Prevention and Treatment of Cytomegalovirus Infections in Solid Organ Transplant Recipients

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KEYWORDS

• CMV • Cytomegalovirus • Herpesvirus infection • Solid organ transplantation
• CMV prophylaxis • CMV treatment

KEY POINTS

- Cytomegalovirus (CMV) prophylaxis and preemptive monitoring have reduced the incidence of early CMV disease in solid organ transplantation, but late disease has emerged as a significant problem.
- CMV-specific cell-mediated immunity (CMI) is required to control CMV in the absence of antiviral therapy, and achieving strong CMI without coincident allograft rejection is the ultimate goal of CMV management strategies.
- Measurement of CMV-specific CMI may help refine CMV prophylaxis and preemptive monitoring strategies.
- Valganciclovir remains the mainstay of CMV treatment but comes at the cost of frequent myelosuppression.
- Letermovir is a newly approved antiviral with strong activity against CMV and minimal side effects and may change the landscape of CMV management.

Human cytomegalovirus (CMV) is a double-stranded DNA virus and member of the herpes virus family. Infection prevalence reaches 60% to 80% by adulthood in the United States and nearly 100% in many parts of the world.[1,2] First recognized as a major complication of solid organ transplantation (SOT) 50 years ago, it remains the most common viral infection encountered after SOT and can occur as a primary infection, secondary infection, or reactivation from a latent reservoir.[3] Although humans have evolved to live a lifetime with persistent asymptomatic infection, recipients of SOT

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are challenged to adapt to and control CMV infection while deliberately impairing immune recognition of their allograft.

CYTOMEGALOVIRUS INFECTION AND THE IMMUNE RESPONSE

Primary infection in immunocompetent individuals is most often asymptomatic and transmitted via secretions of an infected individual. CMV disseminates from the respiratory epithelium, most commonly via mononuclear cells and polymorphonuclear cells to endothelial, epithelial, and fibroblast of tissues and organs.[1] Prolonged shedding in saliva and urine after primary infection provides evidence for coincident chronic viral replication in some sites but emergence of latency elsewhere.

The innate immune system provides initial antiviral activity until the adaptive immune response can exert more definitive control of infection. Both CD4 and CD8 T-cell responses are instrumental for control of CMV and guard against replication and infection of new cells.[4,5] CMV establishes lifelong latency in endothelium, epithelium, smooth muscle, and fibroblasts by evading immune detection.[5,6] Infections with CMV variants and intermittent viral replication from latency expand the breadth of CMV recognition over a lifetime.[1,7] Although humoral immunity may restrict viral dissemination early in the primary infection and with reinfection, its role beyond this is debated.[4,8,9] CMV immunoglobulin G (IgG), however, is reflective of past infection.

Cytomegalovirus in Solid Organ Transplant Recipients

Immunologic recognition of acute CMV infection and control of latent infection require many of the same mechanisms that are disabled by the immunosuppression that prevents allograft rejection. **Fig. 1** depicts the evolution of CMV infection in the normal host and the impact of transplantation.

RISK FACTORS FOR CYTOMEGALOVIRUS DISEASE

Risk for CMV disease is associated with past CMV infection, new CMV exposure, the degree of T-cell impairment, and the type of organ being transplanted (**Table 1**).

Cytomegalovirus Immunoglobulin G Donor/Recipient Status

About 20% to 30% of adult transplant recipients are CMV IgG negative and are at greatest risk for primary infection. The donor organ is the most common source for primary infection, but it can also occur through blood products and community exposures (eg, healthy children with salivary shedding). CMV IgG results can be falsely positive or negative. Direct testing for CMV-specific cell-mediated immunity (CMI) is more sensitive and more specific than antibody testing at identifying those with latent infection but is not practical in the transplant donation process and is not currently recommended as a screening tool for recipients.[10] False-positive CMV IgG is most often due to passive antibodies via blood products, usually intravenous immunoglobulin (IVIG). False-negative CMV IgG testing can occur rarely from waning antibody over time or from insensitive testing methods.[10]

Type and Degree of Immunosuppression

T-cell depleting agents are highly associated with CMV disease. High doses of steroids and higher levels of calcineurin inhibitors, mycophenolic acid, and azathioprine are also associated with CMV disease. CMV uses mammalian target of rapamycin (mTOR) pathways for viral replication, and the use of mTOR inhibitors have been associated with a lower risk for CMV infection and CMV syndrome (but not consistently

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