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CLINICAL AND PATHOGENETIC ASPECTS OF INFECTIOUS MONONUCLEOSIS

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Summary : *For many physicians, the terms Epstein-Barr virus and infectious mononucleosis are synonymous. Epstein-Barr virus causes approximately 90% of infectious mononucleosis cases, with the remainder being caused primarily by cytomegalovirus, human herpes virus type 6, toxoplasmosis, HIV infection, and adenovirus.*

The aim is to analyze the pathogenetic, clinical and epidemiological features of infectious mononucleosis of Epstein-Barr viral etiology, as well as problems of diagnosis and treatment.

Material and methods. The article presents a review of domestic and foreign literature data on infectious mononucleosis of Epstein-Barr viral etiology. Results and their discussion. Due to a significant increase in the incidence of infectious mononucleosis caused by the Epstein-Barr virus, in recent years, the improvement of methods of specific diagnostics and antiviral therapy will allow us to successfully solve the problem of stopping the pathological process in the early stages of the disease. But the problem of protracted forms of the disease requires a more in-depth study.

Conclusions. The key to success in the treatment of patients with infectious mononucleosis is timely diagnosis, correct and strictly individual approach to both etiotropic and pathogenetic therapy, as well as timely hospitalization of patients with severe forms of infectious mononucleosis.

Key words: infectious mononucleosis, Epstein-Barr virus, hepatitis

Abstract. Epstein – Barr virus and infectious mononucleosis are synonymous for many physicians. Epstein – Barr virus causes approximately 90% of cases of

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infectious mononucleosis, while the rest of the cases are associated mainly with cytomegalovirus, human herpesvirus type 6, toxoplasmosis, HIV infection and adenovirus. Aim. Pathogenetic, clinical and epidemiological features of Epstein – Barr virus infectious mononucleosis have been analyzed as well as the problems of its diagnosis and treatment.

Materials and methods. The article presents an overview of Russian and foreign literature data on Epstein – Barr virus infectious mononucleosis. Results and discussion. In connection with a significant increase in the incidence of infectious mononucleosis caused by Epstein – Barr virus in recent years, improvement of specific diagnostic methods and antiviral therapy will successfully solve the problem of arresting pathological process at the early stages of the disease. However, the problem of chronic forms of the disease requires in-depth study.

Conclusion. The key to success in treatment of patients with infectious mononucleosis is timely diagnosis, correct individual approach to etiotropic and pathogenetic therapy, as well as timely hospitalization of patients with severe forms of infectious mononucleosis.

Key words: infectious mononucleosis; Epstein – Barr virus; hepatitis.

The relevance of studying infectious mononucleosis (IMN) is due to the high circulation of the pathogen among the population, the specific tropism of the herpes virus to immunocompetent cells, lifelong persistence of the virus in the body and often a latent course [1]. More than 95% of people worldwide are infected with the Epstein-Barr virus, mainly in the higher socio-economic groups of industrialized countries, primarily becoming infected at the age of 1 to 5 years [2]. In the last 10 years, the incidence of IMN caused by the Epstein-Barr virus has increased 5-fold not only in adults but also in infants. This is due to both a true increase in the incidence due to the impact of various exogenous and endogenous factors, and the improvement of laboratory diagnostic methods for this infection [3]. Infectious mononucleosis was first described as a generalized inflammation of the lymph nodes by the famous Russian pediatrician N.F. Filatov in 1885. Later, descriptions of outbreaks of glandular fever appeared, presented by K.L. Pfeiffer (1888) and N.S. Korsikov

