

World Journal of *Hepatology*

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJH* as 0.61. The *WJH*'s CiteScore for 2020 is 5.6 and Scopus CiteScore rank 2020: Hepatology is 24/62.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Lin-YuTong Wang; Production Department Director: Xiang Li; Editorial Office Director: Xiang Li.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

February 27, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Cytomegalovirus infection in liver-transplanted children

Norrapat Onpoaree, Anapat Sanpavat, Palittiya Sintusek

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Yellanthoor RB

Received: February 28, 2021

Peer-review started: February 28, 2021

First decision: March 29, 2021

Revised: April 17, 2021

Accepted: January 15, 2022

Article in press: January 15, 2022

Published online: February 27, 2022



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Abstract

Cytomegalovirus (CMV) infection is a common complication of liver transplantation in children. The CMV serostatus of recipients and donors is the primary risk factor, and prophylaxis or pre-emptive strategies are recommended for high-risk patients. Graft rejection, coinfection and Epstein-Bar virus reactivation, which can lead to post-transplant lymphoproliferative disease, are indirect effects of CMV infection. Assessment of CMV infection viral load should be routinely performed upon clinical suspicion. However, tissue-invasive CMV disease is not associated with CMV viraemia and requires confirmation by tissue pathology. Oral valganciclovir and intravenous ganciclovir are equivalent treatments, and the duration of treatment depends on factors including CMV viral load, tissue pathology, and clinical response. Risk stratification by donor and recipient status prior to transplantation and post-transplantation antiviral prophylaxis or pre-emptive therapy are recommended. Adult guidelines have been established but additional study of the effectiveness of the preventive guidelines in children is needed. This review summarizes the burden, risk factors, clinical manifestations, laboratory evaluation, treatment, and prevention of CMV infection in children after liver transplantation.

Key Words: Cytomegalovirus; Children; Liver transplantation; Pediatric; Infection

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Core Tip: Cytomegalovirus (CMV) infection after liver transplantation in children is a serious complication, with high morbidity resulting from direct and indirect effects. Despite risk stratification, pre-emptive therapy and antiviral prophylaxis, late CMV infection frequently occurs in transplant recipients. If CMV infection is suspected during outpatient visits, then prompt detection is key. If CMV infection is detected, then decreasing immunosuppressants should be prioritized before initiation of antiviral therapy. Oral valganciclovir and intravenous ganciclovir are the mainstays of treatment, with variable duration depending on CMV manifestations, viral load, histopathology, and clinical response.

Citation: Onpoaree N, Sanpavat A, Sintusek P. Cytomegalovirus infection in liver-transplanted children. *World J Hepatol* 2022; 14(2): 338-353

URL: <https://www.wjgnet.com/1948-5182/full/v14/i2/338.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v14.i2.338>

INTRODUCTION

Cytomegalovirus (CMV) infection is common in both immunocompetent and immunocompromised hosts, and the manifestations of primary infection in adolescents and young adults can be serious. In immunocompromised hosts, both primary and latent CMV infection can cause serious disease. The indirect effects of mixed infection, post-transplant lymphoproliferative disease, and graft rejection, are all of great concern. Hence, prevention and prompt management of incident CMV infections are necessary and rapid access to measures to predict and detect CMV infections with high accuracy are required.

TERMINOLOGY

CMV infection is defined as evidence of CMV replication regardless of symptoms. The evidence may involve isolation and identification of the CMV virus or detection of viral proteins or nucleic acids in any specimen. The detection of CMV in the blood may be by standard or shell techniques, CMV pp65 antigen, CMV DNA, or CMV RNA, with CMV viraemia, antigenaemia, DNAemia, or RNAemia[1-3].

CMV reinfection is CMV infection by a different strain from an exogenous source documented by molecular techniques or sequencing of specific regions. Patients with CMV reinfection develop new immune responses to the viral epitopes that are different from the previous primary CMV infection, known as a polymorphic gene[3].

CMV reactivation is a CMV infection that results from reactivation of latent endogenous CMV.

CMV disease includes evidence of CMV infection in combination with attributable symptoms that can be classified as CMV syndrome and tissue-invasive CMV disease or compartmentalized CMV disease. CMV syndrome, which includes fever, malaise, and/or myelosuppression[3], has no organ- or tissue-specific manifestations. Tissue-invasive CMV disease has primary organ-specific pathology and organ-specific manifestations.

PREVALENCE

CMV seroprevalence, or evidence of infection, varies worldwide (from 45% to 100%) in reproductive-age women[4]. Seroprevalence is highest in South America, Africa, and Asia and lowest in Western Europe and the United States. Factors related to high seroprevalence are older age, low socioeconomic status, crowded or unsanitary living conditions, and low education level[5,6]. The age-adjusted seroprevalence of CMV infection was reported as 50.4% in the United States[5] and as 20.7%-28.2% in children aged 1-5 years and as 36.3%-37.5% in those aged 6-11 years[7].

CMV infection can be serious in recipients who were seronegative prior to liver transplantation. Consequently, the risk of infection is stratified by recipient and donor serostatus as seropositive donors with seronegative recipients (D⁺/R⁻), seropositive donors with seropositive recipients (D⁺/R⁺), seronegative donors with seropositive recipients (D⁻/R⁺), and seronegative donors with seronegative recipients (D⁻/R⁻). A study of a series of 146 liver transplant patients reported a higher incidence of post-transplant CMV infection in the 14 children (71.4%) than in the 132 adults (33.4%)[8] because of the high proportion of CMV-naïve recipients. The children also developed CMV infection significantly sooner than the adults, with a mean time to viraemia of 11.5 *vs* 30 d[8].

