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Review

Cytomegalovirus in Lung Transplant

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Abstract

Lung transplantation is a therapeutic option for patients with advanced lung diseases. Lung transplant outcomes have improved over time with improvements in the management of these complex patients. Cytomegalovirus is a common opportunistic organism affecting all solid organ transplant recipients. Characteristics unique to lung transplantation can make this virus difficult to manage, with myriad complications including graft failure and death. Ongoing research into and understanding of cytomegalovirus has opened exciting new avenues of management. We discuss the various manifestations of CMV related pathologies in the lung transplant recipient. We discuss current mainstays of risk stratification, diagnosis, and treatment, as well as present new and evolving concepts. Current medications are highly effective at preventing and treating CMV manifestations, but may be poorly tolerated. A new generation of therapies carry the promise of efficacy, with a greater safety profile and improved tolerance of adverse effects. We discuss host-virus immune interactions, specifically how these can be utilized in clinical practice to individualize the cytomegalovirus related care of lung transplant recipients. Finally, we turn our attention to the near horizon as we continue to evolve the care of this unique population.

Keywords
Cytomegalovirus; lung transplantation; review; immunity; treatment

1. Literature Review

1.1 Introduction

Cytomegalovirus (CMV) remains the most common opportunistic infection following lung transplantation, responsible for a substantial burden of morbidity and mortality [1]. Despite decades of increasing short and long-term lung transplantation success, CMV management has remained relatively static. However, new diagnostic, prophylactic and therapeutic strategies are becoming available and bring with them promise to improve the care of this immunosuppressed population. In this review, we discuss current standards of management for CMV related pathologies and examine how these standards may soon change.

1.2 Background

CMV is a DNA virus, a member of the beta-herpesviridae family that is highly prevalent throughout populations. CMV is ubiquitous throughout society, with general seropositivity between 30 and 97%, and prevalence correlated with age and socioeconomic factors [2-4]. CMV may spread via close contact, body fluids exposure, sexually or perinatally [5, 6]. In immunocompetent individuals, initial (lytic phase) infection may be asymptomatic, or cause a febrile illness that can resemble Epstein-Barr Virus (EBV) mononucleosis [7]. Lytic phase infection leads to the synthesis of a number of CMV specific proteins, including immediate-early (IE), early, and late viral proteins [8], all of which have been exploited in developing new diagnostic tests to evaluate CMV specific immunity. The initial immune response to CMV involves innate immunity, before transitioning to an adaptive immune response characterized by humoral and CMV-specific T cell responses [9]. While early studies pointed to the prominence of the cytotoxic (CD8+) T-cell in controlling CMV infection, the CD4+ T-cell response is necessary for lasting viral control [10]. Regardless, after immune control, this virus, like other members of the Herpesviridae family, enters a state of latency. As latent virus tends to reside in monocytes, macrophages, lymphocytes, endothelial cells and bone marrow progenitor cells [9], viral DNA has consequently been isolated from myriad body fluids including saliva, urine, blood, and genital secretions [5]. In individuals who lose immune control of latent virus, CMV may reactivate, entering a lytic phase and potentially resulting in recurrent clinical disease.

As a group, lung transplant recipients are at an increased risk of CMV related disease compared to other solid organ transplant (SOT) recipients. Many factors exist to explain this finding. First, donor seroprevalence has increased over time by transplant era, increasing from 55.3% between January 1992 and December 2000 to 61.6% in the most recent era (January 2010 through June 2018). This increasing seroprevalence is perhaps due to increasingly aggressive donor acceptance practices, and an increase in mean donor age from 30 to 40 years over the same time period [11]. Secondly, when compared to kidney, liver, or heart, the lung may carry a higher burden of donor CMV infected

cells allowing more opportunity for reactivation [9]. Thirdly, compared to these other organ transplants, lung transplants tend to require the highest amounts of maintenance immunosuppression which may also increase the odds of recrudescence of viral disease. Finally, episodes of acute rejection in lung transplant recipients may necessitate high doses of corticosteroids, or lymphocyte depleting therapies which predispose recipients to increased risk of CMV reactivation [9].

