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Review

Cytomegalovirus Management in Solid Organ Transplant Recipients

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Abstract

Cytomegalovirus (CMV) remains a significant cause of morbidity and mortality in solid organ transplant (SOT) recipients. Despite advancements in prophylaxis and antiviral therapy, CMV continues to pose clinical challenges in transplant medicine. This review provides a comprehensive overview of CMV, exploring its pathophysiology, epidemiology, and clinical presentation in SOT patients, in whom CMV infection can lead to direct organ involvement and systemic symptoms. Additionally, CMV has indirect effects, including graft dysfunction and an increased risk of opportunistic infections. We examine the immune responses to CMV, focusing on the roles of both innate and adaptive immunity. The importance of personalized prophylaxis and preemptive therapy is emphasized based on serostatus and individual risk factors. Furthermore, this review discusses resistance mechanisms to standard therapies exploring alternative treatments.

Keywords

Cytomegalovirus; solid organ transplantation; immunosuppression; CMV prophylaxis; antiviral resistance; immune response; CMV disease; transplant recipients; CMV management

1. Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus belonging to the Herpesviridae family, which infects humans worldwide across all age groups. Since CMV is present in various body fluids, including saliva, semen, urine, tears, feces, cervicovaginal secretions, breast milk, and blood, it carries the risk of transmission through sexual contact, blood transfusion, organ or bone marrow transplantation, breastfeeding, and close contact with infected individuals. CMV can also be transmitted vertically from an infected mother to the fetus. The primary infection is often asymptomatic in immunocompetent individuals. However, infectious mononucleosis cases rarely have been reported with clinical manifestations such as hepatitis, encephalitis, transverse myelitis, thrombocytopenia, hemolytic anemia, pericarditis, myocarditis, uveitis, and pneumonia [1, 2]. After primary infection in immunocompetent individuals, CMV remains a latent infection within myeloid cells with the potential for reactivation.

The uncontrolled CMV replication in immunosuppressed patients is a significant cause of mortality and morbidity [3]. CMV can cause severe presentations in individuals who have undergone hematopoietic stem cell transplantation, patients with acquired immunodeficiency, solid organ transplant (SOT) recipients, and immunocompromised fetuses [4]. Additionally, the indirect effects of CMV disease in SOT recipients are graft dysfunction or rejection, increased risk of opportunistic infections, and accelerated coronary artery atherosclerosis. These complications can negatively affect long-term patient survival and transplant success [5-7]. The management of CMV in transplant recipients is guided by several consensus statements and guidelines, including the Third International Consensus Guidelines on CMV in Solid Organ Transplantation (2018) and the UK Guidelines on CMV Prevention and Management in Solid Organ Transplantation (2020).

A systematic literature search was conducted using PubMed, Scopus, and Web of Science to identify relevant studies on CMV management in SOT recipients. Inclusion criteria encompassed studies focusing on antiviral therapies, prophylaxis, immunological responses, and resistance mechanisms, prioritizing peer-reviewed research and clinical trials. Articles in English with full-text availability were considered. Studies were excluded if they focused on non-transplant populations, had incomplete data, were duplicates, or lacked methodological rigor. Two independent reviewers conducted the selection, resolving discrepancies through discussion.

2. Epidemiology

CMV seroprevalence varies geographically, with higher rates in developing countries. In the 2010s, rates as high as 100% were reported in developing countries, likely due to poor socioeconomic conditions and overcrowded living environments that facilitate viral transmission [8]. The highest seroprevalence in the United States is 50% among women, elderly individuals, and those with lower income levels [9]. The incidence and prevalence of CMV are notably higher in specific transplant populations. The incidence of CMV is reported to range between 50% and 75% in patients undergoing lung or heart-lung transplantation and around 50% in pancreas or kidney-pancreas transplanted patients. Conversely, CMV incidence varies from 9% to 23% in heart transplants, 22% to 29% in liver transplants, and 8% to 32% in kidney transplants [3, 10, 11]. CMV disease develops

in approximately 30% of allogeneic and 5% of autologous hematopoietic stem cell transplantation (HSCT) recipients.

3. Immunology

CMV is a DNA virus with a genome size of approximately 230 kilobases (kb) that consists of long (UL) and short (US) segments. The UL segment contains homologous regions encoding DNA polymerase, glycoprotein B (gB), and glycoprotein H (gH). The remaining portion of the genome comprises CMV-specific genes [4]. CMV strains have frequent mutations, deletions, and rearrangements in these genes [12].

CMV enters host cells, specifically fibroblasts, through interactions between viral glycoproteins and integrins or growth factor receptors on the cell membrane [13]. CMV proliferates slowly within endothelial cells. Within the first 0-4 hours after infecting the cells, viral transcription is regulated by early genes, which then facilitate DNA replication and further transcriptional regulation between 4 and 48 hours. Then, the structural proteins are encoded by late genes. While CMV encodes a functional DNA polymerase, it utilizes the host's RNA polymerase [14].

Both innate and adaptive immune responses play a role in controlling CMV infection [15]. Among innate immune mechanisms, type I interferons (IFNs), and natural killer (NK) cells play a crucial role during the early stages of infection [16]. CD8 and CD4 T cells are active in the late stages of acute infection. Cytotoxic CD8+ T cells are essential for inhibiting viral replication in most tissues. Additionally, CD4 T cells effectively resolve persistent infections in tissues such as salivary glands, which are necessary for viral dissemination. When CMV infects the host, it encounters a coordinated immune response within lymphoid tissues, such as lymph nodes and the spleen [17]. Despite fully activating the immune response, CMV can successfully establish latency in the bone marrow, spleen, and lymph nodes [18]. In non-lymphoid organs, the initial immune response to CMV infection begins with the activation of tissue-resident macrophages. Kupffer cells in the liver, alveolar macrophages in the lungs, and histiocytes in the intestinal tissue rapidly respond to infection [19]. Kupffer cells secrete type I interferon (IFNαβ) during the innate immune response to infection in the liver, stimulating the production of Monocyte chemoattractant protein-1 (MCP-1). MCP-1 activates inflammatory macrophages, which produce Macrophage Inflammatory Protein-1α (MIP-1α), to recruit natural killer (NK) cells to the sites of infection. NK cells control the viral infection in the liver through an IFNγ-dependent mechanism. However, NK cells can also secrete TNFα, which may contribute to the persistence of the viral infection [20] (Figure 1). CD8 T cells exhibit cytotoxic activity, a key component of the adaptive immune response, in the liver. On the other hand, the CD8 T cell response can become pathologically exaggerated. Regulatory T cells (Tregs, $CD4^+$ $Foxp3^+$ T cells) and activated NK cells suppress the immune response, which can lead to an excessive CD8 T cell response. Tregs accumulate and exert their effects in response to IL-33, which is produced by macrophages. Besides Treg, NK cells also contribute to the regulation of cytotoxic immunopathology by secreting IL-10 and perforin [21].

