 hours. • If treatment is started with intravenous administration of ganciclovir, then with clinical and virological improvement, you can switch to taking valganciclovir.	• Reduce the level of immunosuppression. • The duration of treatment is individual. Preferably within 2 weeks after the end of the period of viremia and clinical regression.
CMV disease	• Ganciclovir 5 mg/kg IV every 12 hours. • Valganciclovir 900 mg orally 2 times/day (drugs should not be used orally if there are malabsorption or severe somatic disorders). • You can start treatment with intravenous ganciclovir and switch to valganciclovir with clinical and virological improvement.	• Reduce the level of immunosuppression. • The duration of treatment is individual. Treatment should be carried out within 2 weeks after clinical and virological cure. • In some cases, CMV disease can affect different tissues and organs (for example, the small intestine), and blood testing for CMV may not be consistent with the severity of the disease.
Cytomegalovirus pneumonia	• Ganciclovir 5 mg/kg IV every 12 hours.	• Reduce the level of immunosuppression. • Valganciclovir is not preferred as a first-line drug due to CMV pneumonia's potentially severe complications and death. • Possible switch from intravenous administration of ganciclovir to oral administration of valganciclovir. • In some cases, antibodies to CMV are added, especially when the patient is in serious condition.

Indications	Drugs*	Recommendations
Gastrointestinal diseases	• Ganciclovir 5 mg/kg IV every 12 hours. • Alternatively: valganciclovir 900 mg orally 2 times/day for 2 weeks.	• Reduce the level of immunosuppression. • Valganciclovir is not preferred as a first-line drug for severe gastrointestinal diseases due to malabsorption. • Possible switch from intravenous administration of ganciclovir to oral administration of valganciclovir (900 mg 2 times/day) with clinical stabilization. • In some cases, gastrointestinal diseases can fall into different categories, and CMV blood testing may not correspond to the severity of the disease.
Cytomegalovirus retinitis	• Ganciclovir 5 mg/kg IV every 12 hours or valganciclovir 900 mg orally 2 times/day.	• Reduce the level of immunosuppression. • The duration of treatment is determined after a second examination by an ophthalmologist.
CNS lesions	• Ganciclovir 5 mg/kg IV every 12 hours.	• Reduce the level of immunosuppression. • Intravenous ganciclovir is prioritized over valganciclovir as a first-line drug.
Severe diseases	• Ganciclovir 5 mg/kg IV every 12 hours.	• Reduce the level of immunosuppression. • In some cases, therapy can be supplemented with anti-CMV antibodies. • Valganciclovir has not been studied for the treatment of severe diseases associated with CMV. • Possible switch from intravenous administration of ganciclovir to oral administration of valganciclovir (900 mg 2 times/day) with clinical stabilization.
Ganciclovirresistant diseases	• Reduce immunosuppression and give ganciclovir 7.5–10 mg/kg IV every 12 hours (for low resistance UL97).	• To determine the treatment plan, a test for UL97 and UL54 genetic mutation is carried out. • Therapy can be supplemented with anti-CMV antibodies.

* These doses are for patients with normal renal function. With a decrease in GFR, it is necessary to reduce the drug dose.
** CMV infection detected in blood by PCR or antigen detection, but without visible clinical manifestations.

HUMAN HERPESVIRUS 6 (HHV-6)

Human herpesvirus type 6 can cause multiple sclerosis, encephalitis, infectious mononucleosis, “sudden exanthema”, chronic fatigue syndrome, and with prolonged persistence, the virus manifests itself in the form of lymphoproliferative diseases.

HHV-6 is a DNA virus of the ***Betaherpesvirinae*** subfamily, the genus ***Roseolovirus***. The virion diameter is 160–200 nm, the type of symmetry is icosahedral, contains 162 capsomeres, and has a supercapsid lipid-containing envelope [18].

HHV-6 is unstable to physical and chemical factors; it is destroyed by organic solvents, as well as at a temperature of 50–52°C after 30 minutes, at 100°C – instantly. Viruses are inactivated by ultrasound, UV, repeated freezing and thawing, low pH, resistance to low temperatures: they are stored for 1–2 years at –24°C; in a lyophilized state, they do not lose activity for 10 years or more [7].

There are two subtypes of HHV-6: HHV-6A and HHV-6B. Both variants are 88% identical at the nucleotide sequence level but differ in cell tropism in vitro, restriction endonuclease profile, reactions with monoclonal antibodies, seroepidemiology, and involvement in various diseases [142].