Risk of CMV related complications can be stratified according to the serostatus of donor and recipient. Seronegative recipients receiving organs from seropositive donors are at greatest risk, followed by seropositive recipient of seropositive organs. In this instance, though seropositive recipients may have pre-transplant immunity to CMV, donors may still transmit novel CMV strains, or recipients may lose immunity to CMV over time [12]. Seropositive recipients of seronegative organs are at lesser risk, and finally, seronegative recipients of seronegative donor organs are at the lowest risk of developing CMV disease; their risk of de novo CMV viremia mirroring the general population. To this end, it may be important to follow CMV serostatus of this population to document their exposure and risk to CMV over time. These risk categories provide guidance for duration of post-transplant CMV prophylaxis. Recently, testing to determine the presence of recipient CMV immunity following lung transplant has been studied to better stratify risk of CMV reactivation and to personalize duration of CMV prophylactic measures [13]. While many of these studies have been performed in non-lung transplant populations, a few studies have looked specifically at lung transplant recipients and have yielded promising results.

The consequences of CMV infection are not minor. The most common direct end organ manifestations of CMV disease in lung transplant patients include CMV pneumonitis and CMV colitis. In each instance, management typically necessitates invasive diagnostics, histopathologic demonstration, and intravenous therapy with ganciclovir. CMV has also been shown to have indirect effects on the host, possibly by altering the host immune response with subsequent increases in rates of bacterial, fungal, and viral infections [14-16]. A correlation with chronic lung allograft dysfunction has been observed [17], though a direct causation has yet to be shown [18, 19]. CMV has been identified as the cause of death in about 1% of lung transplant recipients and a significant cause of graft failure during the first three years following transplant [1, 20-23]. In an early series of 59 lung transplant recipients not receiving CMV prophylaxis, 32 (54%) patients developed CMV infection, including 95% of CMV seropositive recipients [24]. Survival and significant complications were worse in CMV seronegative recipients who developed infection. Additionally, post-transplant CMV infection is an economic burden on health care systems in terms of cost and number of hospital days [25-27].

2. CMV Manifestations

Cytomegalovirus (CMV) infection or viremia differs from CMV syndrome or disease. Viremia is defined as the detection of CMV in a tested specimen. While viremia in the most traditional sense may be defined as CMV isolated by culturing, this is rarely performed. Detection of antigens may be referred to as antigenemia. Most commonly, viral DNA is detected using PCR based techniques in blood or serum samples, and isolation of viral nucleic acid sequences is referred to DNAemia or RNAemia [28].

CMV syndrome is a definition exclusively used in SOT patients. This is defined as detection of CMV in the blood and at least 2 of the following criteria:

1. Fever $\geq$ 38°C for at least 2 days.
2. New or worsening fatigue.
3. Leukopenia or neutropenia on 2 separate measurements at least 24 hours apart.
4. $\geq$ 5% atypical lymphocytes.
5. Thrombocytopenia defined as a platelet count of <100,000 cells/μL.
6. Transaminitis $\geq$ 2 times the upper limit of normal [28].

CMV may manifest differently in individual patients. Those who are immunocompetent are generally asymptomatic or may present with mononucleosis syndrome. While mononucleosis is commonly associated with EBV, there are some key similarities and differences between these viral syndromes. Both may present with protracted fevers, fatigue, and a maculopapular rash [29] with lymphocytosis and atypical lymphocytes. By contrast, CMV mononucleosis typically does not present with enlarged cervical lymph nodes or tonsillitis. It may cause exudative tonsillopharyngitis but is heterophile antibody negative [29, 30]. Immunocompromised patients, such as those with HIV, cancer, or SOT, may present with more severe manifestations.

CMV disease is broadly defined as viremia and end organ dysfunction resulting from viral infiltration. Ideally, CMV should be directly evidenced from affected tissue; typically, histopathologic changes are seen on biopsy material. CMV retinitis is an exception, as clinical diagnosis is sufficient without detection of CMV in a tissue sample. It is also recognized that high viral DNA levels in a tissue sample with negative serum levels may represent disease, although organ specific viral level cutoffs have not been established. The most common manifestations of CMV disease in lung transplant patients include CMV pneumonitis and CMV colitis. Additional diseases caused by CMV in both immunocompetent and immunocompromised individuals are also described.