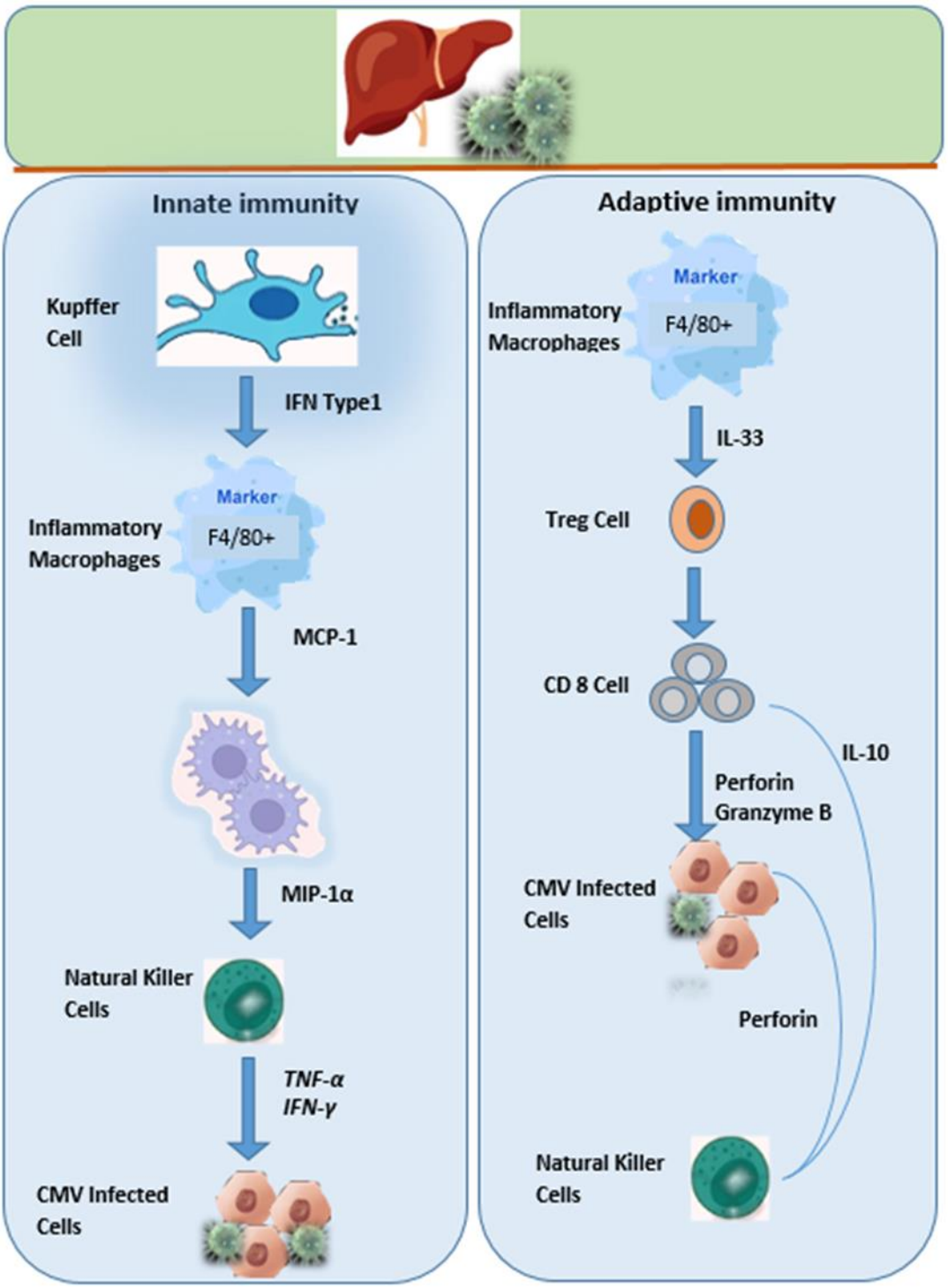

Figure 1 Hepatic immune response against CMV. IFN-γ is a cytokine released by NK and T cells. TNF-α involved in systemic inflammation, while MCP-1 and MIP-1α involved in immune cell recruitment. Perforin and Granzyme (Prf/GzmB) are released by CD8+ T cells, inducing cell death in infected cells. IFN-γ, Interferon-γ; MIP-1α, Macrophage Inflammatory Protein-1α; MCP-1, Monocyte Chemoattractant Protein-1; TNF-α, Tumor Necrosis Factor-α.

The earliest stage of the host immune response to CMV infection involves the release of cytokines and interferons [22]. Both innate immunity (including NK and γδ cells) and adaptive

immunity (mainly $CD8^+$ and $CD4^+$ T cells, with a lesser contribution from B cells) are essential for controlling infection [23]. NK cells are identified by flow cytometry using specific antibodies, including CD3, CD16, CD56, NKG2C, and CD57. In healthy individuals with CMV infection, NK cells with activated CD94/NKG2C receptors are essential [24]. Pre-existing NK memory cells become activated during viremia in CMV-seropositive transplant recipients, and increased expression of activating NK receptors can provide enhanced protection against CMV infection [23].

In humans, γδ T cells are divided into two main subgroups based on the expression of γ and δ T cell receptor (TCR) chains: Vδ1 and Vδ2 T cells. Vγ9Vδ2 T cells express the δ2 chain, while non-Vγ9Vδ2 γδ T cells do not. The presence of non-Vγ9Vδ2 γδ T cells in the peripheral blood of SOT recipients who have experienced CMV infection is notable. Longitudinal monitoring of these cells in kidney transplant recipients has been considered helpful for evaluating CMV treatment efficacy and antiviral drug resistance [23, 25].

CMV-specific $CD8^+$ T cells can be categorized into two subsets based on their cytotoxic potential and proliferative capacity. A central memory T cell population ($CD27^+$ $CD28^-$ $CD45RO^+$) that has low cytotoxic potential but high proliferative ability differentiates early during primary infection [26]. A large percentage (up to 75%) of CMV-specific $CD8^+$ T cells exhibit a TEMRA phenotype ($CD27^-$ $CD28^-$ $CD45RA^+$), characterized by high cytotoxic potential but low proliferative capacity. In healthy CMV-seropositive individuals, CMV-specific $CD8^+$ T cells can account for up to 10% of the memory $CD8^+$ lymphocyte pool following viral clearance [23, 26, 27].

After primary CMV infection in SOT recipients, CMV-specific $CD4^+$ T cells can be detected approximately one week after viremia, exhibiting a $CD4^+$ $CD28^-$ granzyme B^+ phenotype [28, 29]. During the chronic infection phase following viral clearance, CMV-specific $CD4^+$ T cells can comprise as much as 9% of the memory T lymphocyte pool. These $CD4^+$ T cells play a crucial role in anti-CMV immunity by eliminating CMV peptide-loaded cells, supporting B cells in generating specific humoral responses to viral antigens, and enhancing the effector functions of $CD8^+$ T cells [30].

3.1 Immunocompetent Individuals

In immunocompetent individuals, CMV infection is typically asymptomatic and rarely manifests as a mononucleosis-like CMV syndrome. The diagnosis of CMV viral syndrome requires detection of CMV in the blood through viral isolation, rapid culture, antigenemia, or quantitative nucleic acid testing (QNAT), along with the presence of at least two of the following criteria: fever, malaise, fatigue, leukopenia or neutropenia on two separate measurements, thrombocytopenia, ≥5% atypical lymphocytes, or a two-fold elevation in aminotransferase levels [31]. Pericarditis and myocarditis can occur in immunocompetent individuals with acute CMV infection [32]. Some studies suggest that CMV accelerates atherosclerosis following cardiac transplantation [33], but the relationship between CMV infection and atheroma formation is not fully understood.

CMV infection can also manifest with various neurological symptoms in immunocompetent individuals. CMV should be considered in cases of unexplained encephalitis [34]. Guillain-Barré syndrome (GBS) is associated with several infectious agents, including CMV, in which antibodies against ganglioside GM2 play a role. Anti-GM2 IgM antibodies can be detected in CMV infections with or without GBS [35]. The ocular involvement is not typically seen in immunocompetent patients [36], but CMV retinitis can occur in HIV patients. CMV-associated pneumonia is rare in immunocompetent individuals. It is challenging to prove CMV as the etiological agent in patients

with CMV pneumonia. The diagnosis is based on CMV PCR positivity in blood and bronchoalveolar samples and a positive response to CMV-specific treatment [37].

3.2 Immunosuppressed Individuals

CMV disease typically emerges between 30 and 90 days post-transplant in SOT recipients, and cases beyond 180 days are rare. Antiviral prophylaxis can delay the onset of the disease, though it can still develop later in some instances [38-40].

Subclinical transaminitis is the most common finding, though elevated alkaline phosphatase and total bilirubin are not typically expected [41]. Acute CMV hepatitis often presents with prolonged unexplained fever and should be considered in the differential diagnosis of granulomatous hepatitis [41]. It is rarely complicated by portal vein thrombosis [35]. In contrast to hepatitis, gastrointestinal involvement of CMV is uncommon. However, they can lead to significant morbidity and mortality and are associated with a wide range of gastrointestinal conditions, including esophagitis [42], gastritis [43], gastric ulcers [44], gastroparesis [45], Ménétrier's disease [46], ileitis [47], and appendicitis [48]. CMV has also been linked to CMV colitis, typically caused by primary infection in immunocompetents, while it is often the reactivation of a latent infection in immunosuppressed patients [43]. CMV-associated pancreatitis has been reported in several case reports [49].

The symptoms of CMV infection can be localized to a single organ and, in rare cases, may involve multiple systems under immunosuppressive conditions. The most common clinical manifestation in transplant recipients is a viral syndrome characterized by fever, fatigue, leukopenia, thrombocytopenia, and elevated liver enzymes [31]. Gastrointestinal symptoms, particularly abdominal pain, are frequent. Hematochezia is less common but is suggestive of colonic involvement.

4. Risk Factors for the Infection

Several factors, including donor and recipient serology, organ type, immunosuppressive therapies, and genetic predisposition, influence the risk of CMV disease in SOT recipients.

4.1 Serological Risks

The most significant risk factor for SOT is the CMV serostatus mismatch between donor and recipient. The most significant risk factor for CMV disease in SOT is a serological mismatch between the donor (D) and recipient (R). Specifically, CMV-seronegative recipients (R-) receiving organs from seropositive donors (D+) are at the highest risk for primary CMV disease due to the transmission of latent virus through the allograft [50]. CMV D+/R+ and CMV D-/R+ transplants also carry an intermediate risk for disease development, while CMV D-/R- transplants are classified as low-risk groups [51, 52]. Among recipients receiving valganciclovir prophylaxis, the 1-year incidence of CMV disease in high-risk serological groups (D+/R-) was 19.2% after kidney transplantation and 31.3% after liver transplantation [53]. The incidence of CMV infection was found to be 47%, with CMV disease occurring in 7.5% of patients during 1-year follow-up of heart-transplanted patients receiving both prophylaxis and preemptive treatment after the transplantation [54]. On the other hand, in HSCT recipients, the leading risk factor differs—seropositive recipient (R+) status is the

most significant concern, as CMV reactivation can lead to severe disease, particularly within the first 100 days post-transplant [55-57].

