ABSTRACT

Solid organ transplantations save lives in patients affected by terminal organ failures, improve quality of life and are essential for mature health care systems. Organ transplantations have gradually remediated in the last two decades and usually provide excellent results in children, young adults and elderly transplant patients with co-morbidities. However, complications such as infection and allograft rejection, which are related by immunosuppressive therapy, remain major causes of morbidity and mortality following solid organ transplantation. Infections are a major cause of morbidity and mortality in transplant recipients. Among various infections occurring after transplantation, cytomegalovirus is the most frequent and dangerous infection. Cytomegalovirus (CMV) continues to have a tremendous impact in solid organ transplantation despite remarkable advances in its diagnosis, prevention and treatment. It can affect allograft function and increase patient morbidity and mortality through a number of direct and indirect effects. This article reviews the effects of cytomegalovirus on various solid organ transplants, including prophylactic, diagnostic, treatment strategies by providing guidance regarding care of solid organ transplant patients with cytomegalovirus infection.

Keywords: cytomegalovirus (CMV), Solid organ transplantation, risk factors,
INTRODUCTION

Solid organ transplantation is a therapeutic option for many human diseases. Liver, kidney, heart, and lung transplantation have become standard therapy for selected end-stage diseases; pancreas (including islet cell) and small bowel transplantation are also being evaluated in this regard. The quality of life and survival rates following organ transplantation have greatly improved due to advances in surgical technique, immunosuppressive therapy, and medical management.

According to activity data reported to the Global Observatory on Donation and Transplantation (GODT) (World Health Organization 2016), analysis from 2016 transplant activity globally, shows that solid organ transplants were performed 1,35,860 worldwide: 89,352 kidney transplants (40 % from living donors), 30,352 liver transplants (19 % from living donors), 7,626 heart transplants, 5497 lung transplants, 2342 pancreas transplants, and 220 small bowel. This activity was increased 7.25 % when compared with the data of 2015 data, but it is estimated that it is 10% less for global needs. This indicates the significance and emerging need for organ transplantations worldwide.

Transplant rejection is a process in which a transplant recipient's immune system attacks the transplanted organ or tissue. The cause of transplant rejection is immune suppression in the host which is resulted due to antigen-antibody reactions mediated by immune cells of the host on the transplanted organ or tissue.

Infections are a common cause of morbidity and mortality after transplantation, and infections rank second as the cause of death in patients with allograft function. The rate of first infections in the initial 3 years after kidney transplantation is 45.0 per 100 patient-years of follow-up, as estimated using Medicare claims data collected by the U.S. Renal Data System.

CMV infection is the single most frequent cause of infectious complications in the early period following kidney transplantation. Post-transfusion cytomegalovirus infection is of concern in the immune competent as well as in certain categories of immune compromised individuals such as neonates, pregnant women, recipients of bone marrow and other organ transplants and individuals with immune deficiency disorders.

Human cytomegalovirus (CMV) is a vernacular name of the human herpes virus 5, a highly host-specific c virus of the Herpesviridae family. In 1956, Margaret G. Smith recovered the first isolate from the sub-maxillary gland tissue of a dead infant.
Beta Herpes virus i.e., human cytomegalovirus (HCMV) is a widespread opportunistic pathogen that severely affects immune compromised and immune deficient populations. Like all herpes viruses, HCMV undergoes either productive or latent infection. During productive infection, infectious virus is produced, while in latent infection the virus becomes largely transcriptional quiescent. Like other herpes viruses, many events that are critical for productive HCMV replication take place within the nucleus. These include essential steps in viral replication, such as: the transcriptional cascade of immediate-early (IE), early and late viral RNA transcripts, synthesis of viral DNA and the production of DNA-containing capsid.

STATISTICS OF SOLID ORGAN TRANSPLANTATIONS:
The kidney transplantation is indicated in patients with ESRD. According to ERA-EDTA registry the kidney transplants in 2016 are 22,046 out of which the deceased donor percentage is 70% and living donor percentage is 30%. In contrast, the survival probability of donors is maintained at peak level for both genders up to the age of 44 years and glomerulo-nephritis occupied the first place with maximum survival probability.