2.1 Pulmonary

Clinical features of CMV pneumonitis include fever, fatigue, hypoxemia, dyspnea at rest or exertion, tachypnea with a cough that is typically non-productive. Pulmonary infiltrates on imaging can accompany clinical findings and can include non-specific CT findings such as diffuse ground-glass opacities, small pulmonary nodules often in a military pattern, confluent consolidation, and interstitial reticulation without air space opacification. While not easily identified, the finding of large cells with the typical 'owl eye' intranuclear inclusion, also known as Cowdry inclusions, in tissue obtained at biopsy provides a conclusive diagnosis (Figure 1) [31]. And while viral isolation from bronchoalveolar lavage (BAL) is suggestive of infection, strict levels for diagnosis have not been established. BAL testing for CMV can be completed using culture and nucleic acid amplification and quantification. While low levels of CMV DNA in BAL fluid may represent asymptomatic viral replication, higher levels may indicate active disease. Various levels with varying sensitivity and specificity have been reported [32-37], and though there is no specific threshold, it is generally accepted that viral copies > 500,000/mL are more likely associated with CMV pneumonitis [38]. Concurrent histopathology increases sensitivity and specificity of detection of CMV pneumonitis [34]. The higher the viral load, the more likely the patient is to have CMV identified on tissue biopsy, and the more likely the patient is to have clinical features of CMV pneumonia or pneumonitis. CMV pneumonitis may be life threatening in patients who are severely immunosuppressed, causing

severe hypoxemia and progressive respiratory failure by causing transplant failure or rejection. Pneumonitis secondary to CMV is seen less frequently now given improved detection along with modern prophylactic and treatment regimens. Incidence ranges from 3-6% in some reviews, with mortality reported as high as 35% [39]. It is important to note that asymptomatic CMV replication is thought to contribute to the development of bronchiolitis obliterans syndrome (BOS) [16, 40].

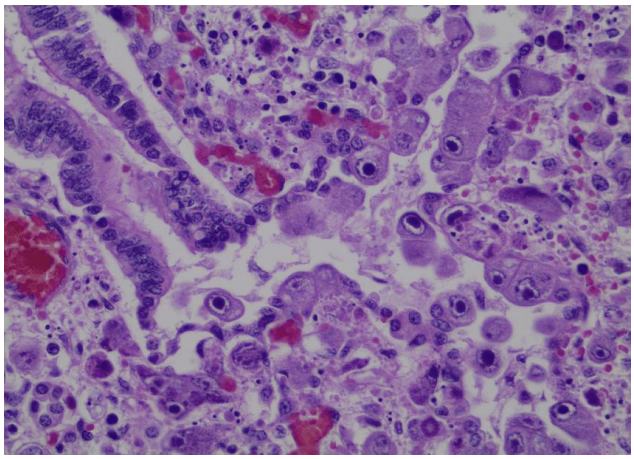

Figure 1 Cowdry Inclusions: Haematoxylin and eosin stain of bronchial epithelial cells with CMV inclusions in nuclei and cytoplasm. Infected cells have an "Owl's eye" appearance.

2.2 Gastrointestinal

Gastrointestinal infection in the form of colitis presents with fever, fatigue, abdominal pain and cramping, diarrhea that is at times bloody, with inflammatory colitis and ulcerations noted on endoscopy. Cowdry inclusions can be seen on pathology [28, 41, 42]. CMV may also cause gastritis [43], esophagitis [44], ileitis [45], obstruction [46], and protein-losing hypertrophic gastropathy [47]. Diagnosis is made with endoscopy and biopsy proven CMV isolation from appropriate mucosa.

2.3 Cardiovascular

CMV has been implicated in both venous thrombosis and coronary atherosclerosis, although causal relationships have not been established. Infection is thought to promote smooth muscle proliferation and increase uptake of lipoproteins, leading to atherosclerosis [48, 49]. Pericarditis and myocarditis have also been reported, and can be confirmed by pericardial or myocardial biopsy and isolation, culture, immunohistochemistry, nucleic acid analysis, or identification of CMV histological features [28, 50].

2.4 Hepatic and Pancreatic

Although hepatitis is a known complication of infection, asymptomatic mild transaminitis is often seen in patients infected with CMV. Disease is diagnosed by liver function test abnormalities and biopsy [28]. Granulomatous hepatitis secondary to CMV has been documented [51, 52], as have portal vein thrombosis [53, 54] and pancreatitis [28, 55].