4.2 Immunosuppressive Risks

The degree of immunosuppression plays a crucial role in CMV susceptibility. Lymphocyte-depleting agents, including Anti-thymocyte globulin (ATG), Anti-lymphocyte globulin (ALG), Anti-CD3 antibody (OKT3), alemtuzumab (anti-CD52 antibody), increase the risk of CMV reactivation when used to treat acute rejection [58-60]. In contrast, mTOR inhibitors (e.g., everolimus) have been associated with a reduced risk of CMV disease [61]. Additionally, proinflammatory conditions from allograft rejection can further trigger CMV activation [55].

4.3 Genetic Risks

Host genetic factors also contribute to CMV susceptibility. Specific genetic polymorphisms affect immune function, including variations in the Toll-like receptor (TLR) gene [62], deficiencies or polymorphisms in ficolin-2 or mannose-binding lectin (MBL) [63], and weak CMV-specific $CD4^+$ and $CD8^+$ T cell responses [64]. Moreover, low complement C3 levels within the first-week post-transplant, hypogammaglobulinemia, low NK cell counts, and pre-transplant lymphopenia have been linked to higher CMV disease risk, particularly in heart and liver transplant recipients [65-68].

5. The Definitions and Terms for Clinical Presentations of Cytomegalovirus

CMV Infection is defined by the detection of viral isolation, viral proteins, or viral nucleic acid in body fluid samples, such as serum, urine, cerebrospinal fluid, bronchoalveolar lavage, whole blood, or in pathological tissue specimens, regardless of whether the patient exhibits CMV-related clinical symptoms [10, 31, 69-71]. CMV infection can present as active or latent infections:

- ***Active Infection*** refers to the period during which active viral replication occurs. This term encompasses asymptomatic CMV infection, CMV disease, and CMV syndrome.
- ***Latent Infection*** refers to a prior exposure to CMV in which the virus remains dormant without ongoing replication.

CMV infection can also be classified as primary or secondary infections:

- ***Primary CMV Infection*** is identified by CMV IgM and IgG serology in an individual not previously exposed to the virus. The antibody responses may be inadequate in immunosuppressed patients, so detecting viral proteins or isolating viruses from body fluids or tissues became critical for diagnosing CMV replication.
- ***Secondary CMV Infection*** refers to the re-detection of CMV infection in a patient who has previously been exposed to CMV and tested seropositive. It can result from the reactivation of a latent infection or reinfection. Diagnosing CMV reactivation requires identifying the initial viral strain as the causative agent through molecular techniques. If a new strain of CMV different from the initial strain is detected, this is referred to as ***CMV reinfection***, indicating that the patient has acquired an exogenous new viral strain.

CMV Disease is defined by the presence of CMV-related symptoms and signs, along with evidence of CMV infection. It can be manifested as either CMV syndrome or target organ disease:

- ***CMV Syndrome*** is characterized by systemic symptoms such as fatigue, fever, lymphocytosis, leukopenia or neutropenia, thrombocytopenia, and elevated liver enzymes, combined with the detection of CMV in body fluids.
- ***Target Organ CMV Disease*** occurs when the virus is pathologically detected in the affected organ and is associated with symptoms related to that organ. Clinical presentations may include pneumonia, colitis, hepatitis, encephalitis, ventriculitis, nephritis, cystitis, myocarditis, and pancreatitis.

Post-transplant CMV (PT-CMV) is a CMV disease that occurs after SOT or HSCT. PT-CMV can develop through three main pathways: transmission from the allograft, reactivation of latent infection, or the onset of primary infection in seronegative transplant recipients [4].

6. Diagnostic Tests

Several methods are used to diagnose CMV infections, including serology, viral culture, immune histopathology, molecular tests (such as quantitative polymerase chain reaction, qPCR), and phosphoprotein 65 (pp65) antigenemia assays.

6.1 Serological Tests

Neutralizing antibodies specific to CMV develop within the first four weeks following primary infection, primarily targeting CMV glycoproteins. These glycoproteins are critical for viral attachment to host cells, membrane penetration, and fusion of the viral envelope with the host cell membrane [72]. It is worth noting that a positive CMV-IgG result does not necessarily indicate protection against viral reactivation or reinfection. Serology is particularly useful for determining the pre-transplant serological status of the donor and recipient, thus helping assess the risk of post-transplant CMV infection. However, serology has limited value after transplantation and does not differentiate active disease or infection [6].

6.1.1 Interpretation of Serological Tests in Immunocompetent Individuals

Serological tests in CMV infections primarily measure CMV IgM and IgG antibodies. CMV IgM is the first antibody detected following primary infection in immunocompetent individuals and can remain in the serum for an extended period. Since it may reappear following CMV reinfection, it is unreliable for diagnosing primary infections [3]. IgG antibodies typically become detectable 6-8 weeks after infection and may remain elevated indefinitely. CMV IgM should be interpreted in conjunction with CMV IgG during the pre-transplant period, as false positivity is possible. This makes CMV IgG the primary test for the CMV status of donor and recipient [70, 73]. If there is a significant gap between serological testing and transplantation, or if blood products have been administered, the serological status of the recipient should be reassessed before transplantation.

6.1.2 Interpretation of Serological Tests in the Post-Transplantation Period

In the post-transplant period, immunosuppression often disrupts humoral immunity, thus complicating the interpretation of serological tests. Additionally, patients may require blood or intravenous immunoglobulin (IVIG) transfusions during this period, further reducing the reliability of serology [3]. However, CMV IgM and IgG seroconversion after transplantation is not a reliable

predictor of CMV disease. In some D+/R- patients, CMV-specific IgG antibodies are present post-transplantation without the occurrence of CMV infection, suggesting the existence of pre-formed CMV-specific memory B cells before transplantation [74].

6.2 Viral Culture

Viral cultures from blood, urine, or sputum are not recommended for diagnosing active CMV infection or disease, as these samples offer limited clinical utility [75]. CMV can be detected using culture techniques such as conventional tube cell culture or the shell-vial assay. Clinical samples are inoculated into culture tubes, where infected cells with cytoplasmic "ground-glass" inclusions are observed under microscopic examination. This appearance indicates the presence of viral cytopathic effects (CPE). Once CPE is observed, the identity of the specific viral isolate is confirmed via immunofluorescence using a specific antiserum. A significant drawback of the conventional tube cell culture test is the slow replication of the virus in culture. The most critical limitation, however, is the low sensitivity of this traditional tube test [76]. In a study examining 47 liver biopsy samples from patients with histopathologically confirmed CMV, the sensitivity of cell culture was found to be 52% [77]. Culture for CMV diagnosis is no longer employed as a first-line method.

6.3 Histopathology

To diagnose invasive CMV disease in tissues, biopsy samples can be obtained via fine-needle aspiration or open surgery for pathological evaluation. The most commonly used samples are from lung, gastrointestinal, and liver tissues, selected based on the patient's clinical presentation. Histologically, viral inclusions can be demonstrated, along with the detection of CMV-specific antigens and viral DNA. Biopsy specimens may be stained with hematoxylin and eosin to reveal the presence of giant cells with characteristic intracellular viral inclusions [76]. Intranuclear and intracytoplasmic inclusions called owl eyes can be observed [78]. To detect the presence of viral antigens in biopsy material, monoclonal antibodies against CMV antigens are used for indirect immunoperoxidase staining [76]. The confirmation of the diagnosis may require in situ hybridization and immunohistochemical tests [79]. Histopathological examination is essential in instances where CMV disease is suspected, yet blood tests for CMV return negative results. This scenario is particularly relevant in a few cases of gastrointestinal CMV disease, where a histological assessment can provide crucial insights for an accurate diagnosis [80].

6.4 Molecular Tests

In situ hybridization methods, such as a biotinylated DNA probe or formalin-fixed CMV-PCR, can be selected to detect CMV DNA in tissue [81, 82]. qPCR is the most widely used method for diagnosing CMV infection, guiding preemptive therapy decisions, and monitoring response to treatment [70]. qPCR detects and quantifies CMV nucleic acid, and its primary limitation is variability in results due to differences in standardization across laboratories. The results should be calibrated according to WHO standards and reported in IU/ml.

qPCR should be performed on plasma or whole blood samples. Thus, qPCR of urine or oral secretions is not recommended for monitoring or diagnosing CMV disease. Serum qPCR values three times or more above the lower detection limit are clinically significant. Serum CMV DNA should be

monitored weekly during treatment in patients requiring antiviral therapy. Therapy should be discontinued once viral loads fall below the detection limit in susceptible tests or based on two consecutive negative results in less sensitive qPCR tests [70].

The definitive diagnosis of target organ CMV disease is made by demonstrating CMV's cytopathic effects and antigens in tissue samples using immunohistochemical methods [69]. CMV DNA levels may be low despite active disease in patients with gastrointestinal disease or pneumonia following lung transplantation [80, 83]. In cases where serum CMV DNA levels are high and treatment is indicated, invasive diagnostic procedures may not be necessary. However, histopathological evaluation is crucial in suspected allograft rejection, co-infection with other pathogens, or when CMV is considered tissue-invasive but undetectable in blood [55].