Liver transplantation (LT) is the second most frequently performed transplant after kidney transplantation. According to 2015 report of the European Liver Transplant Registry, the main indications for Liver transplantation are cirrhosis (56.1%), cancers (16.5%), cholestatic diseases (9.9%), acute hepatic failure (7.6%), metabolic diseases (5.7%), and other diseases (4.2%). Data from the same registry disclosed the survival rate of liver transplants on the basis of 1-year to 20-year follow up. The patient survival of cholestatic diseased patients is better when compared to other primary diseases.

Heart transplantation is indicated in patients suffering from refractory cardiac failure owing to cardiomyopathy (53.5%), coronary artery disease (30.8%), congenital heart diseases (9%),
retransplant because of previous graft failure (2.6%), valvular heart disease (1.4%), and for other entities (2.7%). The median survival age in adults is 10.8 years and in paediatrics is 16.5 years. The main indication for lung transplantation is respiratory insufficiency secondary to idiopathic pulmonary fibrosis (30%), emphysema/chronic obstructive pulmonary disease (26%), and cystic fibrosis (14%). According to International Society For Heart and Lung Transplantation (ISHLT), per year 4661 bilateral lung transplantations performed while single lung transplantations are 920. The median survival age for adults is 6 years and pediatrics is 5.5 years.

**EPIDEMIOLOGY OF CYTOMEGALOVIRUS INFECTION:**

Human Cytomegalovirus (HCMV) is the most frequent reason of congenital infections affecting 0.5% to 2% of all live births in the developed countries. Human Cytomegalovirus (HCMV) has appeared as a major cause of morbidity and mortality in children and immunocompromised adults. It has higher positivity of HCMV infection in females as compared to males.

It is believed that humans are the only reservoir for HCMV and transmission occurs from person to person by direct or indirect, close or intimate contacts. The virus sheds in semen, saliva, urine and other body fluids. Besides contact with seropositive mothers (through genital secretions, breast milk etc.) blood transfusion and organ transplantation are other common modes of postnatal spread of HCMV. It is a ubiquitous virus, the seroprevalence of which reportedly varies between 30 to 100% in different countries.

The seroprevalence of CMV varies geographically and is higher in developing countries, with rates reaching up to 100%, likely resulting from poor socio-economic status and over-crowding which facilitate viral transmission through close contacts.

CMV establishes lifelong latency in a variety of cells following primary infection, which may lead to reactivation and intermittent viral shedding. Prior to implementation of widespread routine CMV prophylaxis among SOT recipients, CMV disease typically occurs during the first three months after transplantation. The epidemiology has changed, as late-onset CMV disease has emerged in high-risk CMV donor-positive/recipient-negative (D+/R-) patients after the completion of antiviral prophylaxis. The incidence of CMV infection and disease varies by the type of organ transplant, the serostatus of donor and recipient, and the prevention strategies used.

In heart recipients who received universal antiviral prophylaxis in the first month after transplant followed by preemptive therapy, the cumulative incidence of CMV infection and disease during the first year was 47% and 7.5% (3.6% in low risk and 25% in high risk group), respectively. The incidence of CMV disease among lung transplant recipients who received
antiviral prophylaxis for 6 to 12 months was 14.9%, with a higher incidence (26.6%) in D+/R group\textsuperscript{14}. Most cases of CMV disease in patients who received antiviral prophylaxis occur after cessation of antiviral drug administration, hence the term “late-onset CMV disease”, and they occur predominantly in CMV mismatch (D+/R) SOT recipients. Late-onset CMV disease remains associated with allograft failure and mortality\textsuperscript{15}.

