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CLINICAL SIGNIFICANCE OF CYTOMEGALOVIRUS INFECTION AFTER LIVER TRANSPLANTATION

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Abstract

Cytomegalovirus is the most common and significant infection in children after liver transplantation with the development of episodes of CMV infection (CMVI) or CMV disease. CMV infection was first described by M. Ribert in 1881, when cytomegalic cells were found in kidney tissue in congenital syphilis. Cytomegalovirus is widely spread both among patients in a state of long-term drug-induced immunosuppression, and among the General population, according to the R. Razonable study, the incidence of cmvi in the population is from 60 to 100%. About half of children attending preschool institutions have suffered an episode of active cmvi, while this indicator increases by 10-15% every year. N. Singh reports a 27% incidence of cmvi, among 139 patients included in the study, all patients received prophylactic antiviral drugs, a higher (50%) incidence rate was observed in the study of I. Lautenschlager without the use of prevention. A. Jain and co-authors reported a 14.3% incidence of active CMV in patients receiving preventive therapy within a year after transplantation, and E. Gane and co-authors reported a 25% incidence of CMV.

During liver transplantation, children should take into account the high risk of developing active cmvi in the postoperative period. Complications of the course of active cmvi are: CMV-a disease with organ damage, CMV-associated rejection of a liver transplant.

The Basis of CMV infection prevention should be a combination of monitoring the activity of the infectious process with long-term drug prevention and treatment of all episodes of active CMVI.

Keywords: *cytomegalovirus, liver transplantation, children.*

Cytomegalovirus is the most common and significant infection in children after liver transplantation with the development of episodes of CMV infection (CMVI) or CMV disease. Cmvi is associated with an increased risk of graft loss. The literature review presents such aspects as the etiology and epidemiology of cmvi after liver transplantation in children, the approaches used for the diagnosis and prevention of cmvi, valganciclovir dosing algorithms, and methods for preventing complications of cmvi. The latest data on current cmvi prevention strategies in the world practice is also presented. Cytomegalovirus is one of the most common viral agents that affects the outcome of liver transplantation. [*Razonable RR et al. 2003, Razonable RR et al. 2004*]. the DNA genomic virus of the genus Cytomegalovirus (Cytomegalovirus hominis) belongs to the subfamily Herpaherpesvirinae of the family Herpesviridae.

CMV infection was first described by Ribert M. in 1881, when cytomegalic cells were found in kidney tissue in congenital syphilis. CMV was isolated from cell culture by Smith M. in 1956. The diameter of CMV virions is 120-150 *nm*. The virion is covered with glikoproteinami shell. The virus has the form of an icosahedron, the protein shell of which consists of 162 symmetrically arranged capsomers. The CMV genome is represented by double-chiral DNA. CMV is thermolabile, inactivated at a temperature of + 56°C, its optimal pH is 7.2-8.0. Currently, three CMV strains have been identified: Davis, AD 169, and Kerr.

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The features of CMV in comparison with other herpetic viruses include: large DNA, the ability to replicate without damaging cells, low cytopathogenicity, slow virus replication, low virulence, low sensitivity to many nucleoside analogues, sharp suppression of cellular immunity.