2.5 Neurologic

CMV is known to cause encephalitis [56], ventriculitis, and Guillain-Barré syndrome (GBS) [57, 58]. Other described neurological deficits associated with CMV include transverse myelitis [59], neuropathies, and cranial nerve palsies [60]. Diagnosis requires relevant clinical symptomatology and viral isolation from cerebrospinal fluid (CSF), culture from nervous tissue biopsy, or encephalitis on electroencephalography (EEG) [28].

2.6 Ocular

CMV is known to cause anterior uveitis in immunocompetent patients when latent CMV is reactivated. While there are differences in the presentation of CMV related chronic anterior uveitis, it is a clinical diagnosis with anterior chamber inflammation, elevated intraocular pressure, and iris atrophy [61]. Retinitis is typically absent in anterior uveitis. Retinitis is diagnosed clinically, however, if the diagnosis is in question, CMV in the vitreous fluid can help support the diagnosis [28].

2.7 Renal

Renal transplantations account for the majority of solid organ transplants performed annually. CMV nephritis is a significant issue in the renal transplant population. While CMV nephritis may theoretically affect lung transplant recipients, there are no published reports of CMV nephritis in this population.

3. CMV Monitoring

There are multiple risk factors for the development of CMV disease in SOT and specifically in LT recipients, prevention is key given high rates of infection and reactivation. Late onset CMV occurs in patients who develop CMV related issues such as DNAemia or end organ complications after they have completed their course of primary prophylaxis post transplantation. This clinical phenomenon is most commonly seen in D+/R- patients between 3-6 months following discontinuation of prophylaxis. Late-onset disease also occurs with greater frequency in patients receiving high levels of immunosuppression, in those with acute rejection, and is seen more in LT compared to other SOTs [12]. Several studies have evaluated duration of prophylaxis [22, 23, 40, 62, 63], and have shown that CMV infection and disease remains frequent, increases mortality, and is decreased using extended prophylaxis [64, 65]. Prevention in the form of CMV prophylaxis and preemptive therapy are discussed below.

3.1 Universal Prophylaxis

Given the high frequency of disease and CMV reactivation following LT, universal prophylaxis is the standard of care for at risk patients following lung transplant. This entails administration of antiviral medication to recipients of seropositive organs, or recipients who themselves are seropositive, for a predetermined length of time. Intravenous ganciclovir and the oral prodrug valganciclovir have been studied for universal prophylaxis and are the most commonly used agents today [12]. Universal prophylaxis effectively prevents disease, is relatively easy to implement, may prevent other opportunistic infections, and may improve survival by preventing rejection secondary

to infection [32]. Universal prophylaxis has been shown to prevent CMV disease in 58-80% of patients [16, 66]. Seronegative recipients who receive transplants from seronegative donors do not typically receive CMV prophylaxis, though may receive anti-viral prophylaxis directed at other pathogens.

3.2 Pre-emptive Therapy

Pre-emptive therapy entails regular CMV monitoring and initiation of antivirals when there is evidence of CMV DNAemia in order to prevent CMV disease [12, 67]. While universal prophylaxis reduces rates of CMV disease as well of that of other herpes viruses, drug costs, potential side effects of antivirals, and development of resistance remain reasons to consider pre-emptive therapy [12].

Prophylaxis against CMV infection in the lung transplant recipient is a central tenet of post-operative care. While debate exists as to the primacy of universal or pre-emptive prophylaxis strategies in hematopoietic and other solid organ transplants, given the risk of developing active CMV following lung transplant universal CMV prophylaxis is provided for all lung transplant recipients with donor or recipient seropositivity for CMV. Duration of CMV prophylaxis is guided by risk of developing active CMV replication in the host. Seronegative recipients transplanted with seropositive donor organs represent the highest risk group and typically receive CMV prophylaxis for a period of at least 12 months [12, 65, 68]. Seropositive recipients will typically receive CMV prophylaxis for a period of at least 6 months [15, 30]. Longer durations of CMV prophylaxis, including indefinite have been implemented at some centers for the highest risk patients, though significant risks include the selection for and breakthrough of resistant CMV strains [69, 70], and medication associated myelotoxicity [71, 72]. After periods of universal prophylaxis, recipients will undergo periods of close pre-emptive monitoring. In the post-prophylaxis period, patients remain at risk for development of a primary viremia, replication of previously latent virus, or infection with a new strain of CMV. Close monitoring enables transplant teams to rapidly identify CMV replication and initiate a therapeutic response.