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(1901). The first report on the characteristic hematological changes in this disease was made by G. Turk in the Vienna Medical Society in 1907. Later, in 1909, D. Berne noticed changes in the "white blood" in glandular fever. In the blood of these patients, he saw an increase in the number of "small mononuclears ". In 1920, scientists from the USA F. Evans and T. Sprunt proposed to introduce the term "infectious mononucleosis". In 1964, M.A. Epstein and J. Barr isolated a virus from the herpes group, which was found with great consistency in patients with infectious mononucleosis and had a tropism for lymphoid tissue, causing blast transformation of lymphocytes [4]. The first representative of the human γ-herpesvirus family was the Epstein-Barr virus (EBV). It was discovered through the study of B-cell lines obtained from patients with African Burkitt lymphoma . EBV is a representative of oncogenic DNA-containing viruses, the capsid diameter is 120-150 nm , surrounded by a membrane, contains lipids. During virus replication, over 70 different virus-specific proteins are expressed. However, to date, groups of immunogenic proteins have been identified, the determination of antibodies to which makes it possible to differentiate the stage of infection (EA - early antigen, EBNA-1 - nuclear antigen, VCA - capsid antigen, LMP - latent membrane protein). As soon as the virus enters the epithelium of the mucous membrane of the oropharynx and upper respiratory tract, infection of lymphocytes occurs. There are a number of differences in the infection of epithelial cells and lymphocytes. In epithelial cells , complete replication of the virus occurs with the formation of a large number of virions, epithelial cell lysosomes , which subsequently infect neighboring cells. At the time of infection of B-lymphocytes, virus replication occurs only in a small percentage of cells, and in the remaining cells the virus is in a latent state. The mechanism of interaction of EBV with B-lymphocytes has been studied most thoroughly. The supercapsid of the virus contains glycoprotein complexes - gp350, 85, 25 and 42. The gp350 complex plays a leading role in interaction with B-lymphocytes. Its structure is similar to the component of the C3 dg complex , and also interacts with the CD21 molecule on the surface of the B-lymphocyte, being a receptor for it. Interacting, adhesion of the virus to the cell and the beginning of endocytosis occur. In order for the virus to penetrate

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the cell membrane, interaction of other glycoprotein complexes with the β-chain of the HLA class 2 molecule is necessary. At the same time, in order for the virus to interact with epithelial cells , the presence of gp85, 25 is necessary, for which there is a special receptor [5, 6, 7]. Antiviral protection of the body is carried out by macrophages and other cells producing interferons (IFN) α, β and γ, they destroy and block viruses. A number of interleukins (IL) [tumor necrosis factor (TNF), IL-6, etc.], natural killers and factors form a specific immune response against a specific virus. Cytotoxic T-lymphocytes (CTL) (CD8+ T-lymphocytes) and B-lymphocytes are responsible for the production of specific antibodies that block viral replication and viruses located outside the cell. In order for cells to function adequately and maintain an immune response, the corresponding production of IFN and IL is necessary [8]. Generalization of viral infection at early stages leads to infection of T- and NK-cells and chronic EBV infection with persistence of the virus in lymphocytes develops. The persistence of EBV, despite its high immunogenicity , indicates the development of special mechanisms by the virus to evade the immune response [5, 6, 7]. The signal for the beginning of secretion of proinflammatory cytokines IL-1β, IL-6, IL-8, IL-12, TNF-α by monocytes is contact with the pathogen. Biologically active molecules (superoxide radicals, leukotrienes , prostaglandins) are produced and secreted during autocrine stimulation of macrophages by cytokines. Endothelial cells of blood vessels, on which the expression of adhesion molecules is induced, become targets of the paracrine action of the same proinflammatory cytokines. Due to the latter, an influx of circulating neutrophils and monocytes into the infection site is ensured. IL-8 functions as an angiogenic factor, being an autocrine chemoattractant for endothelial cells [9, 10]. NK cells, B lymphocytes and cytotoxic T lymphocytes are the main effector cells. NK cells and T lymphocytes participate in the synthesis of proinflammatory mediators and in the direct lysis of infected cells. B lymphocytes, with the help of T helpers, produce antibodies and become specific for viral antigens [11]. The BCRF-1 protein expressed by EBV coincides with the cytokine IL-10 in amino acid sequence and causes its mimicry. Thus, it promotes the suppression of INF-γ synthesis by peripheral mononuclear cells .

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Disruption of interferon formation and activation of secondary flora as a result of the immunosuppressive action of the virus involve various organs and systems in the process [5, 6, 7]. The epidemiological features of EBV mononucleosis are determined, first of all, by a wide range of infection sources: patients with manifest (including protracted and complicated variants) and asymptomatic forms, as well as virus carriers. After an EBV infection, the patient excretes the virus with oropharyngeal secretions for 2-18 months . There is a certain relationship between the immune status and the excretion of EBV into the environment. Airborne transmission is the main route of transmission, but contact-household (with the patient's saliva), parenteral (with donor blood and transplants), and sexual transmission are also possible. IMN most often occurs in the form of sporadic cases. Epidemic outbreaks of the disease are possible in closed groups (in kindergartens, among students and military personnel). The entry point for EBV infection is the epithelium of the oropharynx, from where the virus penetrates into susceptible B-lymphocytes of the lymphoid tissue of the pharynx. The virus can also penetrate through the gastrointestinal tract. Surface receptors of the CD21 molecule for EBV are present on the epithelial cells of the oropharynx and on B-lymphocytes. The virus initially replicates in the epithelium of the mucous membrane of the mouth and nasopharynx, then in the lymphoid formations of the pharynx and salivary gland ducts, as well as in the epithelium of the cervix. After the introduction of the virus, severe hyperemia and swelling of the mucous membranes of the oral cavity and nose appear. Severe hypertrophy of the tonsil tissue and mucous membranes of the pharynx is observed. Clinically, this is manifested by difficulty breathing through the nose and severe pain when swallowing [12].