Antiviral prophylaxis and pre-emptive therapy are intended to decrease CMV infections and disease in liver transplant patients. Without prevention therapy, 18%-85% of adults develop CMV infection and 15%-40% develop CMV disease[9-11], ranging from 1%-2% in D⁻/R⁻ procedures and 44%-65% in D⁺/R⁻ procedures[12]. In young children, the incidence of CMV infection ranged from 44% to 65% within 6 months and up to 2 years in follow-up[13-15]. A study by Saitoh *et al*[13] in Japan reported that in children with pre-emptive therapy, CMV antigenaemia occurred following 63% of the D⁺/R⁻ procedures, 38% of the D⁺/R⁺ procedures, 11% of the D⁻/R⁺ procedures, and 6% of the D⁻/R⁻ procedures. CMV disease occurred with 11% of the D⁺/R⁻ procedures, 2% of the D⁺/R⁺ procedures, 0% of the D⁻/R⁺ procedures, and 6% of the D⁻/R⁻ procedures. A study by Verma *et al*[14] in the United Kingdom, reported late CMV infection in 10.5% and disease in 4.4% of children following liver transplant. None of the D⁻/R⁻ children had late CMV infection or disease 2 years post-liver transplant.

PATHOGENESIS

CMV infection in liver recipients can manifest as a primary infection, reinfection by exogenous virus, or reactivation of endogenous virus in the host cells. After the virus infects the host cells, it replicates slowly, leading to persistent, latent viral infection in recipient cells. Systemic inflammation can cause reactivation of the latent viral state and development of CMV infection. Viral latency at cellular sites may also serve as a route for transmitting the virus to susceptible recipients[12]. The main targets of CMV are epithelial cells[16], with transmission of the virus occurring from host to host *via* mucosal epithelium, as in gastrointestinal CMV infection. Immature dendritic cells underlying the mucosa are also sites of viral replication and shedding, leading to viral spread by lymphatic circulation[17]. In solid organs, the main targets of CMV are mesenchymal and endothelial cells[16,18]. Viral spread within the organ results from infection of connective tissue cells. Infection of endothelial cells contributes to haematogenous spread into organ tissues.

While CMV infection manifests directly as a clinical disease, it can also modulate the host's immune system to lead to indirect effects that cause acute early allograft rejection or late allograft dysfunction. Moreover, immune system dysregulation and immunosuppression associated with impairment of CD4⁺ T cells and macrophages may increase the susceptibility to opportunistic bacterial, fungal, or viral infections including Epstein-Bar virus (EBV) and human herpes virus (HHV)-6[12]. CMV can also infect host vascular endothelial cells and cause the downregulation of genes responsible for the production of extracellular matrix components such as collagen type I and fibronectin, resulting in the development of vascular thrombosis[19].

Protective responses against CMV infection include both innate and cell-mediated immunity. Innate immunity involves Toll-like receptor 2 (TLR2), a pattern recognition receptor that recognizes CMV antigen and consequently promotes antiviral peptide and cytokine production[12]. Tissue dendritic cells are a frontline target of the virus. Cell-mediated immunity is the primary immune response against CMV infection in liver transplant recipients. Interferon-gamma (IFN- γ) produced by CD8⁺ T cells is associated with a decreased risk of CMV disease, and cytokine production is stimulated by recognition of the CMV pp65 antigen by CD8⁺ T cells[20,21]. An enzyme-linked immunosorbent spot assay is available to confirm CD4⁺ and CD8⁺ cell-mediated immune function and quantify IFN- γ produced in response to CMV[22-24]. In addition, humoral immunity against CMV infection develops through production of neutralizing antibodies that target CMV glycoprotein B, which has contributed to the development of a CMV vaccine[25]. Neutralizing antibodies can also be generated against other CMV envelope glycoproteins.

RISK FACTORS OF CMV INFECTION AND DISEASE AFTER LIVER TRANSPLANTATION

CMV serostatus of the recipient and donor

The incidence of CMV infection is generally highest in D⁺/R⁻ liver transplant recipients, and recent studies have reported up to 95% of all recipients with CMV antigenaemia were in either D⁺/R⁻ or D⁺/R⁺ groups[13,14]. The time from transplantation to the onset of CMV viraemia was also shown to be significantly shorter for D⁺/R⁻ patients than for those in the other groups[26]. The evidence supports stratification of liver transplant candidates by the recipient and donor CMV serostatus[27]. D⁻/R⁻ or D⁺/R⁺ patients are considered at low risk, while those who are D⁻/R⁺ are considered intermediate risk and those who are D⁺/R⁻ are considered at high risk[27] (Table 1).

Viral burden

It has been documented that patients with a high initial or an increasing viral load tend to have an increased risk of developing CMV disease after liver transplant[28-30], and early detection is important for clinical management. The viral load cut-off for predicting CMV disease varies with the method of detection. Gerna *et al*[31] found that CMV disease developed in patients with a mean blood CMV viral

Table 1 Risk of cytomegalovirus disease after liver transplantation

Risk factors	
CMV serostatus of recipient and donor	D ⁺ /R ⁻ D ⁺ /R ⁺ and D ⁻ /R ⁺
Viral burden (initial CMV viral load)	High CMV viral load Rate of viral load increasing
Immunosuppressive agents	Antibody to CD3-receptor: OKT3 or muromonab Basiliximab Corticosteroids Mycophenolate mofetil Calcineurin inhibitors: Tacrolimus, sirolimus, and cyclosporine
Recipient immunity	TLR2 gene mutation, mutation of mannose-binding lectin Upregulation of programmed death-1 receptors
Recipient underlying liver disease	Hepatoblastoma with pre-transplant chemotherapy
Other risk factors	Virus-to-virus interaction (HHV6, HCV, fungal infection), transfusion of non-leucocyte-depleted blood products, volume of blood loss, liver transplantation because of fulminant liver failure, older age, non-white race, female sex, CVVH after liver transplant, septic shock, renal insufficiency