**Clinical features:**
CMV infection in solid-organ transplant recipients exhibits a wide range of clinical manifestations, from asymptomatic infection to severe, lethal, CMV disease\textsuperscript{16}. The direct effects of CMV are the clinical manifestations occurring as a result of CMV replication, dissemination and tissue invasion of specific organs\textsuperscript{17}. CMV tends to involve the allograft because of altered immune mechanism locally within the allograft and the presence of the virus within latent cells of the allograft tissue obtained from seropositive donors. Most cases of CMV disease following transplantation are of mild to moderate severity and are rarely fatal in the current decade. Manifestations of mild to moderate disease include fever and malaise without additional signs or symptoms. Leukopenia with or without thrombocytopenia may be present. Myalgias, arthralgias, and at times frank arthritis may occur, but the mononucleosis syndrome seen in immunocompetent hosts is rarely seen in transplant recipients. The majority of viremic episodes accompany clinical symptoms. Viremia, as documented by surveillance cultures, can be the sole indication of CMV infection in the absence of clinical symptoms. However, asymptomatic CMV infection as documented by surveillance cultures may impact the posttransplantation course indirectly by being associated with other (e.g., bacterial) infections\textsuperscript{18}.

A) **CMV IN RENAL TRANSPLANT PATIENTS:**
Cytomegalovirus is the most common virus which is responsible for graft rejection in kidney transplantation. In Indian scenario, the prevalence of Cytomegalovirus is 98%. Probability of primary infection and reactivation was 2% and bulk of CMV infection in post transplant was 96\%\textsuperscript{19}.

Cytomegalovirus (CMV) infection is the most common opportunistic infection in kidney transplant recipients, occurring in 8\% of patients\textsuperscript{20}. Additionally, CMV infection within 100 days of transplant is an independent risk factor for overall recipient mortality, and early CMV disease is associated with increased cardiovascular mortality beyond 100 days\textsuperscript{21}. Reischig and colleagues found that CMV disease is an independent risk factor for biopsy proven acute rejection in the first 12 months\textsuperscript{22}. CMV disease is also associated with post-transplant lympho proliferative disorder (PTLD), transplant renal artery stenosis, post-transplant diabetes mellitus
irrespective of immunosuppressive drugs, and recurrent thrombotic micro-angiopathy after kidney transplant\textsuperscript{23}.

In renal transplant recipients, systemic CMV is associated with a glomerulopathy characterized by enlargement or necrosis of endothelial cells and accumulation of mononuclear cells and fibrillar material in glomerular capillaries\textsuperscript{24}.

B) CYTOMEGALOVIRUS IN LIVER TRANSPLANT PATIENTS:

CMV is frequently detected in our patients after liver transplantation\textsuperscript{25}. In liver transplants, it is associated with nonspecific hepatitis. CMV hepatitis typically manifests as elevated concentrations of gamma-glutamyltransferase and alkalinephosphatase are seen with in 2 to 4 days later than aminotransferase levels, with only minimally increased bilirubin levels\textsuperscript{26}.

CMV exhibits direct and indirect effects on liver transplantation\textsuperscript{27} which are shown in table 1.

<table>
<thead>
<tr>
<th>Direct effects</th>
<th>In-direct effects</th>
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<tbody>
<tr>
<td>CMV syndrome</td>
<td>Acute allograft rejection</td>
</tr>
<tr>
<td>Fever</td>
<td>Chronic allograft rejection</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Vanishing bile duct syndrome</td>
</tr>
<tr>
<td>Malaise, Tissue-invasive CMV disease</td>
<td>Chronic ductopenic rejection</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>Hepatitis C virus recurrence</td>
</tr>
<tr>
<td>(colitis, esophagitis, gastritis, enteritis)</td>
<td>Allograft hepatitis, fibrosis</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Allograft failure</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Opportunistic and other infections</td>
</tr>
<tr>
<td>CNS disease</td>
<td>Fungal superinfection</td>
</tr>
<tr>
<td>Retinitis</td>
<td>Nocardiosis</td>
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<tr>
<td>Mortality</td>
<td>Bacterial superinfection</td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr virus and PTLD</td>
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<tr>
<td></td>
<td>HHV-6 and HHV-7 infections</td>
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<tr>
<td></td>
<td>Vascular thrombosis</td>
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<td></td>
<td>New onset diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
</tr>
</tbody>
</table>

In a study authored by Margaret J. Gorensek et al. identified positive donor cytomegalovirus serology as the single most important risk factor for subsequent development of cytomegalovirus infection, regardless of recipient cytomegalovirus serological status\textsuperscript{28}.