In 2012, the International Committee on Viral Taxonomy classified HHV-6A and HHV-6B as different viruses (Human herpesvirus 6A and Human herpesvirus 6B). However, almost all studies indicate that HHV-6B is the predominant strain isolated from conventionally healthy and immunocompromised individuals. Presumably, HHV-6A strains are neurovirulent, while HHV-6B is the primary etiology of sudden exanthema and is more often detected in patients with lymphoproliferative and immunosuppressive diseases [60].

Both viruses are tropic to neural tissue, while HHV-6B increases the severity of neuro infections caused by HHV-6A. HHV-6A DNA is more common than HHV-6B in patients with neuroinflammatory diseases such as multiple sclerosis and thromboencephalitis. HHV-6A was detected in 72% of childhood glial tumors [107, 131].

The American Association for Cancer Research in 2010 published information that HHV type 6 triggers this process with the help of the DR7 oncoprotein. With a high frequency, HHV type 6 DNA was detected in biopsy specimens from gliomas, and high levels of interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor α, and transforming growth factor β (TGF-β) in the exudate of cystic gliomas were observed. Japanese scientists argue that the data from these studies strongly suggest the involvement of type 6 HHV infection in the pathogenesis of glioma [53].

At the same time, HHV-6B and HHV-6A have differences in tropism to human glial cells, suggesting that the latter can cause various forms of the disease. HHV-6A, which more often causes multiple sclerosis, causes infection of astrocytes with a cytopathic effect and high viral DNA load, while HHV-6B does not cause morphological changes when astrocytes are affected. Meeuwsen et al. determined that HHV-6B exposure on astrocytes leads to a change in the response of infected cells to proinflammatory cytokines and other immunomodulatory factors during inflammation, which can lead to epileptogenesis. These results suggest that HHV-6B can persist at a low level of activity for many years, leading to dysregulation of astrocyte activity and increased glutamate-induced excitotoxicity, while HHV-6A is associated with direct exposure destruction of critical components of the nervous system [53].

PCR in primary infection with febrile seizures in the acute period of the disease allows detecting viral DNA in cerebrospinal fluid, brain tissue, lung tissue, which indicates the enormous organotropy of the virus [4].

Direct and central replication of HHV-6B occurs in the salivary glands, which determines the main route of transmission of the virus – airborne droplets.

The penetration of the virus into the host cell occurs after binding to the receptors on the cell surface. The fusion of the viral envelope with the cell membrane leads to the subsequent degradation of the capsid in the cytoplasm and the release of viral DNA. Next, HHV-6 DNA enters the nucleus, where the expression of early and late structural protein genes necessary for the assembly of new virions occurs. After the formation of a daughter

cell, the virus leaves the host cell by exocytosis. Thus, the entire life cycle of the virus takes 4–5 days [100, 105].

In the acute form of infection, the genome of the virus exists in three forms: circular (as part of the virion), in the form of an episome (in the nucleus), and concatemers (linear forms of DNA) formed during the replication of the pathogen. Unlike other human herpes viruses, HHV-6A and HHV-6B can integrate the viral genome into human chromosomes.

In 1993, Luppi et al. demonstrated the presence of a full-length integral HHV-6 genome, or part of it, in the DNA of isolated peripheral blood mononuclear cells. This condition has been designated chromosomally integrated HHV-6 (ciHHV-6). A covalent bond between viral and cellular DNA occurs in subtelomeric regions of chromosomes, probably by the mechanism of homologous recombination [36, 37].

It has been established that about 1% of the population has a chromosomally integrated HHV-6 infection. When the viral DNA is inserted into the human chromosome, the pathogen loses part of the genome and can replicate further, passing into a latent state. However, only the binding of the chromosome to the concatemer leads to the complete replication of the virus. Thus, not every penetration of HHV-6 into the cell leads to productive infection and the formation of infectious virions. Therefore, it is necessary to differentiate HHV-6 in the active phase from ciHHV-6 to assess the therapeutic intervention to avoid polypharmacy [40, 64, 83, 133].

Integration is an effective way to avoid immune surveillance. It is known that an integrated virus can be displaced from the host genome and return to the lytic phase of the life cycle, but this mechanism is not entirely understood [87].