Molecular tests can identify three key genomic regions responsible for CMV antiviral treatment resistance due to mutations. Mutations in the UL97 region (which encodes phosphotransferase) cause resistance to ganciclovir and maribavir, while mutations in the UL54 region, encoding DNA polymerase, confer resistance to ganciclovir, foscarnet, and cidofovir. Additionally, mutations in the UL56 region, encoding part of the viral terminase complex, can cause resistance to letermovir [84].

6.5 Antigenemia Tests

The CMV antigenemia test detects the presence of CMV by identifying polymorphonuclear leukocytes (PMNLs) that have phagocytosed the virus in peripheral blood. Monoclonal antibodies against the CMV pp65 protein are used as early and specific markers of active infection. The number of infected cells is quantified proportionately to the total number of PMNLs. The antigenemia test can be performed immediately after blood collection, providing rapid results useful for early detection. However, the test may yield inaccurate results in patients with neutropenia [3]. This test is beneficial for CMV detection and correlates with the severity of disease based on the number of infected cells. In this regard, it has a predictive value comparable to qPCR. Since significant infections can occur even with low viral cell counts, the antigenemia test determines when to initiate therapy and assess antiviral treatment response [3].

Based on the literature, when patients from different risk groups were evaluated using various tests at other times, the results were not evenly distributed across all scenarios. CMV-specific cell-mediated immunity (CMI) tests contribute to predicting individual risk for CMV infection and to personalizing the management [23, 85]. However, the most appropriate use of CMV-CMI tests is to personalize prophylaxis duration. Besides donor and recipient's CMV serostatus, CMV infection risk primarily depends on the status of the recipient's CMI [86]. Measuring CMV-specific T-cell responses can help predict individual risk for post-transplant CMV disease and guide prophylactic or preemptive therapy [70].

Most CMV CMI tests assess interferon-gamma (IFN-γ) production after whole blood or peripheral blood PMNL stimulation with CMV-specific antigens or peptides [87, 88]. Combining IFN-γ analysis with markers such as IL-2 and Programmed cell death protein 1 (PD-1) can enhance the ability to predict viremia risk. This approach allows for a more comprehensive evaluation of the CMI response, improving the accuracy of CMV viremia prediction [89]. Commercially available tests for assessing CMV-CMI responses include QuantiFERON-CMV, T-SPOT CMV, and T-SPOT.TB CMV.CMV, and CMV inSIGHT T-Cell Immunity Panel. All these tests measure T cell-mediated effector immune responses to two key CMV immunogenic antigens, pp65 and Immediate early protein 1 (IE-1), by evaluating

IFN-γ production [90]. QuantiFERON-CMV is an ELISA-based test that measures IFN-γ release by CMV-specific $CD8^+$ T cells after in vitro stimulation of whole blood with immunogenic viral peptides presented by MHC class I molecules [44]. It can help identify viremia risk in transplant patients, especially when pre-transplant results are negative [91]. However, its sensitivity may be reduced in lymphopenic patients due to insufficient cells for IFN-γ production [70]. T-Track CMV and T-SPOT.CMV are ELISpot tests that measure IFN-γ production without differentiating between $CD4^+$ and $CD8^+$ T cells [85]. inSIGHT T-Cell Immunity Panel uses intracellular cytokine staining (ICS) and flow cytometry to detect IFN-γ production in CMV-stimulated $CD4^+$ and $CD8^+$ T cells. This approach enables the quantitative and qualitative assessment of CMV-specific T cells, providing an advantage over ELISpot or QuantiFERON tests [70].

During the induction phase in SOT recipients, agents such as ATG and high-dose steroids can suppress CMV-CMI levels for 1-3 months, and their use during rejection episodes can be considered a risk factor for CMV disease [92, 93]. Tacrolimus inhibits the release of CMV-specific cytokines, thereby reducing T-cell activation and proliferation [94]. Mycophenolic acid has been associated with dysfunctional T cell profiles, whereas everolimus may activate T cell function, leading to improved CMV control [95].

7. Treatment

In immunocompetent patients, symptomatic CMV infection is typically benign and self-limiting, with observation without treatment generally recommended. However, in cases of primary CMV infection, symptoms may persist for a prolonged period in immunocompetent individuals [96]. In a study with a follow-up period of two and a half years, the average duration of symptoms in 124 immunocompetent patients with CMV infection was 7-8 weeks [97]. Additionally, severe CMV infection can lead to life-threatening complications [1]. Numerous studies indicate that patients experience rapid symptom resolution following antiviral therapy, demonstrating its morbidity-reducing effects [34, 98]. Therefore, antiviral therapy may be reconsidered for immunocompetent patients if there is clinical deterioration, need for immunosuppressive therapy, intensive care requirements, or prolonged symptom duration. Further prospective studies are required on this topic.

The action mechanisms of antiviral agents used in the treatment of CMV disease are summarized in Figure 2. Intravenous ganciclovir and oral valganciclovir are considered the standard first-line therapies for managing CMV in transplant recipients [99]. However, some patients cannot tolerate these treatments due to side effects or develop resistance to them. For patients who develop resistance to ganciclovir, second-line therapies such as foscarnet or cidofovir should be considered, though both agents carry the risk of nephrotoxicity [100].

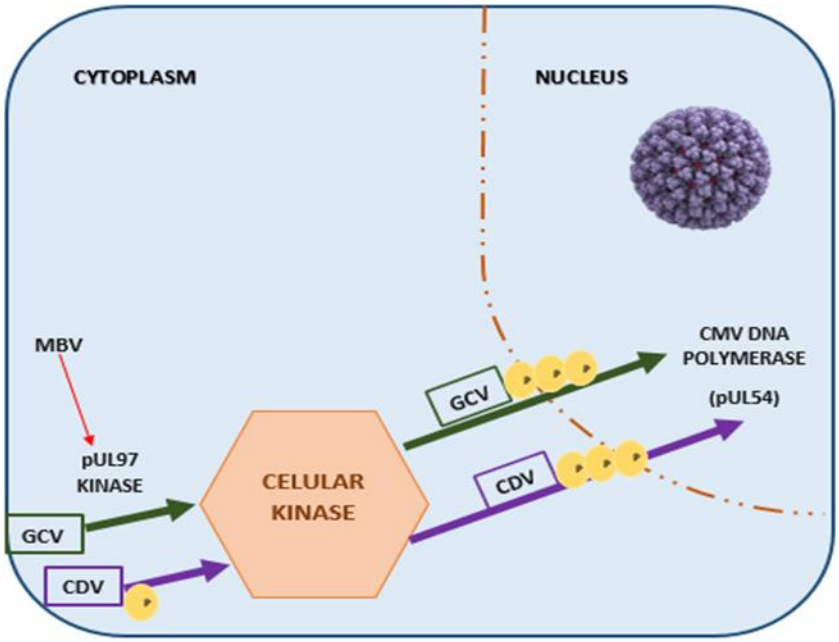

Figure 2 The action mechanisms of anti-CMV drugs. The specific action and resistance mechanisms of ganciclovir (GCV), cidofovir (CDV), and maribavir (MBV) are illustrated, highlighting their interactions with cellular kinases and the pUL97 kinase in the cytoplasm, as well as CMV DNA polymerase within the nucleus.

Ganciclovir is a DNA polymerase inhibitor and is used as an intravenous treatment for severe or life-threatening infections, very high viral loads (>5000-10,000 IU/ml), or patients with inadequate gastrointestinal absorption [101]. To prevent treatment failure and the development of refractory or resistant CMV disease, drug dosages should be optimized based on renal function. The recommended dose for intravenous ganciclovir is 5 mg/kg every 12 hours [84]. Close monitoring for adverse effects, such as leukopenia and renal impairment, is essential. Guidelines recommend a minimum treatment duration of 2 weeks, with therapy continuing until CMV DNA levels fall below detectable limits and clinical signs of CMV disease have resolved [31].

Valganciclovir is a widely used nucleoside reverse transcriptase inhibitor that halts viral replication. Common side effects include leukopenia, anemia, thrombocytopenia, and gastrointestinal symptoms. Due to its known myelosuppressive and nephrotoxic effects, regular monitoring of complete blood counts and serum creatinine levels is essential during treatment [102]. The recommended oral treatment dose for valganciclovir is 900 mg twice daily [84].

Foscarnet is a pyrophosphate analog that directly blocks the pyrophosphate binding site on DNA polymerase [103]. Foscarnet can be administered intravenously at a dose of 60 mg/kg over one hour using peripheral lines. The infusion time should be extended to 2 hours for higher doses (90-120 mg/kg). Renal toxicity typically manifests around the second week of therapy, although it can occur at any time. Foscarnet may also cause electrolyte imbalances, anemia, and QT prolongation [102]. Its benefits outweigh the risks in refractory or antiviral-resistant CMV cases, high viral loads, patients with severe diseases like gastritis, retinitis, or encephalitis, and patients who cannot tolerate oral medications [102].

Cidofovir, like ganciclovir, is a DNA polymerase inhibitor. It is a cytidine monophosphate analog. Unlike foscarnet, cidofovir is not directly active and requires kinase activation to exert its effect

[103]. Cidofovir should be infused over 1 hour in 100 mL of normal saline, with dose adjustments based on renal function. Patients should be monitored for potential side effects such as metabolic acidosis, neutropenia, neurological symptoms, anemia, and vision changes. Cidofovir is effective against CMV strains with UL97 mutations but not those with UL54 mutations. Like foscarnet, it is preferred for severe disease, high viral loads, and patients intolerant to oral therapy [102].