According to Liang-Hui Gao et al, cytomegalovirus incidence may cause the progression of VBDS (vanishing bile duct syndrome), which is responsible for transplant rejection\textsuperscript{29}.

Risk factors for chronic liver rejection include transplantation for primary sclerosing cholangitis (PSC) primary biliary cirrhosis (PBC) certain patterns of HLA match between donor and recipient positive lymphocyte cross-match, cytomegalovirus infection, transplantation between donor and recipient of different ethnic origins, sex mismatch, and absence of azathioprine from the immunosuppressive regimen\textsuperscript{29}.

C) CMV IN LUNG TRANSPLANTATION:
Cytomegalovirus (CMV) infection remains a serious problem in lung transplant recipients. The incidence of CMV infection and disease following lung transplantation in the post ganciclovir era ranges from 30 to 86% with an associated mortality rate of 2–12%30. The Pap worth group showed that seronegative heart–lung recipients of CMV-positive organs are at the highest risk of developing severe, sometimes fatal, disease31. Lung transplantation involves the transfer of large amounts of lymphatic tissue harboring greater amounts of latent CMV than other organs, theoretically increasing the risk and severity of CMV infection32. Therefore, some authors recommend that all lung transplant recipients should be considered high-risk. Co-infection with other beta herpes viruses (HHV-6 and HHV-7) with inherent immune-modulating properties enhances CMV replication33. Use of anti-lymphocytic antibodies for induction therapy or treatment of steroid-resistant rejection increases the rate of CMV reactivation34.

In lung transplantation CMV pneumonitis results in fever, dyspnoea, and cough with findings of hypoxemia and pulmonary infiltrates. Radiographic appearances include bilateral interstitial, unilateral lobar and nodular infiltrates. The lung recipients of lung allografts are particularly prone to CMV pneumonitis, which may be severe in this population35. D. Thomas et al, stated that CMV reactivation in exposed patients undergoing lung transplantation was surprisingly high and was associated with a significantly higher risk of subsequent BOS and a trend towards a poorer 3 year survival36.

MECHANISM OF GRAFT REJECTION:

The explosion of new discoveries in the field of immunology has provided new insights into mechanisms that promote an immune response directed against a transplanted organ. Central to the allograft response are T lymphocytes. Rejection of solid organ allografts is the result of a complex series of interactions involving coordination between both the innate and adaptive immune system with T-cells central to this process. The ability of recipient T cells to recognize donor derived antigens, called Allorecognition, initiates allograft rejection. Once recipient T cells become activated, they undergo clonal expansion, differentiate into effector cells, and migrate into the graft where they promote tissue destruction. In addition, CD4 T cells help B cells produce alloantibodies. Here, we will review the components of an anti-allograft adaptive immune response37.

There is a bidirectional relationship between CMV and allograft rejection. Allograft rejection creates a pro-inflammatory environment that can reactivate CMV, and the treatment for allograft rejection severely impairs the ability to mount an immune response to control viral replication. Allograft rejection was strongly associated with the occurrence of late onset CMV
disease in CMV D+/R- liver and kidney transplant patients. Conversely, CMV up-regulates antigens and results in alloreactivity and facilitates allograft rejection\textsuperscript{38}.

\textbf{Figure 2: Role of Cytomegalovirus (Cmv) Infection In Transplant Recipients}\textsuperscript{39}.

In Immuno-suppressed solid-organ transplant recipient, CMV has three major effects. It (i) causes infectious diseases syndromes; (ii) has been implicated in causing increased immune-suppression, which may explain the frequent association of CMV with other opportunistic infections and (iii) has been associated with allograft rejection in the form of early-onset allograft rejection in renal transplant recipients and chronic allograft rejection (allograft atherosclerosis) in cardiac transplant recipients\textsuperscript{40}.

**RISK FACTORS OF CMV INFECTION IN SOTS:**

The risk of infection for the recipient at any point in time after transplantation is a function of two factors:

- The \textit{epidemiologic exposures} of the patient and the organ donor including recent, nosocomial, and remote exposures.
- The patient’s “\textit{net state of Immunosuppression}”\textsuperscript{41}.