4. CMV Testing

Serologic testing and viral cultures are no longer recommended methods of testing for the presence of CMV given the lack of specificity. Molecular testing has made monitoring CMV status and testing for disease much easier. Quantitative tests include antigen staining of leukocytes and PCR assays. Antigen testing is semiquantitative, where higher levels of antigenemia correlate with likelihood and severity of disease [73]. This test, however, is labor intensive, is less sensitive than PCR testing, and becomes less sensitive in neutropenic patients [74].

PCR assays are more sensitive quantitative tests for CMV, where higher levels correlate with disease [75]. Previously, each laboratory had their own standards and cutoffs - extraction method, amplification target, probe, non-standardized quantification of secondary standards, and amplicon size previously led to intra-lab variability [76]. These, however, have now been standardized through the 2010 WHO international standard for CMV QNAT [12]. Changes in CMV DNA levels should be normalized to log scale, and significant changes are recognized as 1 log increases or decreases in viral copies per mL of sample [12, 77]. Either plasma or whole blood can be used for PCR testing, although consistency in sampling should be considered, as CMV DNA is detected at higher levels in

whole blood as compared to plasma. Whole blood testing has the advantage of detecting latent and replicating virus and is a more sensitive test, while CMV plasma levels are more specific for active DNAemia [12, 74]. It is important to also note that changes in viral loads are useful to determine viral burden and control. Decreasing viral loads, whether in serum or other samples, may indicate improving disease control.

4.1 CMV Agents (Figure 2) [78]

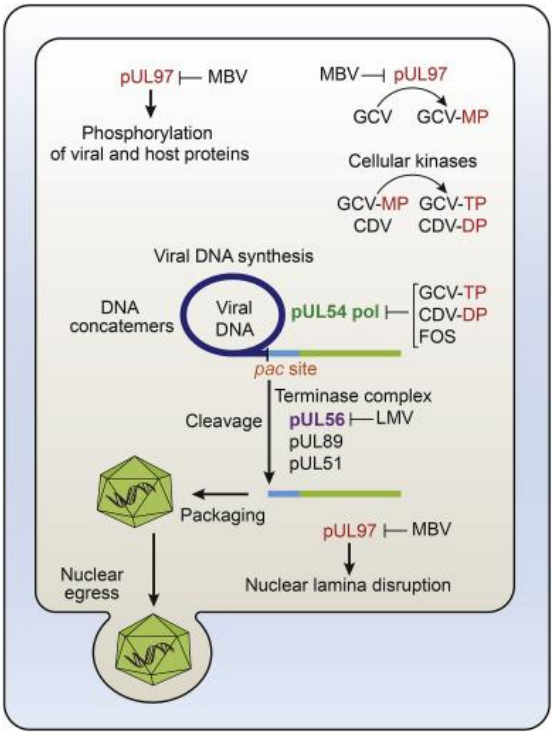

Figure 2 Mechanism of action of antiviral agents against cytomegalovirus: The viral UL97 kinase phosphorylates viral and host proteins involved in viral DNA synthesis. This enzyme enables the initial phosphorylation of ganciclovir (GCV), which is then further phosphorylated by cellular kinases to the active form, GCV-triphosphate (GCV-TP). GCV-TP incorporates into viral DNA where it impedes DNA chain elongation. Maribavir (MBV) also interferes with UL97 by inhibiting nuclear egress of viral particles, and may also limit the initial phosphorylation. Cellular kinases are also responsible for conversion of cidofovir (CDV) into its active state, which incorporates into viral DNA, and leading to termination of chain elongation. The viral DNA polymerase coded by UL54 produces DNA multimers. The activity of this enzyme is directly inhibited by foscarnet (FOS). DNA multimers are then cleaved to monomers and prepared for packaging by the viral terminase complex. Letermovir (LMV) interferes with this activity by inhibiting the UL56 subunit of the viral terminase complex [78].