Cytomegalovirus is widely spread both among patients in a state of long-term drug-induced immunosuppression, and among the General population, according to the R. Razonable study, the incidence of CMVI in the population is from 60 to 100% [*Razonable RR et al. 2003, Razonable RR et al. 2004*].About half of children attending preschool institutions have suffered an episode of active cmvi, while this indicator increases by 10-15% every year [*Dobbins JG et al., 1994*]. The reservoir of CMV in nature is only a person. From the infected body, the virus is released with urine, saliva and tear fluid. A serious problem is the possibility of CMV infection in blood recipients. it is known that blood transfusions from seropositive donors infect from 15 to 40% of children and 2-3% of adults. Even more complex problems are associated with organ transplantation, since the factor of infection transmission can be not only transfusion of blood components, but also the transplanted organ [*Tsirulnikova OM, et al., 2010*]. The incidence of cmvi in patients after liver transplantation is in a wide range from 13 to 75%, which is associated with different schemes for preventing cmvi, the degree of immunosuppression, different methods for confirming the presence of infection, as well as different periods of follow-up after transplantation [*Seehofer D et al. 2002, Indolfi G et al. 2012, Singh N et al., 2005, Fishman JA et al. 1998, Singh N et al., 2006 Müller V et al. 2012*]. According to a review by Fishman JA in 1998, about 75% of patients after liver transplantation experienced primary or recurrent cmvi. Such a high level of prevalence was associated more with the approach to prevention: the administration of intravenous ganciclovir occurred either in the case of CMV detection to prevent the clinical manifestation of CMV disease, or in the case of the need for antilymphocytic immunosuppressive therapy [*Fishman JA et al. 1998*]. According to American researchers, the incidence of cmvi among recipients after liver transplantation is at a level exceeding 50% [*Seehofer D et al., 2002, Singh N et al., 2006*]. In the V. Müller study, CMV viremia was detected in 51 patients (32%), a total of 159 patients after liver transplantation were included in the study. CMV was diagnosed by PCR testing of blood serum, and the reaction was considered positive when more than 400 copies/ml were detected. CMV-the disease was diagnosed in 12% of CMV-infected patients [*Müller V et al. 2012*].

N. Singh reports a 27% incidence of cmvi, among 139 patients included in the study, all patients received prophylactic antiviral drugs [*Singh N, et al., 2005*], a higher (50%) incidence rate was observed in the study of I. Lautenschlager without the use of prevention [*Lautenschlager I, et al., 2006*]. A. Jain and co-authors reported a 14.3% incidence of active CMV in patients receiving preventive therapy within a year after transplantation [*Jain A, et al., 2005*], and E. Gane and co-authors reported a 25% incidence of CMV [*Gane E, et al., 1997*]. Different levels of infection were observed among centers where combined prevention with ganciclovir and specific antibodies was used [*Seehofer D, et al., 2002*]. A. Tzakis reported a 13% incidence rate of active cmvi in this prevention scheme [*Tzakis AG, et al., 2001*]. In the N. Nierenberg study, which included 276 patients from 1999 to 2009, the incidence of active cmvi within five years after transplantation was 52%, and 8% of patients developed CMV disease in the first 2 years after liver transplantation [*Nierenberg NE, et al., 2014*]. In the Korean study of J. Kim, the frequency of active cmvi was demonstrated at 55.7%, CMV-diseases at 5.5%, such data were obtained when analyzing 618 patients for the period from 1996 to 2009, prevention and treatment methods varied [*Kim JM et al.,*

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

2011]. The pediatric group of patients after liver transplantation should be considered separately. In a study by J. Bowman in 1991, the detection rate of active cmvi among children after liver transplantation who did not receive preventive antiviral therapy was 40%, with a mortality rate of about 19% **[***Bowman III J. S., et al. 1991*]. According to the Japanese study Y. Kawanoa among children after a related liver transplant, the CMV infection rate was 36.3%, and the average incidence of CMV diseases was 60.6%. This study included 93 patients in whom antiviral prophylaxis was not used, and preventive therapy was prescribed when cmvi was detected by the diagnosis of pp65-positive lymphocytes **[***Kawano Y et al., 2014*]. According to the study G. Indolfi among children within 21 days after liver transplantation, the rate of reactivation of infection was obtained at the level of 29%, and together with the primary infection, the frequency of viremia was 44% **[***Indolfi G et al. 2012*].

Thus, the prevalence of cmvi can reach 100% both in the General population and in patients after liver transplantation. Such a high incidence among patients after liver transplantation is due to the current lack of unified approaches to the diagnosis and prevention of cmvi. In the early period after transplantation, the most important indicators are: the frequency of infection manifestation, the frequency of CMV recurrence, and the frequency of development of the clinical picture with the development of CMV disease. Minimum rates of cmvi recurrence are achieved in centers that adhere to three main principles: first, the intensity of prevention should be higher, the higher the degree of drug - induced immunosuppression, second, prevention should be initiated before reactivation of cytomegalovirus, and third, in order to prevent the recurrence of infection, prevention should continue for at least three months after the end of therapy for an active episode of CMVI.