In the latent phase, the virus remains in the cells of the lymphoreticular system, monocytes/macrophages, and the central nervous system cells. HHV-6 can also be transmitted sexually, intra-, and postnatally. Infection is possible through blood transfusions, organ transplantation, and the use of medical instruments contaminated with the virus. HHV-6A and HHV-6B are found in the vitreous fluid and may be involved in inflammatory eye diseases. It has been established that the virus is not transmitted via breast milk [60, 142, 172].

The main feature of HHV-6 is its ability to be present in every germ cell of the body. HHV-6 is the only human herpesvirus whose genome is inserted into germline cells. Due to the implantation into gametes, ciHHV-6 can be inherited with a 50% probability in accordance with Mendel's laws. It has been established that in 86% of cases of vertical infection, the virus is transmitted in the form of ciHHV-6 and much less often – transplacentally (without integration into the host genome) [82, 98].

The systemic spread of the virus is by the hematogenous route and through the lymphatic vessels. This leads to active, abortive, or latent infection in susceptible cells and organs. In most cases, the primary condition is selflimited, a specific immune response develops, and viremia decreases [60, 94].

Nevertheless, HHV-6, like other herpesviruses, has a range of mechanisms to evade the immune response. Thus, HHV-6 can stimulate the effectors of innate immunity – the secretion of proinflammatory cytokines (IL-1β, TNF-α, and IFN-α) in peripheral blood mononuclear cells – while HHV-6A additionally stimulates the production of IL-15, which activates the proliferation of natural killer cells. Furthermore, an increase in the production of proinflammatory cytokines is associated with the suppression of the synthesis of IL-2 by the virus, which subsequently leads to a decrease in the activity of T-lymphocytes, and an increase in the production of anti-inflammatory IL-10 (an IL-12 antagonist) leads to a shift from Th1 to Th2 lymphocytes [60].

It was found that HHV-6 reduces the expression of HLA I class molecules on dendritic cells. In parallel, HHV-6 infection has a potent suppressive effect on the growth and differentiation of bone marrow progenitors, affecting the subsequent differentiation of macrophages and the formation of the thymocyte progenitor population.

Moreover, HHV-6A infection induces the expression of a tolerant nonclassical class I MHC molecule HLA-G in primary human mesothelial cells, which leads to impaired recognition and destruction of infected cells by natural killer cells. At the same time, HHV-6B inhibits the activating receptor NKG2D in infected cells [81, 156].

Many of these effects are mediated explicitly by HHV-6 proteins, which act as analogs to cellular chemokines and are thought to promote viral growth and spread, bypassing the host's immune system. For example, the U83 gene encodes a chemotactic protein that is an agonist for multiple human chemokine receptors (CCR); the U24 gene product induces the internalization of the T cell receptor/CD3 complex. Taken together, this "capture" of receptors changes the patterns of T-cell activation and reduces the strength of the immune response to viral infection [60, 71].

Specific IgM antibodies usually appear within the first five days. In the next 1–2 months, the titer decreases and, in the future, is not determined at all. Specific IgM may be present in small amounts when the infection is reactivated. Specific IgG begins to be produced two to three weeks after infection, with low avidity antibodies being determined first and then high avidity IgG. IgG to HHV-6 is detected for a long time, while antibody levels may fluctuate after a primary infection, possibly due to latent virus reactivation. According to the results of some studies, a significant increase in the antibody levels is observed in the case of infection with other viruses with similar DNA, for example, HHV-7 and CMV [36].

The spectrum of diseases associated with HHV-6 is broad, which is related to the virus strain. HHV-6 is associated with the development of sudden exanthema in newborns and older children, infectious mononucleosis in adolescents and adults, etiologically unrelated to EBV infection, histiocytic necrotizing lymphadenitis, malignant lymphoma, peripheral T-cell leukemia, and B-cell lymphoma. About half of all cases of first-ever fever in newborns are associated with primary HHV-6 infection, more often HHV-6B. Reinfection with HHV-6 is observed in patients with an impaired immune system (after transplantation, AIDS) [7, 57].

Most babies are seropositive at birth due to maternal antibodies, which decrease by 5 months of age. By the end of the first year of life, the percentage of seropositive infants is the same as among older children and adults. A high detection rate of antibodies and an early infection age indicate the virus's presence in the immediate environment [7].

The infectious process can occur in the form of an acute primary infection in young children, primary latent infection in children and adults, reactivation of latent infection, or reinfection in immunocompromised individuals. However, the classic clinical picture of illness in children is sudden exanthema (exanthema subitum, sixth disease, baby roseola) [18, 175].