Letermovir is a viral terminase inhibitor that inhibits CMV replication by targeting the CMV DNA terminase complex (pUL51, pUL56, pUL89). It does not require renal dose adjustment, although data are insufficient for patients with creatinine clearance below 10 mL/min [102]. Letermovir is not recommended in patients with severe liver disease (Child-Pugh class C). Side effects are generally mild and include atrial fibrillation, tachycardia, peripheral edema, abdominal pain, diarrhea, and thrombocytopenia [102]. Due to its low resistance threshold (UL56), letermovir should only be considered a last-resort option for low-level CMV viremia [104].

Maribavir is a benzimidazole riboside that shows anti-CMV activity by competitively inhibiting UL97 protein kinase activity, thereby preventing protein phosphorylation and inhibiting CMV replication. Maribavir has recently been approved for the treatment of refractory or resistant CMV infections and is available in oral form. Maribavir is generally well tolerated, with common side effects including diarrhea, nausea, vomiting, anemia, thrombocytopenia, and taste disturbances. The absence of renal and bone marrow toxicity is a crucial advantage over other agents. Maribavir is a substrate for CYP3A4 and a weak inhibitor of CYP3A4 and p-glycoprotein, so dose adjustments may be required when used with CYP3A4 inducers [102]. Maribavir is effective against CMV strains that have developed resistance to ganciclovir, foscarnet, or cidofovir due to UL54 or UL97 kinase mutations, making it a valuable alternative for managing resistant CMV infections [105, 106].

In summary, ganciclovir and valganciclovir have comparable high efficacy, with valganciclovir preferred for oral administration, while ganciclovir is administered intravenously for severe cases. Foscarnet and cidofovir are effective against ganciclovir-resistant CMV but carry high nephrotoxicity risks. Letermovir is primarily used for prophylaxis, with a better safety profile but lower efficacy in active infections. Maribavir is effective against drug-resistant CMV, with fewer bone marrow toxicities, but can cause GI symptoms and taste disturbances.

8. Vaccine Development

Recent advancements in cytomegalovirus (CMV) vaccine development have yielded promising candidates aimed at preventing CMV infections, particularly in immunocompromised individuals. Currently, there are two types of vaccines against CMV infection:

8.1 Triplex Vaccine

Triplex is a CMV vaccine designed to elicit robust T-cell responses against CMV. In a Phase II clinical trial involving pediatric HSCT recipients, Triplex vaccination resulted in high levels of functional CMV-specific T cells, potentially contributing to protective antiviral immunity. Notably, vaccinated pediatric recipients did not require preemptive therapy to control CMV reactivation [107].

8.2 mRNA-1647 Vaccine

Developed by Moderna, mRNA-1647 is an mRNA-based vaccine targeting multiple proteins of CMV. A Phase II, randomized, observer-blind, placebo-controlled, dose-finding trial demonstrated that mRNA-1647 elicited strong humoral and cellular immune responses in healthy adults aged 18-40 years. The vaccine was generally well-tolerated, with an acceptable safety profile [108]. These developments represent significant progress in CMV vaccine research, offering hope for effective prevention strategies in populations at risk for CMV-related complications.

Prophylaxis and preemptive therapy are two different strategies used to prevent CMV infection in SOT recipients. Prophylaxis involves the proactive administration of antiviral drugs to all high-risk patients for a defined period after transplantation, regardless of evidence of CMV infection. In contrast, preemptive therapy involves initiating antiviral treatment as soon as early signs of CMV replication are detected, typically through a positive antigenemia test or when the viral load exceeds a specific threshold [109].

Both prophylaxis and preemptive therapy have proven practical approaches for preventing CMV infection in SOT recipients. However, no consensus exists on which strategy is superior [110]. The choice of approach often depends on clinical factors, including the patient's risk profile, the donor and recipient's serostatus, the level of immunosuppression, and the type of organ transplant (Table 1). Prophylaxis offers several advantages over preemptive therapy, including improved graft survival, lower rates of rejection, and enhanced protection against other opportunistic infections. However, it is associated with a higher incidence of late-onset CMV disease and more significant risks of drug toxicity [55, 86]. This distinction between the two strategies underscores the importance of individualized decision-making tailored to the patient's condition and specific transplant circumstances.

Table 1 CMV Serostatus Combinations and Associated Risks in Solid Organ Transplantation.

CMV Serostatus	Donor (D)	Recipient (R)	Risk of CMV Infection	Clinical Considerations	Recommended Strategy
High Risk (D+/R-)	Positive	Negative	Highest risk (Primary infection)	No pre-existing immunity; CMV transmission from donor likely	Prophylaxis with valganciclovir or letermovir for 3-6 months, close monitoring
Intermediate Risk (D+/R+)	Positive	Positive	Moderate risk (Reinfection or reactivation)	Pre-existing immunity, but reinfection or reactivation is possible	Preemptive therapy or short-term prophylaxis, depending on the immunosuppression level
Intermediate Risk (D-/R+)	Negative	Positive	Moderate risk (Reactivation)	CMV is already present in the recipient, and there is a risk of reactivation under immunosuppression	Preemptive therapy, monitoring viral load
Low Risk (D-/R-)	Negative	Negative	Lowest risk	No CMV exposure in donor or recipient, but risk from community exposure	No routine prophylaxis, but monitor for de novo CMV infection

8.3 Prophylaxis

Prophylaxis for CMV infection in SOT recipients involves administering antiviral medications within 10 days after transplantation and continuing for 3-6 months. Common antiviral agents used for prophylaxis include acyclovir, valacyclovir (particularly in kidney transplant recipients), intravenous ganciclovir, and valganciclovir. These drugs are also effective against other herpesviruses. However, late-onset CMV disease can still occur after discontinuation of prophylaxis, particularly in high-risk D+/R- patients [55, 111]. High-dose valacyclovir has effectively prevented CMV disease in both D+/R- and D±/R+ kidney transplant recipients [112, 113]. Valganciclovir prevents CMV infection by halting viral replication, especially in transplant patients [84]. The recommended prophylactic doses are oral valganciclovir 900 mg once daily, oral valacyclovir 2 grams four times daily, and intravenous ganciclovir 5 mg/kg/day [71]. Dose adjustments based on renal function are necessary for all antiviral agents.

Letermovir is available in both oral and intravenous forms and is approved for the prevention of CMV infection among allogeneic hematopoietic stem cell transplant (HSCT) recipients. In a randomized D+/R- kidney transplantation trial, letermovir was as effective as valganciclovir for CMV prophylaxis. Since rates of leukopenia and neutropenia were lower, fewer patients discontinued letermovir due to side effects [114]. Another study comparing valganciclovir and maribavir for preemptive treatment responses yielded similar results. However, the incidence of serious adverse events was higher in the maribavir group, with common side effects including acute graft-versus-host disease, diarrhea, renal failure, and urinary tract infections [115]. Since letermovir and maribavir do not cover herpes simplex virus (HSV) and varicella-zoster virus (VZV), additional antiviral prophylaxis is required when using these agents. Additionally, their use for SOT prevention is not yet approved; further studies are needed to assess their efficacy in this population.

The decision for prophylaxis should be made based on the donor and recipient's CMV serostatus and the type of transplantation. For patients with D-/R- serostatus, the risk of CMV infection is minimal, and routine prophylaxis is not recommended. However, considering the risk of HSV and VZV infection, antiviral prophylaxis with acyclovir, famciclovir, or valacyclovir should be regarded as [70]. For D+/R- kidney transplant recipients, a 6-month prophylaxis is recommended, whereas liver, heart, and pancreas recipients may receive prophylaxis for 3 to 6 months. In D+/R- lung transplant recipients, extended prophylaxis (6 to 12 months) is advised to prevent late-onset CMV disease, as early discontinuation of prophylaxis may increase the risk of delayed disease onset. In D±/R+ recipients, a 3-month prophylaxis strategy is generally recommended for kidney, pancreas, liver, and heart transplant recipients, though this may be extended to 6 months in those receiving intensive immunosuppressive therapy [70].

Routine CMV prophylaxis in SOT recipients typically prevents CMV disease within the first three months post-transplant. However, in high-risk serological patient groups, late-onset CMV disease may occur. In these cases, CMV disease often emerges after the cessation of antiviral prophylaxis [55, 87]. Risk factors for late-onset disease are D+/R- serostatus, short duration of prophylaxis, high levels of immunosuppression, allograft rejection, and lung transplantation [60, 111, 116]. In D+/R- lung recipients, longer prophylaxis may be necessary. A study that included both D+/R- and R+ lung transplant recipients found that extending valganciclovir prophylaxis to 12 months significantly reduced CMV infection and disease compared to 3 months of prophylaxis [117]. However, even with

6 months of prophylaxis, nearly 50% of D+/R- lung transplant recipients developed late-onset CMV infection or disease [116].