Ganciclovir and Valganciclovir have proven to be the workhorses of CMV directed therapies, applied as first line agents for both prophylaxis and treatment of CMV. Ganciclovir was first introduced in 1988, and in addition to its role in organ transplantation has found application in the treatment of congenital CMV and CMV in other immunocompromised states [7]. Ganciclovir is an acyclic nucleoside analogue that is administered in an inactive state and undergoes phosphorylation

by viral UL97 protein kinase in CMV infected cells to ganciclovir monophosphate. Subsequent phosphorylations are mediated by cellular kinases, generating the active form of this drug - ganciclovir triphosphate. Ganciclovir triphosphate inhibits the viral UL54 encoded DNA polymerase by competing with deoxyguanosine as a substrate for this enzyme. Incorporation of ganciclovir triphosphate during DNA elongation results in the premature termination of CMV DNA synthesis [7]. Ganciclovir is available in IV form, dosing and duration are dictated by indication – treatment or prophylaxis. An oral form of ganciclovir is no longer available in the United States. Ganciclovir is excreted by glomerular filtration and active tubular secretion, and dose adjustment is necessary in impaired renal function. In addition to the need for intravenous access, ganciclovir usage is limited by side effects, most notably bone marrow toxicity, manifested as leukopenia, neutropenia, anemia, and thrombocytopenia [79].

Valganciclovir is an oral prodrug of ganciclovir, that once absorbed is metabolized to ganciclovir by hepatic and intestinal esterases [9]. When appropriately dosed, serum concentrations of valganciclovir can be equivalent to IV ganciclovir and prevent CMV viremia [80, 81]. Valganciclovir has been shown to be an effective agent for CMV prophylaxis and treatment of mild or moderate CMV related diseases [82]. Despite the efficacy of valganciclovir, IV ganciclovir remains the agent of choice for patients with severe manifestations of CMV, due to its superior bioavailability [12].

Cytomegalovirus can be refractory or resistant to treatment with ganciclovir. When CMV is susceptible to ganciclovir, appropriately dosed regimens should lead to a significant decline, defined as a >1 log10 decrease in CMV viral load within 2 weeks of initiation. Patients with an increase in viral load are described as having probable refractory (less than 1 log10 increase) or refractory (greater than 1 log10 increase) CMV [12]. Detection of refractory CMV should lead to testing for CMV resistance. CMV resistance is diagnosed upon detection of mutations with genotypic testing of the UL97 and UL54 genes and can be low-level or high-level. CMV resistance is seen in up to 4% of solid organ transplant recipients [83]. Risk factors for CMV resistance include over-immunosuppression, insufficient ganciclovir dosing [84], and CMV donor positive-recipient negative mismatch status [83, 85]. Patients with ganciclovir resistant CMV have increased mortality, number of hospital days and decreased renal function when compared to patients treated for ganciclovir sensitive CMV [83].

In some instances, low-level ganciclovir resistance may be overcome by increased dosing of ganciclovir, However, in the setting of high-level ganciclovir resistance or severe CMV disease, alternative agents should be deployed to treat CMV viremia and disease [12]. Guideline recommended secondary agents include foscarnet and cidofovir [12]. Both of these agents demonstrate a broad spectrum of activity against DNA viruses. Cidofovir bypasses the need for UL97 mediated phosphorylation, relying on cellular kinases present in high levels in CMV infected cells. Once activated, cidofovir competes with deoxycytidine triphosphate as a competitive substrate for viral DNA polymerase and leads to termination of viral DNA elongation. Resistance to cidofovir occurs in the setting of viral DNA polymerase mutations and occurs at a frequency similar to that of ganciclovir. Foscarnet inhibits the activity of the UL54 encoded viral DNA polymerase by competing at the pyrophosphate binding site, inhibiting the elongation of DNA chains, and inhibiting DNA synthesis [13]. Both agents require IV infusion, and suffer from similar adverse effects profiles, most notably a high incidence of renal injury and electrolyte derangement, albeit via different mechanisms [7, 9]. Brincidofovir was developed as an oral prodrug of cidofovir, however a randomized control trial comparing this medication to placebo for CMV prophylaxis in stem cell

transplant patients showed increased mortality and a higher burden of serious adverse effects [86]. Subsequently, brincidofovir is no longer being developed for management of CMV related purposes [13].