CMV: Cytomegalovirus; CVVH: Continuous venovenous haemofiltration; D: Donor; HCV: Hepatitis C virus; HHV-6: Human herpes virus-6; R: Recipient; TLR2: Toll-like receptor 2.

load of 1740 copies/mL. Assay of CMV DNA by real-time quantitative polymerase chain reaction (PCR) [32-34] showed a cut-off value of 180 copies/mL (164 IU/mL) is associated with an increased incidence of severe CMV disease in adult liver transplant recipients[35]. The lack of an international reference standard limits the generalization of study cut-off values for worldwide use. The World Health Organization (WHO) has a reference standard for plasma quantitative nucleic acid testing (QNAT) that transplantation centres can use for calibration[36,37]. International references are needed for other assay methods (Table 1).

Immunosuppressive agents

Drugs that interfere with host immune function also influence the risk of CMV disease. Generally, immunosuppressive agents involving the cytotoxic immune response cause a loss of CMV infection control. They include lymphocyte-depleting drugs used in the induction and rejection phases. OKT3, or muromonab, a murine monoclonal antibody against the CD3 receptor found in mature T lymphocytes, has been correlated with an increased risk of CMV infection[15]. Other drugs that increase the risk of CMV infection include corticosteroids[38], mycophenolate mofetil[39,40], and basiliximab[41]. Calcineurin inhibitors, such as tacrolimus, sirolimus, and cyclosporine, which are commonly used in paediatric patients, have also been associated with an increased risk of CMV disease[41,42]. Tacrolimus and sirolimus concentrations have been correlated with increased viral load in whole blood and plasma from paediatric liver recipients[42]. Monitoring drug levels in patients receiving tacrolimus or sirolimus was recommended, as the correlation between circulating levels and the administered dose was not strong. The assay may be performed with either whole blood or plasma, as the viral load results obtained with each type of sample were highly correlated[42]. Newer drugs, such as mechanistic target of rapamycin inhibitors, have a weaker association with the risk of CMV infection[12] (Table 1).

Recipient immunity

The immune status of liver transplant recipients also contributes to the risk of CMV infection[12]. Defects in innate immunity, such as TLR2 gene mutations, are correlated with an increased risk of tissue-invasive disease[43]. Other defects in innate immunity associated with the risk of CMV infection include mutation of mannose-binding lectin and upregulation of programmed death-1 receptors[44,45] (Table 1).

Underlying liver disease in the recipient

Some underlying liver diseases in recipients before liver transplantation have been associated with the risk of CMV infection. Acute liver failure and hepatoblastoma patients receiving post-transplant chemotherapy had significantly increased risk of CMV infection[13,46]. Recipients with cholestatic liver

disease before transplantation had a decreased risk of CMV infection and those with biliary atresia were reported to have a lower risk of CMV infection[13], with a reported odds ratio of 0.288[15] (Table 1).

Other risk factors

Other risk factors include virus-to-virus interaction [HHV-6, hepatitis C virus (HCV)], fungal infection, transfusion of non-leucocyte-depleted blood products, blood loss volume, liver transplantation because of fulminant liver failure, older age, non-white race, female sex, haemodialysis, septic shock, and renal insufficiency[47,48] (Table 1).

CMV MANIFESTATIONS

Primary infection, reinfection, and reactivation can occur in liver transplant recipients. Primary infection is the development of CMV viraemia in a previously unexposed seronegative recipient, excluding cases with the passive acquisition of CMV antibodies from blood products or immunoglobulin (Ig). The manifestations of primary CMV infection are more severe than CMV reinfection or reactivation from latent endogenous virus[49]. Current guidelines consider D⁺/R⁻ children to be the most prone to developing severe CMV disease from primary infection[50].

Direct effect of CMV or CMV disease

Patients can manifest CMV syndrome or CMV tissue-invasive disease.

CMV syndrome: Systemic manifestations include the detection of CMV in the blood, together with at least two of the following: Fever; new-onset malaise or fatigue; leukopenia or neutropenia in two separate measurements; 5% atypical lymphocytes; thrombocytopenia; and transaminitis three-times the upper normal limit. Fever is defined by a body temperature > 38 °C for at least 2 d within a period of 4 d. Some patients develop lymphadenopathies, hepatosplenomegaly, pharyngitis, and a mononucleosis-like syndrome consisting of a rubelliform rash associated with febrile illness. Less common manifestations include migratory polyarthritis, mainly involving the fingers, knees, and toes[51-53].

CMV tissue-invasive disease: The most common organ involvement in post-liver transplant includes the gastrointestinal tract, liver, and lungs[12]. Gastrointestinal CMV disease may manifest with clinical features such as odynophagia, dysphagia, abdominal pain, diarrhoea, haematochezia, and severe iron deficiency anaemia that could imply gastritis, oesophagitis, enteritis, or colitis (Figure 1)[12]. CMV may also infect the liver allograft, causing CMV hepatitis in which an abnormal liver function test may not clearly distinguish it from allograft rejection. Other less common CMV manifestations include central nervous system (CNS) disease, retinitis, nephritis, cystitis, myocarditis, pancreatitis and cholangitis[54]. However, the diagnosis of tissue-invasive disease is challenging and often requires invasive investigations. Confirmation of CMV CNS disease requires the presentation of CNS symptoms and evidence of CMV infection in cerebrospinal fluid or brain biopsy. CMV retinitis is diagnosed by fundoscopic examination. The diagnosis of CMV nephritis, cystitis, myocarditis, or pancreatitis requires the detection of CMV together with cytopathological evidence in biopsies of the involved organ.