8.4 Preemptive Therapy

Despite effective antiviral prophylaxis in SOT recipients, many patients develop CMV viremia or disease after discontinued prophylaxis. Monitoring CMV viral load weekly can detect early viral replication, allowing for timely intervention. It is recommended that patients be monitored for at least 3-4 months [70]. This approach enables a more targeted use of antiviral therapy, ensuring that only patients at a significant risk of progressing to CMV disease receive treatment.

Preemptive therapy aims to reduce the incidence of late-onset CMV disease, selectively use antiviral medications, and minimize the associated costs and toxicities of these drugs. There is no universally agreed-upon threshold for initiating preemptive therapy. However, decisions should be made based on observed increases in viral load during weekly monitoring and the individual patient's risk of developing CMV infection. The highest-risk patients, such as D+/R- recipients or those receiving T-cell suppressive therapies, should have a lower threshold for starting treatment [70].

9. Conclusion

CMV remains a significant challenge in managing SOT recipients, with a substantial impact on patient outcomes and graft success. Understanding the complex interplay between CMV and the immune system is essential for developing effective prophylactic and therapeutic strategies. Current evidence supports the implementation of personalized approaches to CMV management by considering the donor and recipient serostatus, the type of organ transplanted, and the level of immunosuppression. While antiviral prophylaxis has proven effective in reducing the incidence of CMV disease, there is still a risk of late-onset infections, particularly in high-risk populations. Ongoing research into antiviral resistance and alternative treatment options is crucial for improving the management of CMV in transplant recipients. Ultimately, a multidisciplinary approach that includes vigilant monitoring and tailored therapy can enhance patient safety and improve long-term outcomes of CMV infection in SOT patients.

Author Contributions

I.N.S: Literature search, data collection, manuscript preparation, visualization. B.K: Literature search, data collection, manuscript preparation. H.Y.B: Literature search, data collection, manuscript preparation, visualization, final edition.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: A systematic review. Virol J. 2008; 5: 47.

2. Momin N, Telisinghe PU, Chong VH. Cytomegalovirus colitis in immunocompetent patients. Singapore Med J. 2011; 52: e170-e172.
3. Azevedo LS, Pierrotti LC, Abdala E, Costa SF, Strabelli TM, Campos SV, et al. Cytomegalovirus infection in transplant recipients. Clinics. 2015; 70: 515-523.
4. Boeckh M, Geballe AP. Cytomegalovirus: Pathogen, paradigm, and puzzle. J Clin Invest. 2011; 121: 1673-1680.
5. Pérez-Sola MJ, Castón JJ, Solana R, Rivero A, Torre-Cisneros J. Indirect effects of cytomegalovirus infection in solid organ transplant recipients. Enferm Infecc Microbiol Clin. 2008; 26: 38-47.
6. Kotton CN, Kumar D, Caliendo AM, Åsberg A, Chou S, Danziger-Isakov L, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013; 96: 333-360.
7. Stern M, Hirsch H, Cusini A, van Delden C, Manuel O, Meylan P, et al. Cytomegalovirus serology and replication remain associated with solid organ graft rejection and graft loss in the era of prophylactic treatment. Transplantation. 2014; 98: 1013-1018.
8. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2010; 20: 202-213.
9. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: The national health and nutrition examination surveys, 1988-2004. Clin Infect Dis. 2010; 50: 1439-1447.
10. Andrews PA, Emery VC, Newstead C. Summary of the British transplantation society guidelines for the prevention and management of CMV disease after solid organ transplantation. Transplantation. 2011; 92: 1181-1187.
11. Simon DM, Levin S. Infectious complications of solid organ transplantations. Infect Dis Clin North Am. 2001; 15: 521-549.
12. Bradley AJ, Lurain NS, Ghazal P, Trivedi U, Cunningham C, Baluchova K, et al. High-throughput sequence analysis of variants of human cytomegalovirus strains Towne and AD169. J Gen Virol. 2009; 90: 2375-2380.
13. Isaacson MK, Juckem LK, Compton T. Virus entry and innate immune activation. In: Human cytomegalovirus. Berlin, Germany: Springer; 2008. pp. 85-100.
14. Gupta M, Shorman M. Cytomegalovirus. StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2025.
15. Berry R, Watson GM, Jonjic S, Degli-Esposti MA, Rossjohn J. Modulation of innate and adaptive immunity by cytomegaloviruses. Nat Rev Immunol. 2020; 20: 113-127.
16. Piersma SJ, Brizić I. Natural killer cell effector functions in antiviral defense. FEBS J. 2022; 289: 3982-3999.
17. Boehm T, Bleul CC. The evolutionary history of lymphoid organs. Nat Immunol. 2007; 8: 131-135.
18. Goodrum F. Human cytomegalovirus latency: Approaching the Gordian knot. Annu Rev Virol. 2016; 3: 333-357.
19. Hu W, Pasare C. Location, location, location: Tissue-specific regulation of immune responses. J Leukoc Biol. 2013; 94: 409-421.

20. Hokeness KL, Kuziel WA, Biron CA, Salazar-Mather TP. Monocyte chemoattractant protein-1 and CCR2 interactions are required for IFN-α/β-induced inflammatory responses and antiviral defense in liver. J Immunol. 2005; 174: 1549-1556.
21. Popovic B, Golemac M, Podlech J, Zeleznjak J, Bilic-Zulle L, Lukic ML, et al. IL-33/ST2 pathway drives regulatory T cell dependent suppression of liver damage upon cytomegalovirus infection. PLoS Pathog. 2017; 13: e1006345.
22. Marshall EE, Geballe AP. Multifaceted evasion of the interferon response by cytomegalovirus. J Interferon Cytokine Res. 2009; 29: 609-620.
23. Bestard O, Kaminski H, Couzi L, Fernández-Ruiz M, Manuel O. Cytomegalovirus cell-mediated immunity: Ready for routine use? Transpl Int. 2023; 36: 11963.
24. Venema H, Van Den Berg AP, Van Zanten C, Van Son WJ, Van Der Giessen M. Natural killer cell responses in renal transplant patients with cytomegalovirus infection. J Med Virol. 1994; 42: 188-192.
25. Kaminski H, Garrigue I, Couzi L, Taton B, Bachelet T, Moreau JF, et al. Surveillance of γδ T cells predicts cytomegalovirus infection resolution in kidney transplants. J Am Soc Nephrol. 2016; 27: 637-645.
26. Appay V, Dunbar PR, Callan M, Klenerman P, Gillespie GM, Papagno L, et al. Memory $CD8^+$ T cells vary in differentiation phenotype in different persistent virus infections. Nat Med. 2002; 8: 379-385.
27. Sylwester AW, Mitchell BL, Edgar JB, Taormina C, Pelte C, Ruchti F, et al. Broadly targeted human cytomegalovirus-specific $CD4^+$ and $CD8^+$ T cells dominate the memory compartments of exposed subjects. J Exp Med. 2005; 202: 673-685.
28. Rentenaar RJ, Gamadia LE, van Diepen FN, Boom R, Weel JF, Wertheim-van Dillen PM, et al. Development of virus-specific $CD4^+$ T cells during primary cytomegalovirus infection. J Clin Invest. 2000; 105: 541-548.
29. van Leeuwen EM, Remmerswaal E, Vossen M, Rowshani AT, Wertheim-van Dillen PM, van Lier RA, et al. Emergence of a $CD4^+$ $CD28^-$ granzyme B^+, cytomegalovirus-specific T cell subset after recovery of primary cytomegalovirus infection. J Immunol. 2004; 173: 1834-1841.
30. Casazza JP, Betts MR, Price DA, Precopio ML, Ruff LE, Brenchley JM, et al. Acquisition of direct antiviral effector functions by CMV-specific $CD4^+$ T lymphocytes with cellular maturation. J Exp Med. 2006; 203: 2865-2877.
31. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-guidelines of the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019; 33: e13512.
32. Magno Palmeira M, Umemura Ribeiro HY, Garcia Lira Y, Machado Jucá Neto FO, da Silva Rodrigues IA, Fernandes da Paz LN, et al. Heart failure due to cytomegalovirus myocarditis in immunocompetent young adults: A case report. BMC Res Notes. 2016; 9: 391.
33. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: Is there a link? Lancet. 1997; 350: 430-436.
34. Eddleston M, Peacock S, Juniper M, Warrell DA. Severe cytomegalovirus infection in immunocompetent patients. Clin Infect Dis. 1997; 24: 52-56.
35. Bertoni M, Squizzato A, Foretic M, Zanieri S, Di Natale ME. Cytomegalovirus-associated splanchnic vein thrombosis in immunocompetent patients: A systematic review. Thromb Res. 2018; 168: 104-113.