The disease begins acutely, the temperature rises to 38–40°C, moderately pronounced signs of intoxication develop, sometimes there is slight hyperemia of the pharynx. Noteworthy is the child's satisfactory state of health, preserved appetite, and excellent response to antipyretic drugs.

Pathognomonic for this disease is that on the 3–5th day of the disease, the temperature normalizes, and at this time (sometimes after 1–2 days) roseolous (less often roseolous-papular or small-spotted) exanthema appears throughout the body, usually more pronounced on the face, neck, and trunk. No itching. After 1–3 days, the rash disappears without a trace without treatment. A detailed clinical blood test shows changes typical for most viral infections: in the first 1–2 days, neutrophilic leukocytosis is noted with a slight shift to the left or without it, then leukopenia with lymphocytosis [52].

HHV-6 can cause exanthema even without temperature and intoxication. However, in this case, the absence of pathognomonic signs requires serological confirmation (detection of IgM or an increase of IgG in dynamics) or detection of viral DNA in the blood using PCR.

HHV-6 is the cause of almost one-third of all seizures recorded in children under 2 years of age, as evidenced by the tropism to the cell lines of neuroblastoma, glioblastoma, and embryonic glia. This explains the ability of the virus to cause meningitis, encephalitis, sometimes combined with exanthema [7].

In addition, viral reactivation is often seen in AIDS patients. HHV-6 has been shown to increase HIV replication by regulating specific cytokines and transactivating long terminal repeat regions of the HIV genome, which leads to an increase in viral load and a more aggressive onset of AIDS [99, 134, 146].

The relationship between the development of the graft versus host reaction (GVHR) and the infection caused by HHV-6 was established. Like other herpes viruses after primary infection, HHV-6 becomes latent and can be reactivated in immunodeficient con-

ditions. Thus, reactivation of HHV-6 is observed in the first months after allogeneic bone marrow transplantation (allo-BMT). In the study of peripheral blood cells and skin biopsies of patients with GVHR using immunohistochemistry and PCR, HHV-6 was detected in more than 70% of patients: in 92% of patients with a severe course and 56% of patients with a mild course of the pathological process [40, 137].

It has been proven that the reactivation of HHV-6 also leads to post-transplant complications in liver transplantation, provoking the development of hepatitis, encephalitis, and transplant rejection. In addition, the virus is a factor contributing to the development of opportunistic infections, including CMV- and EBV-associated lymphoproliferative diseases, invasive fungal infections, and mycobacterial infection [88, 140, 145].

Laboratory diagnosis of HHV-6

For the detection of HHV-6 DNA, qualitative PCR is used. Determination of viral load can be associated with the false diagnosis of active HHV-6A/B infection, which is associated with ciHHV-6A/B. This is because individuals with ciHHV-6 have the viral genome in every germ cell in their body. The latter determines a high level of viral DNA in the blood and tissues of these patients, even in the absence of infection. During active disease, the number of copies of HHV-6A/B per milliliter of blood is usually lower than in individuals with ciHHV-6. Thus, the viral load associated with active HHV-6A/B infection usually ranges from 103 to 104 HHV-6A/B copies/ml of blood. At the same time, the diagnosis of ciHHV-6 is likely when the viral load is more than 500 000 (> 5.5 lg) copies/ml of whole blood, or more than 3.5 lg copies/ml of serum, or more than 4 lg copies/ml of CSF [40, 148].

In general, when a high viral load is detected, a second test (e.g., quantitative PCR of HHV-6A/B copies on hair follicles) should be performed to confirm or exclude ciHHV-6A/B. If ciHHV-6A/B infection is excluded, the patient should be treated with antiviral drugs. However, inappropriate use of antiviral medications can increase the risk of side effects, especially in patients undergoing hematopoietic stem cell transplantation. For this reason, it is essential to distinguish between active HHV-6A/B infection and ciHHV-6A/B [160].

Another way to distinguish acute HHV-6 infection from ciHHV-6 is by performing reverse transcription PCR (RTPCR), which will be positive only with active viral replication in acute infection, since the main target will not be DNA, but RNA of the virus [82, 169].

There is a technique to determine patients with inherited chromosomally integrated HHV-6 - droplet digital PCR. The assay uses digital PCR technology to identify integration from cell samples by accurately analyzing the relationship between HHV-6 and cellular genomic DNA [160].

Treatment of HHV-6 infection

In the last decade, studies on the antiviral action of some drugs have shown that HHV-6 is insensitive to nucleoside analogs. However, no medications have been found that would be effective enough to treat HHV-6 infections.