Indirect effects of CMV

Apart from CMV disease, indirect effects such as CMV-associated graft failure, vanishing bile duct syndrome, allograft fibrosis, chronic ductopenic rejection, vascular thrombosis, and new-onset diabetes mellitus may occur[12]. CMV-associated graft failure may be difficult to distinguish from graft failure from other causes, including immune-mediated graft rejection, haematologic disease, drug toxicity, or other infections, such as HHV-6, EBV, and adenovirus. A diagnosis of exclusion is required[3]. Some patients may manifest with coinfection reactivation or opportunistic HCV, HHV-6, HHV-7, fungal, nocardial, or bacterial infections, or EBV-associated post-transplant lymphoproliferative disease, infections.

INVESTIGATION

A definitive diagnosis of invasive tissue disease requires the detection of CMV in a tissue specimen from the affected organ[55]. The gold standard for testing is the detection of either CMV cytopathology or CMV antigen by immunohistochemistry. Other methods of detecting CMV infection and disease are described below (Tables 2 and 3).

Cell culture

In conventional cultures, human fibroblast cells are inoculated with a clinical specimen and have an incubation period of 2 d to 21 d. In shell vial assays, the incubation time is shortened to approximately

Table 2 Cytomegalovirus assays and clinical use

Investigation	Sample	Uses	Properties
Cell culture			
Traditional cell culture (human fibroblast cells)	Tissue or non-tissue (blood, urine, oral secretion) sample	Not widely available	Highly specific
Shell vial assay (centrifugation-amplification technique)			Can be tested for phenotypic susceptibility; Takes a long time (2 to 21 d), more rapid with the shell vial assay (16 h)
Histopathology of organ-specific tissues			
Plain histological microscopy	Tissue sample	Gold standard for diagnosis of tissue-invasive CMV disease	Low sensitivity but very high specificity
Immunohistochemistry		Used for reference of endpoint of treatment of tissue-invasive CMV disease	
Molecular diagnosis (detection of viral genome)			
Plasma quantitative nucleic acid testing (plasma QNAT)	Blood (plasma or whole blood)	Used to detect CMV DNAemia with high sensitivity; used in diagnosis, surveillance to guide pre-emptive antiviral treatment, and therapeutic monitoring	Generally high sensitivity but less sensitivity in R ⁺ patients
Tissue QNAT	Tissue sample	Need more clinical trial studies	Better specificity but a lack of studies
Real-time PCR	Blood	Alternative to conventional plasma QNAT	More rapid and precise
NASBA assay	Blood	Under study as an alternative to conventional quantitative antigenaemia as a guide for starting pre-emptive therapy	Increased sensitivity for detection of CMV viraemia
Direct viral pp65 antigen detection	Whole blood or plasma	Diagnosis of CMV infection by detecting antigenaemia; Quantitative result, can guide initiation of pre-emptive therapy	After the blood collection, the sample must be processed within 6 h; False-negatives in patients with neutropenia
Serological analysis (viral antibody detection)			
CMV IgG antibody testing	Plasma	Diagnosis of CMV infection	Better sensitivity and specificity; also positive in past infection
CMV IgM antibody testing		Pre-transplant assessment for serostatus of the donor and the recipient	Low sensitivity and specificity for diagnosis
Viral cellular response detection			
QuantiFERON-CMV assay: IFN- γ released measurement	Plasma	Prognostic marker for risk of developing CMV disease: a positive result is associated with a lower incidenceMonitoring during prophylaxis or pre-emptive therapy	High positive predictive value but low negative value

CMV: Cytomegalovirus; D: Donor; IFN- γ : Interferon-gamma; NASBA: Nucleic acid sequence-based amplification; QNAT: Quantitative nucleic acid testing; R: Recipient; PCR: Polymerase chain reaction; Ig: Immunoglobulin.

16 h by a centrifugation-amplification technique. CMV can be cultured from any type of sample, but non-tissue samples have low sensitivity. The current guidelines do not recommend viral culture of blood, urine, or oral secretions for diagnosing active CMV infection[45]. Viral culturing of tissue samples has high sensitivity but is not widely available[1] (Tables 2 and 3).

Histopathology

Histopathological diagnosis of CMV infection requires the finding of typical cytopathic changes including foci of flat and swollen cells. Immunohistochemistry of tissue biopsies has high specificity but low sensitivity depending on the distribution of infected tissues. Frozen sections of biopsy samples or preparations made by centrifuging cells onto a slide can be stained with fluorescently-labelled antibodies to early CMV antigens. CMV infection is confirmed by the CMV antigen-positive inclusion bodies (Figure 2) (Tables 2 and 3).

Molecular diagnosis (detection of viral genome)

QNAT of CMV viral load in blood plasma samples has high sensitivity for detection of CMV DNAemia,

Table 3 Uses of available cytomegalovirus assays

Use	Assay
Diagnosis	CMV viral load by plasma QNAT; CMV viral load by real-time PCR assay; pp65 antigen testing; CMV IgG/IgM antibodies
Diagnosis of tissue-invasive CMV disease	Histopathology
Pre-transplant risk stratification	CMV IgG/IgM antibodies
Threshold for initiation of pre-emptive therapy	CMV viral load by plasma QNAT; Quantitative pp65 antigen measurement; NASBA assay
Monitoring or endpoint (prophylaxis, pre-emptive or treatment)	CMV viral load by plasma QNAT; QuantiFERON-CMV assay
Endpoint of treatment of tissue-invasive CMV disease	Histopathology
Prediction of developing CMV disease	QuantiFERON-CMV assay

CMV: Cytomegalovirus; Ig: Immunoglobulin; PCR: Polymerase chain reaction; QNAT: Quantitative nucleic acid testing.