36. Karkhaneh R, Lashay A, Ahmadraji A. Cytomegalovirus retinitis in an immunocompetent patient: A case report. J Curr Ophthalmol. 2016; 28: 93-95.
37. Gonçalves C, Cipriano A, Santos FV, Abreu M, Méndez J, e Castro RS. Cytomegalovirus acute infection with pulmonary involvement in an immunocompetent patient. IDCases. 2018; 14: e00445.
38. Humar A, Limaye AP, Blumberg EA, Hauser IA, Vincenti F, Jardine AG, et al. Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: Two-year results of the IMPACT study. Transplantation. 2010; 90: 1427-1431.
39. Legendre C, Pascual M. Improving outcomes for solid-organ transplant recipients at risk from cytomegalovirus infection: Late-onset disease and indirect consequences. Clin Infect Dis. 2008; 46: 732-740.
40. Blyth D, Lee I, Sims KD, Gasink LB, Barton TD, Van Deerlin VM, et al. Risk factors and clinical outcomes of cytomegalovirus disease occurring more than one year post solid organ transplantation. Transpl Infect Dis. 2012; 14: 149-155.
41. Cohen JI, Corey GR. Cytomegalovirus infection in the normal host. Medicine. 1985; 64: 100-114.
42. Venkataramani A, Schlueter AJ, Spech TJ, Greenberg E. Cytomegalovirus esophagitis in an immunocompetent host. Gastrointest Endosc. 1994; 40: 392-393.
43. Yeh PJ, Chiu CT, Lai MW, Wu RC, Kuo CJ, Hsu JT, et al. Cytomegalovirus gastritis: Clinicopathological profile. Dig Liver Dis. 2021; 53: 722-728.
44. Beany A, Rainis T. CMV-related gastric ulcer and gastroduodenitis in an immunocompetent patient: A case report and literature review. Case Rep Gastrointest Med. 2021; 2021: 3513223.
45. Solito S, di Prampero SF, Bulajic M, Battista S, Tomassini G, Panic N, et al. Cytomegalovirus-related gastritis in an immunocompetent host presenting with infectious gastroparesis. ACG Case Rep J. 2023; 10: e01231.
46. Lalazar G, Doviner V, Ben-Chetrit E. Unfolding the diagnosis. N Engl J Med. 2014; 370: 1344-1348.
47. Taniwaki S, Kataoka M, Tanaka H, Mizuno Y, Hirose M. Multiple ulcers of the ileum due to cytomegalovirus infection in a patient who showed no evidence of an immunocompromised state. J Gastroenterol. 1997; 32: 548-552.
48. Canterino JE, McCormack M, Gurung A, Passarelli J, Landry ML, Golden M. Cytomegalovirus appendicitis in an immunocompetent host. J Clin Virol. 2016; 78: 9-11.
49. Saeed MI, Stephens R, Nwogbo O, Gani IY, Kapoor R, Doroodchi A. Cytomegalovirus pancreatitis in an immunocompetent patient. IDCases. 2020; 22: e00932.
50. Razonable RR. Strategies for managing cytomegalovirus in transplant recipients. Expert Opin Pharmacother. 2010; 11: 1983-1997.
51. Fishman JA, Emery V, Freeman R, Pascual M, Rostaing L, Schlitt HJ, et al. Cytomegalovirus in transplantation-challenging the status quo. Clin Transplant. 2007; 21: 149-158.
52. Humar A, Snydman DA, AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplant recipients. Am J Transplant. 2009; 9: S78-S86.
53. Harvala H, Stewart C, Muller K, Burns S, Marson L, MacGilchrist A, et al. High risk of cytomegalovirus infection following solid organ transplantation despite prophylactic therapy. J Med Virol. 2013; 85: 893-898.

54. Mendez-Eirin E, Paniagua-Martín MJ, Marzoa-Rivas R, Barge-Caballero E, Grille-Cancela Z, Cañizares A, et al. Cumulative incidence of cytomegalovirus infection and disease after heart transplantation in the last decade: Effect of preemptive therapy. Transplant Proc. 2012; 44: 2660-2662.
55. Ramanan P, Razonable RR. Cytomegalovirus infections in solid organ transplantation: A review. Infect Chemother. 2013; 45: 260-271.
56. Fishman JA. Overview: Cytomegalovirus and the herpesviruses in transplantation. Am J Transplant. 2013; 13: 1-8.
57. Razonable RR, Hayden RT. Clinical utility of viral load in management of cytomegalovirus infection after solid organ transplantation. Clin Microbiol Rev. 2013; 26: 703-727.
58. Requião-Moura LR, Ferraz E, Matos AC, Tonato EJ, Ozaki KS, Durão MS, et al. Comparison of long-term effect of thymoglobulin treatment in patients with a high risk of delayed graft function. Transplant Proc. 2012; 44: 2428-2433.
59. Luan FL. Six-month low-dose valganciclovir prophylaxis in cytomegalovirus D+/R- kidney transplant patients receiving thymoglobulin induction. Transplant Proc. 2013; 45: 175-177.
60. Razonable RR, Rivero A, Rodriguez A, Wilson J, Daniels J, Jenkins G, et al. Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. J Infect Dis. 2001; 184: 1461-1464.
61. Brennan DC, Legendre C, Patel D, Mange K, Wiland A, McCague K, et al. Cytomegalovirus incidence between everolimus versus mycophenolate in de novo renal transplants: Pooled analysis of three clinical trials. Am J Transplant. 2011; 11: 2453-2462.
62. Fernández-Ruiz M, Corrales I, Arias M, Campistol JM, Giménez E, Crespo J, et al. Association between individual and combined SNPs in genes related to innate immunity and incidence of CMV infection in seropositive kidney transplant recipients. Am J Transplant. 2015; 15: 1323-1335.
63. de Rooij BJ, van der Beek MT, van Hoek B, Vossen AC, Ten Hove WR, Roos A, et al. Mannose-binding lectin and ficolin-2 gene polymorphisms predispose to cytomegalovirus (re) infection after orthotopic liver transplantation. J Hepatol. 2011; 55: 800-807.
64. Cummins NW, Deziel PJ, Abraham RS, Razonable RR. Deficiency of cytomegalovirus (CMV)-specific $CD8^+$ T cells in patients presenting with late-onset CMV disease several years after transplantation. Transpl Infect Dis. 2009; 11: 20-27.
65. Sarmiento E, Jaramillo M, Calahorra L, Fernandez-Yañez J, Gomez-Sanchez M, Crespo-Leiro MG, et al. Evaluation of humoral immunity profiles to identify heart recipients at risk for development of severe infections: A multicenter prospective study. J Heart Lung Transplant. 2017; 36: 529-539.
66. Yamani MH, Avery R, Mawhorter SD, McNeill A, Cook D, Ratliff NB, et al. The impact of CytoGam on cardiac transplant recipients with moderate hypogammaglobulinemia: A randomized single-center study. J Heart Lung Transplant. 2005; 24: 1766-1769.
67. Fernández-Ruiz M, Silva JT, López-Medrano F, Allende LM, San Juan R, Cambra F, et al. Post-transplant monitoring of NK cell counts as a simple approach to predict the occurrence of opportunistic infection in liver transplant recipients. Transpl Infect Dis. 2016; 18: 552-565.

68. Nierenberg NE, Poutsiaka DD, Chow JK, Cooper J, Price LL, Freeman RB, et al. Pretransplant lymphopenia is a novel prognostic factor in cytomegalovirus and noncytomegalovirus invasive infections after liver transplantation. Liver Transplant. 2014; 20: 1497-1507.
69. Ljungman P, Boeckh M, Hirsch HH, Josephson F, Lundgren J, Nichols G, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. Clin Infect Dis. 2016; 64: 87-91.
70. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2018; 102: 900-931.
71. Torre-Cisneros J, Aguado JM, Caston JJ, Almenar L, Alonso A, Cantisán S, et al. Management of cytomegalovirus infection in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. Transplant Rev. 2016; 30: 119-143.
72. Genini E, Percivalle E, Sarasini A, Revello MG, Baldanti F, Gerna G. Serum antibody response to the gH/gL/pUL128-131 five-protein complex of human cytomegalovirus (HCMV) in primary and reactivated HCMV infections. J Clin Virol. 2011; 52: 113-118.
73. Delforge ML, Desomberg L, Montesinos I. Evaluation of the new LIAISON® CMV IgG, IgM and IgG Avidity II assays. J Clin Virol. 2015; 72: 42-45.
74. Lúcia M, Crespo E, Melilli E, Cruzado JM, Luque S, Llaudó I, et al. Preformed frequencies of cytomegalovirus (CMV)-specific memory T and B cells identify protected CMV-sensitized individuals among seronegative kidney transplant recipients. Clin Infect Dis. 2014; 59: 1537-1545.
75. Pillay D, Ali AA, Liu SF, Kops E, Sweny P, Griffiths PD. The prognostic significance of positive CMV cultures during surveillance of renal transplant recipients. Transplantation. 1993; 56: 103-107.
76. Dioverti MV, Razonable RR. Cytomegalovirus. In: Diagnostic microbiology of the immunocompromised host. 2nd ed. New York, NY: John Wiley & Sons, Inc.; 2016. pp. 97-125.
77. Paya CV, Holley KE, Wiesner RH, Balasubramaniam K, Smith TF, Espy MJ, et al. Early diagnosis of cytomegalovirus hepatitis in liver transplant recipients: Role of immunostaining, DNA hybridization and culture of hepatic tissue. Hepatology. 1990; 12: 119-126.
78. Kasprzak A, Zabel M, Wysocki J, Biczysko W, Surdyk-Zasada J, Olejnik A, et al. Detection of DNA, mRNA and early antigen of the human cytomegalovirus using the immunomax technique in autopsy material of children with intrauterine infection. Virchows Arch. 2000; 437: 482-490.
79. Razonable RR, Paya CV, Smith TF. Role of the laboratory in diagnosis and management of cytomegalovirus infection in hematopoietic stem cell and solid-organ transplant recipients. J Clin Microbiol. 2002; 40: 746-752.
80. Eid AJ, Arthurs SK, Deziel PJ, Wilhelm MP, Razonable RR. Clinical predictors of relapse after treatment of primary gastrointestinal cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2010; 10: 157-161.
81. Denijn M, Schuurman HJ, Jacobse KC, de Weger RA. In situ hybridization: A valuable tool in diagnostic pathology. Apmis. 1992; 100: 669-681.
82. Lautenschlager I, Halme L, Höckerstedt K, Krogerus L, Taskinen E. Cytomegalovirus infection of the liver transplant: Virological, histological, immunological, and clinical observations. Transpl Infect Dis. 2006; 8: 21-30.