Both non-specific factors and specific immune mechanisms are involved in the formation of anti-cytomegalovirus immunity. Non-specific protection factors – the interferon, complement, and natural killer cells (EC, NK) - slow down the rate of pathogen spread at the first stages of the infectious process, and further potentiate the activity of specific immunity and prevent infection of non-infected cells. The most effective defense against CMV is the formation of specific immunity: the formation of specific anti-CMV antibodies and specific “killer cells” (specific anti-CMV t - lymphocytes CD8). Cmvi causes CMV-specific cellular-mediated immune response, which is the principal factor controlling the presence of the virus in the human body. A specific immune response during initial contact with the cytomegaly virus is formed within 14-28 days. When the virus is first infected, specific antibodies appear and rapidly increase in the first weeks after infection - IgM, IgA, and IgG-antibodies are detected in the serum shortly after symptoms appear. Within 2-3 weeks, the titers of these antibodies constantly increase. Starting from the 2nd month after infection, the concentration of IgM antibodies gradually decreases, IgM and IgA antibodies remain in the body usually for 6-12 weeks. The concentration of IgG-antibodies remains at a high level indefinitely, in decreasing titers for life. In the case of superinfection with another CMV strain, The IgM antibody titer may rise again temporarily. However, the antibodies are devoid of protective properties, which is manifested, in particular, by the easy isolation of the virus from infected people (despite the presence of antibodies). With repeated contact of the body with the same strain of virus, the “protective level” of specific immunity, both antibody and cytotoxic, is formed in a shorter time – up to 7-14 days. CMV is characterized by significant antigenic diversity. Therefore, when a seropositive person is infected with another CMV strain, the formation of secific immunity against this pathogen will occur, as with primary contact. Previously developed type-and group-specific anti-CMV-at to other CMV strains will restrain active replication of the virus.

Whole virions are a weak signal for the immune system, since the main set of pathogen antigens is “hidden” under the viral envelope. More effectively, the immune system recognizes virus antigens that are “exposed” when it is destroyed.

Pathogen antigens are presented to the immune system only when there is a friendly interaction of factors of non-specific protection and, first of all, phagocytosis. As a result of presenting information to lymphocytes about the antigenic features of the pathogen, clones of B-lymphocytes (CD19) synthesizing anti-CMV-at are formed, and clones of specific T-lymphocytes (CD8) whose cytotoxic activity is directed against specific antigens of the cytomegaly virus.

It is assumed that in some cases of intrauterine infection (including cmvi), the fetal immune system perceives the antigen determinants of the pathogen as its own, which is accompanied by the development of immunological tolerance to them. At the same time, specific questions about the possibility, options and consequences of tolerance to pathogens of perinatal infections, including CMV, are under study. There is reason to believe that immunoediting period, i.e. the period of formation of tolerance to CMV antigens during the maturation of immunological reactivity is very long and continues also in the postnatal period of the child's life. This fact is confirmed by the detection of virus antigens in a number of children without any indicators of the formation of a specific anti-CMV-humoral immunity. Similar ratios occur in 7-15% of children examined for suspected intrauterine infection. Insufficient immune response is also found in cases of simultaneous virus persistence with a slight increase in the titer of anti-CMV-at. There is a close relationship between the state of the main indicators of humoral and cellular immunity of fetuses at the time of birth, children in the early neonatal period and the mother's body, regardless of the gestation period and the presence of risk factors for intrauterine infection. When studying the content of immunoglobulins in the blood serum of newborns with intrauterine infection in some studies, a significant increase in IgM and IgA levels was detected, the IgG content remained within the normal range. In other studies, there was a significant increase in IgM, IgA, and IgG, with intrauterine infection causing an increase in the level of IgG and IgA in newborns, while the IgM level reached values in adults. Normalization of indicators was registered only at the age of 1-3 years. The level of serum IgG in newborns with cytomegalovirus infection was significantly lower than in the control group. In subsequent follow-up periods, IgG values were characterized by a pronounced increase in indicators and exceeded similar parameters in healthy children. Low IgG rates in newborns with cytomegaly are probably due to a high percentage of premature babies, as well as significant consumption of maternal IgG delivered via the placenta. Serum IgA indices in congenital cytomegalovirus infection were 1.5-2 times higher than similar parameters in healthy children. The rapid growth of immunoglobulin levels in infected children was determined by early antigen stimulation, as well as a large number of concomitant infections that developed postnatally. A significant increase in the content of immunoglobulins in the blood of a newborn can be a marker of chronic infection in the prenatal period and repeated in the postnatal period. An increase in the concentration of specific IgM antibodies in the serum of the umbilical cord or peripheral blood of a newborn child above 20 *mg/DL* makes it possible to suspect the fact of intrauterine infection. However, it is believed that an increase in the level of IgM in the cord blood is not an indicator of the infectious process in the newborn, but reflects the antigenic stimulation of the fetus in the antenatal period. Low IgG levels in newborns born to mothers at risk for intrauterine infection of the fetus are considered only as evidence of a low level of passive immunity in this category of newborns, which increases the risk of bacterial complications in the postnatal period. Some authors have identified newborns from mothers with infectious pathology with Hypo-G-immunoglobulinemia, enhanced synthesis of their own IgM and IgA both in utero and in the first days of life. In 20% of newborns after intrauterine antigen stimulation or in cases of purulent-inflammatory diseases in the early neonatal period, increased synthesis of their own IgG was observed from the first days of life. There is evidence of increased IgM and decreased IgG levels in cord blood and throughout the early neonatal period. At the same time, significantly lower IgG