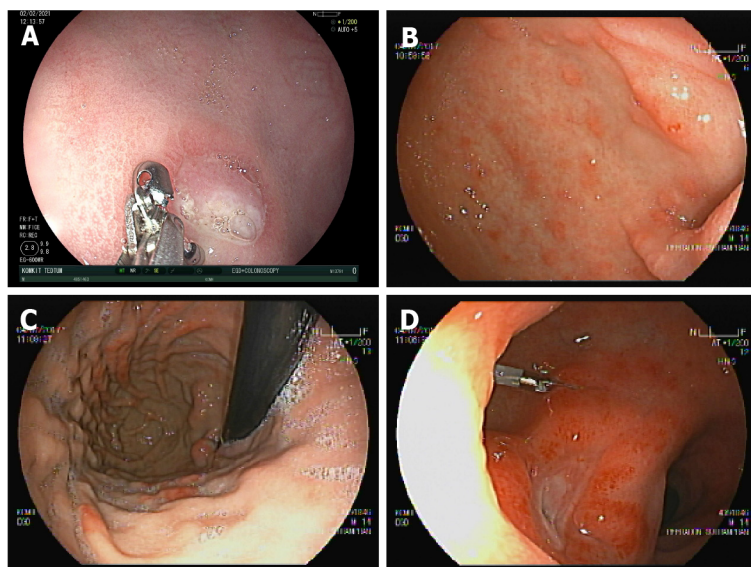


Figure 1 Cytomegalovirus tissue infection of the stomach and duodenum in a 13-mo-old boy and a 14-year-old boy with D⁺/R⁻ serostatus at transplant. Neither patient received antiviral prophylaxis. A and B: The 13-mo-old boy with D⁺/R⁻ serostatus at transplant presented with severe anaemia at 3 mo; C and D: The 14-year-old boy presented with haematemesis at 2 mo after liver transplantation.

especially in D⁺/R⁻ patients, but the sensitivity may be lower in R⁺ patients[56,57]. Current guidelines recommend using plasma QNAT for diagnosis, surveillance to guide pre-emptive antiviral treatment, and therapeutic monitoring. The assay must be calibrated according to WHO standards and reported as IU/mL. The absolute value and rate of increase indicated by plasma QNAT are both correlated with the risk of progression to CMV disease and are predictive of CMV disease[28,51]. QNAT may be performed in either plasma or whole blood specimens, but it is recommended to use the same type of specimen and the same type of assay during monitoring of a patient[55]. Tissue QNAT has greater specificity than plasma QNAT, but the available evidence is not adequate to identify a recommended threshold for routine diagnosis[55]. Other specimens, including urine and oral secretions are not recommended for the surveillance and diagnosis of CMV disease by QNAT[55]. In addition to its usefulness in diagnosis, CMV viral load correlates with the duration of treatment and risk of relapse[58].

Other diagnostic assays are real-time PCR and nucleic acid sequence-based amplification (NASBA) [59]. Real-time PCR targets the conserved region of the CMV DNA polymerase gene, regardless of the presence of any viral mutation, allows the quantitative measurement of viral nucleic acids, and is more rapid and precise than conventional quantitative PCR[60]. NASBA detects unspliced viral mRNAs located in a background of DNA and has been studied as an alternative to quantitative antigenaemia as a guide for starting pre-emptive therapy and as a more sensitive assay for the detection of CMV isolation in blood (Tables 2 and 3).

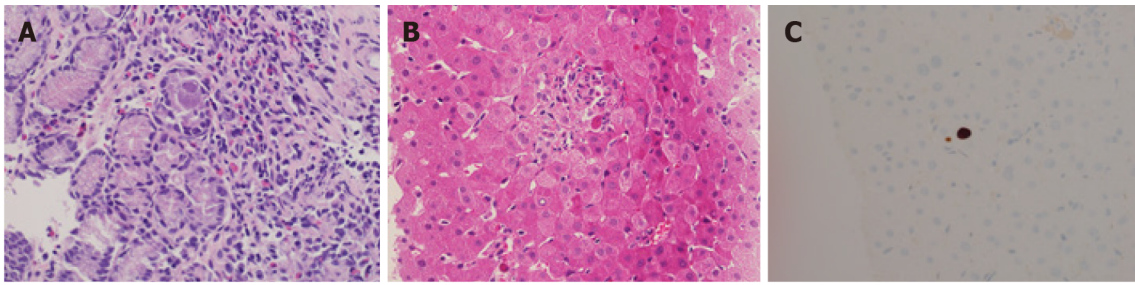


Figure 2 Biopsies showing chronic active gastritis. A: Cytomegalovirus inclusion bodies are seen within mucous cells. The gastric biopsy is characterized by enlarged cells with basophilic nuclear and cytoplasmic inclusions; B: Liver biopsy shows a neutrophilic microabscess surrounding a hepatocyte with granular basophilic cytoplasmic cytomegalovirus inclusions; C: Positive cytomegalovirus immunohistochemistry in liver tissue.

Direct assay of viral antigen

Direct assay of CMV antigen in whole blood or plasma can detect antigenaemia. The pp65 protein antigen is synthesized by the virus in infected host cells, and the sample should be processed within 6 h after collection, as the number of antigen-positive cells significantly decreases with time[61]. Fluorescence-labelled anti-pp65 antibody binds to the pp65 antigen in peripheral blood leucocytes, and the quantitative results are reported as the number of positive cells in 2×10^5 peripheral blood leucocytes. False-negative results are usually obtained in patients with neutropenia[62]. In clinical practice, the detection of CMV antigenaemia can diagnose CMV infection and guide the initiation of pre-emptive therapy (Tables 2 and 3).