In the uncomplicated course of primary HHV-6 infection, specific antiviral therapy is not indicated. It is prescribed only in cases of damage to the central nervous system or infection reactivation in patients with immunosuppression. At the same time, further research is needed to develop methods for choosing drugs, doses, and timing of treatment. Ganciclovir and foscarnet have been used with some success to treat HHV-6 infection. Cidofovir is proposed as an alternative drug due to its pronounced toxicity [4, 139].

HUMAN HERPESVIRUS TYPE 8 (HHV-8)

HHV-8 (Kaposi's sarcoma herpesvirus (KSHV)) belongs to the γ-herpesvirus, the genus Rhadinovirus. HHV-8 is a DNA virus with tropism for lymphoid, epithelial, and dendritic cells and the granular epithelium of the prostate [90].

There is an association between Kaposi's sarcoma and herpes simplex virus type 8, so the presence of the virus in the body is a risk factor for the development of a tumor.

The main routes of HHV-8 transmission are sexual (with seminal fluid, vaginal secretions), horizontal (with saliva, especially in children), hematogenous (with blood transfusions and intravenous injections of infected blood), and transplacental (in newborns infected with infected mothers). In addition, the occurrence of neoplastic processes in patients after organ transplantation from HHV-8-positive donors is possible [150, 151].

As with other herpes viruses, gene expression depends on the stage of infection – latent or lytic. During latent infection, the HHV-8 genome is presented as an episome, and the products of 3 viral genes are expressed: viral cyclin D, which inhibits apoptosis of infected cells; LANA-1, which promotes the spread and transcription of the virus in cells and inhibits the transcriptional activity of p53, and vFLIP, which protects cells latently infected with HHV-8 from apoptosis by blocking the Fas receptor and being destroyed by cytotoxic T lymphocytes [26].

The RTA gene product initiates the lytic phase of the HHV-8 life cycle. After initiation of lytic replication, gene products are produced in an ordered sequence typical of other human herpes viruses. It has been established that up to 10% of HHV-8 viruses detected in Kaposi's sarcoma foci are in the lytic phase. However, HHV-8 in peripheral blood lymphocytes is seen only in patients with severe immunosuppression (AIDS-associated and immunosuppressive types of the disease). The oropharynx is the site of the most pronounced viral replication: saliva contains many HHV-8 copies [26].

It was found that HHV-8 produces a wide range of protein compounds with anti-cytokine activity, capable of inducing cell proliferation and inhibiting apoptosis. In addition, the virus makes many IFN-regulatory factors (vIRFs), through which the functions of both the innate and acquired immune systems are impaired [42].

The latency-associated nuclear antigen produced by the virus in the latency phase ensures the integration of the HHV-8 into the host cell genome. It alters the function of the tumor suppressor of the p53 protein. Activation of the viral G protein-coupled receptor, which has a high affinity for the interleukin-8 receptor, leads to overproduction of vascular endothelial growth factor (VEGF), stimulating cell proliferation and directly to tumor transformation [42, 154].

Viral FLICE inhibitory protein is the next potential oncogenic protein. Its main target is NF-κB factor, a protein responsible for the transcription of genes for the immune response and the cell cycle.

It is known that a significant increase in the expression of IL-6 is observed in various lymphoproliferative diseases. It has been shown that the level of IL-6 increases during the proliferation of tumor cells and is an autocrine growth factor in Kaposi's sarcoma. In HHV-8genome, a gene that is 25% homologous to IL-6 was found. Most likely, its function is to enhance the proliferative effect. In addition, HHV-8 expresses several proteins (vFLIP, vBcl-2, vIAP) that inhibit apoptosis, which ensures the persistence of the virus [42, 154].

It has been proven that HHV-8 may be an etiology of human neoplasms: Kaposi's sarcoma, multiple myeloma, non-Hodgkin B-cell lymphomas, primary exudative B-cell lymphoma (or lymphoma of the body cavities), and Castleman disease. These neoplastic disorders are most often associated with immunocompromised states, including HIV infection, iatrogenic immunodeficiency, and aging, post-transplant conditions [9, 114].

The onset of Kaposi's sarcoma is typical at 35–39 years in men and 25–39 years in women. A high incidence of Kaposi's sarcoma is observed in countries located on the Mediterranean coast and central Africa (endemic Kaposi's sarcoma). In developed countries, in patients infected with human immunodeficiency virus-1 (HIV-1) (observed in 20% of AIDS patients), the incidence of HHV-8 is highest among homosexual and bisexual men. In

addition, the socalled iatrogenic form of Kaposi's sarcoma is observed during transplant-related immunosuppression; in patients on long-term therapy with corticosteroids and chemotherapy [19, 154].