Infectious mononucleosis can occur in typical (acute) and atypical (latent, asymptomatic) forms. The typical clinical picture includes febrile fever, tonsillitis, generalized lymphadenopathy , hepatosplenomegaly , exanthema, the appearance of atypical mononuclear cells in the blood, headache, fatigue, loss of appetite, respiratory syndrome and myalgia [13, 14]. In atypical forms, the manifestations of the main symptoms of the disease are less pronounced [12]. The duration of fever is

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from 10 days to 1 month or more, the severity varies from 37.5 to 40.5 ° C. Involvement of the lymph nodes in IMN is usually symmetrical and includes the submandibular, anterior cervical and posterior cervical groups [12]. Damage to the oropharynx can manifest as granular pharyngitis, catarrhal, lacunar, follicular, ulcerative necrotic tonsillitis. Acting specifically, the virus activates the bacterial flora. Changes appear either from the first days of the disease or somewhat later – on the 4th–6th day against the background of fever, lymphadenopathy and other symptoms of the disease [12]. In the first days of the disease, moderate leukopenia and neutropenia , lymphocytosis and plasma cells can be seen in the peripheral blood. Characteristic changes in blood tests can be detected after the 5th day of the disease. Leukocytosis up to 13×109/l (hyperleukocytosis up to 18–20×109/l is possible), lymphomonocytosis and the appearance of atypical mononuclear cells (10–60% and higher) are observed. Clinical symptoms increase by the 4th–6th day, hepatosplenic syndrome can be observed [12]. Acute hepatitis develops in approximately 50% of patients with infectious mononucleosis, manifested by hepatomegaly (10–25%) and increased transaminase activity. However, hepatitis also develops more frequently (in 80–90% of mononucleosis cases), as well as a more significant (10–20 times) increase in alanine aminotransferase (ALT). Enzymatic activity increases gradually (within 1–2 weeks from the onset of the disease), and in most patients the transaminase level normalizes within a month in accordance with the resolution of disease symptoms. An increase in cholestatic markers – alkaline phosphatase (ALP) levels and slight hyperbilirubinemia – is noted in 5–10% of cases, with the development of jaundice in approximately 45% of cases. In this case, virus-induced intrahepatic cholestasis is indicated by an increase in the activity of ALP and lactate dehydrogenase (LDH), often more significant than ALT and aspartate aminotransferase (AST) [15]. Another important, but rare (0.5–3% of cases) cause of increased bilirubin may be autoimmune hemolytic anemia. A fragment of viral origin is fixed to the erythrocyte membrane.

The resulting haptens transform the red blood cells into foreign target cells for the immune system, which ultimately leads to hemolysis. Hemolysis occurs primarily in the extravascular mononuclear phagocytic system of the liver and in the cells of the