Serological assay of viral antibodies

CMV infection can also be detected by serological assay of viral antibodies. CMV IgG antibody testing is recommended. Tests for IgG combined with IgM and for IgM exclusively are not recommended because of their low specificity[55]. IgM antibodies can persist for months in patients with a previous primary CMV infection, and even though IgG has better sensitivity and specificity than IgM, the results must be interpreted with caution in patients with past CMV infection. The techniques available currently are complement fixation, enzyme-linked immunosorbent assay (ELISA), anti-complement immunofluorescence, radioimmunoassay, and indirect haemagglutination. The primary clinical use of serologic assays is in the pre-transplant assessment of donor and recipient CMV serostatus (Tables 2 and 3).

Viral cellular response detection

The QuantiFERON-CMV assay is an ELISA that detects IFN- γ production following stimulation by CMV antigen. The assay reflects cell-mediated immunity by measuring IFN- γ levels following *in vitro* stimulation of CD8 $^{+}$ T cells by CMV peptides. The subsequent incidence of CMV disease in immunocompromised patients is significantly lower among those with a positive result than those with a negative result[21,50,63]. A multicentre cohort study showed that the positive and negative predictive values of the assay were 0.90 and 0.27, respectively[50]. Many assays are in use in some centres for monitoring during prophylaxis or pre-emptive therapy[55] (Tables 2 and 3).

TREATMENT

Early detection of CMV infection is necessary for the management of transplant patients, and reflects the index of suspicion from clinical features of tissue-invasive CMV disease or CMV syndrome and the results of monitoring blood for CMV DNA in asymptomatic CMV infections. A lower total intensity of calcineurin inhibitors is associated with better early CMV DNAemia eradication[64]. Consequently, if significant CMV viraemia or tissue-invasive CMV disease is diagnosed, then reducing current immunosuppressive therapy, especially in those with severe CMV disease or a high viral load, is the priority.

Medication

Specific antiviral drugs against CMV infection are intravenous ganciclovir and oral valganciclovir. If tolerated, oral drugs are preferred for mild to moderate CMV disease and asymptomatic CMV DNAemia because they are associated with shorter hospital stays and fewer complications than intravenous drugs. Oral valganciclovir is preferred to oral ganciclovir because of its better bioavailability[65]. A study found that oral valganciclovir is safe and noninferior compared with intravenous ganciclovir[66], but in life-threatening CMV disease, intravenous ganciclovir is preferred to reach the optimal drug level rapidly. The current guidelines recommend the administration of 5 mg/kg intravenous ganciclovir every 12 h as initial therapy, with dosage adjustments in patients with renal

insufficiency. After the desired clinical response has been achieved, switching to oral therapy may be considered if it is well tolerated[55]. In cases of asymptomatic CMV infection and CMV syndrome, after a duration of treatment of a minimum of 2 wk with clinical resolution and no evidence of CMV DNAemia, eradication is defined as a CMV viral load of < 200 IU/mL in one or two consecutive weekly samples[55]. Patients with tissue-invasive CMV disease usually have minimally detectable or undetectable viraemia; it is not recommended to use CMV PCR to assay serum viral load as a guide for antiviral discontinuation. The decision to discontinue antiviral medication should be based on the clinical response, including the histopathology of the involved tissue. In patients with gastrointestinal CMV disease, clinicians should consider colonoscopy or upper endoscopy with histologic evidence of invasive CMV infection to indicate disease eradication instead of using serum CMV viral load[65].

Monitoring and alternative regimens

During treatment, patient surveillance includes complete blood count for leucopenic side effects, renal function monitoring to guide antiviral dosage adjustment, and weekly quantitative CMV nucleic acid testing to assess medication response. Apart from renal adjustment, lowering the antiviral dosage is not recommended because of concern of treatment failure. Antiviral switching because of leucopenia is considered after discontinuation of other myelosuppressive agents or the addition of granulocyte colony-stimulating factor. The use of foscarnet or cidofovir as an alternative antiviral medication can then be considered[1,55].

Ganciclovir-resistant CMV disease

If the patient's CMV DNAemia remains persistently positive or is recurrently positive despite prolonged antiviral therapy for more than 6 wk of cumulative exposure to ganciclovir or more than 2 wk of ongoing full-dose therapy[55], then antiviral drug resistance testing should be considered. Factors that increase the risk of developing resistant strains include prolonged use of ganciclovir, typically for more than 5 mo, high-risk pairs, especially D⁺/R⁻, a history of exposure to strongly immunosuppressive agents, or inadequate drug delivery. Paediatric cohort studies have reported an incidence of ganciclovir resistance of approximately 2%-4%, which might have been under-reported[67,68].

Current guidelines recommend medications much like those used in adults[55], but because of a lack of controlled trials, the drug of choice has not yet been identified. Current guidelines include an algorithm to select appropriate medications[55]. The regimen includes the addition or switching of antiviral medication to intravenous foscarnet or a dosage escalation of intravenous ganciclovir. The regimen is then adjusted after genetic testing for antiviral drug resistance. Cidofovir is considered if genetic testing shows resistance to foscarnet. In the case of multidrug resistance, a combination of intravenous antiviral drugs is recommended[55]. The guidelines suggest a combination of intravenous foscarnet and high-dose ganciclovir[55]. Other medications, including brincidofovir, letermovir, and maribavir, are still under clinical study[1,55].