CMV immunoglobulin (CMV-Ig) preparations contain a standardized amount of purified human antibody to CMV, and may serve as an adjunct to prophylactic or treatment protocols [87]. CMV-Ig has been shown to delay the onset of CMV DNAemia and disease in high risk lung transplant recipients [88], and may reduce the risk of chronic lung allograft dysfunction [89]. Additionally, CMV-Ig has been shown to be an effective addition to antivirals as rescue therapy for life threatening CMV diseases [90]. However, the utility of CMV-Ig is debated as data supporting its use are mostly single-center, retrospective reports and a potentially diminishing role in the current era of improved CMV detection and treatment [91]. A Cochrane review found that there was no benefit to the use of CMV-Ig in prophylaxis of CMV related outcomes in solid organ transplant recipients [92].

Recently, new options for management of CMV which seek to resolve some of the most vexing issues associated with the traditional therapies have become clinically available. Letermovir is a non-nucleoside inhibitor of the UL56 encoded DNA terminase complex. It prohibits cleavage of CMV DNA multimers into monomers, thereby inhibiting packaging of viral DNA into the virion. Letermorvir was approved in 2017 by the FDA for prophylaxis of CMV infections in hematopoietic stem cell transplant patients [93]. An ongoing randomized control trial is comparing the efficacy of letermovir versus valganciclovir to prevent CMV disease in adult kidney transplant recipients [94]. Though not yet indicated in lung transplant recipients, this medication has been used when resistance or side effects limit the use of traditional agents [95, 96]. Letermovir may be especially useful in the setting of CMV that is cross resistant to ganciclovir, foscarnet and cidofovir, though resistance to letermovir has already been demonstrated [97]. Letermovir is eliminated through hepatic uptake, has mild described adverse effects, does not cause myelosuppression nor does it impair renal function, though an interaction with calcineurin inhibitors may be expected [9]. Importantly, letermovir's spectrum of anti-viral activity is limited to CMV, thus additional anti-viral therapies may be indicated during letermorvir use.

Maribavir is another new agent, with a potential role in treating CMV related diseases. Maribavir is a selective inhibitor of the UL97 encoded protein kinase, acting as a competitive inhibitor of ATP binding [98], and impedes nuclear egress of viral capsids [99]. Early trials failed to show efficacy of maribavir, though these used a low dosing regimen. With higher dosing, a phase 2 trial in both HSCT and solid organ transplant patients has demonstrated non-inferiority of maribavir to valganciclovir for CMV prevention [99]. Though UL97 mutations can cause cross resistance to ganciclovir and maribavir [78, 100], maribavir may have a role in treating CMV infections that are refractory or resistant to first and second line therapies [101]. Maribavir is well tolerated, without significant myelosuppression or nephrotoxicity, though complaints of GI distress and dysgeusia have been relatively common. Maribavir is specific for CMV and EBV, and additional antiviral coverage may be indicated in select patients while on maribavir.

An intact T cell response to CMV is integral to long term control of this virus. As such, in patients with recurrent or refractory CMV infections, reduction of immunosuppression may be considered to allow for a degree of immune reconstitution. This of course increases the risk of allograft rejection. Adaptive T-cell transfer of CMV specific T cells has been used successfully in the hematopoietic stem cell transplant population for control of CMV [13]. This technique has also been used in solid organ transplantation, including lung transplant recipients, with success in recent years [102-104]. In stem

cell transplant recipients, donor T cells may be used to induce viral immunity, however this is not effective in solid organ transplants. In solid organ recipients, current efforts center around stimulation of recipient peripheral blood mononuclear cells with purified CMV proteins, in vitro enhancement of an immune response and subsequent reinfusion of newly CMV immune cells to generate CMV immunity [105]. Subsequent changes in recipient T cell repertoire are predictive of successful adoptive T cell transfer [106]. Transfer of third party CMV-specific T cells is another paradigm currently being explored [107]. To date, Adoptive T cell therapies in solid organ transplant recipients have been shown to be generally safe and well tolerated, with minimal serious adverse effects. This technique may also allow for resumption of full dose immunosuppression, which may have previously been decreased to allow a host response to CMV to develop. Continued research in the use of adoptive transfer of CMV specific immunity in solid organ transplant recipients is ongoing [108].

Alternative approaches to managing CMV infection are in varying stages of clinical readiness. An immunosuppression regimen including mTOR inhibitors has been shown to reduce the incidence of CMV viremia in transplant recipients, although the mechanisms underlying this association are poorly understood [109-112]. Leflunomide impairs virion assembly and inhibits pyrimidine synthesis and has been used off label for resistant and refractory CMV [113]. A monoclonal AB, RG7667 is undergoing clinical trials and has shown promise as potential therapy to prevent CMV infection in solid organ transplant recipients [114].