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reticulohistiocytic system of the spleen. Changes in liver function tests can be detected as early as the 5th day of the disease. Typical histological changes usually develop between the 10th and 30th days of the disease. Pleomorphic infiltration of the portal tracts, periportal zone and sinusoids with lymphocytes and monocytes with the formation of lymphocytic foci is detected in the liver. Minimal swelling and vacuolization of hepatocytes are typical. Proliferation of Kupffer cells and bile capillary epithelium, bile stasis, as well as focal necrosis and granulomas can also be recorded . Hepatitis in infectious mononucleosis usually occurs in accordance with the severity of the disease. Cases of fulminant course with a fatal outcome have been described. They were mainly due to immunosuppression : immunodeficiency in Duncan's disease, lymphoproliferative diseases or liver transplantation (as a result of primary EBV infection or reactivation). Like other manifestations of mononucleosis, hepatitis is more severe in people over 30 years of age. Sometimes such patients develop severe jaundice, fever, pain in the right hypochondrium, which may suggest mechanical jaundice. Ascites may develop in severe hepatitis, as well as autoimmune liver damage after EBV infection, which occurs lightning fast, accompanied by cirrhosis, liver failure, portal hypertension. Rarely, jaundice is caused by hemophagocytic syndrome, which sometimes develops in patients with EBV infection. It is characterized by fever, hepatosplenomegaly , impaired synthetic function of the liver, cytopenia and significant hyperbilirubinemia . Hemophagocytic syndrome is a result of dysregulation of T-killers, which leads to proliferation and activation of lymphocytes with uncontrolled hemophagocytosis and cytokine production. In rare cases, hemophagocytic syndrome is severe and can be fatal [15]. Some patients may experience specific skin rashes. They typically appear after taking penicillin antibiotics. Delayed-type hypersensitivity reaction causes exanthema. The rash may vary in morphology: maculopapular, roseolous , urticarial , punctate, hemorrhagic, petechial . It may tend to merge. Enanthems and hemorrhages can often be seen during examination of the mucous membrane of the hard palate [16].

New studies have shown that Epstein-Barr virus can be a trigger for many hematological and oncological diseases, such as thrombocytopenia, agranulocytosis,

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autoimmune hemolytic anemia, acute leukemia, nasopharyngeal carcinoma, Burkitt lymphoma and Hodgkin lymphoma . Splenomegaly and splenic rupture in patients with EBV usually manifests by the third week of the disease. Splenic rupture is a rare but potentially fatal threat. Neurological complications include Guillain -Barré syndrome, facial and other cranial nerve palsy, polyradiculoneuritis , meningoencephalitis, aseptic meningitis, transverse myelitis, peripheral neuritis, encephalomyelitis. Other complications, which occur in less than 1% of patients (pneumonia, pleural effusion, myocarditis, pancreatitis, glomerulonephritis, otitis, sinusitis, formation of Stevens -Johnson syndrome as a variant of exanthema progression), usually occur from two to four weeks after the onset of the disease and are bacterial complications [12, 17, 18, 19, 20, 21]. Traditionally, the diagnosis of IMN is based on clinical and hematological changes [22]. Currently, specific diagnostics of IMN consists in determining the DNA of the pathogen by PCR and various classes of specific antibodies by enzyme-linked immunosorbent assay (ELISA). Epstein-Barr virus has specific antigens: early (EAD, EAR), capsid (VCA), nuclear (EBNA), membrane (MA). If we know the time of appearance of a particular antigen in the blood, we can diagnose acute, latent or chronic forms of infectious mononucleosis caused by the Epstein-Barr virus [23, 24]. As soon as the virus enters the body, the production of IgM and IgG antibodies against the capsid antigen (VCA) begins. IgM are transient, and IgG antibodies persist for life. In the acute form of IMN, early antigens appear: diffuse (EAD) antibodies disappear after 6 months , and localized (EAR) antibodies persist for several years after IMN. Nuclear antibodies (EBNA) are detected 1–6 months after the onset of IMN, the titer increases during recovery. The appearance of capsid or early antibodies in the presence of nuclear antibodies indicates reactivation of this infection [25].

The immunoblot method is also used , it allows to determine antibodies to individual antigens of the pathogen [12]. An indirect sign of infectious mononucleosis is an increase in the blood content of aminotransferases (ALT, AST) and organ-specific liver enzymes (LDH'5, urokinase) [22, 26]. Recovery occurs in 2-4 weeks , but lymphadenopathy , hepatosplenomegaly , and atypical mononuclear cells in the

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blood may persist , which indicates a protracted course of IMN [12]. During the acute phase, patients are isolated, bed rest is prescribed and any physical activity is excluded. It is necessary to adhere to a mechanically and thermally sparing diet rich in proteins and vitamins [27]. Treatment of IMN is mainly based on symptomatic therapy. In case of high fever, antipyretic drugs (paracetamol, ibuprofen) are prescribed [28].