The net state of immune suppression depends on several factors which are included in table 2.
Table 2: Factors Affecting Net State of Immune Suppression

- Immunosuppressive Therapy: Type, Temporal Sequence, and Intensity
- Prior therapies (Chemotherapy or Antimicrobials)
- Mucocutaneous Barrier Integrity (catheters, lines, drains)
- Neutropenia, Lymphopenia, Hypogammaglobulinemia (often drug-induced)
- Technical complications (graft injury, fluid collections, wounds)
- Underlying immune defects (e.g. Genetic polymorphisms, autoimmune disease)
- Metabolic conditions: uremia, malnutrition, diabetes, alcoholism/cirrhosis, advanced age
- Viral infection (e.g., herpesviruses, hepatitis B and C, HIV, RSV)

Three patterns of CMV transmission are observed in solid organ transplantation recipients.

1. Primary infection develops when a CMV-seronegative individual receives cells latently infected with the virus from a seropositive donor followed by viral reactivation.
2. Secondary infection or reactivation infection develops when endogenous latent virus is reactivated in a CMV-seropositive individual post transplantation.
3. Superinfection or reinfection occurs when a seropositive recipient receives latently infected cells from a seropositive donor and the virus that reactivates post transplantation is of donor origin.

Following primary infection with CMV, long-term cellular and humoral immunity usually develop but CMV remains latent or persistent within the host. Viral persistence is controlled in the immunocompetent host by an intact cellular immune system. Immunosuppression administered following transplantation may lead to uncontrolled viral replication and consequently to symptomatic CMV infection.
Antilymphocyte antibody is associated with a two- to five-fold increase in rate of CMV. The incidence of CMV disease in donor CMV-seronegative/recipient CMV-seronegative (CMV D-/R-) is 5%\(^{44}\).

DIAGNOSTIC PROCEDURES:

The laboratory tests that are available for screening and diagnosis of CMV include histopathology, serological assays, pp65 antigenemia, and nucleic acid tests (NAT). Measures for immunity to CMV such as serology and novel immunology assays detecting CMV specific cellular immunity may be used to assess the risk of CMV infection in SOT recipients\(^{45}\).

1) ANTIGENEMIA:

The CMV antigenemia test is a rapid method for the detection of CMV phagocytized by neutrophils in the peripheral blood. In particular, monoclonal antibodies to CMV pp65 protein are used as an early and specific marker of active infection. The blood sample should be collected with anticoagulant, and the results are expressed as the number of polymorphonuclear cells infected in relation to the total number of polymorphonuclear cells counted. The antigenemia assay is also used to evaluate the response to antiviral treatment, and its disappearance from the bloodstream is considered as a marker of therapeutic efficacy\(^{46}\).

The advantages of the antigenemia assay are that it can be performed soon after blood collection and has a short processing time (approximately 6 hours), enabling early diagnosis of the infection, and that it does not require sophisticated and expensive equipment and can be performed in medium-capacity laboratories.

The disadvantages include the following:

- The test needs to be conducted immediately after the collection of blood samples (no more than 6 hours later).
- Its quantification is subjective and dependent on the expertise of the person who performs the test.

Table 3: Risk Factors for The Development of CMV

- Donor seropositivity
- Use of induction immune suppression (T cell–depleting antibodies)
- Simultaneous kidney-pancreas transplantation
- Older donors (>60 years)
- Presence of allograft rejection
- Concurrent infection from other viruses
• It is not an uniformly standardized method, with extensive variability in its practice, which can compromise reproduction of the method in different laboratories.
• It can only be applied if there is an adequate number of circulating cells, which limits its use in patients with leukopenia (the neutrophil count must be greater than 200/mm3), particularly in HSCT recipients.
• The result may specifically be doubtful in patients with a neutrophil count below 1,000/mm3.

2) HISTOPATHOLOGY:
Histopathology is used to confirm tissue-invasive CMV disease. However, its invasive nature has limited its use in certain clinical settings. For example, in a patient with gastrointestinal CMV disease, a biopsy may not be done if the patient’s blood contains high levels of CMV. Certain situations that would warrant biopsy and histopathology are (1) when allograft rejection is suspected (which requires more immunosuppression, whereas treatment of CMV disease requires a reduction in immunosuppression), (2) when co-infection with other pathogens is suspected (when symptoms do not resolve with treatment), and (3) when “compartmentalized” disease is suspected due to the absence of detectable virus in the blood47.

