Cytomegalovirus Infection in Liver Transplant Recipients: Current Approach to Diagnosis and Management

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Cytomegalovirus (CMV) infection is the most common viral infection in liver transplant recipients, affecting post-transplant patients and graft survival. Recent advances in diagnosis and management of CMV have led to marked reduction in incidence, severity, and its associated morbidity and mortality. CMV DNA assay is the most commonly used laboratory parameter to diagnose and monitor CMV infection. Current evidence suggests that both pre-emptive and universal prophylaxis approaches are equally justified in liver transplant recipients. Intravenous ganciclovir and oral valganciclovir are the most commonly used drugs for treatment of CMV disease. Most of the centre use valganciclovir prophylaxis for prevention of CMV disease in liver trasplant recipient. The aim of this article is to review the current standard of care for diagnosis and management of CMV disease in liver transplant recipients. (J Clin Exp Hepatol 2017;7:144–151)

Cytomegalovirus (CMV) is a ubiquitous double-stranded DNA virus that infects 50–100% of humans depending upon the population studied. It is the most common viral infection in liver transplant recipients and influences the outcome of liver transplantation.[1,2]

Types of CMV infection:

CMV infection can be primary CMV infection, CMV reactivation, or CMV disease. CMV infection is defined as evidence of CMV replication regardless of symptoms (differs from latent CMV and reactivation).

Primary infection is defined as occurrence of CMV viremia in a previously unexposed transplant recipient. Transplant recipients with donor seropositive and recipient seronegative status are at higher risk of primary CMV infection.

CMV disease is defined as evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as a viral syndrome with fever, malaise, leukopenia, and/or thrombocytopenia or as tissue-invasive disease.

CMV reactivation is defined as evidence of CMV replication in patients who were previously positive for CMV serology.

Overall, 18–29% of all liver transplant recipients will develop CMV disease in the absence of prevention strategy.[3] In the absence of antiviral preventive strategy, CMV disease among liver recipients occurs most commonly during the first 3 months after transplantation.[4] Its incidence varies widely depending upon donor and recipient CMV serologic status; the incidence is as high as 44–65% in CMV D+/R−, 8–19% among CMV-seropositive (CMV R+), and 1–2% among CMV D−/R− patients. The CMD D−/R− patients usually acquire the virus from natural transmission or through blood transfusion.[3,5,6]

PATHOPHYSIOLOGY OF CMV INFECTION

Primary infection results in viral latency mainly in lymphoid and myloid cells and ensures the persistence of the virus throughout the life of the host. This viral latency plays an important role in liver transplant recipients who develop CMV infection. The cellular sites of viral latency become reservoirs for reactivation during periods of inflammation (such as allograft rejection and critical illness) and immunosuppression.

CLINICAL MANIFESTATION OF CMV INFECTION

The classic illness caused by CMV after liver transplantation is CMV disease in the form of fever and bone marrow suppression (most commonly, leukopenia and neutropenia) and accounts for 60% of CMV diseases after liver transplantation. Occasionally, CMV infection may manifest as tissue-invasive disease, which mainly involves the gastrointestinal tract (in the form of CMV gastritis, esophagitis, enteritis, and colitis). Gastrointestinal CMV disease accounts for more than 70% of tissue-invasive CMV disease cases in liver and other solid organ transplant recipients.[7] The transplanted liver allograft is also susceptible to develop CMV hepatitis, and this often manifests with symptoms that may be clinically indistinguishable from acute rejection.[8]

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Abbreviations: CMV: cytomegalovirus; HCV: hepatitis C virus; HHV: human herpes virus; IV: intravenous; LT: liver transplantation; NAT: nucleic acid test
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Table 1 Effect of CMV on Liver Transplant Recipients.