To resolve nocturnal snoring, severe nasal congestion, and in severe cases of the disease, it is reasonable to prescribe glucocorticosteroids in a short course [29, 30]. Prescribing antihistamines is not justified because the occurrence of such a complication as exanthema is not associated with an IgE -dependent immune response. An increase in transaminases in IMN may be the reason for prescribing hepatoprotectors and choleretic drugs. Etiotropic therapy with acyclic nucleosides is theoretically justified, since the virus in the lytic cycle phase (which occurs in acute productive infection) secretes thymidine kinase . With the help of this enzyme, acyclic nucleosides are converted from an inactive prodrug form to an active form that disrupts the synthesis of viral linear DNA [31]. The use of antibiotics is justified in the case of bacterial flora layering, as well as in the development of complications. When prescribing antibacterial drugs, preference should be given to cephalosporins or macrolides [32, 33]. Conclusions. The key to success in the treatment of patients with IMN is timely diagnostics, correct and strictly individual approach to both etiotropic and pathogenetic therapy, as well as timely hospitalization of patients with severe forms of IMN.

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LITERATURE

1. Infectious mononucleosis, childhood social environment, and risk of Hodgkin lymphoma / H. Hjalgrim , KE Smedby , K. Rostgaard [et al.] // Cancer Res. – 2007. – No. 67 (5). – R.2382–2388 .

2. Luzuriaga , K. Infectious mononucleosis / K. Luzuriaga , JL Sullivan // NEJM. – 2010. – No. 362 (21). – P.1993– 2000.

3. Khodak , L.A. Modern features of infectious mononucleosis / L.A. Khodak , O.A. Rzhevskaya // International Medical Journal. - 2006. - No. 1. - P.84.

4. Odumade , OA Progress and problems in understanding and managing primary Epstein – Barr virus infections / OA Odumade , KA Hogquist , HH Balfour // Clin. Microbiol . Rev. – 2011. – No. 24 (1). – R.193–209.

5. New data on infectious mononucleosis / V.V. Ivanova, I.V. Shildova , E.N. Simovanyan [et al.] // Russian Bulletin of Perinatology and Pediatrics. - 2006. - No. 6. - P. 44-51.

6. Infectious mononucleosis: clinical presentation, pathogenesis, new developments in diagnostics and therapy / V.V. Ivanova, G.F. Zheleznikova, O.A. Aksenov [et al.] // Infectious diseases. – 2004. – No. 4. – P.5–12.

7. Features of clinical manifestations and immune shifts in reactivation of Epstein-Barr virus infection in children / E.N. Simovanyan , L.P. Sizyakina , A.M. Sarychev [et al.] // Current issues of infectious pathology and vaccination in children: Congress of pediatricians-infectious disease specialists of Russia: materials. - M., 2005. - No. 4. - P. 166.

8. Shulzhenko, A.E. Herpes infections – present and future / A.E. Shulzhenko, G.Kh. Vikulov, T.V. Tutushkina // Difficult patient. – 2003. – V. 1, No. 4. – P.6–15.

9. Herpetic infections in patients with immunodeficiency / M.Yu. Kalugina, N.V. Karzhas , V.I. Kozina [et al.] // Journal of Microbiology, Epidemiology and Immunology. - 2009. - No. 1. - P.79-80.

10. Stepanova, E.V. Purulent-septic and opportunistic diseases in HIV infection / E.V. Stepanova, O.V. Panteleeva, V.V. Rassokhin // Bulletin of Hematology. - 2010. - No. 1. - P.64-65.

11. Cytomegalovirus (CMV) infection – related to male and or female infertility factor? / W. Eggert-Kruse, M. Reuland , W. Johannsen [et al.] // Fertil . Steril . – 2009. – No. 91 (1). – R.67–82.

12. Human herpesvirus infections: a guide for doctors / V.A. Isakov, E.I. Arkhipova, D.V. Isakov. - St. Petersburg: SpetsLit , 2013. - 670 p.

13. Behavioral, virologic, and immunologic factors associated with acquisition and severity of primary Epstein-Barr virus infection in university students / HH Balfour, OA Odumade , DO Schmeling [et al.] // J. Infect. Dis . – 2013. – No. 207. – R.80–88.

14. Infectious diseases: atlas: manual / V.F. Uchaikin [et al.]. – M.: GEOTAR-Media, 2010. – 384 p.

15. Zaitsev, I.A. Hepatitis caused by the Epstein-Barr virus / I.A. Zaitsev, V.T. Kiriyenko // Health Ukraine 21 stories : medical newspaper. – 2016. – No. 9. – P.52.

16. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis / A. Chovel -Sella, A. Ben Tov, E. Lahav [et al.] // Pediatrics. – 2013. – No. 131 (5). – R.1424–1427 .