83. Westall GP, Michaelides A, Williams TJ, Snell GI, Kotsimbos TC. Human cytomegalovirus load in plasma and bronchoalveolar lavage fluid: A longitudinal study of lung transplant recipients. J Infect Dis. 2004; 190: 1076-1083.
84. Stewart AG, Kotton CN. What's new: Updates on cytomegalovirus in solid organ transplantation. Transplantation. 2024; 108: 884-897.
85. Hall VG, Humar A, Kumar D. Utility of cytomegalovirus cell-mediated immunity assays in solid organ transplantation. J Clin Microbiol. 2022; 60: e01716-21.
86. Kotton C. CMV: Prevention, diagnosis and therapy. Am J Transplant. 2013; 13: 24-40.
87. Egli A, Humar A, Kumar D. State-of-the-art monitoring of cytomegalovirus-specific cell-mediated immunity after organ transplant: A primer for the clinician. Clin Infect Dis. 2012; 55: 1678-1689.
88. Sester M, Leboeuf C, Schmidt T, Hirsch HH. The "ABC" of virus-specific T cell immunity in solid organ transplantation. Am J Transplant. 2016; 16: 1697-1706.
89. Sester U, Presser D, Dirks J, Gärtner BC, Köhler H, Sester M. PD-1 expression and IL-2 loss of cytomegalovirus-specific T cells correlates with viremia and reversible functional anergy. Am J Transplant. 2008; 8: 1486-1497.
90. MR W. The human cytotoxic T-lymphocyte (CTL) response to cytomegalovirus is dominated by structural protein pp65: Frequency, specificity, and T cell receptor usage of pp65-specific CTL. J Virol. 1996; 70: 7569.
91. Cantisán S, Lara R, Montejo M, Redel J, Rodríguez-Benot A, Gutiérrez-Aroca J, et al. Pretransplant interferon-γ secretion by CMV-specific $CD8^+$ T cells informs the risk of CMV replication after transplantation. Am J Transplant. 2013; 13: 738-745.
92. Kaminski H, Jarque M, Halfon M, Taton B, Di Ascia L, Pfirmann P, et al. Different impact of rATG induction on CMV infection risk in D+ R- and R+ KTRs. J Infect Dis. 2019; 220: 761-771.
93. Banas B, Steubl D, Renders L, Chittka D, Banas MC, Wekerle T, et al. Clinical validation of a novel enzyme-linked immunosorbent spot assay-based in vitro diagnostic assay to monitor cytomegalovirus-specific cell-mediated immunity in kidney transplant recipients: A multicenter, longitudinal, prospective, observational study. Transpl Int. 2018; 31: 436-450.
94. Egli A, Kumar D, Broscheit C, O'Shea D, Humar A. Comparison of the effect of standard and novel immunosuppressive drugs on CMV-specific T-cell cytokine profiling. Transplantation. 2013; 95: 448-455.
95. Kaminski H, Marseres G, Yared N, Nokin MJ, Pitard V, Zouine A, et al. mTOR inhibitors prevent CMV infection through the restoration of functional αβ and γδ T cells in kidney transplantation. J Am Soc Nephrol. 2022; 33: 121-137.
96. Nolan N, Halai UA, Regunath H, Smith L, Rojas-Moreno C, Salzer W. Primary cytomegalovirus infection in immunocompetent adults in the United States-A case series. IDCases. 2017; 10: 123-126.
97. Wreghitt T, Teare EL, Sule O, Devi R, Rice P. Cytomegalovirus infection in immunocompetent patients. Clin Infect Dis. 2003; 37: 1603-1606.
98. Leman JS, Toalson TW, Wlodaver CG. Ganciclovir treatment of systemic cytomegalovirus in an immunocompetent host. J Okla State Med Assoc. 1997; 90: 367-369.
99. Cho SY, Lee DG, Kim HJ. Cytomegalovirus infections after hematopoietic stem cell transplantation: Current status and future immunotherapy. Int J Mol Sci. 2019; 20: 2666.

100. Morris DJ. Adverse effects and drug interactions of clinical importance with antiviral drugs. Drug Saf. 1994; 10: 281-291.
101. Kotton CN, Kamar N. New insights on CMV management in solid organ transplant patients: Prevention, treatment, and management of resistant/refractory disease. Infect Dis Ther. 2023; 12: 333-342.
102. Hardinger KL, Brennan DC. Cytomegalovirus treatment in solid organ transplantation: An update on current approaches. Ann Pharmacother. 2024; 58: 1122-1133.
103. Royston L, Papanicolaou GA, Neofytos D. Refractory/resistant cytomegalovirus infection in transplant recipients: An update. Viruses. 2024; 16: 1085.
104. Linder KA, Kovacs C, Mullane KM, Wolfe C, Clark NM, La Hoz RM, et al. Letermovir treatment of cytomegalovirus infection or disease in solid organ and hematopoietic cell transplant recipients. Transpl Infect Dis. 2021; 23: e13687.
105. Drew WL, Miner RC, Marousek GI, Chou S. Maribavir sensitivity of cytomegalovirus isolates resistant to ganciclovir, cidofovir or foscarnet. J Clin Virol. 2006; 37: 124-127.
106. Chou S, Song K, Wu J, Bo T, Crumpacker C. Drug resistance mutations and associated phenotypes detected in clinical trials of maribavir for treatment of cytomegalovirus infection. J Infect Dis. 2022; 226: 576-584.
107. La Rosa C, Park Y, Yang D, Zhou Q, Kaltcheva T, Karras N, et al. Cytomegalovirus triplex vaccine in pediatric hematopoietic stem cell transplant patients at high risk for cytomegalovirus complications: Evaluation of vaccine safety, immunogenicity and impact on viremia requiring antivirals. Haematologica. 2024; 109: 2303-2308.
108. Panther L, Basnet S, Fierro C, Brune D, Leggett R, Peterson J, et al. 2892. Safety and immunogenicity of mRNA-1647, an mRNA-based cytomegalovirus vaccine in healthy adults: Results of a phase 2, randomized, observer-blind, placebo-controlled, dose-finding trial. Open Forum Infect Dis. 2023; 10: S1272-S1273.
109. Silva Junior HT, Tokat Y, Cai J, Singh I, Sandhu A, Demuth D, et al. Epidemiology, management, and burden of cytomegalovirus in solid organ transplant recipients in selected countries outside of Europe and North America: A systematic review. Transpl Infect Dis. 2023; 25: e14070.
110. Florescu DF, Qiu F, Schmidt CM, Kalil AC. A direct and indirect comparison meta-analysis on the efficacy of cytomegalovirus preventive strategies in solid organ transplant. Clin Infect Dis. 2014; 58: 785-803.
111. Humar A, Lebranchu Y, Vincenti F, Blumberg EA, Punch JD, Limaye AP, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. Am J Transplant. 2010; 10: 1228-1237.
112. Lowance D, Neumayer HH, Legendre CM, Squifflet JP, Kovarik J, Brennan PJ, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. N Engl J Med. 1999; 340: 1462-1470.
113. Hodson EM, Ladhani M, Webster AC, Strippoli GF, Craig JC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev. 2013. doi: 10.1002/14651858.CD003774.pub4.
114. Limaye AP, Budde K, Humar A, Vincenti F, Kuypers DR, Carroll RP, et al. Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: A randomized clinical trial. JAMA. 2023; 330: 33-42.

115. Maertens J, Cordonnier C, Jaksch P, Poiré X, Uknis M, Wu J, et al. Maribavir for preemptive treatment of cytomegalovirus reactivation. N Engl J Med. 2019; 381: 1136-1147.
116. Schoeppler KE, Lyu DM, Grazia TJ, Crossno Jr JT, Vandervest KM, Zamora MR. Late-onset cytomegalovirus (CMV) in lung transplant recipients: Can CMV serostatus guide the duration of prophylaxis? Am J Transplant. 2013; 13: 376-382.
117. Palmer SM, Limaye AP, Banks M, Gallup D, Chapman J, Lawrence EC, et al. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: A randomized, controlled trial. Ann Intern Med. 2010; 152: 761-769.