values are observed in the cord blood of newborns with clinical forms of intrauterine infections.

In CMV infection, the synthesis of immunoglobulins by the fetus is activated primarily due to IgM, but sometimes in intrauterine infection, IgG and IgA synthesis is very sharply activated, and in these cases, an abundance of circulating immune complexes (CIC) is formed during prolonged exposure to CMV, which damage tissues. In the fetus, the organ in whose vessels these complexes and CMV itself settle is the brain, so typical manifestations of intrauterine infection include encephalopathy and encephalitis. In addition, special studies often detect immunoglobulins in brain cells. In the prenatal period, the virus can cause clonal elimination of maturing T and B cells, which disrupts the development of the immune response to this virus. Premature intrauterine stimulation of the immune system can lead to polyclonal activation of B-lymphocytes and the formation of autoantibodies and circulating immune complexes. This is the background for the development of autoimmune and immunocomplex diseases. Long persisting in the child's body, cytomegalovirus contributes to the polyclonal activation of B-lymphocytes, the formation of autoantibodies and immune complexes, which is realized in the further development of allergic and autoimmune pathology. Children with congenital cmvi have disorders of humoral and cellular immunity, long-term CMV excretion and insignificant levels of specific antibodies. The humoral link of the immune system reduces the virulence of CMV, but does not allow you to completely free yourself from the virus. Humoral immune response is also produced in latent infection – complement-binding and virusneutralizing antibodies appear in serums. Against the background of active cmvi, significant immune shifts occur. A special property of CMV is the ability to cause depression in almost all parts of the immune system – to cause macrophage dysfunction, sharply suppress the activity of interleukin production, and inhibit the production of interferon. CMV suppresses the ability of infected immunocompetent cells to synthesize interleukins due to excessive production of prostaglandins, and the reactions of target cells to interleukin-1 and interleukin-2 are also altered.

The main risk of graft loss and death after liver transplantation was shown to reduce the incidence of these complications using prevention in two meta-studies. There is also evidence that without the use of preventive antiviral drugs, approximately 44-65% of cases develop cmvi within the first year after liver transplantation.