17. Rinderknecht , AS Spontaneous splenic rupture in infectious mononucleosis: case report and review of the literature / AS Rinderknecht , WJ Pomerantz // Pediatr . Emerg . Care. – 2012. – No. 28 (12). – P.1377–1379.

18. Jappe , U. Amoxicillin induced exanthema in patients with infectious mononucleosis: allergy or transient immunostimulation / U. Jappe // Allergy. – 2007. – No. 62 (2). – R.1474–1475 .

19. Carra Dalliere , C. Isolated palsy of the hypoglossal nerve complicating infectious mononucleosis / C. Carra Dalliere , R. Mernes , R. Juntas-Morales // Rev. Neurol. (Paris). – 2011. – No. 167 (8/9). – R.635–637 .

20. Jenson, HB Acute complications of Epstein-Barr virus infectious mononucleosis / HB Jenson // Curr . Opin . Pediatr . – 2000. – No. 12. – R.263–268 .

21. Agranulocytosis after infectious mononucleosis / T. Yokoyama Y. Tokuhisa , A. Toga [et al.] // J. Clin. Virol . – 2013. – No. 56 (3). – P.271–273.

22. Papesch , M. Epstein-Barr virus infectious mononucleosis / M. Papesch , R. Watkins // With lin. About laryngol . – 2001. – No. 26 (1). – P.3–8.

23. Volokha , A. P. Epstein – Barr in i russian i nfec t i ya at d i tey / A . P. Volokha , L. I. Chernishova // Suchasn i i infection ii. – 2003. – No. 4. – P. 79–92.

24. Chernyshova, L.A. Approaches to the treatment of persistent infections in children / L.A. Chernyshova // News of medicine and pharmacy. - 2005. - No. 316 (176). - P.18.

25. Cohen, JI Epstein – Barr virus infectious / JI Cohen // N. Engl. J. Med. – 2000. – Vol. 343, No. 7. – R.481–492 .

26. Khmilevskaya , S.A. Features of the functional state of the liver in various variants of Epstein-Barr virus infection in children / S.A. Khmilevskaya , I.A. Zaitseva, E.V. Mikhailova // Infectious diseases of the blood. - 2010. - No. 2. - P.30-35.

27. Lavrenova, G.V. Our experience in treating infectious mononucleosis. New technologies in otolaryngology / G.V. Lavrenova // Collection of articles of the interregional scientific and practical conference with international participation dedicated to the 90th anniversary of Professor N.V. Mishenkin . - Omsk, 2016. - P.24-28.

28. Auwaerter , PG Infectious mononucleosis: return to play / PG Auwaerter // Clin. Sports Med. – 2004. – No. 23. – R.485–497 .

29. Should you use steroids to treat infectious mononucleosis / KP Dickens, AM Nye, V. Gilchrist [et al.] // J. Fam. Pract . – 2008. – No. 57 (ll). – R.754–755 .

30. Dexamethasone for the treatment of sore throat in children with suspected infectious mononucleosis: a randomized, double blind, placebo controlled trial / MT Roy, B. Bailey, DK Amre [et al.] // Arch. Pediatr . Adolesc . Med . – 2004. – No. 58 (3). – P.250–254.

31. "Clinical masks" of infectious mononucleosis. Ways of therapeutic correction / A.A. Arova , L.V. Kramar, A.M. Alyushin [et al.] // Department of Children's Infectious Diseases, VolGMU : Volgograd Scientific Medical Journal. - 2011. - No. 2. - P.26-31.

32. Textbook of pediatric infectious diseases / RD Feigin JD Cherry, SL Kaplan [et al.]. – 6th ed. – Philadelphia; PA: Saunders, 2009. – pp . 895–929.

33. Nelson textbook of pediatrics / RM Kliegman , RE Behrman, HB Jenson [et al.]. – 18th ed. – Philadelphia; PA: Elsevier Science Health Science Division, 2008. – pp . 191–196.

34. Ziyodullayevich AM Studies on the Determination of Cytokines in Patients with Chronic Hepatitis C with Criglobulinemia //American Journal of Pediatric Medicine and Health Sciences (2993-2149). – 2023. – T. 1. – No. 10. – pp. 487-495.

35. Oblokulov A., Abdulloev M. STUDY OF THE EFFECTIVENESS OF DIRECT-ACTING ANTIVIRAL DRUGS IN THE TREATMENT OF CHRONIC VIRAL HEPATITIS C // Journal of the Vestnik Vracheva. - 2020. - V. 1. - No. 3. - P. 70-73.