There are four clinical types of the disease: classic (Mediterranean), endemic (African), epidemic (AIDS-associated), immunosuppressive, or iatrogenic (transplant-related, which occurs against the background of active treatment with cytostatics and immunosuppressants). In several patients, in addition to typical manifestations in the form of reddishcyanotic spots, nodules and nodes, vegetation, granulation, and verrucous growths develop, rarely – bullous and vesicular rashes located on edematous legs and feet and clinically resembling lymphangioma [42].

The histological picture depends on the stage and duration of the disease. Histologically, Kaposi's sarcoma is characterized by two main features: incomplete angiogenesis and proliferation of fusiform cells. The origin of spindle-shaped cells remains not fully understood. The study of their ultrastructure has demonstrated the characteristics of endothelial cells and fibroblasts. Angiomatous and fibroblastic variants of Kaposi's sarcoma are also histologically distinguished [26, 42].

Laboratory diagnosis of Kaposi's sarcoma by clinical guidelines includes verifying the diagnosis based on histological examination of skin biopsies and detection of HHV-8 using molecular biology techniques.

Despite a large variety of antiherpetic drugs, the treatment of HHV-8 infection presents significant difficulties.

Ganciclovir and foscarnet have been used with some success.

Valganciclovir is a possible way to suppress HHV-8 replication. The drug is better tolerated than the well-known foscarnet, but there are no data on its clinical efficacy in HIV-associated Kaposi's sarcoma. An excellent response to therapy was obtained in the II phase of clinical trials using IL-12. However, drugs that would be sufficiently effective in treating HHV-8 infection have not yet been found [16].

DNA-Technology offers the following kits for detecting herpesvirus infections by PCR (Table 11).

Table 11. Kits produced by DNA-Technology for detection of causative agents of herpesvirus infections

Etiologic agent	Number of tubes in the kit			Registration*
	Forez	Flash	Rt	
Ibu Kit for detecting herpes simplex virus 1,2 DNA by polymerase chain reaction (HSV 1,2) profen	100	100	96	CE/IVD
Kit for detecting varicella-zoster virus DNA by polymerase chain reaction (VZV)	50	50	48	CE/IVD
Kit for detecting Epstein-Barr virus DNA by polymerase chain reaction (EBV)	100	100	96	CE/IVD
Kit for detecting human cytomegalovirus DNA by polymerase chain reaction (CMV)	100	100	96	CE/IVD
Kit for detecting human herpesvirus type 6 DNA by polymerase chain reaction (HHV 6)	100	100	96	RU/IVD
Kit for detecting human herpesvirus type 8 DNA by polymerase chain reaction (HHV 8)	100	100	96	RU/IVD
Kit for detecting herpes simplex virus 1,2, cytomegalovirus DNA by polymerase chain reaction (HSV1, HSV2, CMV Multiplex)	–	–	96	RU/IVD

Note.
* RU/IVD – kits for In Vitro diagnostic, which are registered in Russia only
CE/IVD – kits for In Vitro diagnostic, which are registered in the EU

Kit format:
Kits are aliquoted into test tubes:
- Forez – single tubes 0.5 ml;
- FLASH – single tubes (0.5 ml or 0.2 ml; except HSV 1,2 and CMV kits – 0.5 ml only);
- Rt – single tubes 0.2 ml or strip tubes (8 pcs. 0.2 ml each).

Storage temperature: +2...+8 °C.

Shelf life:
- Forez – 9 months (except HSV 1,2 and CMV kits – 12 months);
- FLASH – 12 months;
- Rt – 12 months.

Kits for DNA extraction:
- PREP-RAPID;
- PREP-NA;
- PREP-GS.