The entrance gates for primary infection are the mucous membranes of the mouth, gastrointestinal tract, and genitals. The virus that has entered the blood is reproduced in white blood cells and the system of mononuclear phagocytes or persists in the lymphoid organs. CMV virions are adsorbed on cell membranes, penetrate the cytoplasm and induce cytomegalic cell metamorphosis. Viral DNA is detected in T-helpers and T-suppressors even at long-term periods of reconvalescence. The virus has a pronounced tropism to the epithelium of the salivary glands and kidney tubules, where it is able to replicate for a long time and secrete from the body with saliva and urine. CMV causes significant disturbances in the regulation of the immune response, which are based on damage to the interleukin system. As a rule, the ability of infected immunocompetent cells to synthesize interleukins due to excessive production of prostaglandins is suppressed, and the reactions of target cells to interleukin-1 (IL-1) and interleukin-2 (IL-2) are also changed. Virus-induced immunosuppression develops with a sharp inhibition of the function of natural killers. Primary CMV infection in immunocompetent patients usually occurs asymptomatically or as a mononucleosis-like syndrome with fever, after which the virus latently persists in various cells throughout life **[***Razonable RR et al., 2004, Razonable RR et al., 2003*]. The described features of the virus play an important role in the pathogenesis of cmvi in liver recipients: CMV is reactivated from the latent state when the cytokine response is activated during graft rejection and during the course of systemic inflammation.in this situation, tumor necrosis factor and other Pro-inflammatory cytokines are produced, which in turn activate intracellular replication factors (such as

nuclear transcription factor NF-kB), viral DNA replication and activation of latent cmvi **[***Fishman JA et al., 2007*]. A characteristic pathomorphological feature of CMV is giant cells detected in tissues, saliva, sputum, urine sediment and cerebrospinal fluid. Cells have intracellular and cytoplasmic inclusions and contain a multiplying virus. Changes in the cell nucleus give it the appearance of an owl's eye. Giant cells are localized mainly in the epithelium of the excretory ducts of the salivary glands, in the epithelium of the distal parts of the nephron in the kidneys, in the epithelium of the bile ducts in the liver, in the epithelium of the ventricles of the brain. In response to CMV exposure, lymphohistiocytic infiltrates occur in the surrounding interstitial tissue, sometimes having the character of nodules. In the generalized form, more often there is a lesion of the lungs, kidneys and intestines, less often — the liver and other organs. Along with giant cells and lymphohistiocytic infiltrates, interstitial pneumonia is detected in the lungs, interstitial nephritis in the kidneys, ulcerative enterocolitis in the intestines, and cholestatic hepatitis in the liver. Latent CMV carrier can cause infection of the recipient during blood transfusion, liver transplantation, pharmacologically-induced suppression of the immune system in the liver recipient is also a serious risk factor for reactivation of endogenous infection or primary activation of the virus in the graft cells, leading in a short time to fever and tissue-invasive disease, and in the long term to graft dysfunction and reduced patient survival **[***Gane E. et al., 1997, Ljungman P et al., 2002, Razonable RR, et al., 2003, Razonable RR et al, 2004, Arthurs SK, et al., 2007*].

The early period after transplantation is the most significant for the development of cmvi, relapse most often occurs in the first three months after transplantation, most viremia occurs in the first 6 weeks after transplantation, which is primarily due to the need to maintain a high level of drug-induced immunosuppression.

Thus, children after liver transplantation have a higher risk of primary CMV infection compared to the group of adult recipients.in this situation, the child first encounters infection during the period of maximum immunosuppression, which contributes to the development of clinical manifestations of CMV disease.

Infectious complications after liver transplantation in children currently remain one of the main causes of morbidity and mortality. Thus, in the R. Shepherd study, which included 2,291 children after liver transplantation, the incidence of infectious complications in the first 15 months after surgery was at the level of 52% **[***Shepherd RW et al., 2008*]. In the Kim J. study, which included 534 liver transplants, the incidence of cmvi was at the level of 24% (128 cases) **[***Campbell AL, et al., 2004*]. The incidence of cmvi among children after liver transplantation is higher than among adult recipients, which is primarily associated with a high probability of primary infection, especially in young children. Some researchers in the United States also divide cmvi with the development of clinical manifestations into early (up to 120 days after transplantation) and late (more than 120 days after transplantation). This approach also involves dividing the effects of CMV viremia into primary, secondary, and tertiary complications. The primary complications in this classification include CMV-syndrome and CMV-disease with damage to internal organs. Secondary complications include: acute graft rejection, opportunistic infections, and sepsis. Tertiary complications include: thrombocytopenia, leukopenia, neutropenia **[***Bedel AN et al., 2012*].