PREVENTION

Pre-organ transplant screening

Pre-organ transplant screening helps to detect patients at risk of CMV disease and who require prophylaxis and patients with clinically significant occult CMV infection requiring pre-emptive therapy. Pre-transplant serostatus screening is thus necessary for risk stratification. The modalities rely on recipient age. Either urine/saliva for CMV shell culture or serum/whole blood for CMV QNAT combined with CMV IgG antibody testing are recommended for recipients younger than 18 mo of age [26]. Single CMV IgG antibody testing is not recommended because maternal CMV IgG antibody can be found in some patients younger than 18 mo of age who acquire passive immunization during the perinatal period. In recipients are older than 18 mo of age, CMV IgG testing alone can be used[27]. If either CMV culture or CMV QNAT is positive, the patient is considered seropositive. However, donors younger than 18 mo of age who are seropositive for CMV IgM are also assumed to be seropositive[51]. As the peak incidence of CMV disease occurs during the first 3 mo after transplantation[8], CMV surveillance with weekly QNAT for the first 12 wk is recommended[55,69].

Pre-emptive therapy

Viral threshold: In pre-emptive therapy, antiviral drugs are provided to asymptomatic patients with evidence of CMV infection. QNAT is the preferred test because of the rapid results with high sensitivity. Patients with a test showing a positive viral load above a clinically significant threshold are given pre-emptive treatment, but there is no universally recommended viral load threshold for management initiation because of a lack of standardized assays[55]. The thresholds are assay- and centre-specific, and it is recommended that each centre establish its own threshold[55]. Paediatric studies at a centre in India used QNAT assays and a cut-off value of 500 copies/mL[8], and a study in Italy used real-time PCR assay of CMV DNA in blood and a cut-off value of 650 copies/mL[70]. pp65 antigenemia has also been

used as a threshold for pre-emptive therapy at many centres. A centre in Japan used a cut-off of 5 pp65-positive cells per 50000 leucocytes to indicate CMV antigenaemia[13].

Medications: Intravenous ganciclovir and oral valganciclovir are recommended for pre-emptive therapy. Oral ganciclovir is less effective than oral valganciclovir. A study reported that despite administration of oral ganciclovir, breakthrough CMV syndrome was observed[71]. In some centres, intravenous ganciclovir is initially given, and switched to oral valganciclovir until the course of the pre-emptive therapy is completed. Intravenous ganciclovir is generally given at 5 mg/kg every 24 h. The recommended valganciclovir dosage is 15 mg/kg once daily for patients who weigh less than 15 kg or 500 mg/m² once daily for patients who weight more than 15 kg. The maximum dose is 900 mg/dose once daily[27]. The dosage of valganciclovir is adjusted to both body surface area and kidney function assessed by creatinine clearance.

The optimal duration of intravenous ganciclovir prophylaxis has not been determined, and varies from 14 d to 3 mo and is extended to 6 mo at some centres[51]. The time from transplantation to onset of CMV viraemia or disease was not significantly different in those who received ≤ 14 d or > 14 d of postoperative ganciclovir prophylaxis[26]. The treatment duration for low-risk D⁻/R⁻ patients should be assessed by clinical follow-up. The intermediate-risk group should be treated for 3 mo, and the high-risk group should be treated for 6 mo. Because of the lack of a recommended optimal cut-off duration, the treatment duration can be adjusted according to the physician's judgment. A negative blood CMV viral load in two samples taken 2 wk apart can also be considered a guide for discontinuation of therapy[8]. The efficacy of the pre-emptive protocol has been studied in some trials. In the study by Pappo *et al*[72], liver-transplanted children were given oral valganciclovir 17 mg/kg/d for 3-6 mo, leading to a decrease in the incidence of CMV infection. A study by Ueno *et al*[73], reported that the incidence of CMV infection in patients with 1 year prophylaxis decreased by more than 80.5% compared with a regimen of less than 1 year. The pre-emptive regimen decreased the cost of treating CMV infection and disease[70].

Monitoring

Drug toxicity should be monitored by complete blood counts, kidney function tests, such as blood urea nitrogen and creatinine, and hepatic transaminase enzymes every 1-2 wk in the first month post-transplant and then monthly until completion of prophylaxis.

A study on post-prophylactic delayed-onset CMV disease found that the peak incidence in paediatric patients occurred at about 3 mo after cessation of antiviral prophylaxis following liver transplantation[51]. This finding led to the recommendation of post-prophylaxis surveillance of CMV for at least the first 3 mo of treatment in high- and moderate-risk recipients[27]. The surveillance can be by either quantitative CMV PCR or QNAT monthly for 12 mo post-prophylaxis. Low-risk recipients may not need surveillance; however, if any febrile illnesses occur, quantitative PCR is required regardless of the recipient risk status.

Systemic antiviral prophylaxis: Patients selected for systemic antiviral prophylaxis include those at high risk as D⁺/R⁻ serostatus. Patients with D⁻/R⁻ serostatus may not require prophylaxis, but universal systemic antiviral prophylaxis is given to all patients at some transplant centres regardless of their serostatus.

Medication

The antiviral medications used for prophylaxis include acyclovir, valacyclovir, intravenous or oral ganciclovir, and valganciclovir. Valganciclovir is the most frequently used agent and ganciclovir is more effective than acyclovir in reducing the incidence of CMV disease[74]. Because of the clinical trials with high power, the effectiveness of oral valganciclovir and oral ganciclovir remain controversial. Some studies found that oral valganciclovir contributed to a lower incidence of early-onset CMV disease than oral ganciclovir[75], but valganciclovir has a higher incidence of tissue-invasive and late-onset CMV disease than oral ganciclovir[76]. The duration of systemic prophylaxis in clinical practice is typically 3-6 mo after transplantation. Current guidelines recommend at least 3-6 mo of treatment in children with a serostatus of D⁺/R⁻ and 3-4 mo or 2-4 wk in other groups, with CMV surveillance at the end of therapy[55]. The summary of management for CMV disease was described in Table 4.