3) SEROLOGICAL ASSAYS:
Serology is useful in determining the serological status of the donor and recipient prior to transplantation to thereby define the post-transplant risk, given that CMV-negative recipients receiving an organ from CMV-positive donors develop more frequent and more aggressive disease. After transplantation, however, the value of serology is limited, and serology has no value for the diagnosis of active disease or infection.
Serological diagnosis of CMV infection can be accomplished by dosing the IgM and IgG antibodies. The first antibody to appear is IgM, which may be present in the patient’s serum for a long period of time after the infection. The IgG antibody appears in the blood after 6 to 8 weeks of infection and can persist indefinitely, although with fluctuation in its levels. For this reason, this antibody is used to define the serological relationship between the donor and the recipient (D/R). It is important to remember that the presence of IgG antibody does not protect the individual from reactivation of a latent viral infection or from a new infection with a different strain of the virus. Serology in immune compromised patients can be difficult to interpret due to the patients’ impaired humoral responses. Moreover, they can present circulating IgG from transfusions or from treatments with immunoglobulin48.

TREATMENT STRATEGIES:
Advances in CMV prevention strategies have resulted in a decrease in CMV related mortality, tissue-invasive disease and detrimental indirect effects in solid organ transplant recipients.
There are two major strategies used to prevent CMV disease in SOT recipients – (1) antiviral prophylaxis and (2) pre-emptive therapy.

ANTIVIRAL PROPHYLAXIS:

1. Antiviral prophylaxis involves administering antiviral drug to all at-risk patients, starting shortly after transplant (usually during the first 10 days), and given up to a pre-defined period of time, usually 3 to 6 months (and even for longer periods after lung transplantation).

2. The advantages of antiviral prophylaxis are ease of medication administration, protection from infections caused by other herpes viruses (HSV, VZV, EBV, HHV-6) and a decreased incidence of CMV related “indirect” effects such as allograft rejection, opportunistic infections and mortality.

3. The main disadvantages of antiviral prophylaxis are drug toxicities (mainly leukopenia and neutropenia from ganciclovir or valganciclovir) and late-onset CMV disease (CMV disease occurring after the completion of antiviral prophylaxis).

<table>
<thead>
<tr>
<th>Preferred Drugs</th>
<th>Antiviral prophylaxis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valganciclovir</td>
<td>900 mg PO once daily</td>
<td>900 mg PO twice daily</td>
</tr>
<tr>
<td>Ganciclovir IV</td>
<td>5 mg/kg once daily</td>
<td>5 mg/kg twice daily</td>
</tr>
<tr>
<td>Alternative drugs</td>
<td>Antiviral prophylaxis</td>
<td>Treatment</td>
</tr>
<tr>
<td>Oral ganciclovir</td>
<td>1 g PO thrice daily</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>2 g PO four times daily</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Not recommended</td>
<td>60 mg/kg IV every 8 h or 90 mg/kg every 12 h</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Not recommended</td>
<td>5 mg/kg once weekly × 2, followed by q 2 weeks thereafter</td>
</tr>
</tbody>
</table>

The drugs used for antiviral prophylaxis are valganciclovir (most common), oral ganciclovir, intravenous ganciclovir, or valaciclovir (in kidney transplant recipients only). Valganciclovir is preferred over oral ganciclovir due to higher oral bioavailability and lower pill burden, and is comparable to oral ganciclovir in preventing CMV disease in solid organ transplant recipients. Valganciclovir was associated with a higher rate of tissue invasive disease in liver transplant recipients compared to oral ganciclovir, but it is still the preferred drug used in liver transplant recipients.

Duration of antiviral prophylaxis depends on the serostatus of the donor and recipient as well as the type of organ transplanted.