J. M. Kim and co-authors divide cmvi into early and late cmvi that occurred in the first 3 months and more than 3 months after transplantation. CMV-disease is divided into CMV-syndrome (antigenemia combined with one or more symptoms - unexplained fever above 38.3, fatigue, myalgia, leukopenia less than 3000/mm^3, thrombocytopenia less than 100 thousand/mm^3) and CMV-disease with tissue invasion (hepatitis, pneumonia, retinitis, gastroenteritis, confirmed by biopsy) **[***Kim JM, et al., 2011*].

Direct effects of cmvi may include flu-like or mononucleosis-like syndrome, often accompanied by neutropenia, and possible damage to the kidneys, liver, heart, lungs, pancreas, and intestines

[*Fishman JA et al., 1998*]. Usually, direct effects are divided into CMV-syndrome and CMV-disease with virus invasion in tissues **[***Ljungman P et al., 2002*]. Non-specific viral syndrome is characterized by fever, hematological changes in the form of leukopenia, atypical lymphocytosis, and thrombocytopenia.

Tissue-invasive disease manifests with damage to internal organs (gastrointestinal tract, liver, lungs) **[***Kelly DA, et al., 2013, Razonable RR, et al., 2004*]. CMV most often affects the gastrointestinal tract: CMV-gastritis, enteritis, esophagitis, colitis, which is more than 70% of all CMV diseases among patients after transplantation **[***Fica A et al., 2007*]. CMV-retinitis is a rare complication of cmvi, can occur without clinical manifestations, especially if the lesion affects the peripheral region of the retina, in some cases, late diagnosis and ineffective treatment can lead to vision impairment **[***Squires JE et al., 2013*]. The study of D. Gotthardt (Germany) demonstrated that CMV can affect the bile ducts and lead primarily to the development of cholangitis, and subsequently to clinically significant narrowing of the ducts outside the zone of anastamosis and micro-damage of the bile ducts after liver transplantation. An interesting fact is that when positive CMV PCR was detected in the bile, a parallel negative result was obtained in the blood test **[***Gotthardt DN et al., 2013*].

In General, CMV disease develops in 18-29% of patients after organ transplantation **[***Paya C et al., 2004, Hoppe L et al., 2006, Gane E et al., 1997*]. A significant influence on the severity of the infection process is provided by the cmvi prevention strategy. According to the results of a number of studies without the use of specific antiviral prevention, cmvi with a characteristic clinical picture develops in 22-60% of patients in the period of 30-90 days after transplantation **[***Ljungman P et al., 2002, Kullberg-Lindh C et al., 2003, Sun HY et al., 2008*]. Also, a significant factor for the development of clinical manifestations of cmvi is the lack of specific immunity before transplantation. According to a study by R. Desai (2015) ten-year survival of patients after liver transplantation with combination of serostatus D+/R- ("D+" is the liver donor antibodies to CMV, "R-" - absence in the recipient of antibodies to CMV) were 13% lower compared to patients of group D-/R-. CMV status was not associated with an increased risk of malignant diseases **[***Kanj SS et al. 1996*].

P. Rebecca, using a hybrid approach of CMV prevention among 34.4% of children with positive CMV PCR, 9.8% had clinical manifestations of CMV disease **[***Madan RP et al. 2009*]. Most researchers conclude that, in addition to the direct effects of invasive infection, CMV is also associated with indirect effects: increased likelihood of graft dysfunction and rejection **[***Fishman JA et al. 2007, John LRF 2013, Kelly DA et al., 2013*]. In patients after liver transplantation, graft survival rates were lower in cases of CMV registration than in patients from the group who did not survive this infection. In the S. Arthurs study, which included 67 observations, found that patients with a clinical picture of cmvi had an approximately 1.5-fold increased risk of death or graft loss **[***Arthurs SK et al., 2007*]. According to the study of P. Gupta, which included 285 children after liver transplantation, a significant relationship between cmvi and chronic graft rejection was confirmed **[***Gupta P et al., 2001*]. The relationship of cmvi with an increased probability of developing chronic rejection was also confirmed in the study by P. Evans, when the duration of viremia for more than 30 days significantly led to an increased risk of developing chronic rejection **[***Evans PC et al., 2000*]. Exposure to cytomegalovirus leads to changes in the immune response, altering the molecules involved in the mechanisms of immune recognition and inflammation. As a result, CMV actions are associated with General non-specific immunosuppression, which leads to an increased risk of opportunistic infections **[***Rubin RH, et al., 1999*]. Cmvi in patients after liver transplantation is a risk factor for bacterial infections, hepatitis C progression, and invasive fungal infections (including Pneumocystis carnii, Aspergillus fumigatus, and Candida albicans) **[***Paya CV et al., 1999, Rubin RH et al., 1999*]. According to the A. Milan study, a statistically significant correlation was obtained between the presence of cmvi and the frequency of