CMV vaccination

Several CMV vaccines have been evaluated in clinical trials, but the results were not promising. Poor protection against infection may be a result of the nature of the virus, which can evade and modulate the immune system. The most promising vaccines are derived from viral glycoprotein B, and are progressing to phase II clinical trials. An initial study in children found that the vaccine was safe and effective in developing immunity, with an efficacy of 43%. The vaccine also reduce the duration of treatment in post-solid organ transplant recipients[80]. Virus-like particles consisting of a fusion product of extracellular domain glycoprotein B and vesicular stomatitis virus G-protein induced high titres of neutralizing antibodies[81]. Live-attenuated vaccine has shown a good safety profile, inducing both humoral and cell-mediated immunity, and reducing the incidence of severe infection[82,83]. However, vaccines still fail to prevent infection in seronegative solid organ transplant recipients. A disabled

Table 4 Summary of pre-emptive, prophylaxis and treatment of cytomegalovirus disease in post-liver transplant patients

Condition	Pre-emptive	Prophylaxis	Treatment
Monitoring and endpoint	Monitoring: Weekly or every 2 wk CBC, BUN, Cr, AST, and ALT for first month and then monthly; Monthly CMV QNAT for 12 mo. Endpoint: CMV QNAT for VL negative for two samples 2 wk apart	Monitoring: Weekly CMV QNAT. Endpoint: CMV QNAT for VL negative for two samples 2 wk apart	Monitoring: Weekly CBC, BUN, Cr; Weekly CMV QNAT. Endpoint: CMV syndrome: Clinical resolution; VL less than 200 IU/mL on 1-2 consecutive weeks; Tissue-invasive CMV disease: Clinical resolution; Histologic evidence
Cut-off for start medication	Reference Verma <i>et al</i> [8,14]; Saitoh <i>et al</i> [13]; Martin-Gandul <i>et al</i> [77]; Atabani <i>et al</i> [58]; Griffiths <i>et al</i> [78] Values Non-specific: VL 500 copies/mL; VL 650 copies/mL; pp65 Ag 5 per 50000 leucocytes. D ⁺ /R ⁺ : Plasma VL 1500 IU/mL. D ⁺ /R ⁺ and R ⁺ : Plasma VL 2275 IU/mL or 2500 copies/mL; Whole blood VL 2520 or 3000 copies/mL. R ⁺ : VL 3983 IU/mL	-	Kotton <i>et al</i> [55] VL > 200 IU/mL for 2 consecutive weeks
Duration	Reference Razonable <i>et al</i> [32,38,71]; Razonable[39]; Razonable and Humar[51]; Razonable and Hayden[56]; Razonable[79]; Pappo <i>et al</i> [72]; Ueno <i>et al</i> [73]; Kotton <i>et al</i> [55] Values Non-specific: 14 d to 3 mo; Extended to 6 mo; Extended to 12 mo. High risk: 6 mo. Intermediate risk: 3 mo. Low risk (D ⁺ /R ⁺): Clinical follow-up	Kotton <i>et al</i> [55] D ⁺ /R ⁺ : 3-6 mo. Others: 3-4 mo or 2-4 wk with CMV surveillance	Kotton <i>et al</i> [55] At least 2 wk
Drug/dose/route	First-line: Ganciclovir (5 mg/kg IV q 24 h); Valganciclovir (< 15 kg: 15 mg/kg/dose po once daily; > 15 kg: 500 mg/m ² /dose po once daily); Maximum dose: 900 mg/dose once daily; Combined ganciclovir then valganciclovir	First-line: Ganciclovir (same dose as pre-emptive); Valganciclovir (same dose as pre-emptive)	First-line: Ganciclovir [5 mg/kg IV q 12 h (+/- with dose adjustment for renal function)]. Second-line (ganciclovir-induced leucopenia): Foscarnet [60 mg/kg IV q 8 h or 90 mg/kg IV q 12 h (+/- with dose adjustment for renal function)]; Cidofovir [5 mg/kg once weekly × 2 doses then every 2 wk (+/- with dose adjustment for renal function)]. For ganciclovir-resistant [Ganciclovir: 7.5-10 mg/kg IV q 12 h (+/- with dose adjustment for renal function). Add or switch to Foscarnet. Switch to Cidofovir

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBC: Complete blood count; CMV: Cytomegalovirus; Cr: Creatinine; Ig: Immunoglobulin; QNAT: Quantitative nucleic acid testing; VL: Viral load; D: Donor; R: Recipient.

infectious single cycle vaccine induced neutralizing antibodies and cell-mediated immunity against CMV infection in non-human primates and had an acceptable safety profile[83]. Peptide-based, DNA-based, and vector vaccines are currently under investigation in phase I clinical trials[84,85].

New strategies

Currently, a hybrid strategy of systemic antiviral prophylaxis followed by pre-emptive medication is being used at some centres. Universal prophylaxis with intravenous ganciclovir for at least 2 wk followed by intravenous ganciclovir for at least an additional 2 wk as universal pre-emptive therapy or pre-emptive therapy has been used for patients with detectable CMV DNA[26,69]. The regimen is effective for the prevention of tissue-invasive CMV disease[69], and the effectiveness is similar to that of pre-emptive therapy alone. However, the duration of antiviral treatment was significantly shorter with pre-emptive therapy alone[31]. More studies of the effectiveness of hybrid strategy are needed.

CONCLUSION

Infection after liver transplantation is a common, frequently serious complication. CMV infection that increases the mortality of children with liver transplants because of its direct and indirect effects. Preventive interventions include risk stratification prior to liver transplantation and regular monitoring for prompt diagnosis of CMV infection. If CMV infection is detected, prompt treatment can lead to favourable outcomes.

FOOTNOTES

Author contributions: Onpoaree N and Sintusek P reviewed the literature and wrote the manuscript; Sunpavat A interpreted the histopathological data and provided the histopathology images; Sintusek P provided the endoscopic images; and all authors approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicting interests.

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

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