Samples:

Kit for detecting herpes simplex virus 1,2 DNA by polymerase chain reaction (HSV 1,2)	· peripheral blood lymphocytes · saliva · urine · epithelial cells scraped from the cervical canal, urethra, and posterior vaginal fornix
Kit for detecting varicella-zoster virus DNA by polymerase chain reaction (VZV)	· epithelial cells scraped from the skin and mucosal lesions
Kit for detecting Epstein-Barr virus DNA by polymerase chain reaction (EBV)	· saliva · urine · epithelial cells scraped from the cervical canal, urethra, and posterior vaginal fornix · peripheral blood mononuclear cells
Kit for detecting human cytomegalovirus DNA by polymerase chain reaction (CMV)	· saliva · urine · epithelial cells scraped from the cervical canal, urethra, and posterior vaginal fornix · peripheral blood mononuclear cells
Kit for detecting human herpesvirus type 6 DNA by polymerase chain reaction (HHV 6)	· peripheral blood lymphocytes · liquor · saliva · urine
Kit for detecting human herpesvirus type 8 DNA by polymerase chain reaction (HHV 8)	· peripheral blood lymphocytes · sperm · prostate secretion · biopsy specimens
Kit for detecting herpes simplex virus 1,2, cytomegalovirus DNA by polymerase chain reaction (HSV1, HSV2, CMV Multiplex)	· urine · epithelial cells scrapings (from the posterolateral vaginal fornix, urethra, and cervical canal)

Analytical sensitivity of the kits for detection of causative agents of herpesvirus infections:

a) for all kits, except for “HSV1, HSV2, CMV Multiplex”:

Specimen	Kits for nucleic acids extraction			
	PREP-NA	PREP-GS	PREP-MP-RAPID (with 300 µl elution)	PREP-RAPID
· epithelial cells scrapings in 500 µl of transport medium	50 copies/ sample	100 copies/ sample	300 copies/sample	500 copies/ sample

b) «HSV1, HSV2, CMV Multiplex» – analytical sensitivity per 1.0 ml sample:

- 2000 genome-equivalents DNA Herpes Simplex Virus 1;
- 2000 genome-equivalents DNA Herpes Simplex Virus 2;
- 2000 genome-equivalents DNA Cytomegalovirus.

Recommended additional reagents: reagents for DNA quality control (SIC) determine and estimate the amount of human genomic DNA by real-time PCR in the tube.

Equipment required for analysis:

- for FLASH kits – «Gene», «Gene-4», «Tertsik», produced by DNA-Technology:

«Tertsik»

«Gene»

«Gene-4»

- for Rt kits:

– "DT" series devices, produced by DNA-Technology: "DTlite", "DTprime":

DTlite»

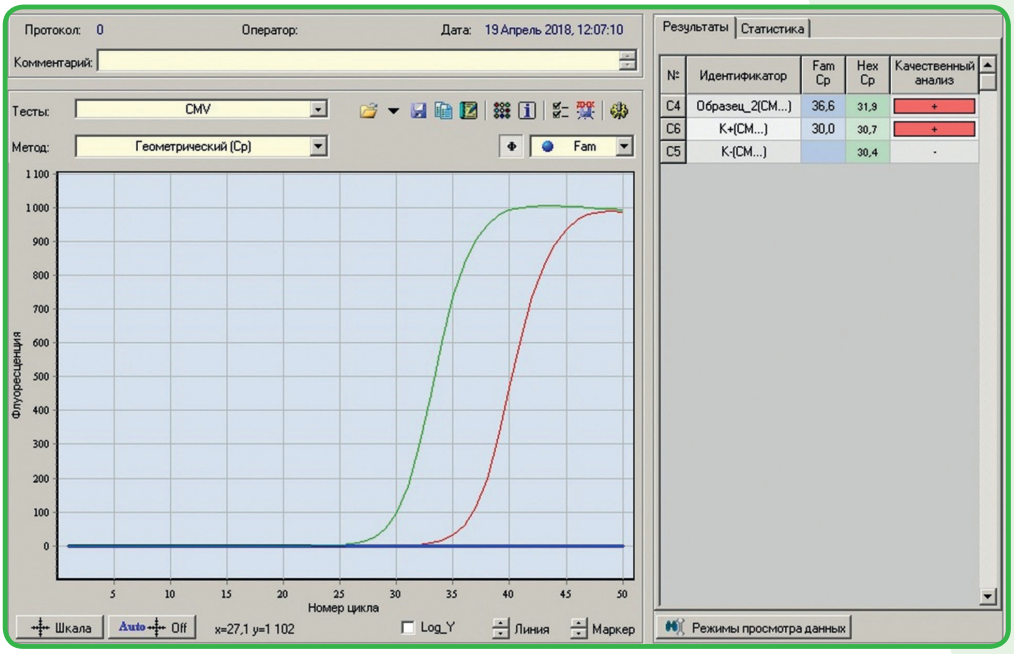
«DTprime»

– IQ5 Cycler device produced by Bio-Rad Laboratories and Rotor-Gene device made by QIAGEN (except for «HSV1, HSV2, CMV Multiplex»).