concomitant bacterial infection, 81% of patients with cmvi had a concomitant infection, and 24% of patients without cmvi [*Milan A et al. 2013*]. It was also found that the presence of cmvi is associated with an increase in cases of Epstein-Barr virus-induced posttransplant lymphoproliferative disease [*Basgoz N et al., 1995, Samanta M et al. 2003, Cobbs CS et al., 2002, Mañez R, et al. 1997, Harkins L et al., 2002*]. It should be noted that there is limited data that does not show a direct link between cmvi and the occurrence of acute rejection reactions [*Arthurs SK et al., 2007, Singh N et al. 2005, Slifkin M et al., 2005, Müller V et al., 2012*]. The relationship of cmvi with increased mortality has not been confirmed in studies. Hoppe et al., V. Müller et al. - five-year survival rate of 85% for the group infected with CMV and 84% for the group without CMV [*Hoppe L et al., 2006, Müller V., et al., 2012*].

The most reliable method for detecting cmvi is quantitative PCR, which is used to detect viral DNA. A routine method of confirming the diagnosis is to measure the level of viral load in the peripheral blood. this method is especially important for detecting subclinical forms of cmvi [*Smith BA et al., 2005*]. Quantitative PCR is a more sensitive method for assessing the degree of infection compared to the determination of the pp65 protein. According to a review by L. Danziger-Isakov in 2014, viral load monitoring was used in the prevention of cmvi in 26 out of 29 centers in the United States and Canada [*Danziger-Isakov L et al., 2014*].

In the United States, the Protocol for monitoring and diagnostics for children after liver transplantation recommends performing CMV PCR in serum every two weeks for the first three months after transplantation and monthly for a year after transplantation [*Bedel, AN et al., 2012*]. X. Chen in a 2013 study showed the advantages of using whole blood for CMV PCR diagnostics, compared to using serum or plasma. The whole blood test method is more sensitive and detects more copies of CMV DNA [*Chen XY et al., 2014*]. Another method used in foreign studies reveals the presence of the protein pp65, which is a specific cytomegalovirus antigen. During the period of active virus replication, this protein accumulates mainly in granulocytes and to a lesser extent in monocytes. Thus, the number of antigen-positive cells per 100 thousand white blood cells is registered. The advantage of quantitative detection of pp65 is that, despite the lower sensitivity of the method, it shows a greater correlation with the development of CMV disease [*Müller V et al., 2012*].

In the J. Kim study, antigenemia was established in the presence of one or more cells containing pp65 antigen among 400 thousand leukocyte cells [*Kim JM et al., 2011, Kim J.M., et al., 2010*]. Japanese researchers widely use this method of diagnosis and positively accept the result when detecting an antigen in one or more lymphocytes among 50 thousand cells.

In 2014, L. Danziger-Isakov conducted a large-scale review study that included data on recommendations and protocols used in 29 centers that perform liver transplantation in children (27 centers in the United States, 2 centers in Canada). As a result, it was found that all centers use serology in the pre-transplant infection screening protocols, 12 centers use serum CMV PCR, 1 center uses urine CMV PCR, 5 centers study urine viral culture, and 3 centers study CMV antigenemia [*Danziger-Isakov L et al., 2014*]. More often used is the monitoring of the presence of viral DNA in the recipient's blood by PCR, less often used is the determination of antigenemia by the detection of pp65 protein. Regardless of the detection method used, there is no uniform and reasonable approach to the frequency of studies conducted and the timing of post-liver transplantation, immunosuppression protocols used, and other significant factors.