A multicenter trial compared the incidence of late onset CMV disease and viremia in high risk lung transplant recipients receiving 3 months versus 12 months of valganciclovir prophylaxis. Patients who received 12 months of antiviral therapy had significantly lower rates of CMV disease and viremia and had a durable, long-term CMV protective benefit.
In the IMPACT trial, which compared the efficacy of 200 days versus 100 days of valganciclovir prophylaxis in D+/ R kidney transplant recipients, late onset CMV disease was significantly lower in the 200 days’ group [56]. This trial resulted in the recommendation of extending valganciclovir prophylaxis to 200 days in high risk (D+/R) kidney recipients. This has also been adapted by the liver, heart, pancreas transplant programs, even if systematic studies have not been performed in these organ recipients [49].

This has also been adapted by the liver, heart, pancreas transplant programs, even if systematic studies have not been performed in these organ recipients. Treatment of established CMV disease requires a multifactorial approach, including reduction of immunosuppressive agents, antiviral agents, and in some cases adjuvant therapy. Intravenous ganciclovir has been considered the mainstay of therapy. However, the Valcyte in CMV Disease Treatment of Solid Organ Recipients (VICTOR) trial found that valganciclovir was as effective as intravenous ganciclovir in at least some solid organ transplant recipients with mild to moderate disease.

Figure 3: Approach To CMV Prophylaxis In Adult Post Liver Transplant Recipients

Among the first antiviral agents to be used in the prevention of CMV infection and disease following solid-organ transplantation, specifically following renal transplantation, were the interferons. Studies with human and fibroblast leukocyte interferon showed mixed effects.
Studies with recombinant interferon demonstrated an unacceptably high rate of steroid-resistant allograft rejection and allograft loss. In theory, one of the simplest interventions for the prevention of CMV disease after transplantation would be immunization of seronegative recipients with a vaccine given once in anticipation of future viral challenge. A live attenuated CMV vaccine, which uses the Towne strain of virus, is both safe and immunogenic; however, there is no significant decrease in the incidence of CMV disease in renal transplant recipients receiving this vaccine.

PREVENTIVE MEASURES:
Careful pre-transplant screening, immunization, and post-transplant prophylactic antimicrobials may all reduce the risk for post-transplant infection. However, because transplant recipients may not manifest typical signs and symptoms of infection, diagnoses may be confounded. Furthermore, treatment regimens may be complicated by drug interactions and the need to maintain immune suppression to avoid allograft rejection.

Pre-transplant screening of potential organ donors and recipients is essential to the success of solid organ transplantation. Guidelines for pre-transplant screening of donor and recipient are outlined by the American Society for Transplantation clinical practice guidelines. These guidelines suggest exclusionary criteria for transplantation (based on conditions associated with poor outcomes after transplantation) and identify groups at high risk for post-transplant infections, thereby allowing for the implementation of preventive interventions.

<table>
<thead>
<tr>
<th>Table 5: Recommended Screening Tests For Donors And Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV antibody IgG</td>
</tr>
<tr>
<td>CMV IgG antibody</td>
</tr>
<tr>
<td>HTLV-1/2 antibody</td>
</tr>
<tr>
<td>HCV antibody</td>
</tr>
<tr>
<td>HBV: anti-HBsAg</td>
</tr>
</tbody>
</table>

Although infections remain a significant cause of morbidity and mortality after transplantation, improved prophylactic, diagnostic, and treatment strategies have decreased the negative effect of infection on transplant outcomes. Ongoing attention to infection prevention beginning before transplantation as well as improved surveillance for infections should be maintained in all patients being considered for transplantation.

CONCLUSION:
A detailed understanding of infections in solid-organ transplant recipients is essential to prevent and treat these sometimes devastating setbacks to an otherwise successful procedure. The epidemiology of infections in this population is changing because of the use of
prophylactic regimens vaccination, new immunosuppressive regimens and careful control of infectious exposures. The morbidity and mortality of CMV in solid-organ transplant recipients have been lowered in the last few years for multiple reasons. Despite, CMV remains at large and continues to have significant impact among solid organ transplant patients. Advances in the field of CMV and solid organ transplantation will be facilitated by the development of (1) optimized threshold for viral diagnosis, (2) effective vaccines for prevention, (3) Pre-transplant screening, and (4) newer antiviral agents with unique mechanisms of action and ideally with much less toxicity.

ACKNOWLEDGEMENT:
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