The additional equipment is needed for analysis using strip tubes: rack and vortex rotor for strip tubes.

Software: registration and interpretation of the PCR results are held in automatic mode (for devices produced by DNA-Technology). (pic. 1).

A

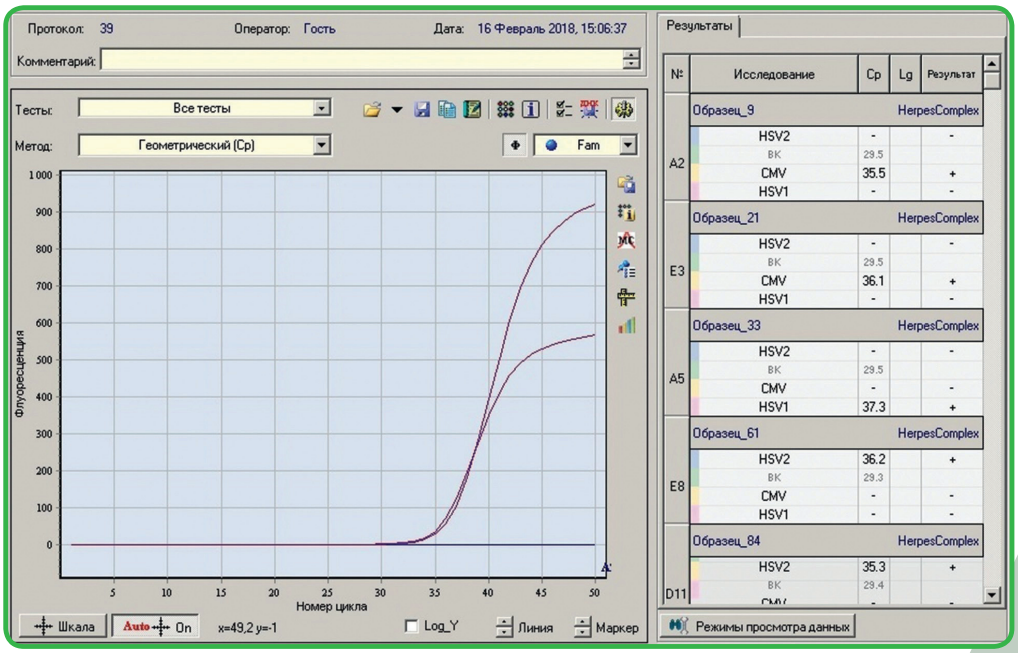


B

Qualitative analysis

Number of the hole	ID of the tube	Cp, Fam	Cp, Hex	Result
C4	Sample_2 (CMV)	36.6	31.9	+
C6	C+ (CMV)	30.0	30.7	+
C5	C– (CMV)		30.4	–

C



D
Sample ID: Sample_0

№	Name of research	Result
1	HSV2	not detected
2	CMV	DETECTED
3	HSV1	not detected

Sample ID: Sample_33

№	Name of research	Result
1	HSV2	not detected
2	CMV	not detected
3	HSV1	DETECTED

Sample ID: Sample_61

№	Name of research	Result
1	HSV2	DETECTED
2	CMV	not detected
3	HSV1	not detected

Pic: 1. Results of Rt analysis
(«DT» series devices, produced by DNA-Technology) using:
a kit for the detection of human cytomegalovirus DNA by real-time PCR («CMV»):
A – optical measurement analysis (Fam channel);
B – analysis results;
a kit for detecting herpes simplex virus 1,2, cytomegalovirus DNA by realtime PCR («HSV1, HSV2, CMV Multiplex»)
C – optical measurement analysis (Fam channel);
D – analysis report

DNA-Technology has been developing, producing, and introducing high-tech equipment and kits for PCR assays since 1993.

Our team brings together leading experts in molecular biology, immunogenetics, medicine, thermodynamics, optics, electronics, programming, which determines the scientific and technological potential of the company, allowing providing high standards of quality and quality control at all stages.

Our production sites meet the requirements of international standards practiced by global companies. The company is certified by the quality management system for medical devices ISO 13485:2016, ISO 9001:2015 and licensed by the Federal Service for Surveillance in Healthcare and Social Development. In addition, the manufactured products conform to regulatory requirements for In-Vitro Diagnostic Medical Devices (Directive 98/79/EC) and CE IVD certified.

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