The most serious risk factor for CMV disease in the post-transplant period is the lack of specific immunity to cytomegalovirus [*Lee S et al., 2013*]. The high-risk group includes recipients who did not have cmvi detected at the stage before liver transplantation, who received an organ from a donor with confirmed cmvi [*Hodson EM et al., 2005, Krampe K et al., 2010*]. Therefore, the most unfavorable combination will be the combination of CMV-positive donor with CMV-negative recipient. in this combination, the risk of CMV-viremia

with the development of the clinical picture and complications is highest [*John, LRF et al. 2013, Lee S et al., 2013*]. With this combination, the recipient is highly likely to encounter cmvi early after transplantation, the source of infection in this case may be the donor liver, and the lack of specific immunity in combination with intensive drug immunosuppression creates conditions for the development of clinically significant early cmvi with direct and indirect manifestations. Patients with a combination of serological status D - /P-showed the lowest probability of cmvi-4.17%, which was significantly less than in patients from the groups D+/P+ (24.1%) and D+/P- (35.7%) [*Müller V et al. 2012*]. Currently, according to the world literature, there are no unified approaches to the methods of diagnosing cmvi both among adult liver recipients and in the group of children's liver recipients. Data on paediatric practice is limited.

CONCLUSION (PRACTICAL RECOMMENDATIONS):

1. During liver transplantation, children should take into account the high risk of developing active cmvi in the postoperative period. Complications of the course of active cmvi are: CMV-a disease with organ damage, CMV-associated rejection of a liver transplant.
2. The Basis of CMV infection prevention should be a combination of monitoring the activity of the infectious process with long-term drug prevention and treatment of all episodes of active cmvi.
3. In the pre-transplant period, the detection of active cmvi in recipients should be performed at least once a week. The frequency of monitoring cmvi activity in the early stages after liver transplantation should be at least once a week, in the long term at least once every 3 months.
4. If active cmvi is detected, antiviral therapy with ganciclovir is indicated at a dosage of 10 mg/kg/day with an interval of 12 hours between injections. In the long term after transplantation, treatment of active cmvi without clinical manifestations should be started with valganciclovir at the calculated dosage (two-time administration).
5. The effectiveness of the therapy active cmvi it is necessary to estimate a periodicity of 7 days. An episode of active cmvi can be considered complete after receiving two consecutive negative CMV PCR results at an interval of 7 days.
6. If a relapse of active cmvi is detected in the recipient before liver transplantation, the administration of antiviral therapy with ganciclovir at a dosage of 10 mg/kg/day with an interval of 12 hours between injections is indicated. After the end of an active cmvi episode, antiviral prophylaxis is indicated with ganciclovir at a dosage of 5 *mg / kg / day*, administered once before liver transplantation.
7. For prophylactic purposes, all recipients, starting from 1 day after liver transplantation, are shown the appointment of ganciclovir at a dosage of 5 mg/kg / day (single administration), followed by conversion to oral valganciclovir at the calculated dosage, (single administration).It is necessary to use long-term medical antiviral prevention: 200 days after liver transplantation, up to 100 days after an episode of active CMV, up to 200 days after an episode of CMV-disease.
8. When prescribing pulse therapy for liver transplant rejection, it is necessary to take into account the nature of the course of cmvi, as well as use antiviral prevention with ganciclovir and additional studies of CMV activity in blood plasma by PCR.
9. When cmvi is resistant to basic therapy, it is recommended to prescribe a double therapeutic dosage of ganciclovir, normal human immunoglobulin, and immunoglobulin against CMV, as well as to reduce the level of medicinal immunosuppression or its temporary cancellation.
10. Given the immunodeficiency condition caused by the use of immunosuppressive therapy, liver recipients may be given immunoglobulins to correct the immune imbalance.
11. According to numerous literature data, cmwi when resistant can be used foscarnet.

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