An effective vaccine against CMV would prove to be a holy grail in the management of transplant recipients, pre-empting the risks associated with CMV diseases and medication related adverse effects. To this end, efforts to develop a vaccine have persisted since the 1970's and have been increased since the turn of the century [115]. An ideal vaccine would provide long lasting immunity by stimulating humoral and cellular arms of the adaptive immune system and lead to development of memory responses that protect against the entire range of CMV strains. Development has been slowed by incomplete understanding of the CMV virus, including its latent state, its unique immune evasion capabilities, an incomplete understanding of necessary immune elements for protection, and lack of good animal models [116]. A myriad of vaccines is currently in varying stages of development, including live, non-living, vectored, and novel vaccines [117], including an mRNA vaccine candidate [118]. There is clearly an important need for a CMV vaccine, both in the transplant community and for prevention of congenital CMV [119, 120]. However, to date, no vaccine is currently in Phase 3 trials.

5. CMV Immunity and Immunity Testing

An evolving understanding of immunity against CMV has opened a new phase of personalized management in the care of lung transplant recipients. Interactions between CMV and the host immune system are complex and dynamic. Following initial viremia, a robust immune response is triggered, eliciting activity from innate and adaptive immunity, including elements of both the humoral and cell mediated arms. Innate immune cells, including natural killer (NK) cells, and proteins such as toll like receptors, characterize the initial response to CMV [121]. CD4, CD8 and antibody producing cells are elicited in the adaptive immune response [122]. Intact cellular immunity provides long lasting protection from active CMV viremia.

Prior to transplant, the presence of a serologic antibody response to CMV indicates prior exposure and therefore likely immune control of CMV replication. Following transplantation, however, the host immune system's ability to control CMV infection may be impaired secondary to induction and maintenance immunosuppression regimens. Immune monitoring of the response to CMV represents a new avenue to personalize management of CMV treatment and prophylaxis. A number of unique tests assessing the T cell response to CMV have been developed and are in varying stages of clinical readiness. Principles of testing vary, though all tests include the in vitro stimulation of immune cells with CMV specific proteins and subsequent assessment of the immune response. ELISpot nonspecifically tests both CD4 and CD8 responses, while QuantiFERON tests primarily monitor CD8 responses [40, 123, 124]. Flow cytometry-based T-cell immune profiles provide specific values for both CD4 and CD8 cellular responses [125, 126]. Ongoing efforts to refine these tests, to best understand appropriate threshold values and when to apply these tests are underway [62]. In short, demonstration of the presence or absence of host immunity to CMV holds great promise to assist the clinical team with decisions to prolong or discontinue CMV therapies.

6. Future of CMV in LTx and Conclusion

Cytomegalovirus has been a vexing concern for lung transplant recipients and their healthcare providers since the inception of routine transplantation. CMV remains a complex and incompletely understood virus and is a burden on patients and health care systems, with direct and indirect affects impacting patient's quality and quantity of life. Major advances have allowed practitioners to better prevent and treat CMV in lung transplant recipients. Increasingly sensitive testing allows us to identify early viremia and risk stratify our patients. New therapies exploit our improved understanding of the virus, are less toxic and easier to administer. The future appears bright, as new therapies emerge, diagnostic strategies evolve, and promising vaccine options continue to be developed.

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JR and MB are responsible for the conception and drafting of this work. DN is responsible for critical revision of this work. All authors approve of the final version of this work.

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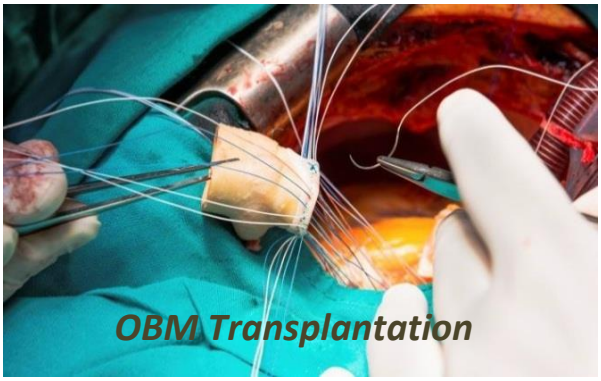

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