Direct effects	Indirect effects
CMV syndrome	Acute allograft rejection
Fever	Chronic allograft rejection
Myelosuppression	Vanishing bile duct syndrome
Tissue-invasive CMV disease	Opportunistic bacterial and viral infections
Gastrointestinal disease	Epstein–Bar virus and PTLD
CMV hepatitis	HHV-6 and HHV-7 infections
CMV pneumonitis	New-onset diabetes mellitus
CNS disease, retinitis	Vascular thrombosis

Adapted from Bruminhent et al.[50]

CMV has not only direct effects on tissue that it infects but also has indirect effects resulting from its ability to modulate the immune system (Table 1). CMV is a potent upregulator of alloantigen, which increases the risk of acute rejection and chronic allograft dysfunction.[9–12] A higher incidence of vascular and hepatic artery thrombosis has been reported in liver transplant recipients with CMV disease and thought to be due to infection of the vascular endothelial cells.[13,14] CMV infection/reactivation is associated with increased risk of bacterial, other viruses, and invasive fungal infection.[15,16] CMV-infected transplant recipients are more likely to develop Epstein–Barr virus-associated post-transplant lymphoid disorder or coinfections with other viruses such as human herpes virus (HHV) 6 and HHV7.[15–17] Similarly, there is significant association between CMV infection and accelerated course of HCV recurrence and allograft loss after liver transplant.[18–23] In a study of 347 HCV-infected liver recipients, CMV infection increased the risk of allograft fibrosis by 1.5 times and CMV disease increased the risk of allograft inflammation by 3.4 times.[24] Recent evidence has suggested possible role of CMV infection in post-transplant metabolic diseases such as post-transplant diabetes mellitus.[25] Therefore, the strategies to reduce the risk of CMV reactivation may help to reduce the risk of related infections, acute or chronic rejection, or HCV recurrence.

DIAGNOSIS

The diagnostic modalities for CMV infection include serology, qualitative and quantitative polymerase chain reaction (PCR), pp65 antiginemia, culture, and histopathology.

Viral culture of blood and urine has limited clinical utility for prediction, diagnosis, and management of CMV disease in adult liver transplant recipients.[26] Similarly, because of immunosuppression, liver transplant recipients have delayed or impaired ability to mount an antibody response and, hence, CMV serology to detect IgG and IgM antibody has limited role for diagnosis in post liver transplant recipients.[27] Although histopathology confirms the presence of tissue-invasive CMV disease, it is not routinely used due to its invasive nature. It may be useful in some cases where CMV is suspected, but CMV testing in blood is negative especially in the case of gastrointestinal CMV disease.[28]

There are several studies supporting the clinical utility of CMV replication assays, particularly plasma or whole blood quantitative PCR assay in managing CMV disease.[27] The combination of viral load in the initial phase of infection and the rate of increase in viral load may help to identify patients at risk of CMV disease. It is commonly used in many centers to diagnose active CMV disease, screen for pre-emptive antiviral therapy and monitor response to antiviral therapy. Quantitative PCR test and CMV pp65 antigenemia test are available for detecting viral DNA and antigen, respectively. Antigenemia has higher sensitivity than culture and is comparable to PCR.[29,30] It is useful to guide pre-emptive therapy for rapid and sensitive diagnosis of CMV disease and to guide treatment response.[29] However, quantitative PCR assays are more commonly used than the antigenemia test because CMV DNA PCR assay has better standardization, increased stability of the specimen, smaller specimen volume, and ability to test patients with leukopenia.[31] Quantitative CMV PCR is useful to guide pre-emptive therapy for rapid and sensitive diagnosis of CMV infection and to guide response to treatment.[31] However, lack of an international reference standard limited the generation and implementation of viral threshold for pre-emptive therapy, disease prognostication, and therapeutic monitoring. Therefore, it recommended that each transplant center should work within their clinical laboratories to define their relevant viral threshold for their clinical applications.[26] In 2011, WHO released the first international reference standard for the quantification of CMV DNA, and commercially available CMV DNA assays should now be calibrated to this standard.[32,33]